労災疾病臨床研究事業費補助金

石綿関連胸膜疾患における個別化治療とケアの確立

令和2年度 総括・分担研究報告書

研究代表者　藤本 伸一

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Ⅰ．　総括研究報告

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総 括 研 究 報 告 書

【石綿関連胸膜疾患における個別化治療とケアの確立】

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研究要旨

「切除不能悪性胸膜中皮腫に対する初回化学療法としてのシスプラチン、ペメトレキセドおよびニボルマブ併用化学療法の第 II 相試験」を医師主導治験として企画、立案し、治験を実施した。平成 30 年 1 月から令和元年 5 月までに予定した 18 例の登録を完了した。主要評価項目である Modified RECIST criteria による奏効率（中央判定）の評価を行ったところ、14 例において部分奏功が確認された（奏効率 77.8%）。化学療法あるいはニボルマブによると思われる消化器毒性、皮膚障害などの有害事象が認められたが既知の頻度、重症度と同等であり、コントロール可能であった。本試験はシスプラチン、ペメトレキセドおよびニボルマブ併用化学療法の有用性と安全性を強く示唆するものと思われた。

またニボルマブの効果を予測するためのバイオマーカーの確立が必須と考え、悪性胸膜中皮腫症例に対するニボルマブ投与における包括的免疫病態の変化を観察した。悪性胸膜中皮腫患者 8 例において末梢血を検体とした包括的免疫機能解析を行い、ニボルマブ投与による治療効果に関わる免疫学的因子の抽出を試みた結果、部分奏効（PR）を示した患者 1 例では治療前よりナチュラルキラー細胞（NK）の IFN-γ 産生誘導能が高く、細胞傷害性 T リンパ球の活性化指標 HLA-DR も高いが、Treg 指標 CTLA-4 も高いことが分かった。抑制されていた高い抗腫瘍免疫機能が解放され明瞭な腫瘍抑制効果に至った可能性が示唆された。さらに、悪性胸膜中皮腫における化学療法の効果あるいはその耐性メカニズムについて、メタボローム解析を用いて検討した。ペメトレキセド耐性化細胞株を樹立し、ペメトレキセド耐性化に伴い thymidylate synthase（TYMS）の発現が増加していることを確認した。さらに、TYMS の発現をノックダウンや過剰発現させたところ、ノックダウンによって薬剤耐性が低下し、過剰発現によって薬剤耐性が増加することがわかり、TYMS の発現増加がペメトレキセド耐性化と関連があることが示唆された。

また石綿ばく露労働者に発症するびまん性胸膜肥厚における著しい呼吸機能障害をより客観的に評価するため、職業性石綿ばく露歴があり、胸部画像検査でびまん性胸膜肥厚と診断された症例を対象に、呼吸機能検査、6 分間歩行試験と ADL の評価を行った。6 分間歩行試験における経皮的酸素飽和度（SpO_2）の最低値は 86.2%、総歩行距離/予測値は 77.3%であった。びまん性胸膜肥厚患者の 6 分間歩行試験において、「SpO_2 最低値が 90%以下、あるいは歩行距離が予測値の 90%以下であること」が、著しい呼吸機能障害の基準になりうると考えられた。

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A．研究目的

胸膜中皮腫に対する新たな治療法として、「切除不能悪性胸膜中皮腫に対する初回化学療法としてのシスプラチン、ペメトレキセドおよびニボルマブ併用化学療法の第 II 相試験」を医師主導治験(以下本治験)として行った。

また胸膜中皮腫におけるニボルマブ治療前後の免疫学的特徴を包括的に解析することにより、治療効果を免疫学的に評価すると共に中皮腫治療の奏功を予測する免疫学的因子群を抽出し、その予測指標の確立を目指す。胸膜中皮腫における代謝産物プロファイルを解析することにより、抗がん剤の効果や耐性機序を予測し、患者を層別化できるバイオマーカーの発見を目的とした。また石綿ばく露労働者に発症するびまん性胸膜肥厚における著しい呼吸機能障害の基準は通常呼吸機能検査と動脈血ガス分析に基づき評価されるが、これらの検査値は良好であるにも関わらず日常生活動作が著しく低下する症例があり、そのような症例を適切に労災認定できるようにするため呼吸機能検査（１次及び２次）に加え６分間歩行、アンケート調査（問診票 P-ADL）を行い、多角的に評価した。

B．研究方法

本治験では、外科的切除不能の進行又は転移性の悪性胸膜中皮腫を対象とし、中央判定による奏効率を主要評価項目として、ニボルマブを含む併用化学療法の有効性と安全性を検討する。主目的は、切除不能の進行又は転移性の悪性胸膜中皮腫に対し、初回化学療法としてシスプラチン(75mg/m^2)、ペメトレキセド（500mg/m^2)、ニボルマブ（360mg/body）を３週間間隔で、最大６コース投与し、以後は中止基準に該当するまでニボルマブによる維持療法を３週間ごとに実施し、有効性及び安全性を多角的に検討する。実施医療機関は、岡山労災病院、岡山大学病院、四国がんセンター、山口宇部医療センターの４施設であり、実施可能性を考慮し、症例数は 18 例と設定した。

石綿による悪性胸膜中皮腫における免疫指標を包括的にスコアリングするため、実際にニボルマブによる治療を行う患者からニボルマブ投与前、投与１週後、また投与３か月後に末梢血を採取し、サイトカイン、単球・CD4 陽性細胞（Th)・CD8 陽性細胞(CTL）およびナチュラルキラー細胞（NK 細胞）の膜表面分子、遺伝子発現を観察した。

悪性胸膜中皮腫細胞株を用い、thymidylate synthase (TYMS) のノックダウン及び、レトロウイルスを用いた TYMS の過剰発現を行い、それらによって薬剤感受性が変化するかどうかを調べた。

胸部単純写真及び CT 検査にてびまん性胸膜肥厚と診断された症例において、呼吸機能検査として、肺機能検査１次（%肺活量や１秒量、１秒率など）・2 次（PaO_2 や $AaDO_2$ など）検査とともに６分間歩行試験を行った。６分間歩行試験では経皮的酸素飽和度（SpO_2）の最低値や歩行距離などをモニタリングした。

C. 研究結果

本治験においては、2018 年 1 月より症例登録を開始し、2019 年 5 月までに予定した 18 例の登録を完了した。主要評価項目である Modified RECIST criteria による奏効率(中央判定) の評価を行ったところ、14 例において部分奏功 (PR) が確認された (奏効率 77.8%)。標的病変の腫瘍径和の変化率を図 1 、図 2 に示す。18 例全例で少なくとも 1 ポイント以上において 30%を超える腫瘍径和の減少が認められた。

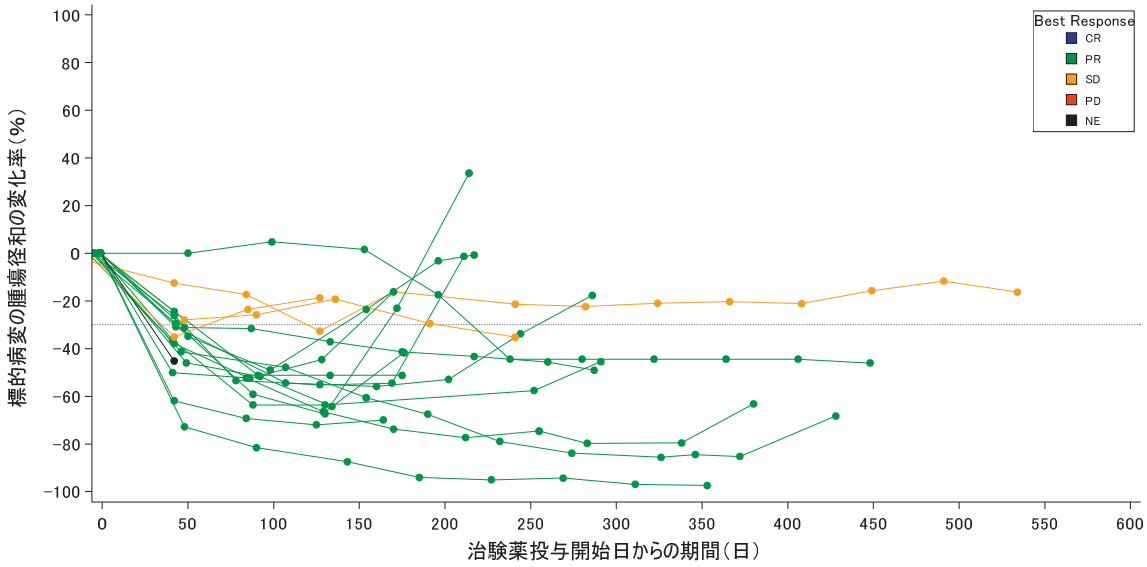

図 1. 標的病変の腫瘍径和の変化率の spider plot

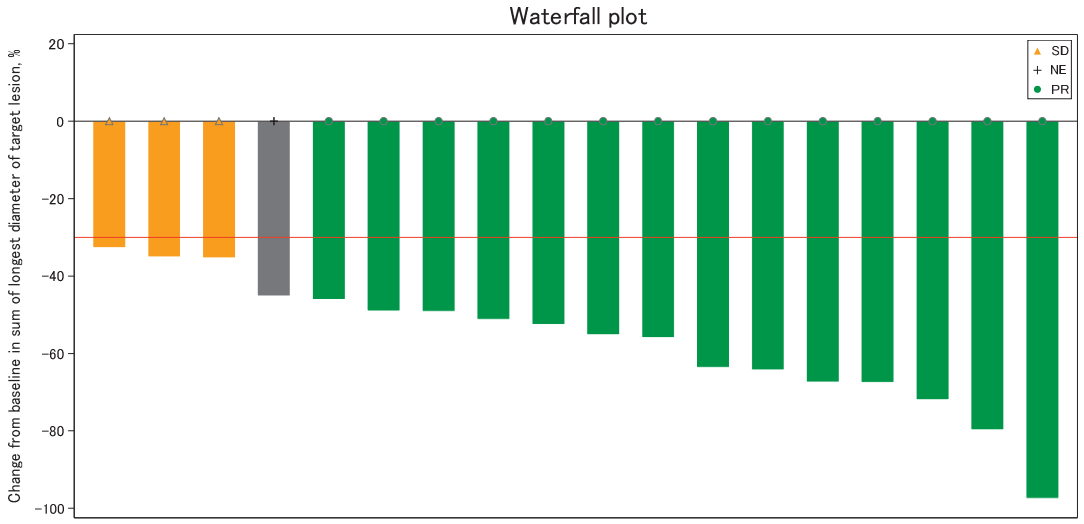

図 2. 最良の標的病変の腫瘍径和の変化率の waterfall plot

解析対象の 18 例全例に有害事象が発現し、主なものは悪心、食欲減退、しゃっくり、便秘、発疹、貧血、倦怠感、好中球数減少、上咽頭炎、不眠症、下痢、発熱、白血球数減少、末梢性ニューロパチーなどであった。有害事象により死亡した症例はなかった。

また実際にニボルマブを投与した悪性胸膜中皮腫患者から供与していただいた末梢血中の免疫担当細胞における免疫指標を解析したところ、CD4+ Th, CD8+ CTL の何れにおいても、SD+PR 群と PD 群の群間の差異および治療前後で共通して変化する指標は確認できなかった。一方、PR を示した MOP-7 (図中の赤色) では、CD4+ Th における CD25 (%) が治療前、１週間後、３か月後の何れにおいても他の症例の何れの測定値よりも高値であった。また、CD4+ Th 上の CTLA-4 (%) も継続して高い傾向であった。一方、CD8+ CTL においては、HLA-DR (%) が高い傾向を示した。PR を示した MOP-7 では刺激後の NK における IFNg mRNA レベルが治療前と治療３か月後において共に高値であることが他とは異なる特徴であった (図３)。しかし、１例のみではあるが PR を示した症例においては、Th 上の CD25%と CTLA-4%および CTL 上の HLA-DR%、加えて刺激後 NK 中の IFN-γ mRNA レベルが継続して高い傾向であることが明らかとなった。

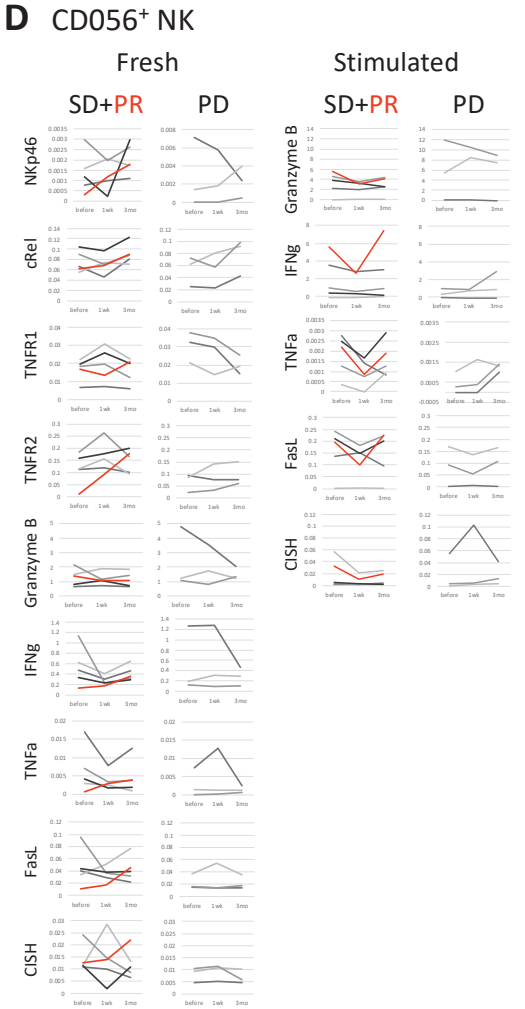

図３．NK 中の mRNA レベルの測定結果

２種のペメトレキセド耐性化株のセルライセートを作成し、ウェスタンブロットを行ったところ、いずれの細胞株でも親株に比べてペメトレキセド耐性化株の方が TYMS の発現が増加していた (図４)。次に、TYMS の発現が増加しているペメトレキセド耐性化株を用いて、siRNA を用いて TYMS をノックダウンしたところ、薬剤耐性が有意に減少していた (図５)。

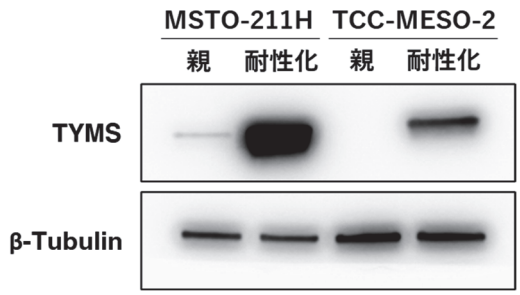

図４．薬剤耐性化によるタンパク質発現の変化

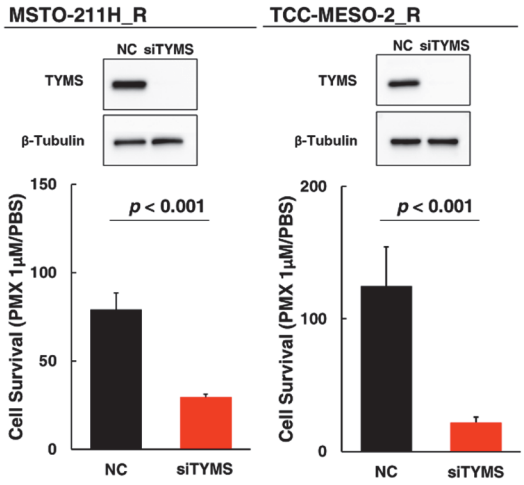

図５．TYMS の KD による薬剤耐性の変化

石綿ばく露によるびまん性胸膜肥厚に関する研究では、研究期間中に 12 名から研究参加同意を得た。12 名全員が男性であり、検査時年齢の中央値は 76.5 歳（67～87 歳）であった。12 名中 10 名が%VC < 60%で呼吸機能障害の基準を満たしていた。SpO_2 について、検査中の最低値は 86.2%（95%信頼区間 82-90%）であった。総歩行距離/予測値は 77.3%（95%信頼区間 63-91%）であった。また、P-ADL によるアンケート調査では、「階段」（24 点満点中, 20.8 点）、「屋外歩行」（20 点満点中，17.5 点）の項目で、他の項目と比較して点数が低かった。

D．考察

本研究は、「石綿関連胸膜疾患における個別化治療とケアの確立」を課題とし、以下の研究項目を掲げている。1．切除不能悪性胸膜中皮腫に対するシスプラチン、ペメトレキセドおよびニボルマブ併用化学療法の医師主導治験、2．石綿ばく露による免疫動態の変化とニボルマブ投与における免疫修飾の観察、3．悪性胸膜中皮腫細胞における細胞内代謝産物プロファイルの解析（メタボローム解析）、４．びまん性胸膜肥厚における重症度を客観的に評価するための指標の作成、である。

悪性胸膜中皮腫に対する薬物治療としては、一次治療としてシスプラチン、ペメトレキセド療法が標準治療とされているがその治療成績は十分とは言えず、また同療法に抵抗性となった患者においては確立した治療法はなく、新たな治療法の開発が切望されている。

本研究では、現在の標準治療であるシスプラチン、ペメトレキセド療法とニボルマブの併用によりさらなる治療効果の上乗せを期待し、初回化学療法における有効性及び安全性を評価した。主要評価項目である中央判定における奏効率において、当初の想定を上回る高い奏効率が得られた。また安全性の評価においては、消化器毒性、皮膚障害などの有害事象が確認されたが、これらの頻度、重症度はこれまでの化学療法や免疫チェックポイント阻害薬をもちいた臨床試験の報告と同様であり、マネジメント可能なものであった。本試験は、シスプラチン、ペメトレキセドおよびニボルマブ併用化学療法の有用性と安全性を強く示唆するものであり、今後胸膜中皮腫におけるあらたな治療選択肢となる可能性がある。

また、実際にニボルマブを投与した８例の悪性胸膜中皮腫患者においてニボルマブ治療前後の包括的免疫機能解析を行った。治療効果の差による群間比較では明瞭な差を捉えることは出来なかったが、PR を示した症例において、Th 上の CD25%と CTLA-4%および CTL 上の HLA-DR%、加えて刺激後 NK 中の IFN-γ mRNA レベルが継続して高い傾向であった。ニボルマブにより PD-1 分子を介した免疫抑制が解除されることで、備えるが抑制されていた強い NK 細胞機能と活性化 CTL の機能が解放され

機能を発揮した結果、明瞭な腫瘍抑制効果に至った可能性が示唆された。

さらに、薬剤耐性化した２つの悪性胸膜中皮腫細胞株においてタンパク質レベルにおけるTYMSの発現増加が確認され、また、TYMS のノックダウンや過剰発現を行い、TYMS の発現を増減させることでペメトレキセドに対する薬剤耐性がそれに反比例して変化することが分かった。つまり、悪性胸膜中皮腫細胞株ではペメトレキセドに暴露され続けることで TYMS の発現が増加し、それが要因となってペメトレキセドに対する耐性を獲得したことが明確となった。今後は、TYMS がどのようにして発現が増加したのか、その制御機構を解明することは引き続き検討課題である。

びまん性胸膜肥厚 12 例に対して肺機能検査、６分間歩行試験、アンケート調査(P- ADL) を行った。６分間歩行試験の解析では、安静時と比較し、労作時の SpO_2 低下が顕著であった。びまん性胸膜肥厚患者の６分間歩行試験において、「SpO_2 最低値が 90%以下、あるいは歩行距離が予測値の 90%以下であること」が、著しい呼吸機能障害の基準になりうると考えられた。また本研究の結果から、びまん性胸膜肥厚の患者は安静時の ADL に大きな障害はないが、労作時の ADL が特に障害されていることがわかった。これまでの評価基準である肺機能検査や動脈血ガス分析では、安静時の評価しか行えなかったが、本研究はいままで明確な数値基準がなかった６分間歩行試験の基準を提示できた点で重要である。

Ｅ．結論

「切除不能悪性胸膜中皮腫に対する初回化学療法としてのシスプラチン、ペメトレキセドおよびニボルマブ併用化学療法の第 II 相試験」を医師主導治験として実施した。

ニボルマブ治療前後の包括的免疫機能解析の結果、治療奏効と関わる特徴として、１）NK の IFN-γ 産生誘導能が高く、２）活性化 CTL が多く、３）Treg 細胞が多いことが捉えられた。ペメトレキセド耐性化細胞株を樹立し、ペメトレキセド耐性化に伴いTYMSの発現が増加していることを確認した。

びまん性胸膜肥厚患者の６分間歩行試験において、「SpO_2 最低値が 90%以下、あるいは歩行距離が予測値の 90%以下であること」を、著しい呼吸機能障害の基準として提唱した。

Ｆ．健康危険情報

抗悪性腫瘍薬の使用に際しては製薬メーカーから提供される取り扱い情報に基づき適正に取り扱った。また実際の投与に際しては、厚生労働省労働基準局より発出された「発がん性等を有する化学物質を含有する抗がん剤等に対するばく露防止対策について」（基安化発 0529 第１号）に則り各施設で定められた抗がん剤ばく露対策マニュアルを遵守し、医師、薬剤師、看護師が薬剤に曝露しないようにした。また患者やその家族に対しても、薬剤の取扱いに関する情報を周知した。

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Ｈ．知的財産権の出願・登録状況（予定を含む。）

1. 特許取得

該当するものなし。

2. 実用新案登録

該当するものなし。

3.その他

特記すべき事項なし。

Ⅱ．　分担研究報告

労災疾病臨床研究事業費補助金
分 担 研 究 報 告 書

【切除不能悪性胸膜中皮腫に対する初回化学療法としてのシスプラチン、ペメトレキセドおよびニボルマブ併用化学療法の第 II 相試験】

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研究要旨

悪性胸膜中皮腫は診断・治療ともに困難な疾患であり、診断から死亡に至るまでの生存期間中央値は 7.9 か月と予後不良である。化学療法治療歴のない悪性胸膜中皮腫の一次治療としてシスプラチンとペメトレキセドの併用療法が標準治療とされているが、同療法に抵抗性となった患者に対する確立した治療法はなく、新たな治療法の開発が切望されている。本研究では、抗 PD-1 抗体の有用性を検討するため「切除不能悪性胸膜中皮腫に対する初回化学療法としてのシスプラチン、ペメトレキセドおよびニボルマブ併用化学療法の第 II 相試験」を医師主導治験として企画、立案し、治験を実施した。平成 30 年１月より症例登録を開始し、令和元年 5 月までに予定した 18 例の登録を完了した。主要評価項目である Modified RECIST criteria による奏効率（中央判定）の評価を行ったところ、14 例において部分奏功（PR）が確認された（奏効率 77.8%）。化学療法あるいはニボルマブによると思われる消化器毒性、皮膚障害などの有害事象が認められたが既知の頻度、重症度と同等であり、コントロール可能であった。本試験は、シスプラチン、ペメトレキセドおよびニボルマブ併用化学療法の有用性と安全性を強く示唆するものと思われた。

Ａ．研究目的

1．治験の主目的

外科的切除不能の進行又は転移性の悪性胸膜中皮腫に対し、初回化学療法として、シスプラチン（75 mg/m^2）、ペメトレキセド（500 mg/m^2）、ニボルマブ（360 mg/body）を３週間間隔で、最大６コース投与し、以後は中止基準に該当するまでニボルマブによる維持療法を３週間ごとに実施したときの有効性（奏効率）を検討する。

2．治験の副目的

設定した有効性の副次評価項目及び安全性の評価項目を用いて、外科的切除不能の進行又は転移性の悪性胸膜中皮腫に対するシスプラチン、ペメトレキセドおよびニボルマブ併用化学療法の有効性及び安全性を多角的に検討する。

Ｂ．研究方法

1..　対象

未治療の外科的切除不能の進行又は転移性の悪性胸膜中皮腫患者

2. 選択基準

登録時に、下記のすべての基準を満たす被験者を選択する。なお、登録から３剤併用化学療法の初回投与前までに下記の基準を満たさないことが明らかとなった場合は、３剤併用化学療法の１コース目の投与を開始しない。

1) 年齢（同意取得時）：20 歳以上
2) 病理学的に悪性胸膜中皮腫と診断された患者
3) 未治療の外科的切除不能の進行又は転移性の悪性胸膜中皮腫患者
4) 登録前 28 日以内の画像診断において、CT 又は MRI により、Modified Response Evaluation Criteria in Solid Tumours (RECIST) criteria に定義される測定可能病変を一つ以上有する患者。ただし、測定可能病変が胸膜病変のみで胸膜癒着術の既往がある場合は、胸膜癒着術後の画像診断において測定可能病変を確認できた患者に限る。
5) PD-L1 発現解析に用いる腫瘍組織（保存組織又は直近で採取した生検組織）を提供できる患者
6) Eastern Cooperative Oncology Group (ECOG) performance status が 0 又は 1 の患者
7) 90 日以上の生存が期待される患者
8) 登録前 7 日以内に酸素補充を行わない状態で、安静時にパルスオキシメーターにて測定した経皮的酸素飽和度が 94%以上の患者。
9) 登録前 7 日以内に実施した最新の臨床検査値が下記の基準を満たす患者。なお、検査日前 14 日以内に顆粒球コロニー刺激因子（G-CSF 製剤）の投与又は輸血を受けていない臨床検査値とする。

① 好中球数が 1,500/mm^3 以上
② 血小板数が 100,000/mm^3 以上
③ ヘモグロビンが 9.0 g/dL 以上
④ AST（GOT）及び ALT（GPT9）が施設基準値上限の 3.0 倍以下
⑤ 総ビリルビンが施設基準値上限の 2.0 倍以下
⑥ クレアチニンが施設基準値上限以下かつクレアチニンクリアランス (Cockcroft/Gault 式による推定値）が 60 mL/min を超える。

10) 妊娠する可能性のある女性（化学閉経などの医学的理由により月経がない患者も含む）
11) 男性の場合、ニボルマブ投与開始後からニボルマブ最終投与後少なくとも７か月間（ニボルマブの５倍半減期と精子の代謝回転に要する期間の合計）の避妊に同意した患者、若しくは完全禁欲に同意した患者
12) 治験責任医師等より、本治験の内容について同意文書及び説明文書を用いて十分に説明を受け、自由意思により本治験参加に同意する患者

3. 除外基準

登録時に、下記のいずれかの基準に該当すると考えられる被験者は除外する。なお、登録から３剤併用化学療法の初回投与前までに下記のいずれかの基準に抵触した場合は、３剤併用化学療法の１コース目の投与を開始しない。

1) 抗体製剤を含む他の薬剤に対する高度の過敏反応の合併又は既往を有する患者
2) 自己免疫疾患の合併又は慢性的あるいは再発性の自己免疫疾患の既往を有する患者。ただし、全身療法を必要としない皮膚疾患（白斑、乾癬、脱毛症など）又は外的誘因の非存在下では再発すると考えられない疾患、ホルモン補充療法により対処可能な甲状腺機能低下症を合併している患者は登録可能とする。
3) 重複がんを有する患者（完全切除された基底細胞がん、Stage I の有棘細胞がん、皮内がん、粘膜内がん又は表在性膀胱がん、あるいは５年間以上再発が認められない他のがんの既往を有する患者は登録可能とする）

4) 脳又は髄膜に転移巣を有する患者。ただし、無症状かつ治療を必要としない患者は登録可能とする。また、本治験への登録の 28 日以上前に同病巣に対する治療を終えて病状が安定しており、かつ本治験への登録の前 14 日間で全身性副腎皮質ホルモンの継続使用を要さない患者は登録可能とする。
5) 画像診断又は臨床所見により診断された間質性肺疾患若しくは肺線維症の合併又は既往を有する患者。ただし、放射線性肺臓炎については、線維化による安定化が確認され、再発の懸念がない患者は登録可能とする。
6) 憩室炎又は症候性消化管潰瘍疾患を合併している患者
7) ２週間に１回を超える頻度で排液を必要とする胸水の貯留を認める患者
8) 治療を必要とする心嚢液又は腹水の貯留を認める患者
9) 腫瘍に関連する疼痛が安定せず、管理不能な患者
10) 登録前 180 日以内に一過性脳虚血発作、脳血管発作、血栓症又は血栓塞栓症(肺動脈塞栓症又は深部静脈血栓症）の既往を有する患者
11) 下記の管理不能又は重大な心血管疾患を有する患者
    ① 登録前 180 日以内の心筋梗塞
    ② 登録前 180 日以内の管理不能な狭心症
    ③ New York Heart Association (NYHA)心機能分類Ⅲ度又はⅣ度のうっ血性心不全
    ④ 適切な治療にもかかわらず管理不能な高血圧（収縮期血圧 150 mmHg 以上又は拡張期血圧 90 mmHg 以上が 24 時間以上持続するなど)
    ⑤ 管理不能な不整脈
12) 抗凝固療法（低用量アスピリンを含む抗血小板療法を除く）を受けている又はそれらを必要とする疾患を有する患者
13) 管理不能な糖尿病を合併している患者
14) 治療を必要とする全身性感染症を有する患者
15) HIV への感染が明らかな患者
16) HTLV-1 抗体検査、HBs 抗原検査又は HCV 抗体検査のいずれかが陽性の患者。また、HBs 抗原検査が陰性であるが、HBs 抗体検査又は HBc 抗体検査のいずれかが陽性かつ HBV-DNA 定量が検出感度以上の患者
17) 過去にニボルマブ（MDX-1106 又は BMS-936558）、抗 PD-1 抗体、抗 PD-L1 抗体、抗 PD-L2 抗体、抗 CD137 抗体、抗 CTLA-4 抗体又はその他の T 細胞制御を目的とした抗体療法若しくは薬物療法の前治療歴を有する患者
18) 登録前 14 日以内に局所又は表面麻酔を伴う手術療法を受けた患者
19) 登録前 28 日以内に全身麻酔を伴う手術療法を受けた患者
20) 登録前 14 日以内に胸膜癒着術を受けた患者（ピシバニールによるものを除く）
21) 登録前 28 日以内にピシバニールによる胸膜癒着術を受けた患者
22) 心膜癒着術あるいは腹膜癒着術の既往のある患者
23) 登録前 14 日以内に疼痛緩和を目的とした放射線療法を受けた患者
24) 登録前 56 日以内に放射性医薬品（検査及び診断を目的とした放射性医薬品の使用を除く）の投与を受けた患者
25) 登録前 28 日（抗体製剤の場合は 90 日）以内に他の未承認薬の投与（悪性胸膜中皮腫に対する効能・効果を有しない承認薬、臨床研究による投与や未承認の配合薬、新剤形薬も含む）を受けた患者
26) 登録前 28 日以内に全身性副腎皮質ホルモン（検査、アレルギー反応に対する予防投与又は放射線療法に伴う浮腫軽減などを目的とした一時的な使用を除く）又は免疫抑制剤の投与を受けた患者
27) 妊娠中、授乳中又は妊娠している可能性のある患者

28) 認知症の合併などにより同意能力を欠く状態であると判断される患者
29) その他、治験責任医師等が治験対象として不適当と判断した患者

4．投与量及び投与方法

本治験は外科的切除不能の進行又は転移性の悪性胸膜中皮腫を対象に、標準療法である PC 療法（シスプラチン、ペメトレキセド療法）にニボルマブを加えた３剤併用化学療法の有効性及び安全性を検討する多施設共同非盲検非対照試験である。本治験はスクリーニング期、治療期及び後観察期からなる。「選択基準」に示す基準を満たし、かつ「除外基準」に示す基準に該当せず、治験責任医師又は治験分担医師が本治験の対象として適格と判断した患者を組み入れる。

試験の概要を図１に示した。治療期は、「３剤併用化学療法期」と「ニボルマブ単独維持療法期」から構成される。初回投与は登録から７日以内に行う。３剤併用化学療法期では、シスプラチン（75 mg/m^2）、ペメトレキセド（500 mg/m^2）、ニボルマブ（360 mg/body）の用量を３週間間隔で静脈内投与する。３週間を１コースとして、２コース間隔で画像診断（CT/MRI など）を実施し、「３剤併用化学療法期の投与継続基準」に示す基準をすべて満たす被験者は３剤併用化学療法を４～６コース行う。３剤併用化学療法期を完了するか、もしくは３剤併用化学療法の投与中止基準のいずれかに該当する場合は、ニボルマブ単独維持療法期への移行基準を確認のうえ、ニボルマブ単独維持療法期に移行する。移行期は「ニボルマブ単独維持療法期の投与中止基準」のいずれにも該当しない場合、３週間間隔で継続可能である。ニボルマブ単独維持療法期に移行できない場合や移行例が「ニボルマブ単独維持療法期の投与中止基準」のいずれかに該当する場合は、後観察期に移行する。

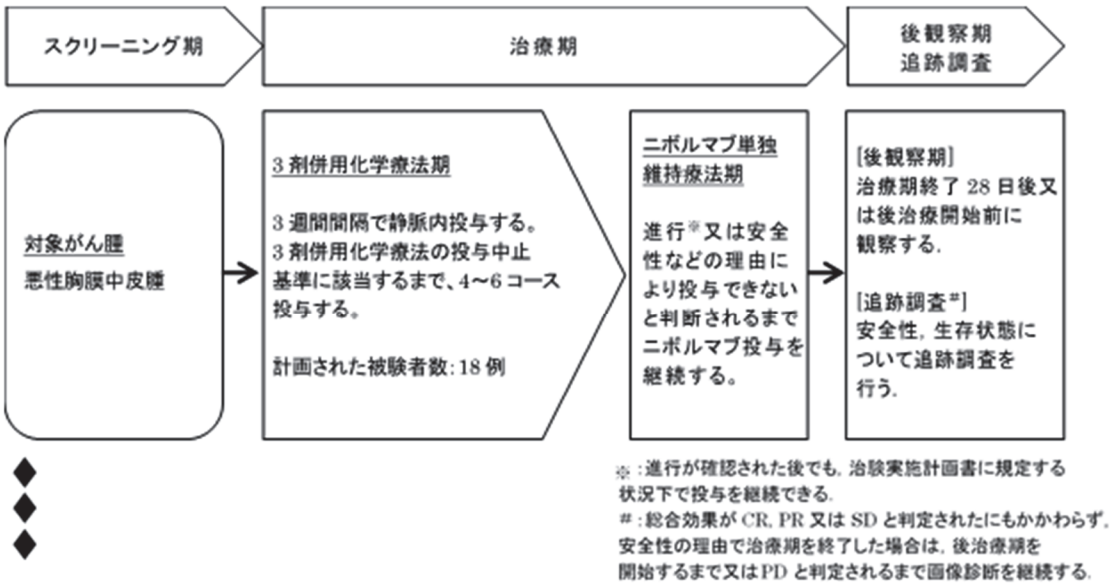

図１．試験の概要

5. 実施医療機関

４施設（岡山労災病院、岡山大学病院、四国がんセンター、山口宇部医療センター）

6. 計画された被験者数とその根拠

国内で施行されたシスプラチン、ペメトレキセド併用療法における奏効率は 36.8%と報告されている（Nakagawa et al. J J Clin Oncol 2008）。本治験を第 II 相試験として実施する場合、実施可能性を考慮のうえ、18 例と設定した。

本治験における奏効例数を５例～10 例と想定すると、奏効率は 35.7%～71.4%となるが、そのとき、奏効率の点推定値と Exact 法による下側信頼限界（信頼係数:両側 90%）の幅は 20%～25%となる。必要被験者数の算出で算出した必要被験者から数名の被験者が早期脱落などにより評価不能となる可能性を考慮し、目標被験者数を 18 名とした。

7. 評価項目

１）有効性の評価項目

①主要評価項目：Modified RECIST criteria による奏効率（中央判定）

②副次評価項目

a. 奏効率（実施医療機関の医師による判定、Modified RECIST criteria）
b. 奏効率（中央判定、Modified RECIST criteria）
c. 病勢制御率（中央判定、Modified RECIST criteria）
d. 全生存期間
e. 無増悪生存期間（中央判定、Modified RECIST criteria）
f. 奏効期間（中央判定、Modified RECIST criteria）
g. 奏効に至るまでの期間（中央判定、Modified RECIST criteria）
h. 最良総合効果（中央判定、Modified RECIST criteria）
i. 標的病変の腫瘍径和の変化率（実施医療機関の医師による判定、Modified RECIST criteria）

２）安全性の評価項目

①有害事象

a. 臨床検査（血液学的検査、生化学的検査、膵機能検査、血液凝固系検査、尿検査、免疫学的検査、ホルモン検査）
b. バイタルサイン（収縮期血圧／拡張期血圧、脈拍数、体温）、体重
c. 12 誘導心電図
d. 胸部 X 線
e. ECOG performance status

３）QOL 評価

QOL（EQ-5D、LCSS-Meso）

４）探索的評価項目

PD-L1 の免疫組織化学的解析

（倫理面への配慮）

本治験は治験実施計画書、ヘルシンキ宣言に基づく倫理的原則、医薬品、医療機器等の品質、有効性および安全性の確保等に関する法律第 14 条第３項、第 23 条の 25 第３項及び第 80 条の２に規定する基準並びに「医薬品の臨床試験の実施の基準に関する省令（GCP）」（平成９年 厚生省令第 28 号）に則り実施するものとする。本治験は、実施に先立ち、各実施医療機関の治験審査委員会において、治験実施計画書、被験者の同意を得るのに使用される方法、治験薬概要書及びその他の必要な文書が審議され、本治験が倫理的及び科学的に妥当であるかどうか、その他、本治験が実施医療機関において行うのに適当であるかどうかの審査を受ける。被験者の登録および症例報告書における被験者の特定はデータ・試料管理担当者によって、被験者識別コード等で行うなど連結可能匿名化を行う。原資料の直接閲覧・取り扱い等においては被験者のプライバシー保護に十分配慮する。患者試料、中央判定のための画像なども、同様に被験者識別コード等で行うとともに、他施設への試料の移送などに際しては、この被験者識別コード等にて識別する。

C．研究結果

2018年1月より症例登録を開始し、2019年5月までに予定した18例の登録を完了した。登録症例の概要を表1に示す。

表1．登録症例の概要

項目	n （%）
性別	
男	15（83.3）
女	3（16.7）
年齢（歳）	
平均値 ± 標準偏差	69.2 ± 4.1
中央値	69.0
最小値 ～ 最大値	64 ～ 78
組織型	
上皮型	14（77.8）
肉腫型	2（11.1）
二相型	2（11.1）
病期分類	
Ⅰ期	8（44.4）
Ⅱ期	0（ 0.0）
Ⅲ期	9（50.0）
Ⅳ期	1（ 5.6）
ECOG Performance Status	
0	3（16.7）
1	15（83.3）
PD-L1 28-8 発現	
なし	1（ 5.6）
あり	17（94.4）

１．主要評価項目

Modified RECIST criteria による奏効率（中央判定）： 18 例中 14 例が奏効と判定され、奏効率は 77.8%であった。なお、Clopper-Pearson 法に基づく 90%信頼区間は[56.1, 92.0]であった。

２．副次評価項目

1) 奏効率（実施医療機関の医師による判定、Modified RECIST criteria）: 18 例中 14 例が奏効と判定され、奏効率は 77.8%であった。
2) 病勢制御率（中央判定、Modified RECIST criteria）: 18 例中 17 例が病勢制御と判定され、病勢制御率は 94.4%であった。
3) 全生存期間 : 全生存期間は最短で 1.7 か月（打ち切り）、最長で 20.8 か月であった。
4) 無増悪生存期間（中央判定、Modified RECIST criteria）: 無増悪生存期間は中央値 8.02 か月［ 90%信頼区間（5.75, 14.06）］、最短で 1.7 か月（打ち切り）、最長で 14.7 か月（打ち切り）であった。
5) 奏効期間（中央判定、Modified RECIST criteria）: 奏効期間の中央値は 6.70 か月[90%信頼区間（4.30, 12.58）]、最短で 2.8 か月、最長で 13.2 か月（打ち切り）であった。
6) 奏効に至るまでの期間（中央判定、Modified RECIST criteria）: 奏効に至るまでの期間の中央値は 1.54 か月[90%信頼区間（1.38, 1.64）]、最短で 1.4 か月、最長で 3.3 か月であった。
7) 最良総合効果（中央判定、Modified RECIST criteria）: 最良総合効果は、CR 0 例、PR 14 例、SD 3 例、PD 0 例、NE 1 例であった。
8) 標的病変の腫瘍径和の変化率（実施医療機関の医師による判定、Modified RECIST criteria）（図２、図３）: 最良総合効果が SD、NE であった症例も含め、18 例全例で少なくとも 1 ポイント以上の PR 評価が得られた標的病変の腫瘍径和の変化率は、PR 相当である 30%を超える減少が認められた。

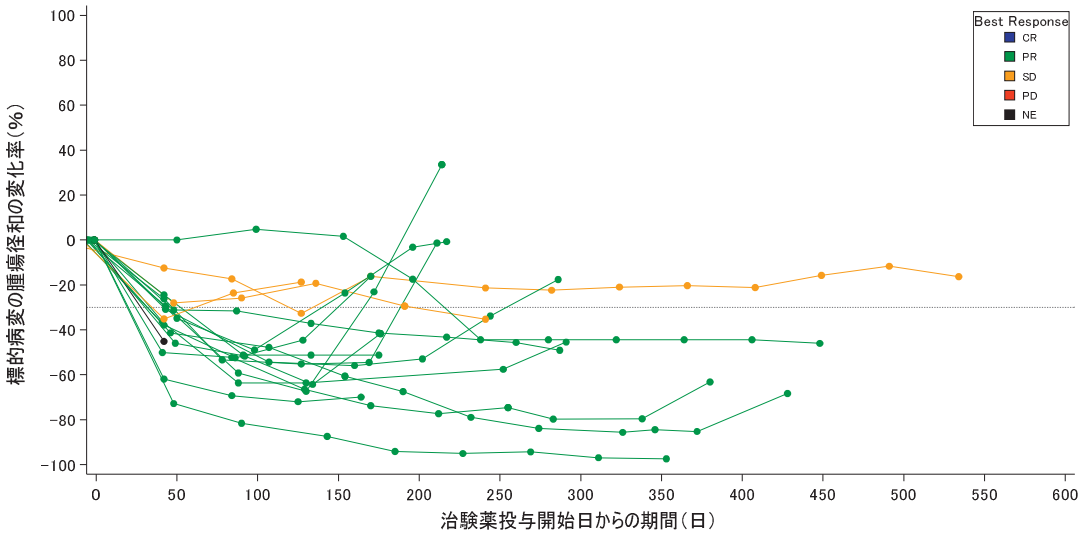

図２．標的病変の腫瘍径和の変化率の spider plot

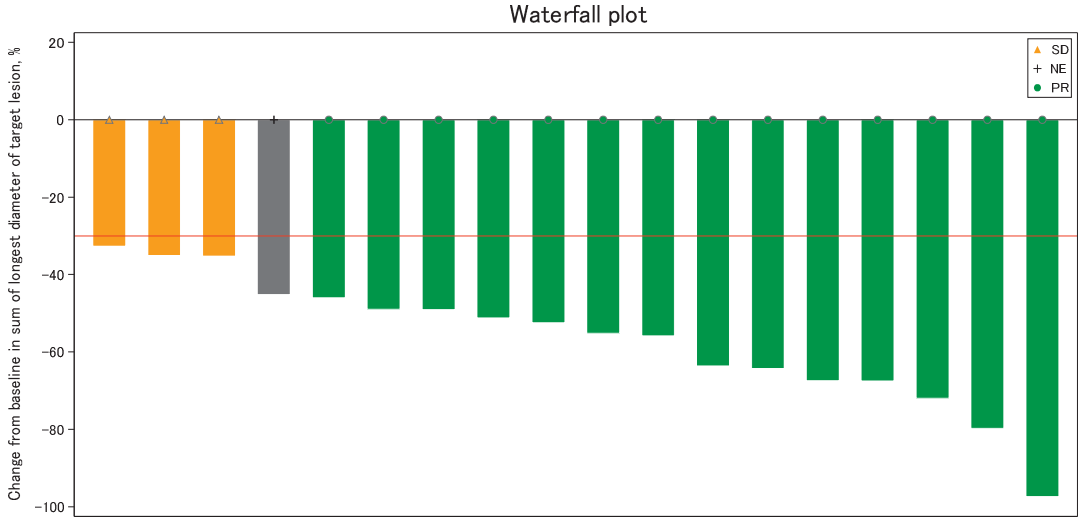

図３．最良の標的病変の腫瘍径和の変化率の waterfall plot

３．安全性の評価項目

解析対象の 18 例全例に有害事象が発現した。なお、有害事象により死亡した症例はなかった。ニボルマブとの関連が否定できない有害事象（副作用）は 16 例(88.9%) に発現した。

解析対象の 18 例の 10%以上で発現した有害事象は悪心 12 例 (66.7%)、食欲減退 11 例 (61.1%)、しゃっくり 11 例 (61.1%)、便秘 9 例(50.0%)、発疹 7 例 (38.9%)、貧血 7 例 (38.9%)、倦怠感 6 例 (33.3%)、好中球数減少 5 例(27.8%)、上咽頭炎 5 例(27.8%)、不眠症 5 例(27.8%)、下痢 4 例(22.2%)、発熱 4 例 (22.2%)、白血球数減少 4 例 (22.2%)、末梢性ニューロパチー 4 例(22.2%)、口内炎 3 例 (16.7%)、肺炎 3 例(16.7%)、味覚障害 3 例 (16.7%)、難聴 3 例(16.7%)、腹部不快感 2 例 (11.1%)、口角口唇炎 2 例 (11.1%)、低ナトリウム血症 2 例(11.1%)、筋肉痛 2 例 (11.1%)、背部痛 2 例(11.1%)であった。

Grade3 以上の有害事象は、18 例中 9 例(50.0%) に発現した。内訳は、「代謝および栄養障害」6 例 (33.3%) ［食欲減退 5 例(27.8%)、低ナトリウム血症 2 例 (11.1%)］、「臨床検査」3 例 (16.7%) ［白血球数減少 1 例 (5.6%)、アラニンアミノトランスフェラーゼ増加 1 例(5.6%)、アスパラギン酸アミノトランスフェラーゼ増加 1 例(5.6%)、リンパ球数減少 1 例(5.6%)］、「感染症および寄生虫症」3 例 (16.7%) ［肺炎 1 例 (5.6%)、憩室炎 1 例 (5.6%)、歯髄炎 1 例 (5.6%)］、「血液およびリンパ系障害」3 例 (16.7%) ［貧血 3 例 (16.7%)］、「胃腸障害」2 例 (11.1%) ［悪心 1 例 (5.6%)、腸炎 1 例 (5.6%)］、「呼吸器、胸郭および縦隔障害」 1 例 (5.6%) ［肺塞栓症 1 例(5.6%)］、「神経系障害」1 例 (5.6%) ［末梢性ニューロパチー 1 例 (5.6%)］、「筋骨格系および結合組織障害」 1 例 (5.6%) ［背部痛 1 例 (5.6%)］ であった。

４．QOL の評価

健康 VAS の平均値は、３剤併用化学療法期開始前に比べて、ニボルマブ単独維持療法期開始前には-5.6±24.2 (-65～30) mm [平均値±標準偏差 (最小値～最大値)、以下同様] 、治療期終了時には 0.5±23.3 (-40～30) mm であった。また、インデックススコアの平均値は、３剤併用化学療法期開始前に比べて、ニボルマブ単独維持療法期開始前には 0.0185±0.1389 (-0.319～0.292) 治療期終了時には、-0.0166±0.1912 (-0.364～0.292) であった。

VAS（全平均）は、3剤併用化学療法期開始前に比べて、ニボルマブ単独維持療法期開始前には-0.01±13.57（-21.1～28.1）mm、治療期終了時には -2.11±21.38（-41.3～36.0）mm であった。これらの結果について、問題となるような QOL の変化はないと考えられた。

D．考察

悪性胸膜中皮腫に対する薬物治療としては、一次治療としてシスプラチン、ペメトレキセド療法が標準治療とされているがその治療成績は十分とは言えず、また同療法に抵抗性となった患者においては確立した治療法はなく、新たな治療法の開発が切望されている。

ニボルマブは、小野薬品工業株式会社とメダレックス社（現、ブリストル･マイヤーズ スクイブ社）が作製した、ヒト PD-1（Programmed cell death-1）に対するヒト型モノクローナル抗体であり、小野薬品及び BMS 社が臨床開発を進めている。国内で行われた臨床試験「2nd/3rd ラインの悪性胸膜中皮腫（MPM）に対するニボルマブの第Ⅱ相試験（MERIT 試験）」において、シスプラチンあるいはカルボプラチンとペメトレキセドの併用療法に不応又は不耐となった悪性胸膜中皮腫 34 例が登録された。患者背景は男/女＝29/5，年齢中央値 68 歳（43-78 歳），PS0/1＝13/21，上皮/肉腫/二相＝27/3/4，前治療レジメン数 1/2＝24/10 であった。観察期間中央値 16.8 か月（1.8-20.2 か月）の時点で奏効率は 29.4％（95％CI：16.8-46.2），無増悪生存期間及び全生存期間の中央値はそれぞれ 6.1 か月（95％CI：2.9-9.9），17.3 か月（95％CI：11.5-NR）であった。この結果に基づき、2 次もしくは 3 次治療としてのニボルマブは有用な治療法であると結論づけられ、2018 年 8 月 21 日に「がん化学療法後に増悪した切除不能な進行・再発の悪性胸膜中皮腫」に対する適応を取得した。

本研究は、現在の標準治療であるシスプラチン、ペメトレキセド療法とニボルマブの併用によりさらなる治療効果の上乗せを期待し、初回化学療法における有効性及び安全性を評価するものである。主要評価項目である中央判定における奏効率において、当初の想定を上回る高い奏効率が得られた。また安全性の評価においては、消化器毒性、皮膚障害などの有害事象が確認されたが、これらの頻度、重症度はこれまでの化学療法や免疫チェックポイント阻害薬をもちいた臨床試験の報告と同様であり、マネジメント可能なものであった。本試験は、シスプラチン、ペメトレキセドおよびニボルマブ併用化学療法の有用性と安全性を強く示唆するものであり、今後胸膜中皮腫におけるあらたな治療選択肢となる可能性がある。

また本試験は、悪性胸膜中皮腫に対する内科的治療において、医薬品の臨床試験に関する基準（Good Clinical Practice, GCP）に準拠する国内で初めての医師主導の臨床試験であり、今後さらに新規治療法を開発していくうえで極めて重要である。

E．結論

「切除不能悪性胸膜中皮腫に対する初回化学療法としてのシスプラチン、ペメトレキセドおよびニボルマブ併用化学療法の第 II 相試験」を医師主導治験として実施した。本試験は、シスプラチン、ペメトレキセドおよびニボルマブ併用化学療法の有用性と安全性を強く示唆するものであり、今後胸膜中皮腫におけるあらたな治療選択肢となる可能性がある。

F．健康危険情報

抗悪性腫瘍薬の使用に際しては製薬メーカーから提供される取り扱い情報に基づき適正に取り扱った。また実際の投与に際しては、厚生労働省労働基準局より発出された「発がん性等を有する化学物質を含有する抗がん剤等に対するばく露防止対策について」（基安化発 0529 第 1 号）に則り各施設で定められた抗がん剤ばく露対策マニュアルを遵守し、医師、薬剤師、看護師が薬剤に曝露しないようにした。また患者やその家族に対しても、薬剤の取扱いに関する情報を周知した。

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H．知的財産権の出願・登録状況（予定を含む。）

1. 特許取得

該当するものなし。

2. 実用新案登録

該当するものなし。

3.その他

特記すべき事項なし。

労災疾病臨床研究事業費補助金
分 担 研 究 報 告 書

【悪性胸膜中皮腫細胞株における葉酸代謝拮抗薬に応答する代謝変化解析】

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研究要旨

メタボローム解析技術を用いたメタボローム解析は、オミクス解析の一つで、疾患における初期診断や薬剤に対するバイオマーカーに応用可能な生体内の代謝産物量を網羅的に測定することが可能である。悪性胸膜中皮腫の早期診断や臨床で治療に使用されている抗がん剤に対するバイオマーカーの探索を目指している。

悪性胸膜中皮腫の化学療法としてペメトレキセドとシスプラチンの併用療法が用いられているが、薬剤耐性による奏効率の低さが課題である。昨年度までにメタボローム解析による悪性胸膜中皮腫細胞株における葉酸代謝拮抗薬処理時の細胞内代謝産物プロファイルの解析や、その結果が薬剤耐性に関連しているのではないかと仮定し、ペメトレキセド耐性化細胞株の樹立及び、ペメトレキセド耐性化によって mRNA レベルで TYMS の発現が増加していることを確認した。

今年度は、昨年度から引き続き TYMS に着目し、耐性株が親株と比較して薬剤耐性化によってタンパク質レベルでも TYMS の発現が増加しているかどうかを確認した。さらに、TYMS と薬剤耐性との関連を調べるため TYMS の発現をノックダウンや過剰発現させたところ、ノックダウンによって薬剤耐性が低下し、過剰発現によって薬剤耐性が増加することがわかり、TYMS の発現増加がペメトレキセド耐性化と関連があることが示唆された。

A．研究目的

質量分析計を用いる生体内の代謝産物を網羅的に解析するメタボローム解析技術は、400 以上におよぶ代謝産物を同定することができ、疾患の早期発見や患者の層別化を可能とするバイオマーカーを発見できる可能性を秘めている。

画像検査において悪性胸膜中皮腫が疑われる場合、胸水細胞診や胸膜生検の病理診断が必要である。中皮腫は、組織学的に上皮型、肉腫型とその両者が混ざり合って存在する二相型の 3 種類に分けられ、病理診断は難しい現状である。血液検査で悪性胸膜中皮腫を早期に発見する腫瘍マーカーの研究も進められているが、これまでのところ確実に診断する腫瘍マーカーは発見されていない。

悪性胸膜中皮腫は非常に治療が難しい病気の一つで、化学療法では葉酸代謝拮抗薬のペメトレキセドとシスプラチンの併用療法である。しかし、ペメトレキセドとシスプラチンの併用療法を受けた患者で奏効が認められる人は全体の 30～40%にとどまり、現在では寛解にいたる効果は期待できない現状である。言い換えれば全体の 60～70%が薬剤耐性であると言える。ペメトレキセドの標的分子は、ピリミジン生合成経路の thymidylate synthase (TYMS)、一

炭素（1C）代謝経路の dihydrofolate reductase（DHFR）、プリン塩基新規生合成経路の glycinamide ribonucleotide formyltransferase（GART）の３種の酵素である。特に TYMS を第一標的としているが、この酵素は dUMP を基質として還元型メチル化反応により dTMP に変換する。シスプラチンの薬剤耐性のメカニズムはいくつか報告があるが、ペメトレキセドについてはよく分かっていない。例えば、TYMS の発現量の増加がペメトレキセド耐性に関与しているという報告がある一方で、臨床結果と TYMS の発現量が必ずしも相関しないとの報告もある。昨年度の研究では、ペメトレキセド耐性化悪性胸膜中皮腫細胞株を２種樹立し、それらの株は TYMS の mRNA の発現だけが有意に増加していることを示した。また、一昨年度、TYMS の下流に存在する代謝産物であるチミジンの細胞内濃度が高い場合、ペメトレキセドの薬効が失活する可能性があることを明らかにしている。今年度は、これまでの結果を基に TYMS の増加がペメトレキセド耐性を誘導したのではないかと推察し、TYMS とペメトレキセド耐性化との関連性を明らかにする。具体的には siRNA を用いた TYMS のノックダウン及び、レトロウイルスを用いた TYMS の過剰発現を行い、それらによって薬剤感受性が変化するかどうかを調べた。

Ｂ．研究方法

市販されている悪性胸膜中皮腫細胞株（MSTO-211H）と国立がん研究センターにおいて patient-derived xenograft（PDX）で樹立された細胞株（TCC-MESO-2）を用いた。また、それらを親株として昨年度樹立したペメトレキセド耐性化株（MSTO-211H_R、TCC-MESO-2 _R）を用いた。

まず、mRNA の発現と同様にタンパク質の発現も変化しているかどうかを確認するため、昨年度樹立したペメトレキセド耐性化株２種とそれぞれの親株からセルライセートを作成し、ウェスタンブロットを行った。次に、ペメトレキセド耐性化株で発現が増加した TYMS が薬剤耐性化に関連するかどうかを確認するため遺伝子のノックダウン及び、過剰発現の試験を行った。TYMS のノックダウンでは、TYMS に特異的に作用する siRNA を用いてペメトレキセド耐性化株２種の TYMS のノックダウンを行い、薬剤感受性が変化するかどうかを WST-8 によってその生細胞数を計測した。TYMS の過剰発現では、プラスミド（コントロール、TYMS）と Plat-A（Platinum Expression System Amphotropic cell）を用いて２種のレトロウイルスを作成し、ペメトレキセド耐性化株の親株である MSTO-211H と TCC-MESO-2 それぞれに感染させ、TYMS の過剰発現株とコントロール株を作成した。レトロウイルス感染後の培養には G418（750 ug/ml）を含む培地で培養した。

（倫理面への配慮）

今年度の研究は、細胞株を用いた研究成果であり、ヒト由来検体を用いていないため、倫理面への配慮は不要である。

Ｃ．研究結果

昨年度樹立した２種のペメトレキセド耐性化株はペメトレキセドに対して強い耐性を有し、mRNA レベルで TYMS の発現が増加していることが分かっている。今年度はタンパク質レベルでも確認するため、MSTO-211H_R と TCC-MESO-2_R 及び、その親株のセルライセートを作成し、ウェスタンブロットを行った。その結果、いずれの細胞株でも親株に比べてペメトレキセド耐性化株の方が TYMS の発現が増加していることが分かった（図１）。

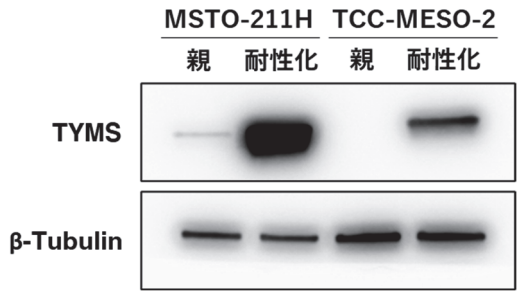

図１．薬剤耐性化によるタンパク質発現の変化

次に、TYMS の発現が増加していることが分かったペメトレキセド耐性化株を用いて、siRNA による TYMS のノックダウンによって薬剤耐性が変化するかどうかを調べた。

2 つのペメトレキセド耐性化細胞株をそれぞれ Negative Control (NC)、TYMS 特異的 siRNA (siTYMS) でトランスフェクションし、48 hrs 後に回収した。回収した細胞の一部は、セルライセートを調製し、ウェスタンブロットを行った。残りの細胞は、PBS 処理とペメトレキセド 1 μM 処理を行い、WST-8 アッセイで生細胞数をカウントし、NC、siTYMS それぞれの PBS 処理群とペメトレキセド処理群との比を算出した。

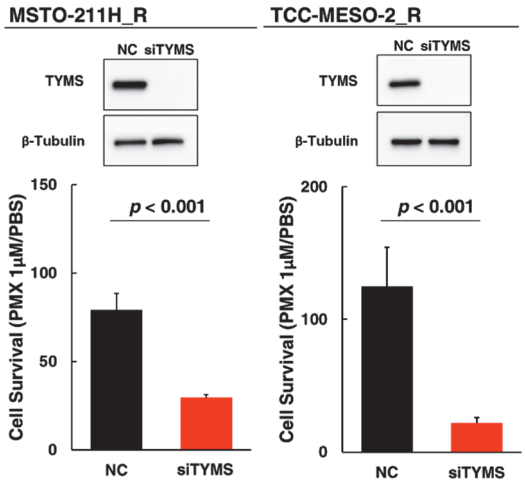

図２．TYMS の KD による薬剤耐性の変化

その結果、NC に比べて siTYMS においてペメトレキセドによって生細胞数が有意に減少していることから、TYMS のノックダウンによって薬剤耐性が有意に減少したことがわかった（図２）。

次に TYMS を過剰発現させた場合、薬剤感受性が変わるかどうかを調べた。レトロウイルス発現システムである Plat-A cell に 2 種のプラスミド（コントロール、TYMS）をそれぞれトランスフェクションし、プラスミド由来の遺伝子を有する 2 種のレトロウイルスを作成した。得られたレトロウイルスを耐性化株の基となった 2 種の悪性胸膜中皮腫細胞株に感染させた。感染した細胞は G418 を含む培地で培養した後、TYMS の発現をウェスタンブロットで調べた。その結果、レトロウイルスを用いた過剰発現系によりタンパク質レベルで TYMS の発現を増加させることができた。さらに、同じ細胞株を用いて、それぞれ PBS 処理、ペメトレキセド 1 μM 処理を行い、その生細胞数を WST-8 アッセイで調べ、PBS 処理群とペメトレキセド処理群との比を算出した。その結果、TYMS を過剰発現させることにより、ペメトレキセドに対する感受性が有意に低下することが分かった（図３）。

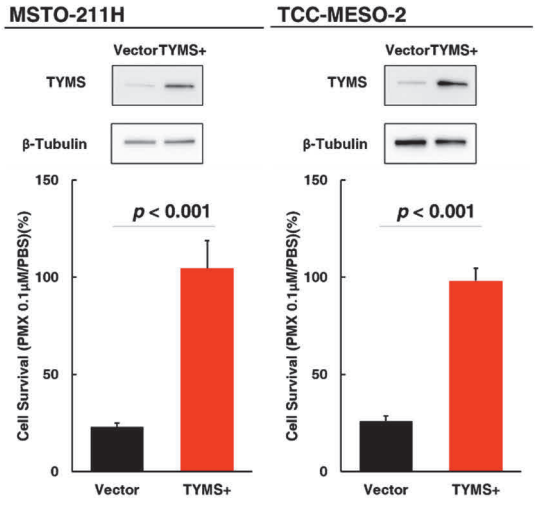

図３．TYMS の過剰発現による薬剤耐性の変化

D．考察

今回の研究では、薬剤耐性化した 2 つの悪性胸膜中皮腫細胞株においてタンパク質レベルにおける TYMS の発現増加が確認

され、また、TYMS のノックダウンや過剰発現を行い、TYMS の発現を増減させることでペメトレキセドに対する薬剤耐性がそれに反比例して変化することが分かった。つまり、悪性胸膜中皮腫細胞株ではペメトレキセドに暴露され続けることで TYMS の発現が増加し、それが要因となってペメトレキセドに対する耐性を獲得したことが明確となった。今後は、TYMS がどのようにして発現が増加したのか、その制御機構を解明することを目的にクロマチン免疫沈降を行う予定である。

今後は、腫瘍組織、胸水や血漿などの生体由来の試料によるメタボローム解析の蓄積よる比較等、また悪性胸膜中皮腫由来の特徴的な代謝産物を示すための比較対象の検討も必要であると考える。

E．結論

本研究成果により、薬剤耐性化については、TYMS が悪性胸膜中皮腫における薬剤耐性化の重要な因子であることを示すことができた。今後は TYMS の発現が増加したメカニズムを明らかにしたい。

今後は、倫理面に配慮しながら胸水や血漿のメタボローム解析や、新たにヒト患者由来の悪性胸膜中皮腫組織や非腫瘍組織のメタボローム解析を行い、その代謝プロファイルを蓄積し、メタボローム解析が悪性胸膜中皮腫に対する TR 研究に貢献できることを明らかにしたい。

F．研究発表

1. 論文発表

記載事項なし。

2. 学会発表

1) Yuzo Sato、Hideki Makinoshima. Metabolic Characterization of Drug Resistance to Antifolate in Malignant Pleural Mesothelioma. 2020 World Conference on Lung Cancer. Poster Presentation. 2021 年 1 月. Online

G．知的財産権の出願・登録状況（予定を含む。）

1. 特許取得

記載事項なし。

2. 実用新案登録

記載事項なし。

3.その他

特記すべき事項なし。

労災疾病臨床研究事業費補助金
分 担 研 究 報 告 書

【悪性中皮腫症例におけるニボルマブ投与療法の奏効に関わる免疫学的特徴】

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研究要旨

悪性中皮腫患者８例について末梢血を検体とした包括的免疫機能解析を行い、ニボルマブ投与による治療効果に関わる免疫学的因子の抽出を試みた。その結果、部分奏効(PR) を示した患者１例では治療前より NK の IFN-γ産生誘導能が高く、細胞傷害性 T リンパ球の活性化指標 HLA-DR も高いが、Treg 指標 CTLA-4 も高いことが分かった。抑制されていた高い抗腫瘍免疫機能が解放され明瞭な腫瘍抑制効果に至った可能性が示唆される。今後の一層の免疫機能解析によるニボルマブ治療効果予測指標の構築が期待される。

Ａ．研究目的

本研究班において、我々の研究目的はニボルマブ治療前後の免疫学的特徴を包括的に解析することにより治療効果の免疫学的評価をすると共に、中皮腫治療の奏功を予測する免疫学的因子群を抽出し、その治療効果予測指標の確立を目指すこととする。中でも、一部に明瞭な治療効果が認められたことから、奏効例とそれ以外の際に注目し、試行した。

Ｂ．研究方法

岡山労災病院または四国がんセンターにて同意された悪性中皮腫患者より末梢血を得た。採血はニボルマブ治療開始前、１週間後、３か月後の３点で行われた。採取された末梢血を川崎医科大学まで輸送し、翌日、血漿を遠心分離により採取した後、lymphoprep を用いて末梢血単核細胞(PBMC) を調整した。PBMC の一部を用いて各種蛍光標識抗体にて染色し、CD4+T ヘルパー細胞（Th)・CD8+細胞傷害性 T リンパ球（CTL)・CD56+ナチュラルキラー細胞(NK)・単球の各細胞集団における細胞表面分子群の発現量をフローサイトメトリー(FCM) により陽性細胞比率（%）または平均蛍光強度（MFI）を測定した。PBMC の残りを FCM により４細胞集団にソートし、一部はそのまま凍結、残りは Th, CTL, NK については PMA/ionomycin 刺激下で、単球は無刺激下にて培養し翌日回収し凍結保存した。後日、凍結細胞を試料として total RNA を抽出し SYBR Green を用いて各種遺伝子の mRNA レベルを測定した。また、血漿については Luminex システムを用いて多項目のサイトカイン濃度を測定した（図１)。最終的に、奏効例における特徴を示す免疫学的指標群について主成分分析を行い、治療効果と免疫学的動態の関わりを考察し、ニボルマブ治療効果予測指標確立の可能性を検討した。統計学的解析には GraphPad Prism9 および SPSS Statistics 27 を用いた。

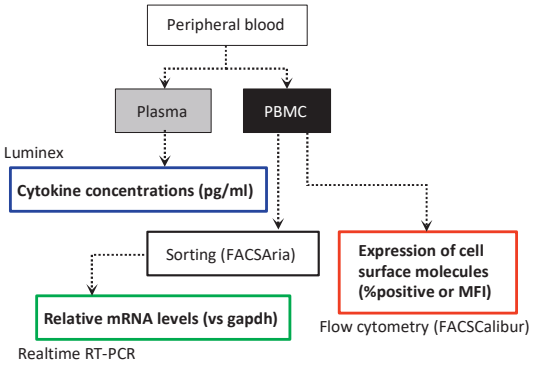

図１．包括的免疫学的解析の作業フロー

表１．患者検体一覧

施設	患者ID	治療効果
岡山労災病院	MOP-1	SD
岡山労災病院	MOP-2	SD
四国がんセンター	MOP-3	PD
岡山労災病院	MOP-4	SD
岡山労災病院	MOP-5	SD
岡山労災病院	MOP-6	PD
岡山労災病院	MOP-7	PR
四国がんセンター	MOP-8	PD

（倫理面への配慮）

本研究については、解析主体である川崎医科大学衛生学･大槻を研究代表者として、研究課題名「前治療不応性悪性胸膜中皮腫症例に対するニボルマブを含む化学療法における包括的免疫病態の変化の観察」として倫理申請を行い承認済みであるが、解析主体の交代に伴い川崎医科大学衛生学・西村を研究代表者とする変更を申請し認められた。

C．研究結果

1)　ニボルマブ治療効果の内訳

令和２年度末までに岡山労災病院からは６名、四国がんセンターからは３名より採血を得た。四国がんセンターの１名については治療開始３か月後の採血が未だであるため、この１例を除く合計８例についての解析結果を報告する（表１）。ニボルマブ治療効果の内訳は、部分奏効（PR）１名、病状安定（SD）４名、増悪（PD）３名であった。そこで、８名を SD+PR 群５名と PD 群３名に分け群間で各指標の値およびその動態を比較すると共に、特に治療効果 PR を示す１名における免疫学的特徴の抽出を試みた。また、PD 症例において３か月を待たずに治療を終了した場合には 1.5-2 か月時に採血が行われた（結果の表記では何れも３か月時と便宜表示）。

2)　各細胞集団における細胞表面分子発現量

CD4+T ヘルパー細胞（Th）・CD8+細胞傷害性 T リンパ球（CTL）・CD56+ナチュラルキラー細胞（NK）・単球の各細胞集団は図２のように FSC, SSC および二重蛍光染色により定義され、それぞれの細胞集団における細胞表面分子発現量を各種 PE 標識抗体染色の陽性細胞比率（%）または平均蛍光強度（MFI）を測定することによって評価した。NK 細胞集団については単球の持ち込みを防ぐために抗 CD14 蛍光標識抗体を同時に染色し、CD14+細胞を gate-out した。

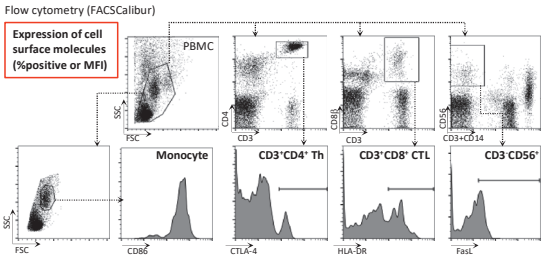

図２．４種の免疫細胞集団の FSC，SSC および二重蛍光染色による定義と、各細胞集団における PE 標識抗体での染色による陽性細胞および平均蛍光強度測定の例示

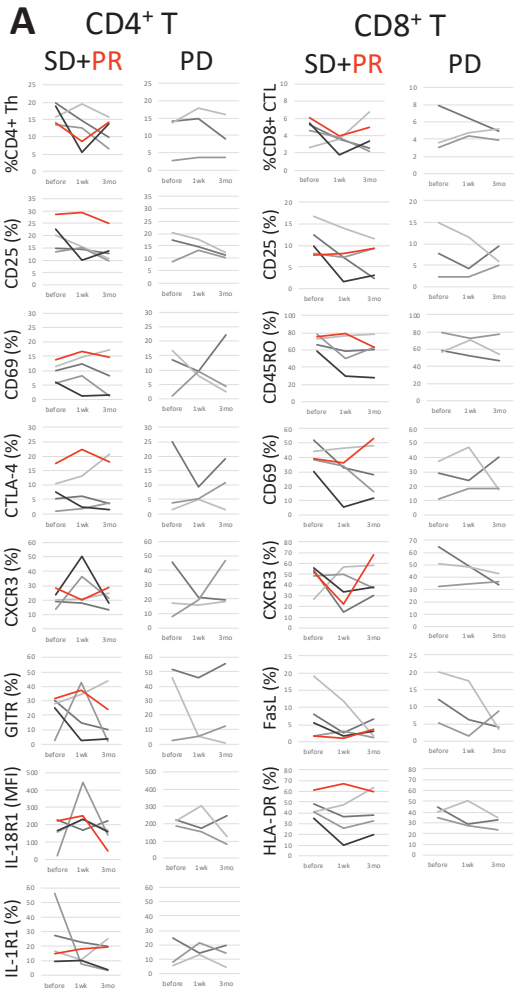

図３Ａ．CD4+ Th および CD8+ CTL における細胞表面分子発現量の測定結果

CD4+ Th については、活性化指標 (CD25, CD69, HLA-DR), 制御性 T 細胞 (Treg) 指標 (CTLA-4, GITR), Th1/遊走機能指標 (CXCR3), サイトカイン受容体 (IL-18R1, IL-1R1) の陽性比率または MFI を測定した。CD8+ CTL については、活性化 (CD25, CD69)およびエフェクター/メモリー指標 (CD45RO), 遊走機能指標 (CXCR3), 細胞傷害機能分子 (FasL) の陽性比率を測定した。CD4+ Th, CD8+ CTL の何れにおいても、SD+PR 群と PD 群の群間の差異および治療前後で共通して変化する指標は確認できなかった。一方、PR を示した MOP-7 (図中の赤色) では、CD4+ Th における CD25 (%) が治療前、１週間後、３か月後の何れにおいても他の症例の何れの測定値よりも高値であった。また、CD4+ Th 上の CTLA-4 (%) も継続して高い傾向であった。一方、CD8+ CTL においては、HLA-DR (%) が高い傾向を示した (図３A)。

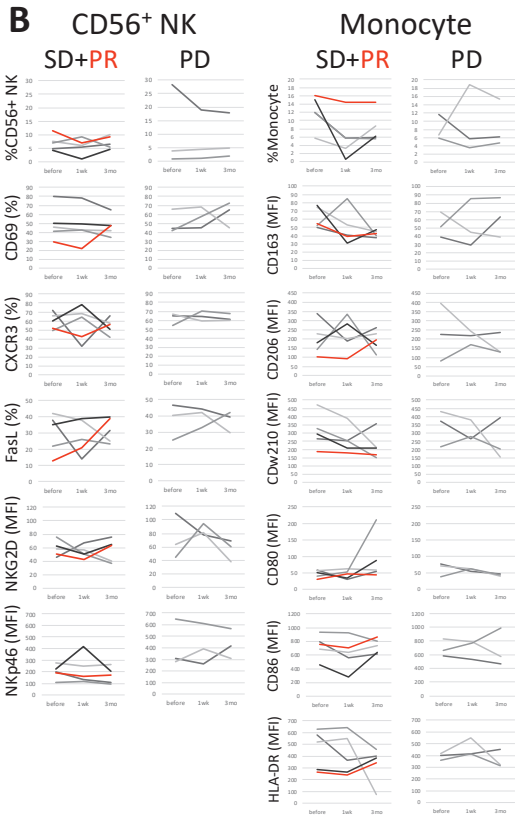

図３Ｂ．NK および単球における細胞表面分子発現量の測定結果

NK 細胞については活性化指標 (CD69), 活性化受容体 (NKG2D, NKp46), 遊走機能指標 (CXCR3), 細胞傷害機能分子 (FasL) の陽性比率または MFI を測定した。単球については、抗原提示機能分子 (HLA-DR) および M1 型 (CD80, CD86) または M2 型 (CD163, CD206, CDw210) マクロファージ指標の MFI を測定した。しかし、NK 細胞と単球については、群間差の特徴も、PR を示す MOP-7 における特徴も、確認することは出来なかった (図３Ｂ)。

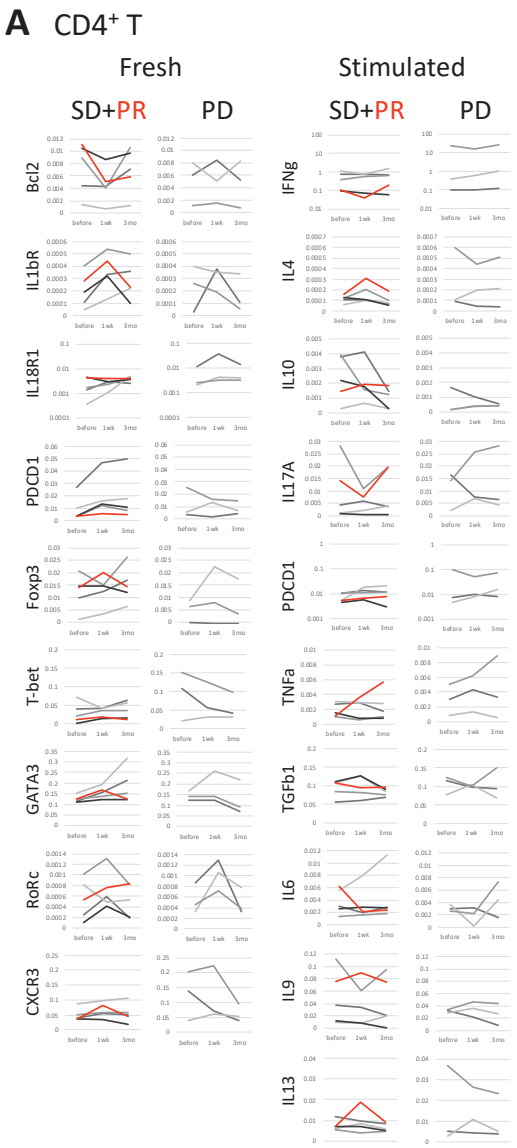

図４A. CD4+ Th 中の mRNA レベルの測定結果

3) 各細胞集団における遺伝子 mRNA レベル

PBMC よりソートされた各細胞集団の遺伝子 mRNA レベルが調べられた。一部は培養後（単球以外は PMA/ionomycin 刺激下で）に回収した細胞について調べられた。CD4+ Th においては、Th1, Th2, Th17, Treg 機能のマスター転写因子（Foxp3, GATA3, T-Bet, RORC), 抑制性に働く PDCD1, Th1 指標である CXCR3, アポトーシス抑制に働く Bcl-2、および炎症性サイトカイン受容体（IL-1R1, IL-18R1）について調べた。また刺激後の Th においては、種々のサイトカイン（IFNg, IL4, IL6, IL9, IL10, IL13, IL17A, TNFa, TGFb1）および PDCD1 について調べた。CD8+ CTL においては、エフェクター細胞機能制御関連遺伝子（Notch1, Eomes, Creb1), 細胞傷害性機能分子（Granzyme B, PRF1, FasL), IL18R1、および細胞株を用いたこれまでの実験で石綿曝露影響との関わりが明らかになった遺伝子 B について調べた。また刺激後の CTL についてはサイトカイン（IFNg, TNFa, IL6）および細胞傷害性機能分子と遺伝子 B について調べた。

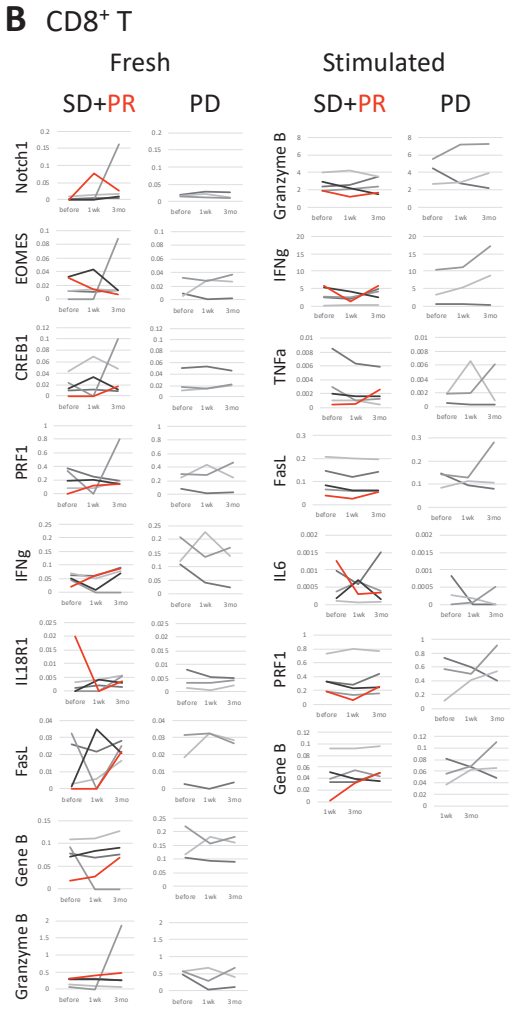

図４B. CD8+ CTL 中の mRNA レベルの測定結果

しかし、Th と CTL いずれにおいても群間での差異や治療前後の変化および PR を示す MOP-7 における特徴を確認することは出来なかった。一方、ソート直後の CD8+ CTL における遺伝子 B mRNA レベルは IFNg mRNA レベルと高い相関性を示した(図４A-C)。

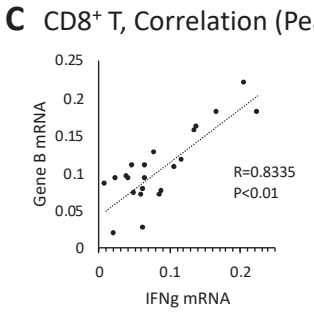

図４C. CD8+ CTL の遺伝子 B mRNA レベルと IFNg mRNA レベルの相関性（Pearson）

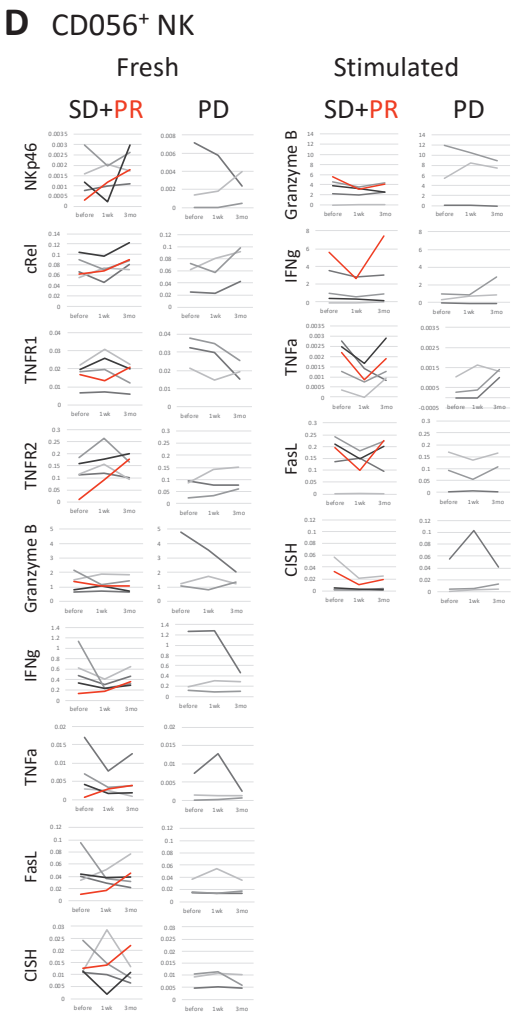

図４D. NK 中の mRNA レベルの測定結果

他方、NK においては PR を示した MOP-7 の特徴を確認することができた。NK についてはソート後の細胞または刺激下培養後の細胞において、NKp46, IFNg, TNFa, Granzyme B, FasL, および機能制御に関わる cRel, CISH や TNFR1, TNFR2 の mRNA レベルを調べた。群間差を捉えることは出来なかったが、PR を示した MOP-7 では刺激後の NK における IFNg mRNA レベルが治療前と治療３か月後において共に高値であることが他とは異なる特徴であった（図４D)。単球においては、幾つかのサイトカイン mRNA レベルについてソート直後または培養後の細胞に関して調べたが、群間差や治療前後の特徴および MOP-7 に

おける特徴を確認することは出来なかった(図４Ｅ)。

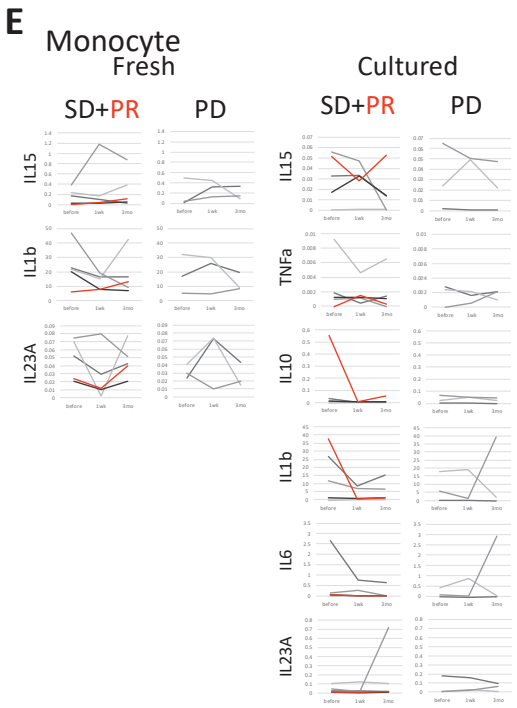

図４Ｅ．単球中の mRNA レベルの測定結果

4)　血漿中の種々のサイトカイン濃度

血漿中のサイトカイン濃度の変化および群間差を調べた。サイトカインは、EGF, Eotaxin, G-CSF, GM-CSF, IFN-a2, IFN-g, IL-10, IL-12p40, IL-12p70, IL-13, IL-15, IL-17, IL-1ra, IL-1a, IL-1b, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IP-10, MCP-1, MIP-1a, MIP-1b, TNF-a, TNF-b, VEGF の 29 種について測定された。しかし、SD+PR 群と PD 群との差、治療前後の差、および PR を示す MOP-7 の特徴を確認することは出来なかった（図５)。

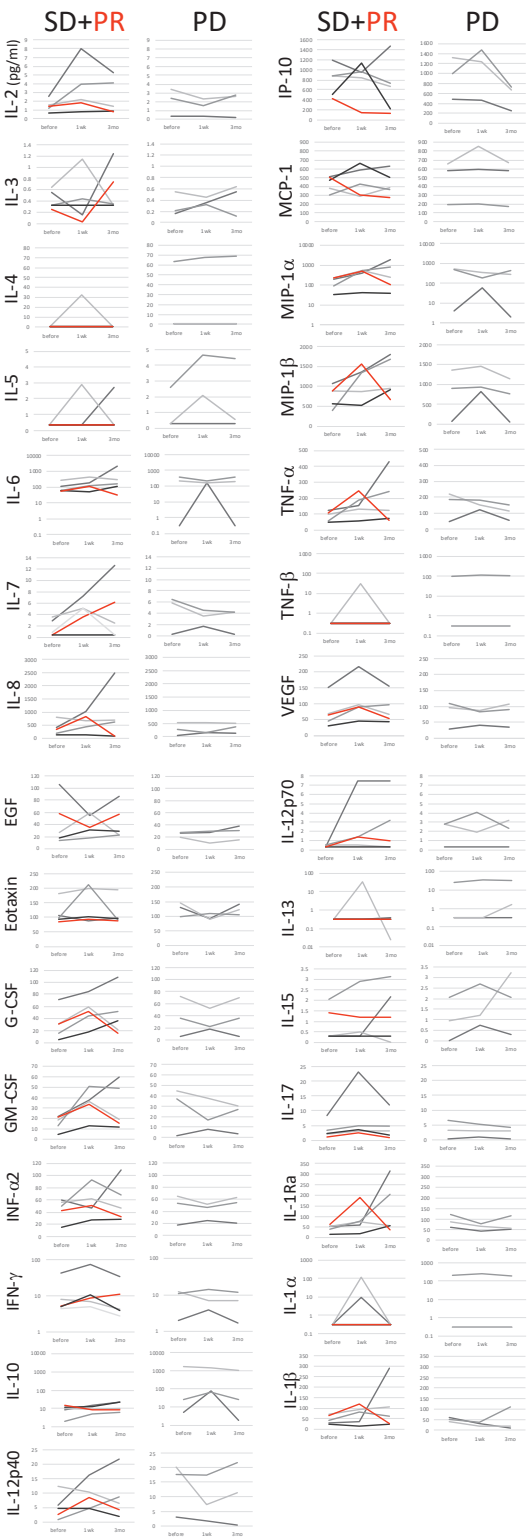

図５．血漿中サイトカイン濃度の測定結果

5) 奏効例における特徴を示す指標群について主成分分析

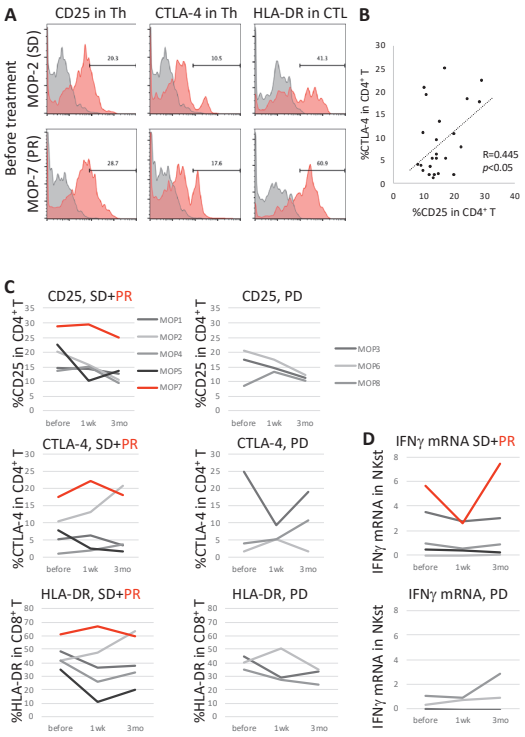

図６．PR を示す MOP-7 における特徴のまとめ

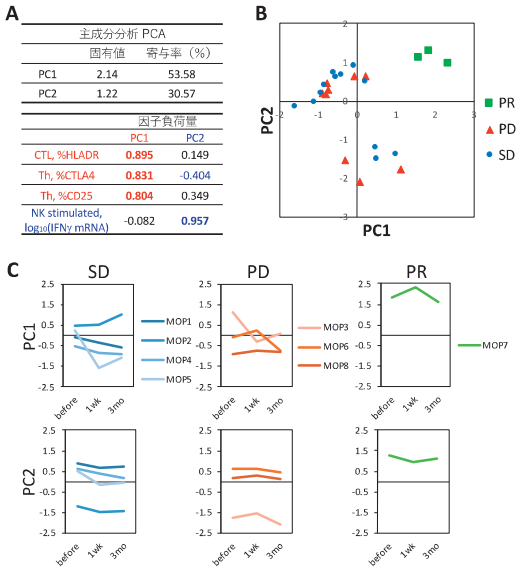

図７．奏効例における特徴を示す指標群について主成分分析の結果．Ａ：主成分分析の分析結果，Ｂ：主成分１，２の各サンプルの得点の二次元プロット，Ｃ：主成分１，２の各サンプルの得点の SD，PD，PR 間の比較

これまでの個別の分析において、PR を示す MOP-7 では、Th 上の CD25％と CTLA-4％および CTL 上の HLA-DR％、加えて刺激後 NK 中の IFN-g mRNA レベルが継続して高い傾向を示すことが確認できた（図６）。そこで、これら４因子について主成分分析を行ったところ、２つの主成分が抽出された。主成分１（寄与率 53.58％）では Th 上の CD25％と CTLA-4％および CTL 上の HLA-DR％が高い正の因子負荷量を示し、主成分２（寄与率 30.57％）では刺激後 NK 中の IFN-g mRNA レベルの log10 対数変換値が高い正の因子負荷量を示し、両成分の累積寄与率は８割を超えた（図７Ａ）。主成分１，２は PR を示した MOP-7 では治療前後に因らず高い値を示し、SD や PD では値は症例間でばらつき SD,PD 群間に差は見られなかった（図７Ｃ）。主成分１，２を二次元プロットした図では、PR を示す MOP-7 の３つの測定値（治療前、１週間後、３か月後）は他の測定値と明瞭に異なる独立した座標に位置した（図７Ｂ）。

Ｄ．考察

８例の悪性中皮腫患者に対するニボルマブ治療前後の包括的免疫機能解析を行った。治療効果の差による群分け SD+PR 群と PD 群の群間比較では明瞭な差を捉えることは出来なかった。しかし、１例のみではあるが PR を示した症例においては、Th 上の CD25％と CTLA-4％および CTL 上の HLA-DR％、加えて刺激後 NK 中の IFN-g mRNA レベルが継続して高い傾向であることが明らかとなった。Th における CD25（IL-2Rα）の発現は活性化の指標であると同時に CD4+CD25+Treg 細胞との関わりも考えることができた。図６Ｂに示すように CD25％は CTLA-4％と有意な正の相関を示すことから、MOP-7 における CD25％の高値は活性化ではなく Treg 細胞の増加を意味していると解釈できる。それらを総合して解釈すると、MOP-7 では自然免疫においては NK 細胞が刺激後の高い IFN-g 産生能を持ち、また獲得免疫におい

ては活性化 CTL が多く血液循環している状況にあるが、増加した Treg 細胞による強い免疫抑制の状態にあることが示唆される。つまり、ニボルマブにより PD-1 分子を介した免疫抑制が解除されることで、備えるが抑制されていた強い NK 細胞機能と活性化 CTL の機能が解放され機能を発揮した結果、明瞭な腫瘍抑制効果に至った可能性が示唆される（図８）。解除すべき免疫抑制の標的が明瞭にあって、且つ発揮すべき潜在的な抗腫瘍免疫細胞の機能が保たれていることがニボルマブ治療の奏効に重要ということでは無いだろうか。一方、PR 例であっても末梢血中の Treg の減少は見られなかった。適切なニボルマブ治療効果には、局所における免疫抑制状態の解除が重要なのであって、寧ろ全身性の免疫抑制状態の解除はニボルマブによる免疫毒性指標（過剰な免疫抑制解除）として理解すべきなのかもしれない。また、細胞株の実験によって石綿曝露と IFN- g 産生能との関わり（負の相関性）が判明している遺伝子 B は本研究での症例解析では逆に IFN- g と正の相関性を示し、矛盾した結果となった。しかしながら、何れの研究結果も遺伝子 B と IFN- g との強い関係を示すことは、未知の免疫機能制御機序の存在を示唆する。

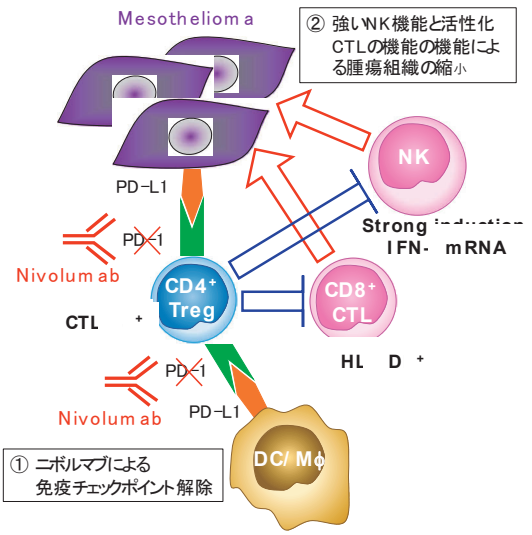

図８．ニボルマブ投与治療の奏効との関連が示唆される免疫学的機序

E．結論

８例の悪性中皮腫患者へのニボルマブ治療前後の包括的免疫機能解析の結果、治療奏効と関わる特徴として、１）NK の IFN-g 産生誘導能が高く、２）活性化 CTL が多く、３）Treg 細胞が多いことが捉えられた。

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G．知的財産権の出願・登録状況（予定を含む。）

1. 特許取得

2020 年度では無し。

2. 実用新案登録

2020 年度では無し。

3.その他

2020 年度では特に無し。

労災疾病臨床研究事業費補助金
分 担 研 究 報 告 書

【石綿ばく露によるびまん性胸膜肥厚の著しい呼吸機能障害に関する研究】

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研究要旨

石綿ばく露労働者に発症したびまん性胸膜肥厚における著しい呼吸機能障害の評価において、呼吸機能検査が出来ない場合には６分間歩行試験を行うが、明確な基準が存在しない。ADL 低下が顕著であるにも関わらず、呼吸機能検査や動脈血ガス分析などの検査値は良好な症例を労災認定できるようにするために、研究を行った。職業性石綿暴露歴があり、胸部画像検査でびまん性胸膜肥厚と診断された症例を対象に、呼吸機能検査、６分間歩行試験と ADL の評価を行った。６分間歩行試験における SpO_2 最低値は 86.2%（95%信頼区間 82-90%）、総歩行距離/予測値は 77.3%（95%信頼区間は 63.4-91.1%）であった。びまん性胸膜肥厚患者の６分間歩行試験において、「SpO_2 最低値が 90%以下、あるいは歩行距離が予測値の 90%以下であること」が、著しい呼吸機能障害の基準になりうる。

Ａ．研究目的

びまん性胸膜肥厚は石綿ばく露によって引き起こされる良性胸膜疾患の一つである。臓側胸膜に起こる非特異的な慢性線維性胸膜炎であり、壁側胸膜との癒着を伴う[1]。良性石綿胸水の約半数がびまん性胸膜肥厚を来すと言われており[2]、拘束性換気障害を呈することが報告されている[3]。胸部レントゲン検査で胸膜肥厚の最も厚いところが５mm 以上あり、胸膜肥厚が片側のみの場合は側胸壁の 1/2 以上、両側の場合は各側胸壁の 1/4 以上であるものと定義されている。石綿曝露作業への従事期間が３年間以上あり、著しい呼吸機能障害を呈する場合は労災認定の対象となるが[4]、その基準は、（1）%肺活量（%VC）が 60%以上 80%未満であって、次の(ア)または(イ)に該当する（(ア) 1 秒率（FEV_1%）が 70%未満であり、かつ%1 秒量（%FEV_1）が 50%未満、(イ) 動脈血酸素分圧（PaO_2）が 60 Torr 以下である場合または肺胞気動脈血酸素分圧較差（$AaDO_2$）が限界値を超える）場合となっている[5]。しかしながら、じん肺法において、著しい呼吸機能障害（閉塞性換気障害）の基準である FEV_1%が 70%未満でなおかつ%FEV_1 が 50%未満であってもその対象となっている。呼吸機能検査が出来ない場合には６分間歩行試験を施行するが[5]、この検査における著しい呼吸機能障害の明確な基準がないのが実情である。

表１．対象者 12 例の肺機能検査，６分間歩行の結果

	性別	測定時年齢（歳）	肺機能検査			6分間歩行試験															
						血圧		Sp02			PR			歩行/無歩行				中断・休息時間			
			%肺活量（%）	一秒率（%）	%一秒量（%）	開始前（mmHg）	終了後（mmHg）	開始前平均値（%）	歩行中最小値（%）	終了後最大値（%）	開始前平均値（bpm）	歩行中最大値（bpm）	終了後最小値（bpm）	実測行数（歩）	総歩行距離（m）	予測値（m）	割合（%）	（分）	（秒）	合計（秒）
1	M	73	60.2	68.4	52.7	128 / 69	144 / 85	94.3	85	97	77.2	105	72	636	385	492	78	0	0	0
2	M	77	39.0	91.7	45.1	123 / 69	137 / 72	97.0	96	98	84.7	131	83	601	371	457	81	0	0	0
3	M	67	47.5	67.3	40.2	169 / 97	196 / 106	97.0	82	98	84.9	108	85	725	401	–	–	0	0	0
4	M	75	63.7	56.1	46.4	158 / 76	176 / 86	97.5	95	99	78.6	106	73	733	469	423	110	0	0	0
5	M	80	52.3	100.0	68.3	133 / 81	136 / 81	96.6	81	98	76.9	116	55	659	369	528	69	0	0	0
6	M	70	32.6	100.0	39.7	157 / 77	147 / 76	96.8	91	98	97.2	113	95	617	345	548	62	0	0	0
7	M	87	59.3	71.8	53.6	169 / 80	168 / 73	94.7	86	97	87.9	112	92	662	325	392	82	0	0	0
8	M	83	48.4	93.5	61.1	167 / 82	172 / 97	93.3	82	94	89.0	116	95	591	262	339	77	0	0	0
9	M	80	35.7	100.0	43.4	114 / 47	116 / 55	94.3	87	96	78.1	95	74	273	106	361	29	3	35	215
10	M	79	37.2	97.1	45.7	134 / 66	146 / 75	91.3	77	92	81.4	104	57	607	375	493	76	0	0	0
11	M	71	50.8	66.7	43.3	185 / 108	229 / 122	95.7	80	97	80.4	128	83	662	420	445	94	0	0	0
12	M	76	57.7	87.4	56.4	146 / 88	140 / 89	96.3	92	98	75.8	94	76	699	415	447	92	0	0	0

ADL 低下が顕著であるにも関わらず、呼吸機能検査や動脈血ガス分析などの検査値は良好であるため労災認定基準を満たさない症例がしばしば存在する。こうした現行の基準で見逃されている呼吸機能障害例を労災認定できるようにするために、本研究によって新たな呼吸機能障害の基準を設けることを目的とした。

対　　象

2019 年４から 2021 年３月にかけて岡山労災病院を受診した患者のうち、職業性石綿暴露歴があり、胸部 X 線検査及び CT 検査でびまん性胸膜肥厚と診断された症例を対象とした。労災認定の有無は問わず、在宅酸素を導入している症例は対象外とした。

B．研究方法

1. 肺機能検査として、１次検査（スパイロメトリーで測定した項目［%VC, % FEV_1, FEV_1%］、予測値）、２次検査（動脈血液ガス分析）とともに６分間歩行試験を行った。６分間歩行試験では血圧、心拍数、酸素飽和度（SpO_2）、歩行数、歩行距離、中断・休憩時間を測定した。歩行距離の予測値は性別、身長、体重、年齢などから [8)9)]、歩行距離の割合は総歩行距離を予測値で除して算出した。歩行路は 30 m の平坦な直線コースを折り返して使用し、対象者には６分間に出来るだけ長く距離を歩くこと、テスト中は６分間に何度休憩しても良いことを伝え、１分毎に決まった内容を声かけした [7)]。なお、６分間歩試験において、前月の不安定狭心症や心筋梗塞は絶対的禁忌とし、安定型狭心症、安静時心拍数 ＞ 120 回/分、収縮期血圧 ＞ 180 mmHg、および拡張期血圧 ＞ 100 mg は相対的禁忌とした [7)]。

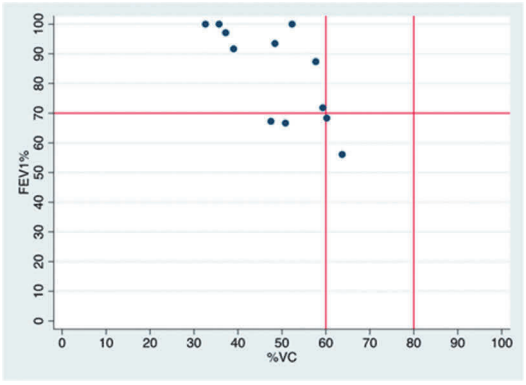

図１．対象者 12 名の呼吸機能分布

2. 日常生活の状況について Pulmonary emphysema ADL [以下 P-ADL] [6]を用いてアンケートを行った。P-ADL は食事・排泄・入浴・洗髪・整容・更衣・屋内歩行・階段・屋外歩行の ADL の 9 カテゴリーを、達成方法・距離・頻度・速度・息切れ・酸素量の 6 つの指標を用いて評価する自記式質問票である [6]。ただし、P-ADL の記入に家族、医療者の助けを借りることは許容した。

（倫理面への配慮）

本研究の実施にあたって、研究の意義、目的、方法、予測される結果、提供者が被る恐れのある不利益、試料保存及び使用方法、研究参加は自由意志によるものである。拒否・中止も自由でそれに伴う不利益もないことについて十分な説明を行った上で書面にて同意を得た。また、個人が特定できないようプライバシーの配慮に努めた。本研究は岡山労災病院倫理委員会により承認された。

C．研究結果

研究期間中に 12 名から研究参加同意を得た。12 名全員が男性であり、検査時年齢の中央値は 76.5 歳（67～87 歳）であった。12 名中 10 名が%VC < 60%で呼吸機能障害の基準を満たしていた。%VC > 60%の 2 名のうち、1 名は FEV_1、$\%FEV_1$ が低いため呼吸障害の基準を満たしていた。もう 1 名はこの度の検査では基準を満たしていなかったが、%VC、$\%FEV_1$、FEV_1%のいずれも基準値下限であり、既に認定も受けていた。そのため、12 名全員がびまん性胸膜肥厚による呼吸障害があるものとして、6 分間歩行試験の結果について検討した。全員が拘束性換気障害を呈しており、4 名は混合性換気障害を合併していた。SpO_2 について 6 分間歩行試験前後（安静時）の平均値は は 95.4%で、健常人に比べると数値はやや低値であった。一方、検査中最低値は 86.2%（95%信頼区間 82-90%）であった。歩行距離は予測値が各個人によって幅広いため総歩行距離/予測値の分布を示した。総歩行距離/予測値は 77.3%（95%信頼区間 63-91%）であった。また、P-ADL によるアンケート調査では、対象者 12 名のうち 11 名より回答が得られ、「階段」（24 点満点中，20.8 点）、「屋外歩行」（20 点満点中，17.5 点）の項目で、他の項目と比較して点数が低かった。

表２．６分間歩行試験の SpO_2，歩行距離

SpO2				
変数	サンプル数(人)	平均(%)	標準誤差	95%信頼区間(%)
6分間歩行前	12	95.4	0.536	94.2–96.6
最低値	12	86.2	1.779	82.3–90.1
6分間歩行後	12	96.8	0.575	95.6–98.1

歩行距離				
変数	サンプル数(人)	平均(%)	標準誤差	95%信頼区間(%)
総歩行距離/予測値	11	77.3	6.207	63.4–91.1

表３．対象者 12 名（11 名回答）の P-ADL ［ ※対象者の点数/満点 ］

	性別	測定時年齢（歳）	食事	排泄	入浴	洗髪	整容	更衣	屋内歩行	階段	屋外歩行	会話
1	M	73	22/24	21/24	21/24	22/24	20/24	16/20	19/24	15/24	14/20	13/16
2	M	77	23/24	22/24	24/24	24/24	24/24	20/20	22/24	18/24	17/20	15/16
3	M	67	24/24	24/24	24/24	24/24	24/24	20/20	24/24	23/24	20/20	16/16
4	M	75	24/24	24/24	22/24	24/24	24/24	20/20	24/24	22/24	14/20	16/16
5	M	80	24/24	24/24	24/24	24/24	24/24	20/20	24/24	20/24	18/20	16/16
6	M	70	22/24	24/24	23/24	24/24	24/24	19/20	22/24	20/24	17/20	15/16
7	M	87	24/24	24/24	24/24	24/24	24/24	20/20	24/24	24/24	20/20	16/16
8	M	83	24/24	24/24	24/24	24/24	24/24	20/20	24/24	19/24	17/20	15/16
9	M	80	24/24	24/24	18/24	24/24	24/24	20/20	24/24	23/24	18/20	15/16
10	M	79	24/24	24/24	24/24	24/24	24/24	20/20	24/24	23/24	19/20	16/16
11	M	71	23/24	24/24	23/24	21/24	23/24	19/20	23/24	22/24	19/20	16/16
12	M	76	回答なし									
平均			23.5/24	23.5/24	22.8/24	23.5/24	23.5/24	19.5/20	23.1/24	20.8/24	17.5/20	15.4/16

D．考察

びまん性胸膜肥厚 12 例に対して肺機能検査、６分間歩行試験、アンケート調査(P- ADL) を行った。６分間歩行試験の解析では、安静時と比較し、労作時の SpO_2 低下が顕著であった。びまん性胸膜肥厚患者における SpO_2 最低値の 95%信頼区間上限が 90%、あるいは歩行距離予測値の信頼区間上限が 90%であるため、６分間歩行試験の結果がそれ以下であれば著しい呼吸障害のある集団と同程度の呼吸機能と結論づけることができる。したがって、以上の結果より、びまん性胸膜肥厚患者の６分間歩行試験において、「SpO_2 最低値が 90%以下、あるいは歩行距離が予測値の 90%以下であること」が、著しい呼吸機能障害の基準になりうると考えられた。またアンケート調査については、一般的な ADL 尺度（機能的自立度評価法 [FIM] ）では呼吸器疾患患者の息切れによる ADL 障害を的確に捉え難いことから[6]、びまん性胸膜肥厚に対しても、呼吸器疾患特異的な ADL 評価「Pulmonary emphysema ADL (P-ADL) 」を用いることとした。本研究の P-ADL の結果から、「階段」や「屋外歩行」などの項目で点数が低く、安静時の ADL に大きな障害はないが、労作時の ADL が特に障害されていることがわかる。したがって、６分間歩行試験における SpO_2 低下あるいは歩行距離の短縮で示される労作時の呼吸障害を「階段」および「屋外歩行」の ADL 低下が裏付けていると考えられる。拘束性換気障害を呈するびまん性胸膜肥厚において、画像診断上指摘困難であっても、閉塞性換気障害を合併している可能性は否定できない。そしてこのことが、今回安静時にはみかけ上あまり異常がなくても、６分間歩行試験で SpO_2 の著明な低下が認められた理由かもしれない。これまでの評価基準である肺機能検査や動脈血ガス分析では、安静時の評価しか行えなかったが、６分間歩行試験では安静時と労作時の両方の評価が可能である。これまで労作時のみ機能が悪い例が見逃されてきたが、６分間歩行によってその部分を補うことができると考えられる。

本研究はびまん性胸膜肥厚の著しい呼吸機能障害において、いままで明確な数値基準がなかった６分間歩行試験の基準を提示できた点が優れていると考えられる。なお、本研究では呼吸機能障害を有するびまん性胸膜肥厚症例のみの検討であったが、明らかな呼吸機能障害のない対照群と比較することができれば、より

詳細な検討ができるかもしれない。今後の症例の蓄積に期待したい。

E．結論

びまん性胸膜肥厚患者の 6 分間歩行試験において、「SpO_2 最低値が 90%以下、あるいは歩行距離が予測値の 90%以下であること」が、著しい呼吸機能障害の基準になりうる。

F．研究発表

1. 論文発表

該当なし

2. 学会発表

該当なし

G．知的財産権の出願・登録状況（予定を含む。）

1. 特許取得

該当なし

2. 実用新案登録

該当なし

3. その他

該当なし

H．参考文献

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Ⅲ.　研究成果の刊行に関する一覧表

＜研究成果の刊行に関する一覧表＞

【 書　籍 】

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
Matsuda A, Fujimoto N	Immunotherapy in malignant pleural mesothelioma.		Advances in Precision Medicine Oncology	Intech Open.	UK	2021	DOI: 10.5772/intechopen.95823
Fujimoto N.	Systemic Chemotherapy for Unresectable Pleural Mesothelioma from Front Line to Salvage Treatment: How Can We Treat the Patients Failed to PD-1/PD-L1 Inhibitors?	Takashi Nakano Takashi Kijima Editor	Respiratory Disease Series: Diagnostic Tools and Disease Managements	Springer Nature Singapore Pte Ltd.	Singapore	2021	253-266

【 雑　誌 】

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Hotta K, Fujimoto N, Kozuki T, Aoe K, Kiura K.	Nivolumab for the treatment of unresectable pleural mesothelioma.	Expert Opin Biol Ther.	20(2)	109-114	2020
Fujimoto N.	An appropriate choice for immunotherapy in malignant pleural mesothelioma.	EBioMedicine.	62	doi: 10.1016/j.ebiom.2020.103057.	2020
Tanaka T, Miyamoto Y, Sakai A, Fujimoto N.	Nivolumab for malignant peritoneal mesothelioma.	BMJ Case Rep.	13(11)	e237721	2020

＜研究成果の刊行に関する一覧表＞

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Kishimoto T, Fujimoto N, Mizuhashi K, Kozawa S, Miura M.	Retrospective investigation on diagnostic process for benign asbestos pleural effusion (BAPE) using checklist.	J Occup Health.	62(1)	e12182	2020
Baas P, Scherpereel A, Nowak AK, Fujimoto N, Peters S, Tsao AS, Mansfield AS, Popat S, Jahan T, Antonia S, Oulkhouir Y, Bautista Y, Cornelissen R, Greillier L, Grossi F, Kowalski D, Rodríguez-Cid J, Aanur P, Oukessou A, Baudelet C, Zalcman G.	First-line nivolumab plus ipilimumab in unresectable malignant pleural mesothelioma (CheckMate 743): a multicentre, randomised, open-label, phase 3 trial.	Lancet.	397(10272)	375-386	2021
Fujimoto N, Okada M, Kijima T, Aoe K, Kato T, Nakagawa K, Takeda Y, Hida T, Kanai K, Hirano J, Ohe Y.	Clinical efficacy and safety of nivolumab in Japanese patients with malignant pleural mesothelioma: 3-year results of the MERIT study.	JTO Clin Res Rep	2（3）	https://doi.org/10.1016/j.jtocrr.2020.100135	2021

Ⅳ.　研究成果の別刷

Chapter

Immunotherapy in Malignant Pleural Mesothelioma

Asako Matsuda and Nobukazu Fujimoto

Abstract

Malignant pleural mesothelioma (MPM) is an extremely aggressive plural malignancy mainly caused by asbestos exposure. Basic research about the immune suppressive tumor microenvironment in MPM has suggested that MPM might be a good candidate for immune therapy. Immunocheckpoint inhibitors have shown some promising results. A phase Ib trial with pembrolizumab, an antibody specific for the programmed cell death 1 protein (anti-PD-1), showed efficacy in patients with programmed death-ligand 1 (PD-L1)-positive MPM. Among 25 patients tested, 5 patients (20%) achieved a partial response. A Japanese group evaluated the efficacy and safety of nivolumab, an anti-PD-L1 antibody, for patients with advanced MPM in a phase II study. Ten (29%) patients showed an objective response. Based on those results, nivolumab was approved in Japan for unresectable recurrent MPM. A phase III randomized study was conducted to compare nivolumab plus ipilimumab to platinum doublet chemotherapy as a first-line therapy in unresectable MPM. The primary endpoint, overall survival (OS), was significantly improved in the nivolumab plus ipilimumab group. Cellular therapies and cancer vaccines are limited by many challenges; therefore, improvements to overcome these difficulties are urgently warranted. Further research is needed, including large-scale clinical trials, to clarify the utility and safety of immunotherapy in MPM.

Keywords: asbestos, ipilimumab, nivolumab, mesothelioma, pembrolizumab

1. Introduction

Malignant pleural mesothelioma (MPM) is an extremely aggressive plural malignancy, which is mainly caused by asbestos exposure [1]. The benefit of surgical resection is controversial, because only a minority of patients with MPM meets the criteria for surgery, and it is unrealistic to assume that surgery will achieve a complete tumor resection without a micro residual tumor. Systemic chemotherapy with platinum plus pemetrexed is the recommended first-line systemic therapy for advanced MPM. However, the median overall survival (OS) is only approximately 12 months [2]. For patients that fail first-line chemotherapy, a standard second-line chemotherapy has not been defined [3]. Hence, it is critically essential to develop a new treatment option.

Recently, immunocheckpoint inhibitors (ICIs) have achieved great success in treating several cancer types [4–7]. Basic research about the immune-suppressive tumor microenvironment in MPM has suggested that MPM might be a good candidate for immune therapy [8, 9]. CD8+ tumor-infiltrating lymphocytes were

reported to predict a favorable prognosis after a resection of MPM [10]. In fact, recently, ICIs have shown promising results for patients with MPM.

In this chapter, we summarize recent studies on immunotherapy for MPM.

2. Anti-cytotoxic T-lymphocyte antigen 4 antibody

Anti-cytotoxic T-lymphoctye antigen 4 (CTLA-4) antibody was the first reported ICI for treating MPM. To date, three clinical trials have tested anti CTLA 4 antibody monotherapy for MPM.

In the first phase II trial (MESOT-TREM-2008), the anti-CTLA-4 monoclonal antibody, tremelimumab (15 mg/kg) was administered intravenously once every 90 days to patients with MPM [11]. Twenty-nine patients with MPM that had failed a first-line platinum-based regimen were enrolled. Of these, no patients achieved a complete response, 2 patients achieved a partial response, and 7 others achieved durable disease control. The median progression-free survival (PFS) was 6.2 months, and the median OS was 10.7 months. The second phase II trial (MESOT-TREM-2012), enrolled 29 patients with MPM that were treated with 10 mg/kg tremelimumab, initially every 4 weeks for 6 doses, then every 12 weeks [12]. The disease control rate was slightly improved after this regimen modification; one patient achieved a partial response, and 11 patients achieved disease control.

Based on these two trials, a large scale, randomized trial (DETERMINE) was conducted [13] with 571 patients with MPM. Of these, 382 patients were assigned to tremelimumab and 189 patients were assigned to placebo. However, there was no significant difference in PFS or OS between these two groups. After the DETERMINE trial, anti-CTLA-4 antibodies were investigated only in combination with an anti-programmed cell death protein 1 (anti-PD-1) antibody or anti-programmed death ligand 1 (PD-L1) antibody.

3. Anti-PD-L1 antibody

Mansfield et al. reported that PD-L1 was expressed in approximately 42 of 106 MPM specimens, and that PD-L1 expression was significantly correlated with poor survival (OS: 5 months in a PD-L1-positive group vs. 14.5 months in a PD-L1-negative group) [14]. Cedrés et al. also reported that PD-L1 expression was a negative prognostic factor in patients with MPM [15]. These results supported the notion that PD-L1 might serve as a potential target for immunotherapy in MPM.

Avelumab is a human IgG1 monoclonal antibody that binds to PD-L1 [16]. Hassan et al. described a phase I trial (JAVELIN Solid Tumor) that enrolled 53 patients with unresectable MPM. Those patients had failed first-line chemotherapy with platinum and pemetrexed. When they were treated with avelumab, the objective response rate was 9% (one complete response and four partial responses) [17]. Responses were durable (median, 15.2 months), and they were observed both in patients with PD-L1-positive tumors (objective response rate [ORR]: 19%) and in those with PD-L1-negative tumors (ORR: 7%). The median PFS was 4.1 months, and median OS was 10.7 months.

Another anti-PD-L1 antibody, durvalumab, was recently evaluated for efficacy in 54 patients with MPM that were not treated previously. Durvalumab was combined with cisplatin and pemetrexed as a first-line chemotherapy (DREAM trial) [18]. The ORR was 48%, and, 31/54 (57%) patients were progression-free at 6 months. Based on the phase II trial results, a phase III trial is currently planned.

4. Anti-PD-1 antibody

4.1 Pembrolizumab

Pembrolizumab is an antibody against PD-1. Pembrolizumab was tested for efficacy in 25 patients with PD-L1-positive MPM in a non-randomized, phase Ib trial [19]. Five patients (20%) achieved a partial response, and 72% of patients achieved disease control. The median OS was 18 months.

A phase II trial of pembrolizumab monotherapy was conducted in 65 patients with MPM that had been treated previously [20]. Among those patients, 19% achieved a partial response to pembrolizumab. The median PFS and OS were 4.5 and 11.5 months, respectively.

Based on these two trials, pembrolizumab was administered, off-label, to 93 patients with MPM in Switzerland and Australia [21]. The ORR was 18%, and the median PFS and OS were 3.1 months and 7.2 months, respectively. Patients with high PD-L1 expression showed improved ORR (44%) and PFS (6.2 months). Recently, a retrospective study from Australia analyzed data from patients with MPM that received pembrolizumab as the first-, second-, or subsequent-line treatment. They found an ORR of 18%, and a disease control rate of 56%. The median PFS was 4.8 months, and the median OS was 9.5 months [22].

4.2 Nivolumab

Nivolumab is a fully humanized monoclonal anti-PD-1 antibody. It was first tested in 34 patients with recurrent MPM in the Netherlands [23]. In that single-center trial, patients with MPM received 3 mg/kg intravenous nivolumab every 2 weeks. Among 34 patients, 8 patients (24%) achieved a partial response, and another 8 patients (24%) displayed stable disease at 12 weeks.

A Japanese group also evaluated the efficacy and safety of nivolumab in 34 patients with advanced MPM. That study tested nivolumab as a salvage therapy in a single-arm phase II study (MERIT study) [24]. Patients received 240 mg nivolumab intravenously every 2 weeks. Ten (29%) patients showed an objective response. The median duration of the response was 11.1 months, and the disease control rate was 68%. The median PFS and OS were 6.1 and 17.3 months, respectively. Among patients with PD-L1-positive tumors (≥1% expression), the ORR was 40%. Based on those results, nivolumab was approved in Japan for unresectable recurrent MPM.

5. Combination therapy with ICIs

Based on the favorable results obtained with ICI monotherapy, recent investigations tested combination treatments, with an anti-PD-1 or anti-PD-L1 antibody combined with an anti-CTLA-4 antibody. This combination was expected to maximize T-cell activation.

NIBIT-MESO-1 was open-label, non-randomized, phase II trial, in which 40 patients with MPM received at least one dose each of tremelimumab and durvalumab [25]. Eleven patients (28%) displayed an objective response. The median PFS was 5.7 months and the median OS was 16.6 months.

IFCT-1501 MAPS2 was a multicenter, open-label, randomized, phase II trial, in which 108 patients with MPM were randomly assigned to receive intravenous nivolumab or intravenous nivolumab plus ipilimumab. In the intention-to-treat population, 12-week disease control (primary endpoint) was achieved by 25/63

Agent	Year	N	ORR (%)	mPFS (mo)	mOS (mo)	Study type	Reference
Anti-CTLA4							
Tremelimumab	2013	29	7	6.2	10.7	2	Calabro et al. [11]
Tremelimumab	2015	20	3	6.2	11.3	2	Calabro et al. [12]
Tremelimumab	2017	571	5	2.8	7.7	2b	Maio et al. [13]
Anti-PD-L1							
Avelumab	2019	53	9	4.1	10.7	1b	Hassen et al. [17]
Anti-PD-1							
Pembrolizumab	2017	25	20	5.4	18	1b	Alley et al. [19]
Pembrolizumab	2018	65	19	4.5	11.5	2	Desai et al. [20]
Nivolumab	2018	34	24	2.6	11.8	2	Quispel-Janssen et al. [23]
Nivolumab	2018	34	29	6.1	17.3	2	Okada et al. [24]
Combination therapy							
Tremelimumab/Durvalumab	2018	40	28	5.7	16.6	2	Calabro et al. [25]
Nivolumab/Ipilimumab	2019	62	28	5.6	15.9	2	Scherpereel et al. [26]
Nivolumab		63	19	4	11.9		
Nivolumab/Ipilimumab	2019	34	29	6.2	NR	2	Disselhorst et al. [27]
Nivolumab/Ipilimumab	2020	303	40	6.8	18.1	3	Baas et al. [28]

ORR: objective response rate; mPFS: median progression free survival; mo: months; mOS: median overall survival; CTLA: cytotoxic T-lymphocyte antigen; PD-L1: programmed death ligand 1; PD-1: programmed cell death protein 1.

Table 1.
Overview of clinical trials that tested immunocheckpoint inhibitors for malignant pleural mesothelioma.

(40%) patients in the nivolumab group and 32/62 (52%) patients in the combination group [26]. The INITIATE study also evaluated the efficacy of nivolumab combined with ipilimumab in patients with MPM. In that study, among 34 patients included in the efficacy assessment, ten (29%) patients achieved a partial response, and 23 patients (68%) achieved 12 weeks of disease control [27]. Based on these favorable results, a phase III randomized study was conducted to compare nivolumab plus ipilimumab to platinum doublet chemotherapy as a first-line therapy in unresectable MPM. In that study, 303 patients were randomized to nivolumab plus ipilimumab and 302 patients were randomized to platinum doublet chemotherapy. With a minimum follow-up of 22 months, the primary endpoint, OS, was significantly improved with nivolumab plus ipilimumab compared to chemotherapy (median, 18.1 vs. 14.1 months; hazard ratio, 0.74; 95% confidence interval, 0.61–0.89; P = 0.002) [28].

Overview of clinical trials of that tested ICIs for MPM was summarized in **Table 1**.

6. Vaccine

Cancer vaccines have been tested for various cancer types. These vaccines have included tumor lysate, attenuated bacteria, and single or multiple peptides. Wilms tumor 1 (WT-1) is one of the most well investigated cancer antigens. WT-1 was expressed in tumors in 97% of patients with MPM [29]. Galinpepimut-S, a multivalent vaccine against the WT 1 peptide, can activate both CD4+ and CD8+ T-cells [30]. The efficacy and safety of galinpepimut-S was investigated in a phase II trial. The pilot study demonstrated that the median PFS was 7.4 months in the placebo group and 10.1 months in the vaccine group. The median OS was 18.3 months in the placebo group and 22.8 months in the vaccine group. Based on th0se findings, a clinical trial is currently ongoing to investigate a combination treatment of galinpepimut-S plus nivolumab in patients with MPM (with WT-1-positive tumors). Combining cancer vaccines with ICIs might improve the clinical outcome and open a new avenue of therapeutic strategies for MPM.

7. Dendritic cell therapy

Vaccination strategies have been developed that involve dendritic cells (DCs), which are antigen-presenting cells for T-cell activation. The DCs are pulsed with tumor lysate to overcome the shortcomings of autologous DCs. These strategies have shown remarkable anti-tumor activity, with low toxicity, in several cancer types. In the area of MPM, 9 patients received three vaccinations of autologous mature DCs loaded with autologous tumor cell lysate [31]. Among these patients, 3 showed a partial response in the first 8 weeks after the DC vaccination. However, two of those three patients had received chemotherapy before the DC vaccination, which might have influenced the anti-tumor effect. In the next step of treatment, they added cyclophosphamide to increase the anti-tumor activity by inhibiting regulatory T cells [32]. Ten patients with MPM received cyclophosphamide and a vaccination of autologous mature DCs loaded with autologous tumor cell lysate. Of those ten patients, seven lived longer than 24 months, and the mean OS was 37 months.

Obtaining autologous tumor cell lysate is time consuming, because patients have to undergo multiple tumor biopsies. In one study, allogeneic tumor lysate obtained from a tumor cell line was applied to autologous DCs [33]. Nine patients with MPM

were treated with DC vaccinations (autologous DCs pulsed with tumor lysate from five mesothelioma cell lines). Of these, two patients experienced a partial response and all nine patients established disease control. The median OS was longer than 22.8 months. Based on those promising results, an ongoing phase II/III study is currently testing DCs loaded with allogeneic tumor cell lysate as a maintenance therapy after chemotherapy (DENIM trial) [34].

8. Chimeric antigen receptor T-cell therapy

Chimeric antigen receptor (CAR) T-cells can be used to target specific tumor antigens directly. CAR T-cell therapy has shown clinical efficacy for hematological malignancies, and it was approved by the United States Food and Drug Administration for B cell acute leukemia and diffuse large B-cell lymphoma. Several clinical trials are ongoing to test CAR T-cell therapy on both hematological malignancies and solid tumors [35]. CAR T-cells that targeted WT-1, fibroblast activation protein (FAP), or mesothelin (MSLN) were tested in a clinical trial on MPM. Hass et al. reported the results of a clinical trial for testing CAR T-cells that targeted MSLN on 15 patients with MPM. The CAR T-cells were applied as a monotherapy or in combination with low-dose cyclophosphamide, for solid tumors [36]. The best overall response was stable disease (11 of 15 patients). Currently, several phase I trials are ongoing to examine the efficacy of CAR T-cell therapy in solid tumors, including MPM.

9. Conclusion

The prognosis of MPM remains poor. A PD-1/PD-L1 blockade is an effective treatment option for MPM. The combination of nivolumab (anti-PD-1 antibody) and ipilimumab (anti-CTLA-4 antibody) could be a standard first-line treatment. Additionally, the combination of an ICI with conventional chemotherapy might be a promising treatment option. Cellular therapies and cancer vaccines must overcome many challenges, such as T-cell migration to the tumor and infiltration into the tumor. Improvements in cancer therapies are urgently needed to overcome these difficulties. Further research with large-scale clinical trials are needed to clarify the utility and safety of these immunotherapies in MPM. In addition, in this new era of precision medicine, we need to develop biomarkers to identify which patients would benefit from ICI-ICI combinations, ICI plus chemotherapy, or cellular therapy.

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Conflict of interest

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Chapter 22
Systemic Chemotherapy for Unresectable Pleural Mesothelioma from Front Line to Salvage Treatment: How Can We Treat the Patients Failed to PD-1/PD-L1 Inhibitors?

Nobukazu Fujimoto

Abstract There are a limited number of randomized clinical trials on systemic chemotherapy for malignant pleural mesothelioma (MPM). The combination of platinum/pemetrexed is considered a standard front-line treatment. There is no established treatment option for those who progressed after initial treatment with platinum/pemetrexed. In recent years, immune checkpoint inhibitors (ICIs), such as pembrolizumab and nivolumab, demonstrated a favorable response, disease control, and survival in phase II trials. In 2018, nivolumab was approved for advanced or metastatic MPM patients who were resistant or intolerant to previous chemotherapy in Japan. Combinations of ICIs or an ICI and conventional chemotherapy are under investigation to further improve response and survival. If these combination regimens that include anti-program death-1 (PD1)/PD-ligand1 (PD-L1) antibodies demonstrate high enough activity, safety, and tolerability as front-line treatments, the standard regimen with platinum/pemetrexed might be replaced. The best treatment regimen to use for patients who failed PD-1/PD-L1 inhibitors has not yet been elucidated. Based on the possible immunotherapy-induced chemosensitization effect that was recently reported, cytotoxic agents, such as pemetrexed, vinorelbine, or gemcitabine, would be the ideal choice. For patients who experienced a certain time to progression after first-line chemotherapy that included pemetrexed, a pemetrexed-based rechallenge might be administered. Combination treatment with immunotherapy and antiangiogenic agents with/without chemotherapy may offer hope, though there are only preclinical studies to support this strategy so far.

Keywords Pemetrexed · Pembrolizumab · Nivolumab · Immune checkpoint · PD-1

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1 Introduction

Malignant pleural mesothelioma (MPM) is a highly aggressive neoplasm with poor prognosis and a median overall survival (OS) of only approximately 12 months. In particular, patients with unresectable, advanced disease are characterized as having a worse prognosis than other patients. This poor outcome is principally due to a lack of effective systemic therapy [1, 2]. There are some guidelines for MPM treatment, including systemic chemotherapy; however, these recommendations are based on very limited evidence. In fact, there are a limited number of randomized clinical trials on systemic chemotherapy for MPM. The current standards for systemic chemotherapy including recent reports of immune checkpoint inhibitors (ICIs) for MPM, are summarized in this chapter, followed by some future perspectives.

2 Front-Line Chemotherapy

2.1 Platinum/Pemetrexed

Systemic chemotherapy consisting of a platinum plus pemetrexed is a recommended first-line systemic therapy for patients with MPM with a good performance status (PS). A single-blind, placebo-controlled, randomized phase III trial compared cisplatin (75 mg/m^2) alone and cisplatin plus pemetrexed (500 mg/m^2) in 456 previously untreated patients with MPM [3]. The combination of cisplatin and pemetrexed achieved a higher response rate (RR) (41.3 vs 16.7%; $P < 0.001$), superior median OS (12.1 vs 9.3 months; $P = 0.020$), and progression-free survival (PFS) (5.7 vs 3.7 months; $P = 0.001$) than single-agent cisplatin (Fig. 22.1). The toxicity was greater with the combination, producing grade 3/4 neutropenia, leukopenia, and nausea in 27.9%, 17.7%, and 14.6% of patients, respectively. Vitamin supplementation was instituted after the first 117 patients were enrolled, resulting in a significant reduction in toxicity. The combination chemotherapy also improved the quality of life (QoL) of the patients. Using the Lung Cancer Symptom Scale instrument to evaluate QoL, the combination of cisplatin plus pemetrexed demonstrated statistically significant improvements in dyspnea and pain. Another phase III trial that compared the antifolate raltitrexed (80 mg/m^2) plus cisplatin (80 mg/m^2) to cisplatin alone in 250 patients similarly demonstrated a higher RR (23.6 vs 13.6%) and a superior median OS (11.4 vs 8.8 months) and 1-year survival (46 vs 40%) for the raltitrexed/platinum combination than for cisplatin alone [4].

Pemetrexed can be administered in combination with carboplatin, with efficacy comparable to that of cisplatin/pemetrexed [5]. Although no randomized study has directly compared carboplatin to cisplatin in MPM, data from multiple phase II series and an expanded access program suggest that they are likely equivalent [6–8]. In a retrospective pooled analysis, patients over 70 years of age who were treated

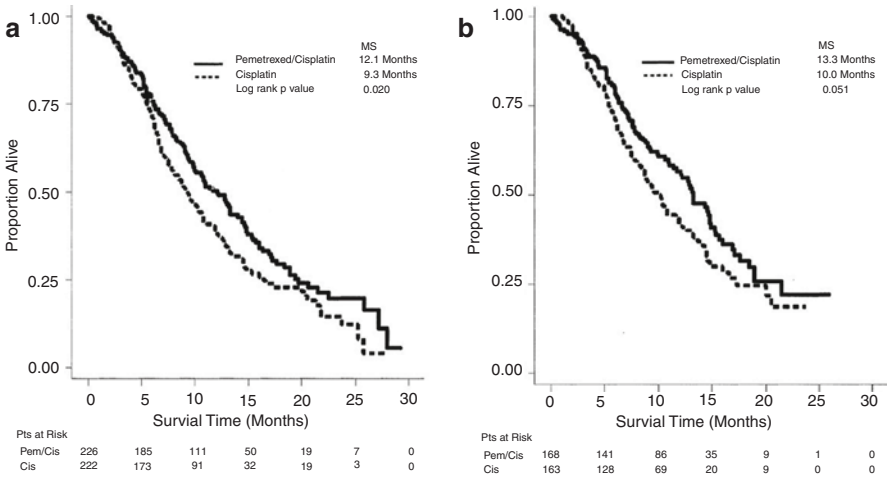

Fig. 22.1 Kaplan-Meier estimates of the overall survival time for all patients (Pts) (**a**) and for fully supplemented patients (**b**) in a phase III study that compared pemetrexed/cisplatin (Pem/Cis) to cisplatin alone (Cis) [3]. *MS* median survival

with pemetrexed and carboplatin achieved similar outcomes to their younger counterparts, though the older patients experienced more frequent hematologic toxicities [9]. MPM usually develops after a long latency period from past asbestos exposure, so there are many older patients who have some comorbidities. The combination of carboplatin/pemetrexed could be a reasonable treatment option for patients who are not candidates for a cisplatin-based regimen [10].

2.2 Beyond Platinum/Pemetrexed

There have been some clinical trials that examined the utility of new agents to further improve the results of platinum/pemetrexed combination chemotherapy. Representative examples are antiangiogenic agents. The Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS), an open-label, randomized, phase III trial, compared cisplatin/pemetrexed with or without the addition of bevacizumab, which targets vascular endothelial growth factor (VEGF) [11]. The three-drug combination demonstrated a longer OS than cisplatin/pemetrexed (18.8 vs 16.1 months; $P = 0.0167$; hazard ratio [HR], 0.77). PFS was also superior to the triplet treatment (9.2 vs 7.3 months; $P < 0.001$; HR, 0.61). Although the addition of bevacizumab increased the rate of grade 3/4 toxicities (71 vs 62%), especially hypertension (25 vs 0%) and thrombosis (6 vs 1%), there was no detriment to the QoL with the addition of bevacizumab [11]. The cisplatin/pemetrexed/bevacizumab regimen is recommended as one of the first-line treatment options in the National Comprehensive Cancer Network (NCCN) guidelines but is still not considered a standard treatment

in most countries. Bevacizumab is not approved in Japan, and there is no plan for its future approval.

Nintedanib targets VEGF receptors 1–3, platelet-derived growth factor (PDGF) receptors α and β, fibroblast growth factor (FGF) receptors 1–3, and the Src and Abl kinases, which are all implicated in MPM pathogenesis. Based on the favorable findings of the phase II LUME-Meso study [12], a double-blind, randomized, placebo-controlled phase III trial was conducted at 120 institutions in 27 countries [13]. Chemotherapy-naive patients with unresectable epithelioid MPM and an Eastern Cooperative Oncology Group (ECOG) PS 0-1 were randomly assigned to receive cisplatin/pemetrexed with or without nintedanib. PFS was not different between the nintedanib group (median 6.8 months [95% confidence interval (C.I.): 6.1–7.0]) and the placebo group (7.0 months [6.7–7.2]; HR 1.01 [95% C.I.: 0.79–1.30], $P = 0.91$).

2.3 Current Standards

Based on these discouraging situations, the platinum/pemetrexed combination is still considered a standard front-line treatment. In a pivotal study on cisplatin/pemetrexed, patients received a median of six cycles of chemotherapy. The percentage of patients who completed at least four, six, or eight cycles was 71%, 53%, and 5%, respectively [3]. A nonrandomized feasibility study with 27 patients suggested that continuous maintenance treatment with pemetrexed was safe and that responses could be achieved after 6 cycles of induction chemotherapy [14]. However, due to the limitations of the study, such as the heterogeneous patient population, the different induction regimens (pemetrexed/carboplatin or pemetrexed alone), and the small number of patients who received maintenance chemotherapy, maintenance treatment with pemetrexed is not recommended. A break from chemotherapy after four to six cycles of platinum/pemetrexed is currently recommended [15].

3 Salvage Chemotherapy

3.1 Pemetrexed

There was no recommended treatment option for MPM that had progressed after first-line treatment with platinum/pemetrexed. A phase III trial in 243 patients who had not previously received pemetrexed demonstrated a higher RR (18.7 vs 1.7%; $P < 0.001$), superior disease control (59.3 vs 19.2%; $P < 0.0001$), and longer PFS (3.6 vs 1.5 months; $P = 0.0148$) in those who received single-agent pemetrexed than in those with best supportive care [16]. Even for patients who had received a first-line treatment containing pemetrexed, retreatment with pemetrexed-based

chemotherapy is a reasonable option for patients who achieved durable disease control with first-line chemotherapy. A single-center retrospective review reported an overall RR of 19% and a disease control rate (DCR) of 48% among 31 patients who achieved disease control with first-line pemetrexed-based chemotherapy for at least 3 months [17]. A multi-institution retrospective analysis of 30 patients documented a 66% DCR and decreased pain for patients who had at least 6 months of disease control with first-line platinum/pemetrexed and were rechallenged with a pemetrexed-based regimen [18]. A multicenter retrospective analysis showed that patients with MPM who experienced a time to progression of at least 12 months after first-line chemotherapy had a greater likelihood of disease control with retreatment with pemetrexed [19].

3.2 Other Cytotoxic Agents

Other treatment options for salvage chemotherapy in MPM include vinorelbine or gemcitabine; however, the median OS with these agents ranges from 5 to 10 months [20, 21]. Vinorelbine is widely used as a second-line therapy, though there are limited data to support its efficacy. A single-center phase II trial of vinorelbine in 63 patients achieved an RR of 16% and a median OS of 9.6 months. Similarly, a single-center retrospective review of 59 patients reported an RR of 15% and a DCR of 49% [22]. In contrast, a retrospective review of 60 patients who received either vinorelbine or gemcitabine in a second- or third-line setting reported no RR for vinorelbine and an RR of 2% for gemcitabine. The median PFS was 1.7 and 1.6 months for vinorelbine and gemcitabine, respectively [23].

3.3 Other Novel Agents

Vorinostat, an oral histone deacetylase inhibitor, showed some evidence of activity in an initial study [24]. However, the efficacy was not confirmed in a phase III trial, in which 661 previously treated patients were randomly assigned to receive either vorinostat or placebo [25]. Other experimental agents, such as angiogenesis inhibitors [26] or tyrosine kinase inhibitors [27], have also not demonstrated efficacy. Recently, YS110, a humanized IgG1 monoclonal antibody with a high affinity for the CD26 antigen, demonstrated preclinical antitumor effects for CD26-expressing solid tumors. The recommended dose was defined, and encouraging prolonged disease stabilization was observed in a first-in human study for patients with CD26-expressing solid tumors, including MPM [28]. A subsequent phase II study is ongoing.

Given the paucity of active agents in this setting, enrollment in some clinical trials is highly recommended for those with a good PS.

4 Immune Checkpoint Blockade

4.1 Anti-Cytotoxic T Lymphocyte–Associated Antigen 4 (CTLA-4) Antibody

Targeting immune checkpoints with immunomodulatory monoclonal antibodies has been proven to be an effective antitumor strategy across a variety of cancers [29]. The immunosuppressive tumor microenvironment in MPM suggests that MPM might benefit from these kinds of immunotherapy [30, 31]. An anti-CTLA-4 antibody was the first ICI reported in MPM. Phase II studies demonstrated that the anti-CTLA-4 monoclonal antibody tremelimumab had favorable activity as a second-line treatment for MPM [32, 33]. However, in the subsequent phase III DETERMINE study, second- or third-line tremelimumab did not improve OS compared with placebo [34].

4.2 Anti-Programmed Death-1 (PD-1) Antibody

4.2.1 Pembrolizumab

Next, pembrolizumab, an anti-PD-1 antibody, paved the way. In a preliminary report of a nonrandomized, phase Ib trial of pembrolizumab in previously treated patients with PD-1-positive MPM, 20% of patients had an objective response, 72% had disease control, and the median OS was 18 months (95% C.I.: 9.4 to not reached) [35]. Then, a phase II trial assessed the activity of pembrolizumab in a nonselected group of 65 MPM patients [36]. The objective RR (ORR) was 19%, and the DCR was 66%. The median PFS was 4.5 months (95% C.I.: 2.3–6.2), and the median OS was 11.5 months (95% C.I.: 7.6–14).

Based on these promising results, pembrolizumab was used off-label in Switzerland and Australia [37]. Pembrolizumab was administered as a second-line treatment in 48 of 93 patients (52%). In the full cohort, the overall RR was 18%, the median PFS was 3.1 months, and the median OS was 7.2 months. The non-epithelioid histological subtype showed an improved ORR (24 vs 16% [$P = 0.54$) and median PFS (5.6 vs 2.8 months [$P = 0.02$]). The toxicities were as expected.

4.2.2 Nivolumab

Another anti-PD-1 antibody, nivolumab, was first tested in recurrent MPM in the Netherlands [38]. In a single-center trial, patients with MPM received nivolumab (3 mg/kg) intravenously every 2 weeks. Of the 34 patients included, 8 patients (24%) had a partial response, and another 8 had stable disease, resulting in a DCR

of 47%. The Japanese investigators also evaluated the efficacy and safety of nivolumab for advanced MPM patients who were resistant or intolerant to prior chemotherapy [39]. Thirty-four patients were enrolled, 10 patients showed a centrally assessed objective response, and the ORR was 29.4% (95% C.I.: 16.8–46.2). Concerning the histological subtypes, the ORRs were 25.9%, 66.7%, and 25.0% for the epithelioid, sarcomatous, and biphasic subtypes, respectively. The median OS and PFS were 17.3 and 6.1 months, respectively (Fig. 22.2). Based on these findings, nivolumab was approved in Japan for advanced or metastatic MPM patients who were resistant or intolerant to previous chemotherapy.

The toxicity of these ICIs was acceptable in MPM. The grade 3 or 4 toxicities included adrenal insufficiency (3%), pneumonitis (3%), skin rash (3%), colitis (1.6%), confusion (1.6%), hepatitis (1.6%), hyperglycemia (1.6%), and grade 5 hepatitis (1.6%) in a study of pembrolizumab [36]. Adverse events of any grade, such as fatigue (29%) and pruritus (15%), occurred in 26 patients (76%) in a study of nivolumab. Grades 3 and 4 treatment-related adverse events were reported in 9 patients (26%), and pneumonitis, gastrointestinal disorders, and abnormal laboratory results were most commonly seen. One treatment-related death occurred due to pneumonitis and was probably initiated by concurrent amiodarone therapy. These toxicity profiles resemble those in other malignancies, such as melanoma and non-small cell lung cancer (NSCLC), and seem manageable.

Although the effect of these ICIs requires confirmation in larger clinical trials, nivolumab and pembrolizumab would offer hope for patients with MPM. Reported studies with an anti-PD-1 antibody in MPM are summarized in Table 22.1.

5 Future Perspectives

5.1 Combination of ICIs

There are still a number of challenges in systemic chemotherapy for MPM. Immune checkpoint blockade could play the main role in addressing these challenges, at least for the time being. An important issue is the combination of an ICI and other agents, including other ICIs. The combination of antibodies targeting PD-1 or PD-ligand1 (PD-L1) and CTLA-4 warrants investigation given the synergistic roles of the PD-1/PD-L1 and CTLA-4 pathways in T-cell activation [40]. The NIBIT-MESO-1 study investigated the efficacy and safety of first- or second-line tremelimumab combined with durvalumab, an anti-PD-L1 monoclonal antibody [41]. In a phase II study, patients with unresectable pleural or peritoneal mesothelioma received intravenous tremelimumab and durvalumab every 4 weeks for four doses, followed by maintenance therapy with intravenous durvalumab. Eleven (28%) of 40 patients had an objective response. The median PFS was 5.7 months (95% C.I.: 1.7–9.7), and the median OS was 16.6 months (95% C.I.: 13.1–20.1). The treatment-related toxicities were generally manageable and reversible.

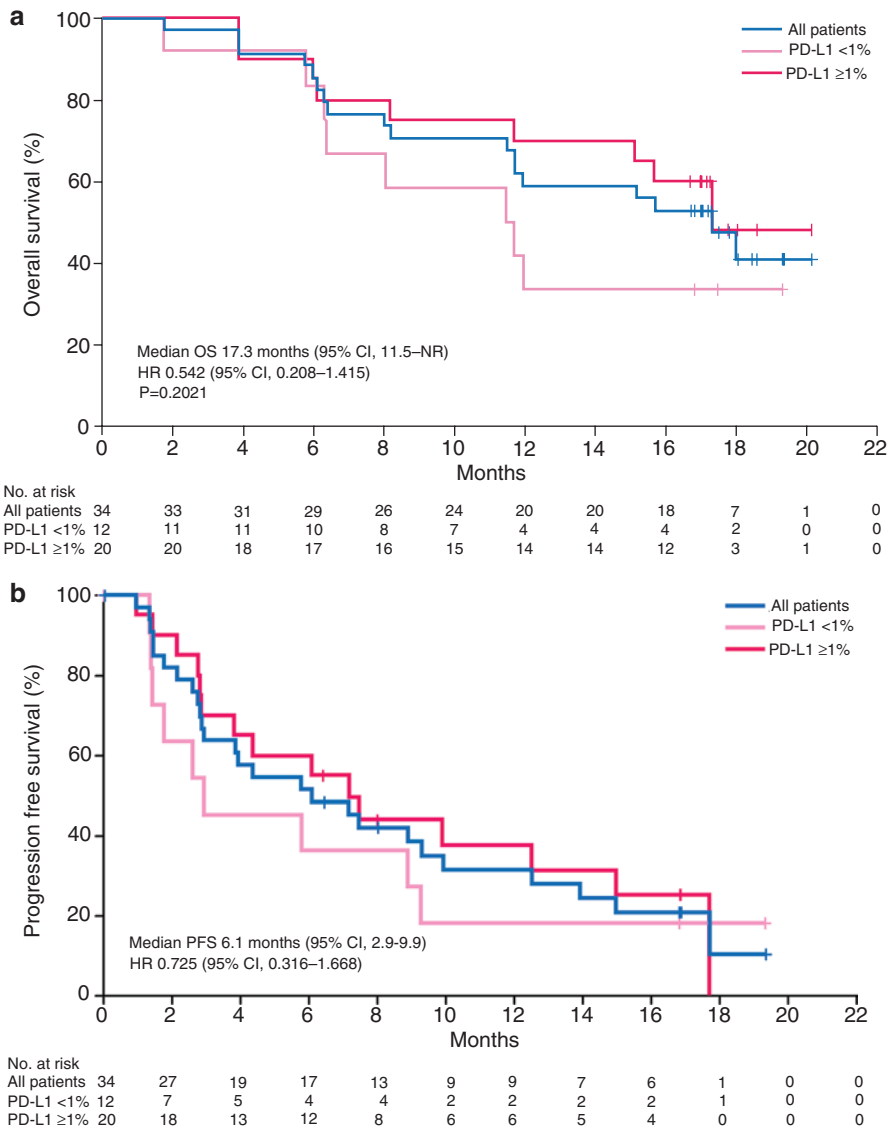

Fig. 22.2 Kaplan-Meier curves for overall survival (**a**) and progression-free survival (**b**) for all patients and according to the PD-L1 expression status in the MERIT study [39]. *HR* hazard ratio, *NR* not reached

Table 22.1 Reported studies with anti-PD-1 antibodies in malignant pleural mesothelioma

Agent	*N*	ORR (%)	DCR (%)	mPFS (m)	mOS (m)	Author	References
Pembrolizumab	25	20	72	5.4	18	Alley et al.	[35]
Pembrolizumab	64	22	61	4.1	10.1	Desai et al.	[36]
Pembrolizumab	93	18	48	3.1	7.0	Metaxas et al.	[37]
Nivolumab	34	26	47	2.6	11.8	Quispel-Janssen et al.	[38]
Nivolumab	34	29	67.6	6.1	17.3	Okada et al.	[39]

DCR disease control rate, *mOS* median overall survival, *mPFS* median progression-free survival, *N* number of cases, *ORR* objective response rate, *PD* programmed death

Another multicenter, randomized, phase II study was performed in France [42]. In that study, patients were randomly allocated to receive nivolumab or nivolumab plus ipilimumab and were treated until progression or an unacceptable toxicity. In the intention-to-treat population, 12-week disease control was achieved by 25 (40%; 95% C.I.: 28–52) of 63 patients in the nivolumab group and by 32 (52%; 95% C.I.: 39–64) of 62 patients in the combination group. The most frequent grade 3 adverse events were asthenia (1 [2%] in the nivolumab group vs 3 [5%] in the combination group), asymptomatic increases in aspartate aminotransferase or alanine aminotransferase (none vs four [7%] of each), and asymptomatic increases in lipase (two [3%] vs one [2%]). These findings indicate that the combination of anti-CTLA-4 and anti-PD1/PD-L1 antibodies appears effective, with a good safety profile in patients with MPM. A phase III, randomized, open-label trial of nivolumab in combination with ipilimumab vs pemetrexed with cisplatin or carboplatin as first-line therapy in unresectable MPM is ongoing. The primary end point of the study, OS, will be reported soon.

5.2 Combination of ICI and Chemotherapy

The advantage of the combination of ICI and chemotherapy has already been demonstrated in NSCLC [43]. The combination of an anti-PD-1/PD-L1 antibody and conventional chemotherapy is also under investigation in MPM. Nowak et al. presented results from a phase II trial of durvalumab with first-line cisplatin/pemetrexed in MPM [44]. The primary end point was PFS at 6 months (PFS6). The proportion of PFS6 was 57% (95% C.I.: 45–68%), and the median PFS was 6.9 months (95% C.I.: 5.5–9.0). The ORR was 48% (95% C.I.: 35–61%). Grade 3–5

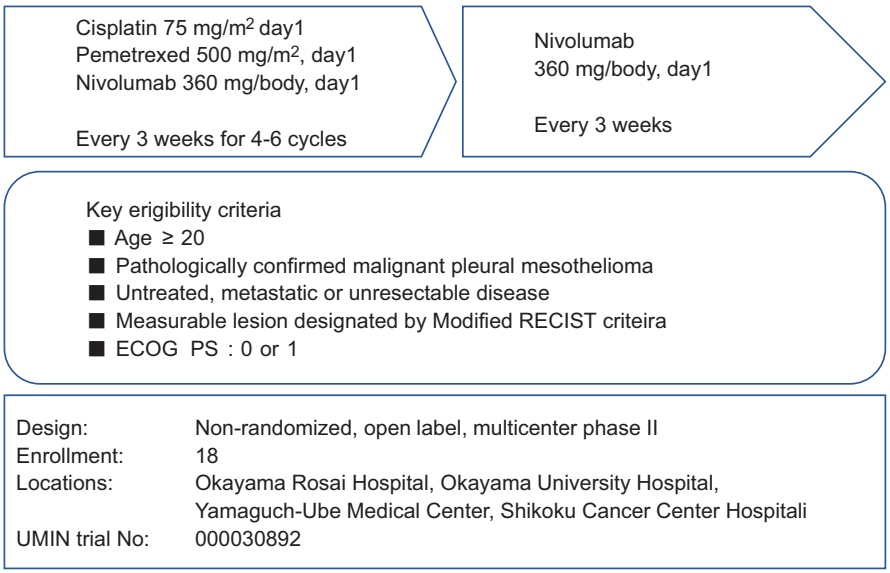

Fig. 22.3 Overview of a phase II trial testing first-line combination chemotherapy with cisplatin/pemetrexed and nivolumab for the treatment of unresectable malignant pleural mesothelioma [45]. *ECOG* Eastern Cooperative Oncology Group, *PS* performance status, *RECIST* Response Evaluation Criteria in Solid Tumors

adverse events occurred in 36 participants, including neutropenia in 13%, nausea in 11%, anemia in 7%, fatigue in 6%, and any grade of peripheral neuropathy in 35%. Another phase II study of the combination of cisplatin/pemetrexed and nivolumab is currently in progress [45] (Fig. 22.3), and the combination of cisplatin/pemetrexed and pembrolizumab is also being evaluated in a large-scale randomized study.

If these combination regimens, including those with an anti-PD1/PD-L1 antibody demonstrate enough activity, safety, and tolerability as a first-line treatment, the standard regimen of cisplatin/pemetrexed might be replaced.

6 How Can We Treat the Patients Failed to PD-1/PD-L1 Inhibitors?

The best treatment regimen to use for patients who failed to PD-1/PD-L1 inhibitors has not yet been elucidated. We could not find any small studies or case series addressing this topic. Based on our experience, currently, cytotoxic agents, such as pemetrexed, vinorelbine, or gemcitabine, would be the best choice. As mentioned in the previous section on "salvage chemotherapy," for patients who experienced a certain time to progression after first-line chemotherapy containing pemetrexed, a pemetrexed-based rechallenge might be administered.

Recently, Schvartman et al. reported that the RR to chemotherapy after exposure to ICIs was higher in advanced NSCLC [46]. Park et al. also reported that ICIs could improve the RR of salvage chemotherapy administered after immunotherapy in patients with NSCLC [47]. The immunomodulatory effects of chemotherapy are considered possible mechanisms of the immunotherapy-induced chemosensitization effect, although the detailed mechanism remains unknown. A prospective study is warranted to examine the effect of rechallenge with pemetrexed or monotherapy with gemcitabine or vinorelbine after the failure of ICI treatment.

Another interesting future prospect is a combination of immunotherapy and other drugs, such as antiangiogenic agents. A recent basic study showed that simultaneous treatment with a PD-1 inhibitor and an anti-VEGFR2 antibody synergistically inhibited tumor growth in vivo [48]. Allen et al. also showed that anti-PD-L1 therapy can sensitize tumors to antiangiogenic treatment and can prolong its efficacy, although this was demonstrated in preclinical models [49]. Combination treatment with immunotherapy and antiangiogenic agents with/without chemotherapy may offer hope.

7 Conclusion

We still have a number of challenges to address in systemic chemotherapy for MPM. Immune checkpoint blockade may play the main role in addressing these challenges. The combination of an ICI and other ICIs and the combination of an ICI and conventional chemotherapy are under investigation. Further study is warranted to investigate whether ICIs could improve the response to salvage chemotherapy administered after immunotherapy.

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DRUG EVALUATION

Nivolumab for the treatment of unresectable pleural mesothelioma

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ABSTRACT

Introduction: Platinum-based chemotherapy is the current first-line standard therapy for unresectable malignant pleural mesothelioma (MPM). Recently, immune-checkpoint inhibitors (ICI) have been intensively investigated as treatment options for this disease. Nivolumab, an anti-programmed cell death (PD)-1 agent, was one of the first drugs used and is representative of available ICIs.

Areas covered: This review discusses previous relevant reports and current ongoing trials of nivolumab. The efficacy and safety of nivolumab have been investigated mostly in second-line or later treatment settings as both monotherapy and in combination with other ICIs. Particularly, nivolumab monotherapy yielded promising efficacy with an objective response rate of 29% and median overall survival of 17.3 months in salvage settings in the single-arm, Japanese phase 2 trial (MERIT). Notably, the study led to Japanese approval of nivolumab for unresectable recurrent MPM. Several trials with monotherapy or cotherapy with nivolumab have commenced, including randomized trials of nivolumab monotherapy vs. placebo in the salvage setting, and cotherapy with nivolumab and ipilimumab vs. the platinum doublet in the frontline setting.

Expert opinion: Nivolumab seems like a reasonable option for unresectable, relapsed MPM despite the lack of randomized trial data. Ongoing pivotal trials will confirm its efficacy.

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1. Introduction

Malignant pleural mesothelioma (MPM) is a rare and aggressive malignancy that occurs in the mesothelial surface of the pleural and peritoneal cavities, and the pericardium [1]. The disease is closely associated with asbestos exposure and approximately 80% of MPM cases are caused by occupational or environmental exposure [2–6]. Despite policies banning asbestos use in Western countries, MPM has continued to increase in many countries where asbestos is still extensively used. It is expected that 500,000 new cases of MPM will be diagnosed in men with occupational exposure in Europe alone [7]. The prognosis of MPM is poor, with a median survival time (MST) of 18 months and a 5-year overall survival (OS) rate of < 5% [8]. In particular, those with unresectable, advanced disease at the initial presentation characteristically have a worse prognosis than patients in earlier stages. This disappointing outcome is principally due to the lack of efficient screening methods and effective systemic therapy [9,10]. Therefore, innovative agents are urgently anticipated and required.

The role of peripheral immune tolerance with the co-inhibitory immune-checkpoint molecules cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed cell death 1 (PD-1) and its ligand (PD-L1) have been extensively investigated. PD-L1 is a transmembrane protein that binds to PD-1 and is expressed on cytotoxic T cells and other immune cells [11,12]. Various types of tumor cells have been shown to exhibit upregulated PD-L1 expression levels, which enables them to escape the immune response and keep proliferating [11]. Based on this background knowledge, anti-CTLA4, PD-1, and PD-L1 antibodies have been widely developed against various advanced malignancies. In this review, among the available immune-checkpoint inhibitors (ICI), we specifically discuss nivolumab, which blocks the PD-1 receptor, focusing on relevant previous trial reports and ongoing trials of unresectable MPM both in the first-line and salvage settings.

2. Basic information on nivolumab

Nivolumab is a human monoclonal antibody (HuMAb; immunoglobulin G4 [IgG4]-S228P) that targets the PD-1 cluster of the CD279 cell surface membrane receptor [13,14] (See Box 1). Nivolumab is expressed in Chinese hamster ovary cells and is produced using standard mammalian cell culture and chromatographic purification technologies. The agent was approved for the treatment of several types of tumors in various countries including the United States of America and Japan in 2014 and the European Union in 2015.

The interaction of PD-1 with its ligands, PD-L1 and PD-L2, can be blocked by nivolumab, leading to enhanced T-cell proliferation and interferon (IFN-γ) release *in vitro* [15].

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The supplementary data for this article can be accessed here.

Nivolumab binds with high affinity to activated human T-cells expressing cell surface PD-1 and cynomolgus monkey PD-1. Through a mixed lymphocyte reaction, nivolumab enhances reproducible IFN-γ release in a concentration-dependent manner [16].

In a population pharmacokinetic model, the overall distributions of nivolumab exposure are comparable after treatment with either 3 mg/kg or 240 mg nivolumab. The predicted range of nivolumab exposure following a 240 mg fixed dose across a 35 to 160 kg weight range is maintained well below corresponding exposure to the well-tolerated 10 mg/kg biweekly dosage of nivolumab. That is why a flat dose has been adopted in more recent nivolumab clinical trials.

The clinical activity and safety of nivolumab have been evaluated in patients with various malignancies including melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma, classical Hodgkin lymphoma, urothelial carcinoma, and head and neck carcinoma as a monotherapy or in combination with chemotherapy, targeted therapies, and other immunotherapies. In contrast, in mesothelioma, the clinical establishment of nivolumab has progressed slowly mainly because of the extremely small patient population and the difficulty associated with their accrual into relevant trials.

3. Nivolumab in the first-line setting

Patients with unresectable disease are often treated with systemic cytotoxic chemotherapy not as a cure but for disease management. Currently, the doublet chemotherapy of cisplatin and pemetrexed, antifolates, is the standard regimen for patients with frontline, unresectable MPM [17], followed by the regular approval in NSCLC [18–25]. However, the efficacy of this regimen is limited, with an objective response rate (ORR) of up to 30–40%, and some cancer-related symptoms can be relieved with the therapy, while the median OS is approximately 1 year in this disease setting [26].

Platinum agents can enhance the effector immune response through modulation of PD-L1 [27]. The observed encouraging results might extend ICI use to first-line treatment of MPM, particularly in combination with the standard platinum-based chemotherapy. Based on this background knowledge, ICIs have been tested in untreated, unresectable mesothelioma. Unfortunately, to date, no nivolumab trials have been reported (Table 1), while the potential benefit of adding durvalumab, a PD-L1 inhibitor, to the cisplatin and pemetrexed standard regimen was tested in 54 patients with untreated, unresectable MPM [28]. The study showed promising results and the primary endpoint of progression-free survival (PFS) at 6 months was 57%, with an ORR of 48% and median duration of response of 6.5 months.

In parallel with this promising trial, in January 2018 we commenced a phase 2 trial of nivolumab as a third agent in combination with the standard chemotherapy of cisplatin and pemetrexed for untreated, unresectable MPM [29] (Table 2). The primary endpoint is centrally reviewed ORR, while the secondary endpoints are disease control rate (DCR), OS, PFS, and adverse events (AEs). This is an exploratory trial with a target enrollment of 18 Japanese patients with good performance status.

As a different approach, the survival advantage of frontline combination immunotherapy with nivolumab and ipilimumab over platinum and pemetrexed is currently under investigation in 606 patients with unresectable MPM. This is the industry-sponsored, large-scaled, randomized phase 3, CheckMate 743 study (NCT02899299), initiated in October, 2016, with an estimated completion date of 15 April 2022.

4. Single-agent nivolumab in the salvage setting

No systemic treatment has been proven effective for mesothelioma refractory to first-line platinum doublet therapy in randomized clinical trials. Although multiple systemic therapeutic options have been investigated, there has been little progress [30]. Cotherapy with vinorelbine or gemcitabine or rechallenge with platinum therapy is often chosen in clinical practice, but is rarely effective [31,32]. Therefore, this challenging situation has created the most reasonable clinical setting for developing new treatment strategies using ICIs.

Currently, four ICIs have been tested in the second-line or later setting, including nivolumab as a monotherapy or in combination with other ICIs. Single-agent nivolumab was evaluated

Table 1. Relevant nivolumab trial results in the salvage setting.

Trial	Year	Phase	RCT	Drug	Primary endpoint	No.	ORR	mPFS (mo)	MST (mo)	Ref.
MERIT	2018	2	No	Nivolumab	OR	34	29%	6.1	17.3	[34]
NivoMes	2018	2	No	Nivolumab	DCR	34	24%	2.6	11.8	[33]
MAPS2	2019	2	Yes	Nivolumab/ipilimumab	DCR	62	28%	5.6	15.9	[36]
				Nivolumab		63	19%	4.0	11.9	
INITIATE	2019	2	No	Nivolumab/ipilimumab	DCR	34	29%	6.2	NR	[37]

Abbreviations: RCT; randomized controlled trial, ORR; objective response rate, mPFS; median progression-free survival, MST; median survival time, DCR; disease control rate, OS; overall survival, NR; not reached.

Table 2. Ongoing relevant nivolumab trials.

Trial	Country	Phase	RCT	Setting	Regimen	Primary endpoint	No. of planned pts	Study start date	Registration No.
CM743	Global	3	Yes	Frontline	Nivolumab/ipilimumab vs. p-pem	OS	606	25/10/16	NCT02899299
JME-001	Japan	2	No	Frontline	cis-pem/nivolumab	OR	18	20/01/18	UMIN000030892
CONFIRM	UK	3	Yes	Salvage	Nivolumab vs. placebo	OS	336	28/03/17	NCT03063450

Abbreviations: RCT, randomized controlled trial; pts, patients; cis-pem, cisplatin and pemetrexed; p-pem, platinum (cisplatin or carboplatin) and pemetrexed; OS, overall survival; OR, objective response.

in a single-center, single-arm phase 2 trial (NivoMes) for patients with recurrent MPM [33]. The study revealed a DCR at 12 weeks, set as the primary endpoint, of 47% (16 of 34), including eight partial responders [33], while PD-L1 expression failed to predict responses in this population. The median PFS and MST were 2.6 and 11.8 months, respectively, and nine (26%) patients developed grade ≥ 3 treatment-related AEs, including gastrointestinal disorders and pneumonitis. The investigators documented that single-agent nivolumab had meaningful clinical efficacy and a manageable safety profile in previously treated patients with MPM.

Japanese investigators conducted the single-arm phase 2 MERIT study, assessing the efficacy of nivolumab monotherapy in 34 previously treated patients with pleural MPM [34]. The primary endpoint was centrally defined ORR while AEs, PFS, and OS were also evaluated. The ORR was 29% (10/34, 95% confidence interval [CI]: 16.846.2), which was clearly affected by PD-L1 expression level, with an ORR of 40 and 8% in PD-L1 ≥ 1% and <1%, respectively. The ORR also seemed to be differently stratified by histologic subtypes: 26%, 67%, and 25% for epithelioid, sarcomatoid, and biphasic histologies, respectively. The survival data were also favorable with median PFS and MST of 6.1 and 17.3 months, respectively while 26 patients (76%) experienced treatment-related AEs. The results of this study led the Japanese government to approve nivolumab monotherapy for unresectable recurrent MPM.

5. Combination nivolumab and anti-CTLA-4 antibody in the salvage setting

Assuming that combining ICIs can enhance their upregulation of tumor immunogenicity [35], the combination of an anti-CTLA-4 antibody with nivolumab was investigated in several clinical trials. A randomized phase 2 trial (IFCT MAPS2) evaluated the benefits of a combination of nivolumab and ipilimumab over nivolumab monotherapy in MPM progression after first-line or second-line pemetrexed and platinum-based treatments (Supplemental Figure 1) [36]. A total of 125 relapsed MPM patients were allocated to the cotherapy or monotherapy arm. The primary endpoint of disease control at 12 weeks in the first 108 patients was met in both groups: 27 (50%, 95% CI: 37–63) of 54 in the combination arm and 24 (44%, 95% CI: 31–58) of 54 patients in the monotherapy arm reached centrally assessed disease control at 12 weeks. The efficacy of both regimens was enhanced especially in high PD-L1-expressing tumors (> 25%), with an ORR of 63% to 71%. Sixteen (26%) of 61 patients in the combination arm and nine (14%) of 63 in the monotherapy arm had grade ≥ 3 toxicities, and the most frequent were hepatic injury, asthenia, and lipase increase. The authors concluded that nivolumab monotherapy or nivolumab plus ipilimumab cotherapy both showed promising activity in relapsed patients with malignant pleural mesothelioma, without unexpected toxicity.

In addition to the MAPS2 trial, the efficacy of nivolumab plus ipilimumab was also investigated in the single-arm, phase 2 INITIATE trial in patients with mesothelioma refractory to platinum-based chemotherapy [37]. The primary endpoint was also set as disease control at 12 weeks. Thirty-four patients were evaluable for the response assessment at 12 weeks, and 10 (29%) and 13 (38%) achieved partial response (PR) and stable disease (SD), respectively, resulting in a DCR of 68% (23/34, 95% CI: 50–83). Notably, this study showed similar safety and efficacy results to those of MAPS2 trial [36,37]. This study also showed the association of tumor PD-L1 expression with the efficacy of the cotherapy. The most common AEs were skin disorders, infusion-related reactions, and fatigue. Grade 3 treatment-related AEs were reported in 12 (34%) of the 35 patients.

Along with these reported trials, UK investigators have commenced a randomized, placebo controlled, double blind trial (CONFIRM) comparing nivolumab monotherapy with a placebo in the salvage setting (NCT03063450). The study will recruit 336 patients with mesothelioma who have a history of at least one prior line of treatment at 25 institutes in the UK over a 4-year period. All patients are to be treated for 1 year. The primary endpoint is set as OS while the secondary endpoints are ORR, safety, and patient-oriented outcome. The actual study start date was 28 March 2017, and the estimated study completion date will be July 2021.

6. Conclusion

We have reviewed clinical trial results and ongoing trials related to nivolumab therapy in unresectable MPM. In the frontline setting, the addition of nivolumab to standard cytotoxic chemotherapy is being investigated to overcome the current poor prognosis. With the expectation of enhancing tumor immunogenicity, the combination of anti-CTLA-4 antibody and nivolumab is also under investigation. In the salvage setting, the single-arm, phase 2 MERIT trial showed a favorable ORR of 29% [34], leading to the approval of nivolumab monotherapy in Japan. Other trials have also successfully demonstrated similar efficacy of this agent. Although, to date, no randomized trials have demonstrated a robust survival advantage of nivolumab over other therapies, ongoing pivotal trial may confirm its efficacy.

7. Expert opinion

Nivolumab has been extensively evaluated for efficacy and safety in treating unresectable MPM (Table 2) [33,34,36,37], similar to investigations conducted in other malignancies [38]. However, in contrast to trials of other tumors, MPM trials were often designed as single-arm studies with small sample sizes and OS or PFS was not set as the primary endpoint [33,34,36,37]. Thus, in terms of activity, it is still unknown whether nivolumab monotherapy possesses true survival advantage over other therapies because of the insufficient efficacy data.

However, the following critical points should be considered a focus: 1) single-agent pembrolizumab, another PD-1 antibody, also showed an ORR of approximately 20% with MST of 12 to 18 months; 2) no clearly effective agents are currently available in the salvage setting; and 3) the ORR in the MERIT study was better than that in studies of other malignancies (i.e. ORR of 19%–20% in the study of nivolumab monotherapy for recurrent NSCLC [39,40]). Thus, some, but not all patients could benefit substantially from anti-PD-1 antibodies in the

Box 1. Drug summary box.

Drug name	Nivolumab (OPDIVO)
Phase	Approved
Indication	OPTIVO is indicated for the second – or later-line treatment of mesothelioma by the Ministry of Health, Labor and Welfare of Japan.
Pharmacology description	See the previously published review article [35].
Route of administration	Intravenous infusion
Chemical structure	See the previously published review article [35].
Pivotal trial	The MERIT study [34], a single-arm, Japanese, phase II clinical trial of nivolumab in the treatment of patients with malignant pleural mesothelioma in the second- or third-line setting. The study showed nivolumab monotherapy showed activity. This directly led to the approval of nivolumab for mesothelioma treatment in Japan.

salvage setting. Moreover, based on the low incidence of mesothelioma, we assume that the approval based only on the results of single-arm phase II clinical trials is reasonable, making the agent available to more patients.

However, it is important to note that after approval, the activity of nivolumab should be cautiously reevaluated through post-market surveillance and relevant research with larger study populations. In addition, verification of the approval in large-scale randomized trials is essential, and it is worth paying special attention to the expected results of the CONFIRM trial (NCT03063450). Whether the Japanese MERIT study results would be reproduced by this trial is of great interest [34].

In addition, Mansfield and colleagues stressed the importance of using contemporaneous synthetic control groups to develop surrogate/predictive markers for efficacy [41]. Such an approach would herald the next potential trend of strategies for designing clinical trials of ICIs in the treatment of rare malignancies including mesothelioma.

Similarly, in other malignancies including melanoma, renal cell carcinoma, and NSCLC [42], cotherapy with nivolumab and ipilimumab may also have a potent survival advantage even in untreated, unresectable MPM. Consequently, the Checkmate 743 trial (NCT02899299) may directly change the existing treatment strategy in the frontline setting. Further accumulation of forthcoming relevant data is strongly needed to improve the use of ICIs in daily clinical practice. Ongoing relevant studies are currently strongly expected to further confirm the role of immunotherapy in several disease settings, in addition to MERIT study results, hopefully leading to changes in the current historical prognosis of mesothelioma.

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Declaration of interest

K Hotta has received honoraria outside the current work from AstraZeneca, Ono Pharmaceutical,

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Commentary

An appropriate choice for immunotherapy in malignant pleural mesothelioma

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In this article of *EBioMedicine*, Mankor and colleagues [1] report the results of immune monitoring of peripheral blood immune cell subsets in patients with malignant pleural mesothelioma (MPM) treated with so-called immune checkpoint inhibitors (ICIs). Combination treatment with anti-PD-1/anti-CTLA-4 antibodies induced an increase in the proliferation and activation of T cells. In addition, patients who responded to the combination treatment had low frequencies of naïve CD8 T cells and high frequencies of effector memory CD8 T cells expressing cytokines, such as granzyme-B and interferon-γ. These findings suggest that immune monitoring of peripheral blood immune cell subsets may provide information for predicting clinical benefit from ICI-ICI combination therapy.

MPM is strongly associated with asbestos exposure and has continued to increase in many developing countries. The combination of platinum and pemetrexed is considered a standard regimen, but median survival is approximately 1 year [2]. There is no established treatment option once cases are refractory or intolerable to the regimen. The immunosuppressive tumor microenvironment in MPM suggests that patients may benefit from this kind of immunotherapy. In recent years, some encouraging results of ICIs have been reported for MPM. In a Japanese single-arm phase II study examining the efficacy and safety of nivolumab monotherapy, the primary endpoint, objective response rate, was 29%, and the median progression-free and overall survival were 6.1 and 17.3 months, respectively [3]. These results led to the approval of nivolumab in Japan for unresectable recurrent MPM. However, the efficacy of anti-PD-1 antibody has not been established in randomised clinical studies.

Recently, the combination of nivolumab and ipilimumab was demonstrated to significantly improve overall survival compared to standard chemotherapy in the Checkmate-743 study [4]. An important clinical issue is to determine which patients can expect a response or unacceptable toxicity, as not all patients could benefit from the treatment, and some specific adverse events have been reported for the ICI-ICI combination. Some studies have revealed the correlation between responses and higher PD-L1 expression. In MPM, however, more established outcome data are needed to confirm the value of PD-L1 expression as a predictive biomarker. The tumor mutation burden and tumor microenvironment are associated with the response to ICIs in some neoplasms, but their roles as biomarkers have not been shown in MPM.

In this study, Mankor and colleagues show that patients who respond to combination treatment with nivolumab and ipilimumab have low frequencies of naïve CD8 T cells and high frequencies of cytokine-expressing effector memory CD8 T cells. A strength of this monitoring is that it can be performed before treatment induction. Notably, there are some limitations in this study, including a limited number of responding patients. However, the findings suggest that immune monitoring of peripheral blood immune cell subsets may act as a biomarker predicting a clinical benefit from ICI combination therapy. A prospective study with more subjects should be planned to validate these findings. In addition, basic or translational research to identify the mechanisms of action of T cells and cytokines against mesothelioma cells is warranted.

As a future perspective, the combination of an anti-PD-1 or anti-PD-L1 antibody and conventional chemotherapy is also under investigation. Nowak et al. recently presented favorable results from a phase II trial testing durvalumab, an anti-PD-L1 antibody, combined with cisplatin/pemetrexed in MPM [5]. A large-scale randomised study for testing the combination of pembrolizumab, another anti-PD-1 antibody, and cisplatin/pemetrexed is also ongoing. Platinum agents can enhance the effector immune response through modulation of PD-L1 [6]. Further development of new biomarkers to determine patients who would benefit from ICI-ICI combinations, ICI plus chemotherapy, or conventional chemotherapy is also needed.

A new era in systemic chemotherapy for MPM has just begun. Immune monitoring would be the key to choosing appropriate treatments.

Contributors

Dr Fujimoto wrote the commentary.

Declaration of Competing Interests

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Nivolumab for malignant peritoneal mesothelioma

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SUMMARY

Malignant peritoneal mesothelioma (MPeM) is a highly malignant neoplasm of the peritoneum, which carries a poor prognosis. A 70-year-old man, who was employed in the shipbuilding industry and exposed to asbestos for 50 years, was found to have a low-density lesion in the peritoneum around the liver and spleen, associated with multiple mediastinal and parasternal lymphadenopathy. Laparoscopic exploration was performed, and biopsy specimen analysis led to a diagnosis of MPeM. Initial systemic chemotherapy comprising cisplatin and pemetrexed yielded a modest cytoreductive effect. However, 4 months later, the patient presented with abdominal distension and anorexia. CT images revealed massive ascites, bowel obstruction and an enlarged intra-abdominal tumour, which was considered progression of the MPeM. The patient was treated with nivolumab. Bowel obstruction was improved after the first administration, and his sense of abdomen distension completely disappeared after the third administration. This case supports the utility of immunotherapy in MPeM.

BACKGROUND

Malignant peritoneal mesothelioma (MPeM) is a highly malignant neoplasm occurring in the peritoneum, which is associated with a poor prognosis. There is no established treatment strategy for this disease, and patients with MPeM are usually treated following the strategy for malignant pleural mesothelioma. In recent years, several encouraging reports have demonstrated that malignant pleural mesothelioma shows a positive clinical response to immunocheckpoint inhibitors. However, no clinical study has examined the utility and safety of immunocheckpoint inhibitors for MPeM treatment. Here, we report a case of MPeM which showed a significant clinical response to nivolumab treatment.

CASE PRESENTATION

A 70-year-old man, who had been employed in the shipbuilding industry and exposed to asbestos for 22 years between 16 and 38 years, was identified as hepatitis B virus-positive by a blood test. Further examination using abdominal CT scan revealed a low-density lesion in the peritoneum around the liver and spleen, associated with multiple mediastinal and parasternal lymphadenopathy. Positron emission tomography/CT scan revealed 18F-fluorodeoxyglucose (FDG) accumulation in the peritoneal lesion. Laparoscopic exploration was performed, and histopathological analyses of the biopsy specimen revealed a sheet-like proliferation of epithelial cells with round nuclei and conspicuous nucleoli. Immunohistochemical analyses demonstrated that these cells were positive for calretinin, D2-40 and cytokeratin 5/6, and negative for desmin, carcinoembryonic antigen and thyroid transcription factor-1. Based on these findings, the patient was diagnosed with MPeM, epithelioid subtype.

INVESTIGATIONS

This patient was referred to our hospital, where he received systemic chemotherapy comprising cisplatin and pemetrexed. Six cycles of this treatment yielded a modest cytoreductive effect. Four months later, the patient was admitted to another hospital due to bowel obstruction. He received conservative treatment, but continued to exhibit abdominal distension and anorexia. CT images showed massive ascites, bowel obstruction and an enlarged intra-abdominal tumour, which was considered to be the progression of the MPeM (figure 1A).

Nivolumab therapy was initiated as a salvage treatment. After the first nivolumab administration, the bowel obstruction was improved. The patient's sense of abdomen distension completely disappeared after the third nivolumab administration. After the fourth administration, CT images demonstrated remarkable reduction of the abdominal tumour (figure 1B). Nivolumab therapy did not result in any specific adverse event, except for grade 1 skin eruption (according to Common Toxicity Criteria of Adverse Event V.5).

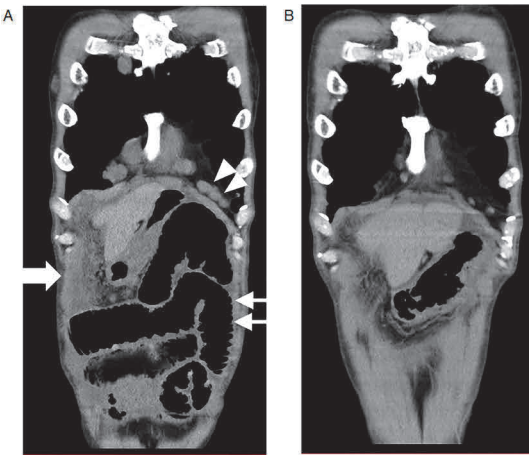

Figure 1 (A) CT images of the abdomen reveal a soft tissue lesion on the omentum (bold arrow); lymphadenopathy adjacent to pericardium fat (arrowheads) and dilatation and fluid accumulation of the small intestine, which indicate intestinal obstruction (narrow arrows). All of these findings suggest the progression of malignant peritoneal mesothelioma. (B) CT images after the fourth administration of nivolumab reveal significant improvement of all of the previous findings.

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OUTCOME AND FOLLOW-UP

The patient was administered 24 courses of nivolumab without disease regrowth. Further administration was suspended due to financial reasons. At this time, the patient had been progression free for 10 months after discontinuation without any cancer treatment.

DISCUSSION

Malignant mesothelioma (MM) is mainly found in the pleura and peritoneum, with some reports indicating that 80% occur in the pleura and 10%–20% in the peritoneum.[1] MPeM arises in peritoneal mesothelium cells, and is classified into epithelioid, sarcomatoid and biphasic subtypes. Yan *et al* found that 92% of cases were the epithelioid subtype and 8% the biphasic subtype.[2] Asbestos exposure is considered a main cause of MPeM, though the association is weaker than with malignant pleural mesothelioma.[3]

No standard MPeM treatment has yet been established. Selected patients receive cytoreductive surgery and hyperthermic intraperitoneal chemotherapy.[4] For patients with inoperable disease, systemic chemotherapy is the most common alternative treatment option, typically using a combination of cisplatin and pemetrexed, since pemetrexed has been approved for malignant pleural mesothelioma. One report of MPeM cases describes a chemotherapy response rate of 38%, and a median overall survival of 15.4 months.[5] In the salvage setting after chemotherapy failure, currently available agents rarely work against MM. In Japan in 2018, nivolumab was approved for malignant pleural mesothelioma that is refractory to primary chemotherapy, based on the favourable results of a phase II clinical study.[6] To date, no report has described the utility of immunocheckpoint inhibitors for MPeM treatment.

The drastic and durable clinical response to nivolumab in the current case of MPeM suggests the utility of immunotherapy in MPeM. A well-designed clinical study is warranted to examine whether nivolumab should be considered as a new treatment option for MPeM.

Patient's perspective

At diagnosis:

I had no symptoms and I was fully active, so I was very shocked when I was given the diagnosis of malignant peritoneal mesothelioma. I was exposed to asbestos when I worked at a shipyard, when I was 17–20 years old. I was afraid of what will happen to me in the future. I was getting in shape by going to the gym, so I was sure to overcome my disease. I want to set myself up as an example to other patients with mesothelioma who can survive long.

At the presentation of disease progression, small intestinal obstruction:

I was informed of the disease progression. My doctor said that there were few treatment options, and he suggested that I receive treatment with nivolumab. I thought it would be far better than doing nothing at all, so I decided to receive the nivolumab treatment.

After the third administration of nivolumab:

My abdomen has dented! I feel grateful that my doctor has treated me with nivolumab. I feel like people on the news, because I have watched the TV news that reported that the researchers who discovered programmed death-1 protein have been given the Nobel Prize. Now I can eat a lot, so I feel the benefit of nivolumab every day.

At the discontinuation of nivolumab:

I was very shocked to hear that I could not continue the nivolumab treatment because Worker's Compensation will not support the treatment anymore. I gradually feel more positive these days, so from now on, I will proactively do what I can.

Learning points

- There is no established treatment strategy for patients with malignant peritoneal mesothelioma (MPeM).
- Immunocheckpoint inhibitors have proven useful for malignant pleural mesothelioma in recent years.
- A well-designed clinical study is warranted to examine whether nivolumab should be considered as a new treatment option for MPeM.

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ORIGINAL ARTICLE

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Retrospective investigation on diagnostic process for benign asbestos pleural effusion (BAPE) using checklist

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Abstract

Objectives: In Japan, benign asbestos pleural effusion (BAPE) has been eligible for industrial accident compensation since 2003 as an asbestos-related disease despite the lack of good criteria. We compiled a criteria into a checklist of essential items and for excluding other diseases inducing pleural effusion as a diagnosis process.

Method: Thoracentesis was performed in order to confirm the presence of pleural effusion at the initial diagnosis, and 105 suspected BAPE patients were retrospectively examined. We complied a checklist comprising the following diagnostic items: (a) occupational asbestos exposure; (b) confirmation of exudate of pleural effusion; (c) exclusion of pleural effusion with malignant tumors based on negative results of CEA and hyaluronic acid, and cytology of pleural effusion; (d) exclusion of rheumatic, bacterial, and tuberculous pleuritis; (d) radiological findings for exclusion of malignancies; and (e) histopathological findings based on thoracoscopy that exclude malignancies (when thoracoscopy was not performed, there was confirmation that no malignancies were present during 3-month follow-up observation). Cases that satisfied all items were defined as BAPE.

Results: Among the 105 suspected cases, there were five cases that had no occupational asbestos exposure; six cases in which transudate of on pleural effusion; one case each of rheumatoid pleuritis and tuberculous pleuritis; and five cases of pleural mesothelioma based on chest radiography and histopathological findings within 3 months after initial diagnosis. Therefore, we excluded 18 cases from the 105 candidates and determined 87 cases of BAPE.

Conclusion: We consider that six items described above are suitable for diagnosing BAPE.

KEYWORDS

benign asbestos pleural effusion, exudative, occupational asbestos exposure, pleural mesothelioma, pleural plaques

1 | INTRODUCTION

Benign asbestos pleural effusion (BAPE) is a non-malignant pleural lesion induced by asbestos exposure, which is also known as asbestos pleuritis. Eisenstadt[1] reported BAPE as a new disease concept for the first time in 1964, and BAPE typically presents unilaterally and with a small volume of pleural effusion.

Epler et al[2] reported diagnostic criteria such as (a) asbestos exposure, (b) presence of pleural effusion by chest radiograph or thoracentesis, (c) no other causes except asbestos exposure, and (d) no appearance of malignancy during a period of 3 years from diagnosis. These criteria were generated for prospective epidemiological observation, and clinical follow-up for 3 years was set in order to exclude pleural mesothelioma. Hillerdal et al[3] showed that clinical follow-up for only 1 year is sufficient if precise checking is followed by diagnostic imaging such as chest computed tomography (CT) scanning in 1989. However, other new criteria have not been proposed since. Therefore, we cannot compare with standard data described the previous studies.

It is speculated that the pathogenic mechanism of BAPE is mechanical irritation of the visceral pleura by asbestos fibers, obstruction of the lymphatic drainage of the parietal pleura induced by pleural fibrosis,[4] or autoimmunity due to the adjuvant effect of asbestos fibers.[5] However, the true mechanism has not yet been established. It may be defined that the inflammation of visceral pleura induced by asbestos fibers induces BAPE.

In Japan, BAPE was approved in 2003 as an asbestos-related disease for industrial accident compensation. However, this compensation to BAPE patients was judged despite the lack of diagnosis criteria. It is suspected that some patients with BAPE have been overlooked because there are no diagnostic criteria for BAPE. Therefore, we examined retrospectively the diagnosis of BAPE based on occupational history, pleura, chest images, and laboratory data of pleural effusion together with data from reported BAPE patients.[6-8] We then established a diagnosis manual for BAPE, and report the findings.

2 | MATERIALS AND METHODS

From 2012 to December in 2019, 105 patients who were diagnosed with BAPE at the initial diagnosis at the Okayama Rosai Hospital, Toyama Rosai Hospital, Yokohama Rosai Hospital, and Tohoku Rosai Hospital in Japan, were examined retrospectively, and the validity of the diagnosis was investigated. These cases were diagnosed as BAPE at the initial diagnosis based on data from laboratory and radiological findings. However, we reinvestigated these cases based on a checklist of proposed new criteria, and some cases were deemed to be diagnosed incorrectly. Therefore, the remaining cases were diagnosed definitely as BAPE. It was made clear that BAPE should be diagnosed based on these procedures containing these exclusion items.

We complied a checklist for diagnosing BAPE as given in Figure 1, and judged retrospectively the validity of the diagnosis depending on this checklist for the 105 cases who were diagnosed as BAPE at the initial diagnosis. The checklist was basically complied based on (a) the presence of occupational asbestos exposure for confirmation of asbestos exposure, (b) pleural effusion findings with thoracentesis and exclusion of other diseases in the criteria defined by Epler et al[2] in 1982.

1. In order to confirm asbestos exposure, we inquired concerning occupational asbestos exposure. In the cases with confirmed asbestos exposure, we inquired concerning the age at first exposure, exposure term, and job duty, and investigated the latent period from the first exposure to the onset of BAPE. We designated cases as questionable exposure to asbestos where pleural plaques appeared in radiographs without confirmation of occupational asbestos exposure. We, therefore, excluded these cases.
2. In order to exclude other diseases that might induce pleural effusion, we checked the past history and present illness. There were 15 cases with heart disease, two cases with kidney disease, and one case with prostate cancer. However, none of these cases were excluded because these diseases were assessed not to cause pleural effusion. In the next step, we examined the pleural fluid. Since pleural fluid results from inflammatory disease with asbestos fibers, the fluid was confirmed to be exudative based on Light's criteria.[9]
3. (a) For exclusion of cases with malignant pleural effusion, cytopathological examination of the pleural effusion as well as assay of carcinoembryonic antigen (CEA) and hyaluronic acid in the pleural effusion were performed. (b) To exclude rheumatoid pleuritis, rheumatoid factors (RFs) in the serum and effusion were examined. (c) For exclusion of bacterial pleuritis, a bacterial check of the pleural effusion was performed and we confirmed that lymphocytes were more than half in the leukocytes of the pleural effusion. (d) Furthermore, to exclude tuberculous pleuritis, adenosine deaminase (ADA) was checked, and a bacterial smear and culture for tuberculosis were performed in addition to polymerase chain reaction for Mycobacterium tuberculosis (Tbc-PCR).
4. At chest imaging, the absence of irregular pleural thickening and no tumorous mass were confirmed in order to exclude pleural mesothelioma.[10]
5. To exclude the early stages for pleural mesothelioma, macroscopic findings based on thoracoscopy and biopsy of the parietal pleura were checked. Histopathological examination had not been performed in some of the cases,

Checklist for diagnosis of benign asbestos pleural effusion

1	Name		Date of birth	MM/DD/YYYY / /	Age	years
2	Occupational asbestos exposure		☐ Yes [Occupational asbestos histories] Exposure term [ ]			☐ Unknown
3	Pleural effusion		☐ Yes [☐ bloody ☐ others ( )]			☐ None
4	Past history and present illness		☐ Heart disease ☐ Kidney D ☐ Collagen D ☐ Malignan ☐ None ☐ Thoracic surgery within 6 months ☐ Others ( )			
5	Pleural effusion		※Light's criteria 1. Effusion TP/Serum TP＞0.5 2. Effusion LDH/Serum LDH>0.6 3. Effusion LDH>Serum LDH 2/3			
	Exudate ☐ Yes ☐ No		Effusion: ☐ T-protein ( ) g/dL ☐ LDH ( ) U/L Serum: ☐ T-protein ( ) g/dL ☐ LDH ( ) U/L			
	Cytological result in PE		☐ Class Ⅰ ☐ Ⅱ ☐ Ⅲ ☐ Negative			☐ None
	CEA in PE less than 5.0 ng/ml		☐ Yes CEA ( )ng/mL			☐ None
	HA in PE less than 100,000 ng/ml		☐ Yes HA ( )ng/mL			☐ None
	Rule out rheumatism and other collagen disease		☐ Yes Effusion RF( )IU/mL , Serum RF( )IU/mL Others( )			☐ None
	ADA in PE less than 40IU/L		☐ Yes Effusion ADA ( )IU/L			☐ None
	Lymphocytes in PE (%)		☐ Yes Lymphocyte ( )%			☐ None
	Bacterial examination in PE	Bacteria	☐ Positive [☐ − ☐ ± ☐ 1+ ☐ 2+ ☐ 3+]			☐ Negative
		Mycobacteria: Smear	☐ Positive			☐ Negative
		Mycobacteria: Culture	☐ Positive			☐ Negative
		Mycobacteria: PCR	☐ Positive			☐ Negative
6	Chest radiological examination					
	Malignant signs by chest CT		☐ None			☐ Yes
	Pleural plaques		☐ Yes [ ]			☐ None
7	Thoracoscopic examination		☐ Yes [☐ Pleural plaques ☐ Susp of malignant chages]			☐ None
	Pleural biopsy		☐ Yes [☐ Malignant findings] Pathological exam [ ]			☐ None
BAPE			☐ OK ☐ NO ☐ Pending			
Registration date			MM/DD/YYYY / /		Confirmer	

HA : Hyaluronic acid , PE : Pleural effusion

FIGURE 1 Checklist for diagnosis of benign asbestos pleural effusion

and no malignant tumor was confirmed in follow-up observation during a period of at least 3 months.

3 | RESULTS

All 105 cases suspected as BAPE at the initial diagnosis were male and aged 60 to 96 years with the median age of 79 years at diagnosis.

1. One hundred cases (95.2%) were confirmed to have occupational history of asbestos exposure and four cases were suspected to have asbestos exposure with pleural plaque imaging without definite occupational asbestos exposure. One case was not confirmed to have occupational asbestos exposure and pleural plaques as indicated in Figure 2.
2. Differential diagnosis of pleural effusion was performed according to the Diagnostic Approach to Pleural Effusion.[11] Thoracentesis was performed on all 105 cases and 79% proved to be bloody effusion.
3. Pleural fluids of 99 cases (94.3%) were proven to be exudative. Among these, 55% satisfied all three items of Light's criteria, 22% satisfied two items, and 17% satisfied one item. Six cases (6%) that did not satisfy any item were determined as transudative, and were excluded at this stage.
4. (a) Only one case showed more than 5 ng/mL of CEA, and the malignant marker threshold was 6.5 ng/mL, but its malignancy was denied. Two point four percent of cases exhibited hyaluronic acid exceeding the 100 000 ng/mL threshold, but did not exceed 120 000 ng/mL, and pleural mesothelioma was denied. For cytology, with regard to Class III diagnosis, 4.9% of cases were Class III, but they were mild (Class IIIa) and malignant tumors such as mesothelioma were not observed during follow-up (Table 1). (b) One case with high levels of serum and effusion RFs was later proven to be rheumatoid arthritis. This case was diagnosed previously with rheumatoid pleuritis. (c) One case with an ADA level in the pleural effusion of 60.5 U/L was proven to be tuberculous pleuritis with detection of *Mycrobacterium tuberculosis* (M. tb) after 2 weeks culture, despite negative results with Tbc-PCR and interferon-γ releasing assay (T-SPOT) as given in Figure 2. (d) In regard to bacterial pleuritis, all cases presented negative in the bacterial test. The majority of cases (97.5%) had more than 50% of lymphocytes among the leukocytes in pleural effusion, and 3.5% increased in eosinophils, but no case increased in neutrophils (Figure 2).
5. For radiological examination, 97.5% of cases presented with pleural plaques, but no pulmonary asbestosis. No tumorous thickening of the pleura was detected at the initial diagnosis; however, three cases exhibited irregular pleural thickening in 1-3 months of follow-up. Figure 3 shows one of these three cases without positive findings in all sites containing the left pleura except pleural effusion on the left side with PET-CT. After 3 months, the left pleura exhibited slight irregular thickening, and distinct narrowing of the left thorax was present as shown in Figure 4. We suspected left pleural mesothelioma and was diagnosed definitively based on thoracoscopy as given in Figure 2.

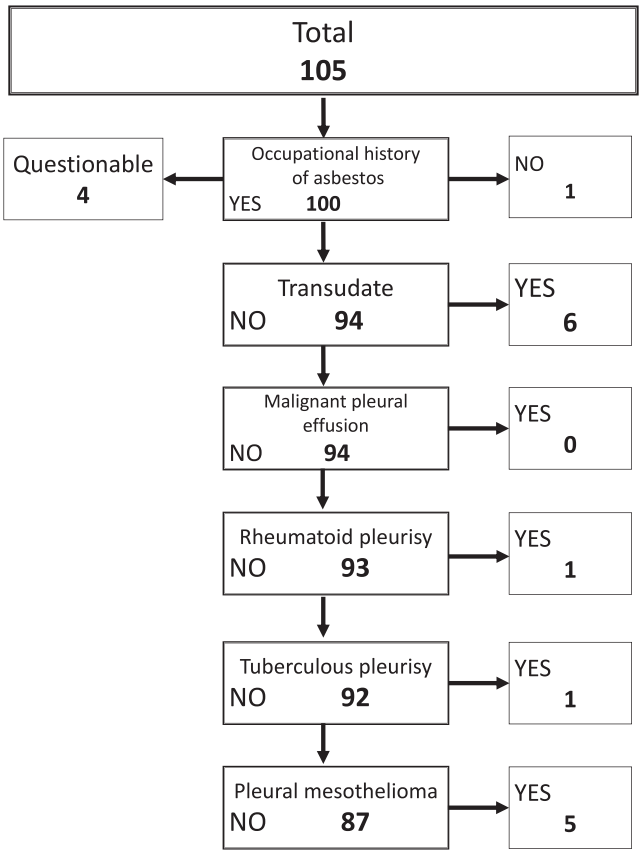

FIGURE 2 Differential diagnosis of BAPE from other diseases

TABLE 1 Laboratory findings in pleural effusion

CEA in PE less than 5.0 ng/mL		Lymphocytes dominant in PE	
YES	98.8%	YES	96.5%
NO	1.2%	NO	3.5%
HA in PE less than 100,000 ng/mL		Exclusion of RA pleuritis	
YES	97.6%	YES	96.4%
NO	2.4%	NO	3.6%
Cytology in PE		ADA in PE less than 40 IU/L	
Class I	30.5%	YES	98.8%
Class II	64.6%	NO	1.2%
Class III	4.9%		

Abbreviations: HA, hyaluronic acid; PE, pleural effusion.

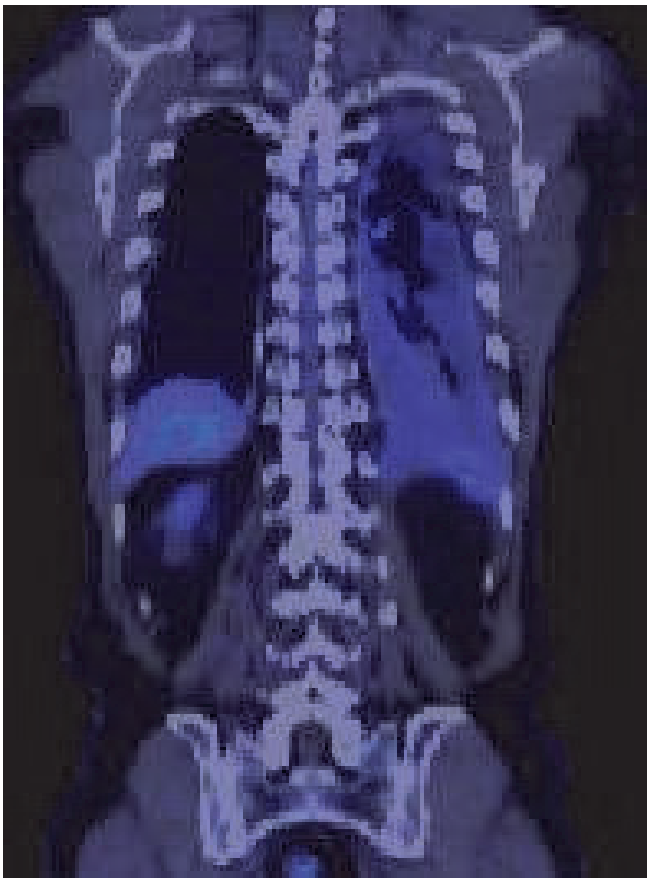

FIGURE 3 PET-CT shows no positive lesions in the left thorax with pleural effusion

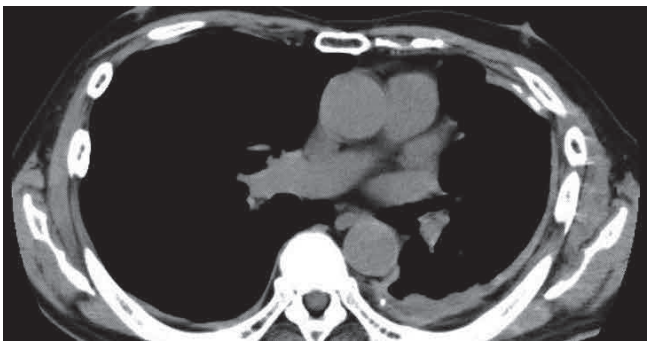

FIGURE 4 Chest CT that was taken 6 mo after first visit shows irregular pleural thickening in the left pleura. The left thorax becomes smaller than the right thorax suggesting left pleural mesothelioma

6. Just after the initial diagnosis, thoracoscopy in three cases among these five cases was performed but biopsy results were negative. However, tumorous pleural thickening appeared during the 3-month follow-up period, and subsequent biopsy proved to be sarcomatoid pleural mesothelioma. The other two cases complained of persistent severe chest pain as a subjective symptom although there were negative radiological findings. Pleural biopsy with thoracoscopy was performed and these cases were proved to be the epithelioid type of pleural mesothelioma. Therefore, we assessed the necessity of more than 3 months of follow-up after thoracentesis for the diagnosis of BAPE.

Based on the exclusion criteria, we determined BAPE induced by occupational asbestos exposure for 87 cases. All of the final defined 87 cases were male and aged 60 to 93 years with the median age of 79 years. In terms of the occupational history, the main occupation was shipbuilder followed by construction worker as indicated in Figure 5. The asbestos exposure term ranged from 2 to 55 years with the median of 38 years. The latency period ranged from 18 to 73 years with the median of 53.5 years.

4 | DISCUSSION

Pleural effusion comprises transudate occurring from impairment of the flow of body fluid such as heart failure or nephrotic syndrome, and exudate induced by local inflammation extending to the pleura or by malignancies. BAPE is visceral pleural pleuritis induced by asbestos fibers penetrating the pleural cavity, and has been considered to be an asbestos-related disease since the 1960s.[1] No new criteria for BAPE have been determined, since Epler et al[2] described criteria in 1982. In Japan in 2003, BAPE was added to the list of asbestos-related diseases for which patients were able to receive industrial accident compensation. Although no new criteria were identified, compensation for this disease was determined. Therefore, we present a new checklist to use as a reference in diagnosing BAPE based on a retrospective reinvestigation of the cases diagnosed as BAPE at the initial diagnosis that screens out the misdiagnosed cases.

Although asbestos exposure history is a criterion reported by Epler, we propose occupational history of asbestos exposure in order to ensure asbestos exposure. For this reason, there are no reports of BAPE induced by environmental asbestos exposure. Almost all cases were induced by occupational asbestos exposure. Based on the checklist, we excluded five cases including four cases whose occupational history of asbestos exposure was unclear from the 105 cases under investigation. Although almost all cases (97.5%) presented with pleural plaques, pleural plaques were considered as a reference item only and occupational asbestos exposure was considered more important.

By confirming the exudate as inflammatory pleural effusion using Light's criteria classification,[9] six cases with transudate were excluded. Ninety-three percent to 96% of cases meeting this criterion were reported to have exudate. Furthermore, the cases that did not satisfy this criterion were determined to be transudative.

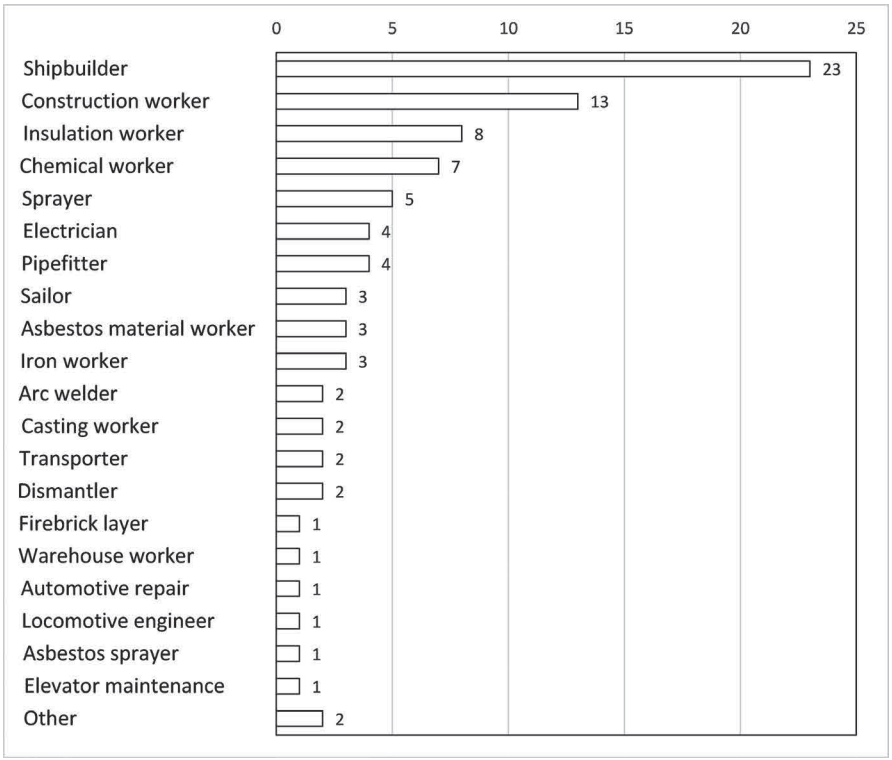

FIGURE 5 This figure shows the number of occupational histories for 87 confirmed BAPE cases. Shipbuilder and construction workers are main components for BAPE cases as reported for asbestos-related lung cancer or mesothelioma cases

For differential diagnosis to exclude malignant tumors, we considered CEA, hyaluronic acid, and cytology data. The CEA concentration in pleural effusion was reported to be less than 1.8 ng/mL for BAPE[12] and useful in identifying BAPE. However, for mesothelioma, CEA is not helpful in distinguishing from pleural mesothelioma because almost all pleural mesothelioma cases were within normal limits. The majority of pleural mesothelioma cases exhibited hyaluronic acid concentrations of greater than 100 000 ng/mL; however, almost all BAPE cases exhibited concentrations of less than 100 000 ng/mL.[6] Fujimoto reported that three cases among 87 cases with BAPE exceeded the concentration of 100 000 ng/mL, but those were less than 120 000 ng/mL.[7] Our results regarding hyaluronic acid in pleural effusion were consistent with this report and we assumed that there were no cases that suggested mesothelioma. It is relatively easy to differentiate malignant effusion using cytological examination. Five cases showed Class III, which was difficult to judge, and these were Class IIIa. We denied malignancies from clinical course. From these results, we judged that there were no cases with findings suggestive of a malignant tumor.

At the next step, differential diagnosis of collagen disease such as rheumatic pleuritis was performed. There was no case affected by these diseases based on past history and present illness. One case presented with high RFs in serum and pleural effusion, and was examined carefully at a later date. This was likely rheumatic pleuritis from diagnosis of rheumatoid arthritis,[13] and was excluded. In addition, to exclude bacterial pleuritis, we performed bacterial examination and assayed the differential count of leukocytes in the pleural effusion. There were no abnormal cases. Although the percentage of lymphocytes in leucocytes in the pleural effusion was greater than 50% in most cases, three cases presented with eosinophilia. BAPE cases with eosinophilia were reported,[14] and these results did not affect this diagnosis.

To exclude tuberculous pleuritis, which presents with many lymphocytes in pleural effusion, we performed ADA assay and bacterial examination. Only one case showed a concentration of greater than 40 U/L (60.5 U/L) of ADA. It has been reported that cases with ADA of greater than 40 U/L are suspected to suffer from tuberculosis.[15] This case presented negative for Tbc-PCR in effusion and serum T-SPOT tests, but culture of pleural effusion proved M. tb positive. We determined that this was tuberculous pleuritis. We excluded 13 cases due to the results so far.

Finally, it is difficult to differentiate diagnosis between BAPE and early stage pleural mesothelioma. Kato et al[10] focused on the thickening of the mediastinal pleura for one of the features of pleural mesothelioma, but no positive cases presented with this indicator in 92 cases examined. Although clinical symptoms during 3 months of follow-up presented only as pleural effusion, two cases complained of severe chest pain and three cases exhibited irregular pleural thickening and narrowing of the affected thorax. In three cases among them pleural biopsy was performed under thoracoscopy. Visual change in the tumors was not observed in these cases, and they were diagnosed with fibrinous pleuritis based on biopsy. However, after manifestation of irregular pleural thickening, the second pleural biopsy indicated pleural mesothelioma. The reason for this discrepancy was that

the biopsied sites were thought not to be suitable for definite diagnosis. Two other cases had no positive radiological abnormality but indicated persistent chest pain. We again performed thoracoscopic biopsy and made a definite diagnosis of epithelioid mesothelioma. The diagnosis of these five cases changed during the 3 months of follow-up, and we assessed the necessity for a 3-month of follow-up observation period after administering a pleural effusion test.

From the report by Metintas et al,[16] in the 287 cases that underwent thoracoscopy, 101 cases diagnosed with fibrinous pleuritis by biopsy were examined more closely, and the rate of false negatives was 18%. All of these cases presented as malignant pleural diseases. Of the 142 cases exhibiting exudate as pleural effusion, 30% to 40% could not be diagnosed based on histopathological data using thoracoscopy. Of that group 8% to 12% were found to have malignant pleural lesions and almost all cases were diagnosed with pleural mesothelioma. The other 25% to 91% were classified as non-specific pleuritis and were treated as idiopathic pleuritis. If a definite diagnosis is reported to be determined, greater accuracy using invasive biopsy is required.[17] For determining BAPE as a diagnosis by exclusion, we consider that a 3-month follow-up period is necessary. Nevertheless, a part of pleuritis in which definite diagnosis is not determined after thoracoscopic biopsy is thought to be grouped as BAPE. Using these criteria, we diagnosed 87 cases as BAPE.

Thus, when BAPE was diagnosed with (a) a history of occupational asbestos exposure and (b) the presence of exudate based on a pleural effusion test as the required main items; and (c) negative results of CEA and hyaluronic acid in pleural effusion, and cytology of pleural effusion for exclusion of malignancy; (d) exclusion of rheumatic, bacterial and tuberculous pleuritis; (e) exclusion of malignancy using radiological images; and (f) exclusion of histopathological malignancy using thoracoscopy (when thoracoscopy was not performed, no malignant tumor was confirmed in follow-up observation during at least 3 months) as required sub-items, BAPE could be determined with a more than 95% if cytology was class III. If some of these six sub-items are no, we should carefully make a differential diagnosis.

The age of BAPE onset induced by asbestos exposure has pointed out the relationship to the volume of asbestos to which the patient was exposed. The number of incidences increases and latency becomes short, if the exposure volume of asbestos increases.[18] The median age of BAPE onset was 66 years at our previous report,[8] but increased to 79 years at this report. Similar to previous reports, the history of occupational asbestos exposure is approximately the same such as No. 1 is shipbuilder and No. 2 is construction worker as shown in Figure 5, and asbestos exposure in these types of work was classified as moderate. The median exposure term was 38 years and the latency from the first exposure was 53.5 years, which was longer than that shown by previous data.[6,8,12] As a reason for this, considered together with many cases of advanced-age patients, it was suggested that the exposure dose was low when they worked with asbestos exposure. Workers were likely affected with BAPE after a long latency period with a low dose of past asbestos exposure.

On the other hand, five cases among those diagnosed as BAPE at the initial diagnosis were determined as pleural mesothelioma in their clinical course. The term of clinical observation was between 1 and 3 months. The reason why we did not confirm pleural mesothelioma was not that pleural mesothelioma changed from BAPE, but that we failed to make a definite diagnosis of pleural mesothelioma at the initial diagnosis due to the presence of only pleural effusion without malignant findings such as tumorous pleural thickening by chest CT and that definite diagnosis could be performed during the progression of the disease. Although we observed parietal pleura in three of the five cases using thoracoscopy and performed a pleural biopsy under thoracoscopy at the initial diagnosis, we failed to reach a definite diagnosis.

If we do not detect malignant findings that suggest mesothelioma based on chest CT, we should pursue more precise observation through thoracoscopy and perform a biopsy at the proper site. In particular, in cases presenting with persistent chest pain, we need to consider early stage pleural mesothelioma based on Positron Emission Tomography-Computed Tomography (PET-CT) scanning and perform biopsy at suitable sites for final diagnosis.

As mentioned above, we are convinced that the presented criteria such as occupational asbestos exposure, exudative pleural effusion, tumor marker in pleural effusion, bacterial test results, radiological findings and histopathological findings are suitable for diagnosing BAPE, and it is valid that cases that satisfied these criteria during the 3 months of follow-up be diagnosed as BAPE.

DISCLOSURE

Approval of the research protocol: N/A. *Informed consent:* All participants provided written informed consent before inclusion in the study. *Registry and the registration no. of the study/trial:* N/A. *Animal studies:* N/A. *Conflict of interest:* N/A.

AUTHOR CONTRIBUTIONS

Takumi Kishimoto was involved in data analysis and writing manuscript. Nobukazu Fujimoto, Keiichi Mizuhashi, Satoko Kozawa, and Motohiko Miura were involved in accumulation of patients for BAPE.

ETHICAL APPROVAL

This study was approved by the 11th research ethics committee of the Japan Organization of Occupational Health and Safety on June 18, 2018 (No. 9).

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First-line nivolumab plus ipilimumab in unresectable malignant pleural mesothelioma (CheckMate 743): a multicentre, randomised, open-label, phase 3 trial

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Summary

Background Approved systemic treatments for malignant pleural mesothelioma (MPM) have been limited to chemotherapy regimens that have moderate survival benefit with poor outcomes. Nivolumab plus ipilimumab has shown clinical benefit in other tumour types, including first-line non-small-cell lung cancer. We hypothesised that this regimen would improve overall survival in MPM.

Methods This open-label, randomised, phase 3 study (CheckMate 743) was run at 103 hospitals across 21 countries. Eligible individuals were aged 18 years and older, with previously untreated, histologically confirmed unresectable MPM, and an Eastern Cooperative Oncology Group performance status of 0 or 1. Eligible participants were randomly assigned (1:1) to nivolumab (3 mg/kg intravenously once every 2 weeks) plus ipilimumab (1 mg/kg intravenously once every 6 weeks) for up to 2 years, or platinum plus pemetrexed chemotherapy (pemetrexed [500 mg/m² intravenously] plus cisplatin [75 mg/m² intravenously] or carboplatin [area under the concentration-time curve 5 mg/mL per min intravenously]) once every 3 weeks for up to six cycles. The primary endpoint was overall survival among all participants randomly assigned to treatment, and safety was assessed in all participants who received at least one dose of study treatment. This study is registered with ClinicalTrials.gov, NCT02899299, and is closed to accrual.

Findings Between Nov 29, 2016, and April 28, 2018, 713 patients were enrolled, of whom 605 were randomly assigned to either nivolumab plus ipilimumab (n=303) or chemotherapy (n=302). 467 (77%) of 605 participants were male and median age was 69 years (IQR 64–75). At the prespecified interim analysis (database lock April 3, 2020; median follow-up of 29·7 months [IQR 26·7–32·9]), nivolumab plus ipilimumab significantly extended overall survival versus chemotherapy (median overall survival 18·1 months [95% CI 16·8–21·4] *vs* 14·1 months [12·4–16·2]; hazard ratio 0·74 [96·6% CI 0·60–0·91]; p=0·0020). 2-year overall survival rates were 41% (95% CI 35·1–46·5) in the nivolumab plus ipilimumab group and 27% (21·9–32·4) in the chemotherapy group. Grade 3–4 treatment-related adverse events were reported in 91 (30%) of 300 patients treated with nivolumab plus ipilimumab and 91 (32%) of 284 treated with chemotherapy. Three (1%) treatment-related deaths occurred in the nivolumab plus ipilimumab group (pneumonitis, encephalitis, and heart failure) and one (<1%) in the chemotherapy group (myelosuppression).

Interpretation Nivolumab plus ipilimumab provided significant and clinically meaningful improvements in overall survival versus standard-of-care chemotherapy, supporting the use of this first-in-class regimen that has been approved in the USA as of October, 2020, for previously untreated unresectable MPM.

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Introduction

Malignant pleural mesothelioma (MPM) is a highly aggressive cancer and typically unresectable at diagnosis, with less than 10% of patients surviving 5 years or beyond.[1,2] Historically, age, sex, tumour grade and stage, and histology have been shown to be independent prognostic factors. Notably, worse prognosis has been reported for non-epithelioid histology versus the epithelioid subtype.[1–3] Until October, 2020, platinum agents plus folate antimetabolites, such as pemetrexed, have been the only approved first-line treatment regimens for MPM since 2004.[4,5] However, long-term survival outcomes remain poor with chemotherapy;[6–9] bevacizumab has been added to these regimens[10] but its use varies across regions. As such, there is an urgent need for new and effective therapeutic options.

Nivolumab, a fully human anti-programmed cell death 1 (PD-1) antibody, and ipilimumab, a fully human anti-cytotoxic T-lymphocyte 4 (CTLA-4) antibody are immune checkpoint inhibitors with distinct but

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Research in context

Evidence before this study

We searched PubMed and abstracts from major oncology congresses for studies published from database inception until Oct 2, 2020, relevant to unresectable malignant pleural mesothelioma (MPM) and cancer immunotherapy regimens, with a focus primarily on first-line phase 3 trials, using search terms that included, but were not limited to ("mesothelioma" AND "nivolumab") OR "chemotherapy" OR "pembrolizumab" OR "atezolizumab" OR "avelumab" OR "durvalumab" OR "ipilimumab" OR "tremelimumab" OR "PD-1" OR "PD-L1" OR "CTLA-4" (full names and abbreviations). Although we identified several studies assessing immunotherapy in MPM, we found no published randomised phase 3 studies investigating the efficacy or safety of immunotherapy regimens in the first-line setting. Various phase 1 and 2 studies in previously treated patients with MPM have suggested that immunotherapy regimens might provide clinical benefit. Notably, the multicentre, open-label, single-arm, phase 2 MERIT study led to the approval of nivolumab monotherapy for unresectable recurrent MPM in Japan. However, with recommended first-line systemic treatments limited to chemotherapy since 2004, with or without bevacizumab, there remains a need for new and effective therapeutic options. In the single-arm phase 2 DREAM study, first-line durvalumab plus chemotherapy exhibited promising activity in 54 patients with MPM, but the combination requires evaluation in a larger, randomised, phase 3 study. CheckMate 743 was designed to investigate the efficacy and safety of nivolumab plus ipilimumab versus chemotherapy. A previous non-comparative phase 2 trial (MAPS2) and single-arm phase 2 study (INITIATE) assessing nivolumab plus ipilimumab in MPM showed that this regimen was tolerable and exhibited encouraging clinical activity.

Added value of this study

Here we provide results from the randomised CheckMate 743 study, which is the first phase 3 study to show significant and clinically meaningful improvements in overall survival with immunotherapy versus standard-of-care platinum plus pemetrexed chemotherapy for first-line treatment of unresectable MPM. This regimen was found to show clinical benefit and tolerability, thus providing patients with a new first-line chemotherapy-free treatment option. Notably, survival with nivolumab plus ipilimumab was similar in patients with both non-epithelioid and epithelioid histologies, suggesting that the regimen could be considered for all patients with unresectable MPM. Responses were durable, with a 2-year duration of response rate of 32% of immunotherapy-treated patients. The safety profile of nivolumab plus ipilimumab was consistent with that observed in first-line non-small-cell lung cancer at this dose and schedule and no new safety signals were reported.

Implications of all the available evidence

Nivolumab plus ipilimumab can provide notable and clinically meaningful improvements in overall survival versus the current standard of care. Data from CheckMate 743 support a favourable clinical benefit–risk profile for nivolumab plus ipilimumab. Nivolumab plus ipilimumab is now indicated in the USA and Brazil as a first-line treatment for unresectable MPM.

complementary mechanisms of action. Ipilimumab induces T-cell proliferation and de-novo anti-tumour T-cell responses, including in memory T cells, whereas nivolumab restores the function of existing anti-tumour T cells.[11] Nivolumab plus ipilimumab is approved in various tumours[12] and has shown durable overall survival benefit in melanoma,[13] renal cell carcinoma,[14] and in non-small-cell lung cancer (NSCLC).[15] Furthermore, National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN guidelines) recommend nivolumab with or without ipilimumab as a preferred treatment option (category 2A) in second-line or later MPM settings based on results from three phase 2 trials,[16–18] including the multicentre, open-label, randomised, non-comparative IFCT-1501 MAPS2 trial that showed encouraging clinical activity of the combination therapy.[16]

CheckMate 743 is a phase 3 study designed to assess efficacy and safety of first-line nivolumab plus ipilimumab versus platinum plus pemetrexed chemotherapy in unresectable MPM. Here we present results from the prespecified interim analysis, which has led to nivolumab plus ipilimumab gaining approval in the USA.[12] Additionally, NCCN guidelines recommend nivolumab plus ipilimumab as a preferred first-line option (category 2A) for patients with biphasic or sarcomatoid histology and is also an option for those with epithelioid histology.

For the **most recent and complete version of the NCCN guidelines** see NCCN.org

See Online for appendix

Methods

Study design and participants

CheckMate 743 is a global, open-label, randomised, controlled, phase 3 study run at 103 hospitals across 21 countries (appendix pp 2–4, 22). Eligible patients were aged 18 years or older with histologically confirmed unresectable MPM that was not amenable to curative therapy (surgery with or without chemotherapy), and an Eastern Cooperative Oncology Group performance status of 0 or 1.[19] Unresectability of the disease was determined by the investigator at individual sites using local standards. Patients must have completed any previous palliative radiotherapy 2 weeks or longer before initiating study treatment, with no residual signs of toxicity, and have measurable disease according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST)[20] for pleural mesothelioma. Patients without measurable pleural lesions but with metastatic non-pleural lesions

measurable per RECIST version 1.1 could be considered for inclusion after consultation with the study's medical monitor. Patients were required to have tumour samples available for programmed cell death ligand 1 (PD-L1) testing. Baseline laboratory tests required to assess eligibility included white blood cell counts, neutrophils, platelets, haemoglobin, serum creatinine, alanine aminotransferase, aspartate aminotransferase, and total bilirubin (appendix p 6).

Exclusion criteria included brain metastases (unless resected or treated with stereotactic radiotherapy and asymptomatic with no evolution within 3 months before study inclusion), autoimmune disease, and previous treatment with drugs targeting T-cell costimulation or checkpoint pathways. Patients were excluded if they presented with primitive peritoneal, pericardial, tunica vaginalis, or testis mesotheliomas. Other exclusion criteria included inadequate haematological, renal, or hepatic function; known HIV infection; or interstitial lung disease that was either symptomatic or might affect the detection or management of suspected drug-related pulmonary toxicity. Patients with current or previous malignancy with less than 3 years of complete remission (except for non-melanoma skin cancers and in-situ cancers) requiring or likely to require concurrent intervention during the study period were ineligible, as were patients requiring systemic corticosteroids (>10 mg daily prednisone or equivalent) or immunosuppressive medication within 14 days of the first dose of study drug. More detail on eligibility criteria are in the appendix (p 5) and study protocol (appendix pp 27–410).

An institutional review board or independent ethics committee at each study centre approved all versions of the protocol. An independent Data Monitoring Committee provided general oversight of efficacy and safety for the trial. The trial was done in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines. All patients provided written informed consent.

Randomisation and masking

Patients were enrolled and randomly assigned (1:1) using an interactive web response system, stratified by sex and histology (epithelioid *vs* non-epithelioid [including sarcomatoid and mixed subtypes]) to nivolumab plus ipilimumab or platinum plus pemetrexed chemotherapy. The trial was open label and so patients and investigators were not masked to treatment assignment.

Procedures

Participants in both treatment groups were pretreated with folic acid (350–1000 µg orally daily) and vitamin B12 (1000 µg intramuscularly) 1 week before administration of the first dose of study drug (appendix p 5). Participants in the experimental group were given nivolumab (3 mg/kg intravenous infusion once every 2 weeks) plus ipilimumab (1 mg/kg intravenous infusion once every 6 weeks). Nivolumab was administered first, followed by ipilimumab. Participants in the chemotherapy group were given an intravenous infusion of cisplatin (75 mg/m²) or carboplatin (area under the concentration-time curve 5 mg/mL per min) plus pemetrexed (500 mg/m²) every 3 weeks for a maximum of six cycles. Treatment was continued until disease progression, unacceptable toxicity, or for 2 years for immunotherapy. Treatment with nivolumab plus ipilimumab was permitted beyond disease progression if prespecified requirements were met (appendix p 7). Dose reductions were permitted for chemotherapy, but not for nivolumab or ipilimumab; concomitant use of corticosteroids was permitted. Patients could receive subsequent therapy upon the discontinuation of study treatment in either group at the discretion of the investigator.

Tumour assessments were done 6 weeks after the date of the first dose of study drug and then every 6 weeks for the first 12 months. After 12 months, tumours were assessed every 12 weeks until blinded independent central review (BICR) confirmed disease progression per mRECIST or RECIST version 1.1 criteria, or both. At the time of investigator-assessed initial radiographic progression, the site had to request the blinded independent central review of progression from a third-party radiology vendor (E-research Technologies in St Louis, MO, USA); if progression was not confirmed, treatment could continue.

Adverse events were assessed at baseline and continuously throughout the study and during follow-up. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0). Select adverse events consisted of a list of preferred terms with potential immune aetiology grouped by specific category (gastrointestinal adverse events, pulmonary adverse events, renal adverse events, hepatic adverse events, skin adverse events, infusion reactions, and endocrinopathies). The definition for serious adverse events is in the appendix (p 6). Treatment-related adverse events were defined as those reported between the first dose of study drug and 30 days after the last dose of study drug. According to study sponsor practice, only events that led to death within 24 h were documented as grade 5 events and reported as deaths here. Events leading to death more than 24 h after onset are reported with the worst grade before death.

Tumour histology was determined by individual sites using local protocols. Archival or fresh formalin-fixed paraffin-embedded tumour samples were collected before randomisation. Optional on-treatment fresh tumour samples were collected at weeks 6–8 and at disease progression, at the discretion of the investigator. Samples were sent to a central laboratory (Cancer Genetics, Rutherford, NJ, USA, and for patients in China, PD-L1 testing was done at Covance, Shanghai) to

determine the proportion of tumour cells showing plasma membrane PD-L1 staining of any intensity using the validated immunohistochemical 28-8 pharmDx assay (Dako, Carpinteria, CA, USA).

Laboratory tests were done within 14 days before randomisation and within 3 days before each dose. Full details of all assessments done are in the appendix (p 6). Hepatitis C RNA and HIV (where locally mandated) tests were done at screening only. All tests had to be done at follow-up visits 1 and 2.

Outcomes

The primary endpoint was overall survival in all patients randomly assigned to treatment after the US Food and Drug Administration provided guidance to change progression-free survival from a coprimary endpoint to a secondary endpoint (protocol amendment April 25, 2019; appendix p 7).[21] Overall survival was defined as the time from randomisation to the date of death due to any cause. Secondary endpoints were progression-free survival, objective response rate, time to response, duration of response, and disease control rate (radiographic tumour assessments per adapted mRECIST for pleural lesisons and RECIST [version 1.1] for the other lesions by BICR) in all patients randomly assigned to treatment, as well as overall survival, progression-free survival, and objective response rate by PD-L1 expression.

Progression-free survival was defined as the time from randomisation to the date of the first documented tumour progression or death due to any cause. Participants who died were considered to have progressed on the date of death. Participants who received subsequent therapy without previous reported progression were considered to have progressed on the date of death or were censored at the date of last evaluable tumour assessment before or on initiation of subsequent therapy. Objective response rate was defined as the proportion of patients with a best overall response of partial response or complete response and disease control rate was defined as the proportion of patients with a best overall response of complete response, partial response, or stable disease. Duration of response was defined as the time between the date of first response to the date of the first documented tumour progression, or death due to any cause, whichever occurred first.

Exploratory endpoints included safety and tolerability in all treated patients. Analysis of other exploratory endpoints that are ongoing but not reported here include pharmacokinetics, biomarkers, patient-reported outcomes, and immunogenicity; a full list is in the appendix (pp 119–122).

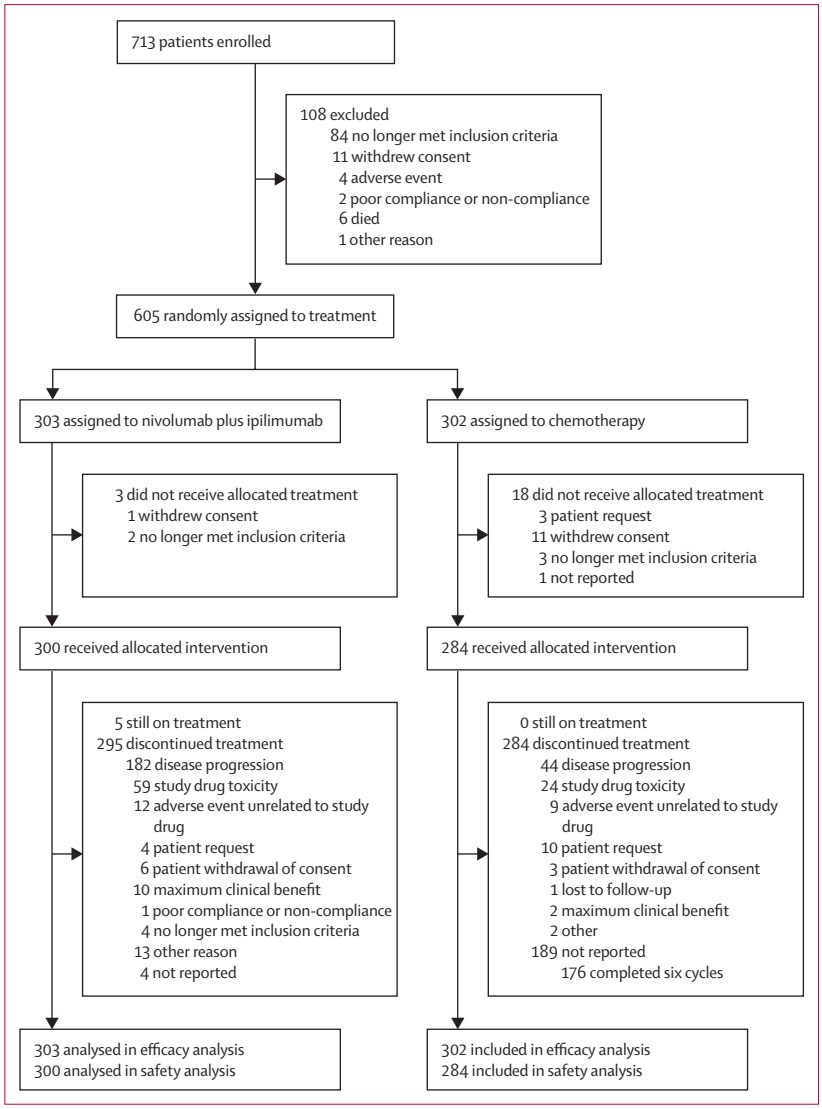


Figure 1: **Trial profile**

Statistical analysis

For the primary endpoint of overall survival, a sample of approximately 600 patients randomly assigned to treatment with 473 deaths would provide 90% power to detect a target hazard ratio (HR) of 0·72 with a two-sided type 1 error of 0·05, by means of a log-rank test. One prespecified interim analysis of overall survival was planned for superiority at approximately 403 deaths (85% of total anticipated events). At the time of database lock for the interim analysis, 419 patients had died (89% of total anticipated events); the boundary for declaring superiority for overall survival was a p value of less than 0·0345, based on the Lan-DeMets alpha spending function with O'Brien-Fleming boundaries. None of the secondary endpoints were included in the testing procedure; therefore, we did no formal statistical testing or allocation of alpha values for progression-free survival, objective response rate, and disease control rate.

We included all patients randomly assigned to treatment in demographic and efficacy analyses. We stratified analyses for overall survival and progression-free survival by sex and histology. We estimated HRs

and CIs (96·6% CIs for the overall survival primary analysis [alpha adjusted for interim analysis], and 95% CI elsewhere) using a stratified Cox proportional hazards model with treatment group as a single covariate. We checked the proportional hazards assumption only for the primary endpoint of overall survival by adding a time-dependent covariate, defined by treatment-by-time interaction, into the stratified Cox regression model of overall survival. We estimated survival curves and rates using the Kaplan-Meier method. We calculated exact two-sided 95% CIs for objective response and disease control rates using the Clopper-Pearson method. We did prespecified descriptive subgroup analyses for overall survival, summarised using HRs (with 95% CIs) calculated using an unstratified Cox proportional hazards model. Safety analyses included all patients who received at least one dose of study drug. We also did exposure adjusted safety analyses, taking into account all on-treatment events on the basis of the total exposure time. We calculated the person-year exposure as the sum over the participants' exposure expressed in years. More details on all analyses are in the appendix (pp 7–8).

We did all statistical analyses using SAS software (version 9.2). An independent Data Monitoring Committee reviewed efficacy and safety data on a periodic basis and at the time of the preplanned interim analysis. This trial is registered with ClinicalTrials.gov, NCT02899299.

Role of the funding source

The study was designed by the funder (Bristol Myers Squibb) and study steering committee. The funder had a role in data collection with the investigators, data analysis and interpretation in collaboration with the authors, and the writing of the report by funding professional medical writing assistance. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

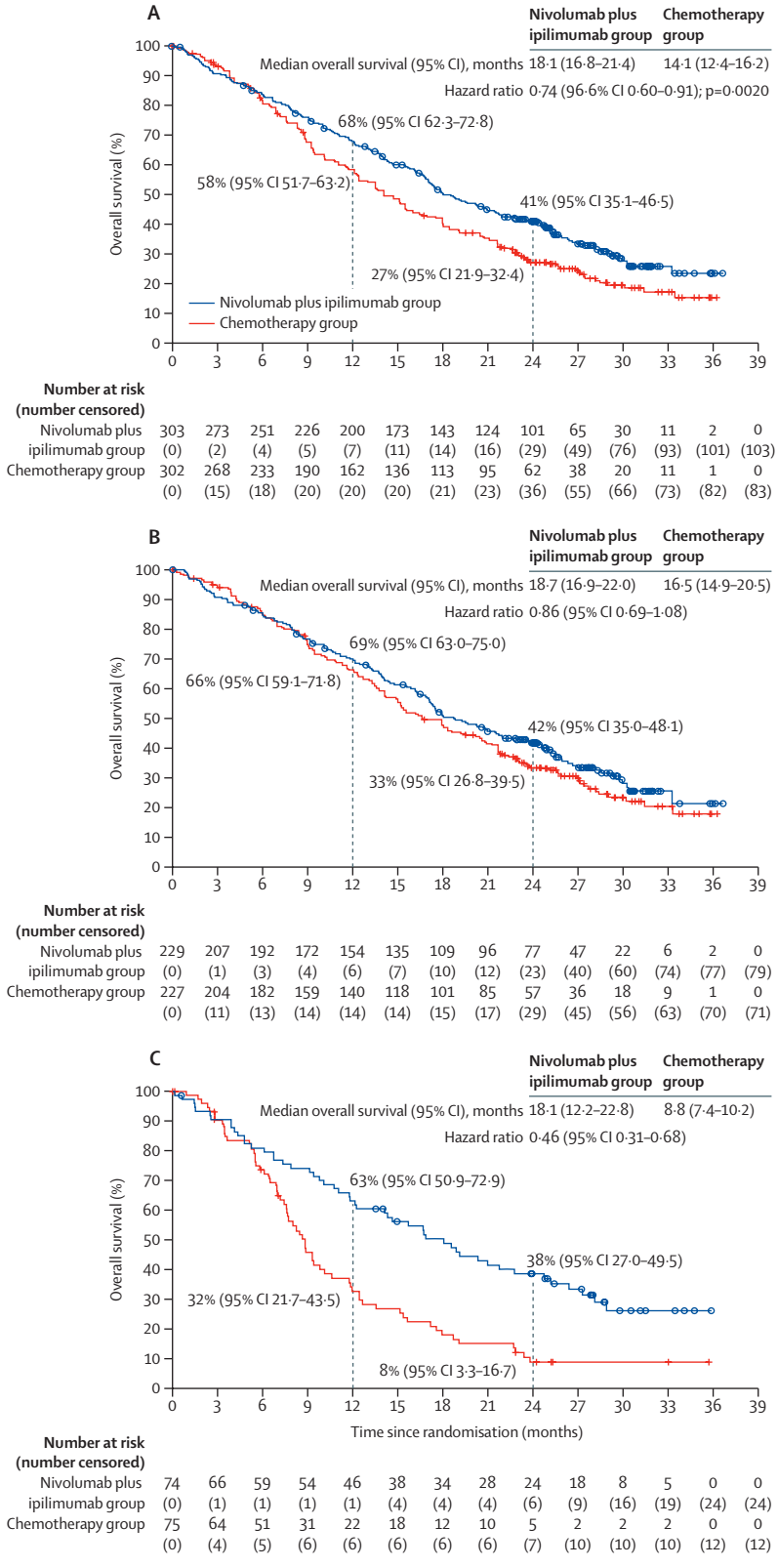
Between Nov, 29, 2016, and April 28, 2018, we enrolled 713 patients, of whom 605 were eligible and randomly assigned to nivolumab plus ipilimumab (n=303) or chemotherapy (n=302). 300 participants in the nivolumab plus ipilimumab group and 284 in the chemotherapy group received at least one dose of study drug (figure 1). At the prespecified interim analysis (database lock April 3, 2020), the median follow-up for overall survival was 29·7 months (IQR 26·7–32·9), with a minimum of 22·1 months. Baseline characteristics were well balanced between treatment groups (table 1). 467 (77%) of 605 participants were male and median age was 69 years (IQR 64–75). Overall, 456 (75%) of 605 patients had epithelioid tumour histology.

As of database lock, five (2%) of 300 patients in the nivolumab plus ipilimumab group who received treatment remained on treatment and no patients in the chemotherapy group remained on treatment (figure 1). The main reasons for treatment discontinuation in the nivolumab plus ipilimumab group were disease progression (182 [61%] of 300) and study drug toxicity

	Nivolumab plus ipilimumab group (n=303)	Chemotherapy group (n=302)
Age, years	69 (65–75)	69 (62–75)
<65	71 (23%)	96 (32%)
≥65 to <75	154 (51%)	127 (42%)
≥75	78 (26%)	79 (26%)
Sex		
Male	234 (77%)	233 (77%)
Female	69 (23%)	69 (23%)
Region		
North America	32 (11%)	27 (9%)
Europe	177 (58%)	175 (58%)
Asia	26 (9%)	39 (13%)
Rest of the world*	68 (22%)	61 (20%)
Eastern Cooperative Oncology Group performance status†		
0	114 (38%)	128 (42%)
1	189 (62%)	173 (57%)
Smoking status		
Current or former	173 (57%)	171 (57%)
Never	127 (42%)	122 (40%)
Unknown	3 (1%)	9 (3%)
Histology		
Epithelioid	229 (76%)	227 (75%)
Non-epithelioid	74 (24%)	75 (25%)
Sarcomatoid	35 (12%)	36 (12%)
Mixed or other	39 (13%)	39 (13%)
Stage		
1	12 (4%)	20 (7%)
2	23 (8%)	22 (7%)
3	103 (34%)	106 (35%)
4	160 (53%)	149 (49%)
Not reported	5 (2%)	5 (2%)
Previous cancer therapy		
Radiotherapy‡	29 (10%)	28 (9%)
Systemic therapy§	1 (<1%)	0
PD-L1 status		
Quantifiable	289 (95%)	297 (98%)
<1%¶	57/289 (20%)	78/297 (26%)
≥1%¶	232/289 (80%)	219/297 (74%)

Data are median (IQR) or n (%). PD-L1=programmed cell death ligand 1. *Includes Australia, Brazil, Chile, and South Africa. †On a score of 0 to 5, with higher scores indicating greater disability. One patient in the chemotherapy group had a baseline Eastern Cooperative Oncology Group performance status of 2 (protocol deviation). ‡Previous radiotherapy was provided for palliative support, pain management, or prophylactic track irradiation for tumour biopsy. §Due to incorrect data entry, one patient was reported as having previous systemic cancer therapy in the nivolumab plus ipilimumab group. ¶Calculated as a proportion of quantifiable patients.

Table 1: **Baseline characteristics**



(59 [20%]); 25 (8%) of 300 patients completed 2 years of immunotherapy. During the study, one patient in the nivolumab plus ipilimumab group discontinued study drug but received subsequent therapy from the investigator before BICR confirmation of disease progression. In the chemotherapy group, 176 (62%) of 284 patients completed all six cycles; 44 (16%) discontinued due to disease progression and 24 (8%) due to study drug toxicity. Median duration of treatment was 5·6 months (IQR 2·0–11·4) in the nivolumab plus ipilimumab group and 3·5 months (IQR 2·7–3·7) in the chemotherapy group (appendix p 9). The median number of nivolumab doses received was 12·0 (IQR 5·0–23·5) and of ipilimumab was 4·0 (2·0–7·0). After randomisation, 104 (34%) of 302 patients in the chemotherapy group were given cisplatin and 180 (60%) were given carboplatin; 29 (28%) of 104 patients given cisplatin switched to carboplatin after the first dose due to investigator decision. The median number of doses of cisplatin was 5·0 (IQR 3·0–6·0), of carboplatin was 6·0 (4·0–6·0), and of pemetrexed was 6·0 (4·0–6·0). Further information on treatment exposure is in the appendix (pp 9–10).

In the nivolumab plus ipilimumab group, 134 (44%) of 303 patients were given subsequent systemic therapy, ten (3%) were given subsequent immunotherapy, and 131 (43%) were given subsequent chemotherapy. In the chemotherapy group, 123 (41%) of 302 patients were given subsequent systemic therapy, 61 (20%) were given subsequent immunotherapy, and 95 (31%) were given subsequent chemotherapy (appendix p 11).

The study met its primary endpoint at the prespecified interim analysis according to the recommendation of the independent Data Monitoring Committee. Given that the study was able to reject the null hypothesis at the interim analysis, this analysis is considered final. Median overall survival was 18·1 months (95% CI 16·8–21·4) with nivolumab plus ipilimumab versus 14·1 months (12·4–16·2) with chemotherapy, with a stratified HR of 0·74 (96·6% CI 0·60–0·91; p=0·0020; figure 2). The p value for the time-dependent covariate was 0·9646, indicating that there was no evidence of a non-constant treatment effect over time. Overall survival rates at 1 year were 68% (95% CI 62·3–72·8) versus 58% (51·7–63·2) and at 2 years were 41% (35·1–46·5) versus 27% (21·9–32·4). Overall survival was similar between chemotherapy regimens: median overall survival was 13·7 months (95% CI 11·8–17·9) with pemetrexed plus cisplatin, and 15·0 months (12·2–17·9) with pemetrexed plus carboplatin (appendix p 25). Overall survival favoured nivolumab plus ipilimumab across most

Figure 2: **Overall survival in all randomised patients (A) and in patients with epithelioid tumour histology (B) and non-epithelioid tumour histology (C)**
The hazard ratio in part A is stratified by sex and histology. The hazard ratios in parts B and C are from unstratified Cox proportional hazard models.

subgroups, although survival in patients aged 75 years and older (n=157) was similar between treatment groups (figure 3). Notably, overall survival was improved with nivolumab plus ipilimumab versus chemotherapy regardless of histology (study stratification factor; figure 2). We found some evidence of higher treatment effect in patients with non-epithelioid histology (HR 0·46 [95% CI 0·31–0·68]) than in those with the epithelioid subtype (0·86 [0·69–1·08]). Median overall survival with nivolumab plus ipilimumab was similar between non-epithelioid and epithelioid subtypes (18·1 months [95% CI 12·2–22·8] *vs* 18·7 months [16·9–22·0]), as were 2-year overall survival rates (38% [95% CI 27·0–49·5] *vs* 42% [35·0–48·1]). By contrast, median overall survival with chemotherapy differed substantially between non-epithelioid and epithelioid subtypes (8·8 months [95% CI 7·4–10·2] *vs* 16·5 months [14·9–20·5]), as did 2-year overall survival rates (8% [95% CI 3·3–16·7] *vs* 33% [26·8–39·5]). Overall survival benefit by tumour PD-L1 expression level for nivolumab plus ipilimumab versus chemotherapy was greater in patients with tumour expression of PD-L1 of 1% or higher (HR 0·69 [95% CI 0·55–0·87]) than in patients with expression of less than 1% (0·94 [0·62–1·40]; figure 3; appendix pp 23–24). Nonetheless, median overall survival with nivolumab plus ipilimumab was similar in patients with tumours with PD-L1 expression of 1% or higher (18·0 months [95% CI 16·8–21·5]) and of less than 1% (17·3 months [95% CI 10·1–24·3]); 1-year survival rates were 70% (95% CI 63·4–75·3) and 59% (45·5–70·9); and 2-year survival rates were 41% (34·3–47·2) and 39% (25·9–51·3; appendix pp 23–24). Conversely, median overall survival with chemotherapy differed between patients with PD-L1 expression of 1% or higher (13·3 months [95% CI 11·6–15·4]) and less than 1% (16·5 months [13·4–20·5]); 1-year survival rates were 55% (95% CI 48·2–61·8) and 64% (52·3–73·9); and 2-year survival rates were 28% (22·1–34·7) and 25% (15·5–35·0; appendix pp 23–24).

The minimum follow-up for progression-free survival was 19·8 months. Median progression-free survival was similar between treatment groups: 6·8 months (95% CI 5·6–7·4) with nivolumab plus ipilimumab and 7·2 months (95% CI 6·9–8·0) with chemotherapy (HR 1·00 [95% CI 0·82–1·21]). However, progression-free survival rates at 2 years were numerically greater with nivolumab plus ipilimumab (16% [95% CI 11·7–21·5]) versus chemotherapy (7% [4·0–11·7]; figure 4).

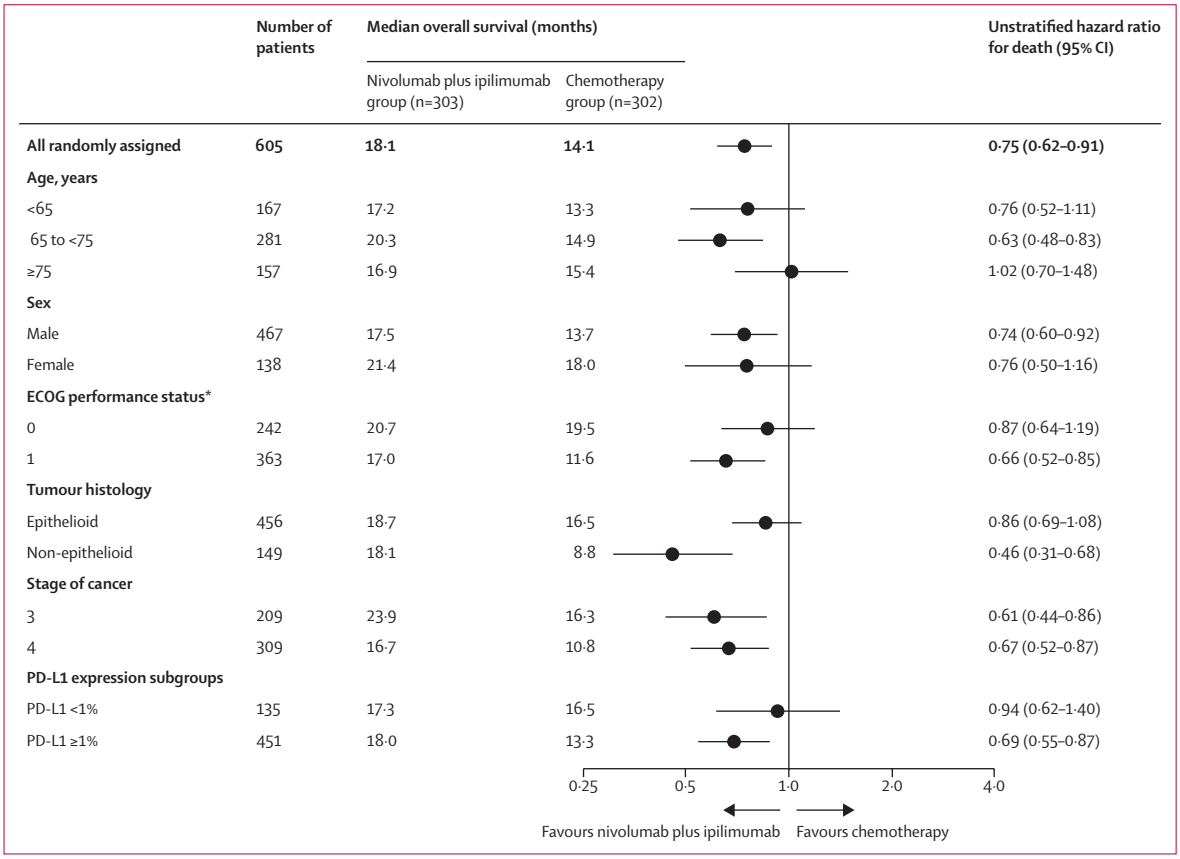


Figure 3: **Overall survival in predefined patient subgroups**
ECOG=Eastern Cooperative Oncology Group. PD-L1=programmed cell death ligand 1. *One patient in the chemotherapy group had a baseline performance status of 2 (protocol deviation).

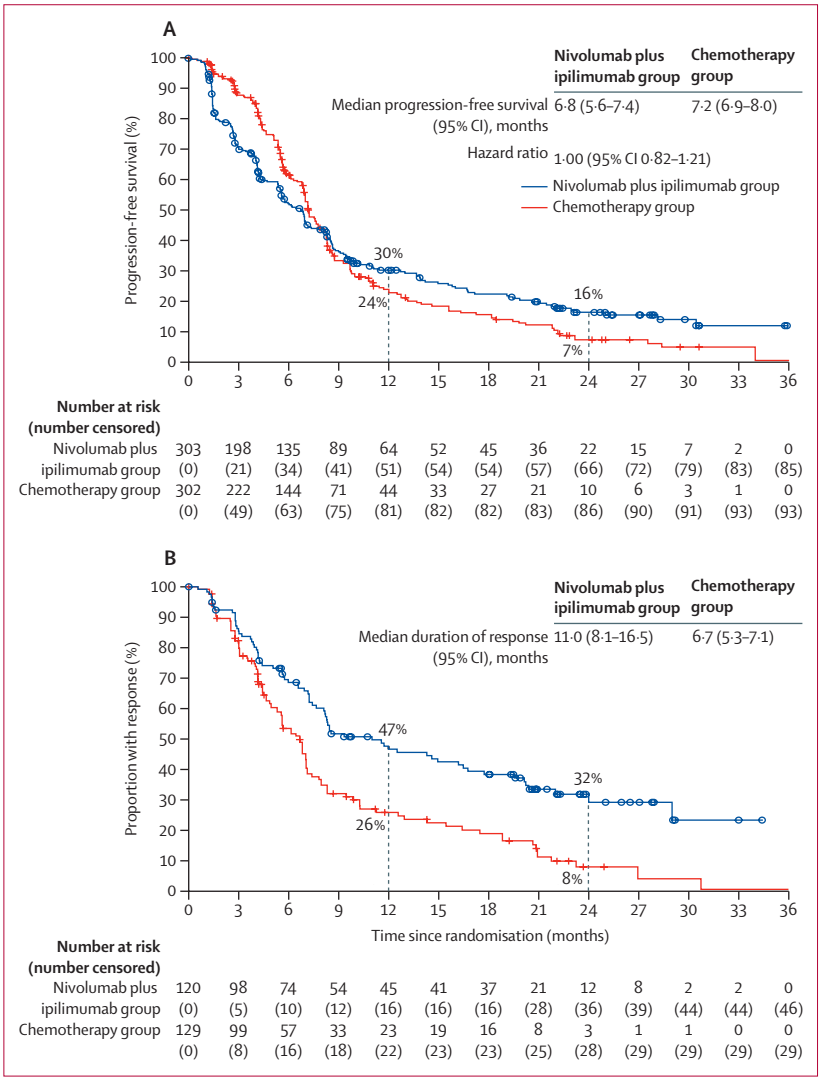


Figure 4: **Progression-free survival in all patients randomly assigned to treatment (A) and duration of response in confirmed responders (B)**

Progression-free survival and duration of response are both per blinded independent central review. The hazard ratio in part A is stratified by sex and histology.

	Nivolumab plus ipilimumab group (n=303)	Chemotherapy group (n=302)
Objective response rate		
n (%)	120 (40%)	129 (43%)
95% CI	34·1–45·4	37·1–48·5
Best overall response		
Complete response	5 (2%)	0
Partial response	115 (38%)	129 (43%)
Stable disease	112 (37%)	125 (41%)
Non-complete response and non-progressive disease	0	3 (1%)
Progressive disease	55 (18%)	14 (5%)
Unable to determine	4 (1%)	5 (2%)
Not reported	12 (4%)	26 (9%)
Disease control rate		
n (%)	232 (77%)	257 (85%)
95% CI	71·4–81·2	80·6–88·9
Time to response, months		
Median	2·7	2·5
IQR	1·45–3·27	1·41–3·02
Duration of response, months		
Median	11·0	6·7
95% CI	8·1–16·5	5·3–7·1
Proportion of patients with a response of at least 1 year or 2 years*		
At 1 year	47%	26%
95% CI	37–56	18–34
At 2 years	32%	8%
95% CI	23–41	3–15

Data are n (%), unless indicated otherwise. Minimum follow-up for objective response rate was 19·8 months. *Estimates are based on Kaplan-Meier estimates of duration of response.

Table 2: **Tumour response, as per blinded independent central review, in all patients randomly assigned to treatment**

An objective response was reported in 120 of 303 patients (40%; 95% CI 34·1–45·4) in the nivolumab plus ipilimumab group versus 129 of 302 patients (43%; 95% CI 37·1–48·5) in the chemotherapy group (table 2). Complete responses were only observed in the nivolumab plus ipilimumab group (five [2%] of 303 patients). Disease control was seen in 232 of 303 patients (77%; 95% CI 71·4–81·2) with a median time to response of 2·7 months (IQR 1·45–3·27) for the nivolumab plus ipilimumab group versus 257 of 302 (85%; 95% CI 80·6–88·9) with a median time to response of 2·5 months (IQR 1·41–3·02) for the chemotherapy group. Median duration of response in all confirmed responders was 11·0 months (95% CI 8·1–16·5) in the nivolumab plus ipilimumab group versus 6·7 months (95% CI 5·3–7·1) in the chemotherapy group (figure 4). The 2-year duration of response rate was 32% (95% CI 23–41) in the nivolumab plus ipilimumab group versus 8% (95% CI 3–15) in the chemotherapy group.

Safety is summarised in table 3, and all reported grade 3 and 4 treatment-related adverse events are listed in the appendix (pp 13–16). Of 300 patients treated with nivolumab plus ipilimumab, 28 (9%) discontinued ipilimumab early. In the chemotherapy group, dose reductions occurred in 89 (31%) of 284 participants who were given pemetrexed, 18 (17%) of 104 patients who were given cisplatin, and 85 (41%) of 209 participants who were given carboplatin, whereas dose reductions were not permitted for the nivolumab plus ipilimumab group. Grade 3–4 treatment-related adverse events were reported in 91 (30%) of 300 participants treated with nivolumab plus ipilimumab and 91 (32%) of 284 participants treated with chemotherapy. Any-grade serious treatment-related adverse events were reported in 64 (21%) patients treated with nivolumab plus ipilimumab versus 22 (8%) patients treated with chemotherapy; grade 3–4 treatment-related serious

	Nivolumab plus ipilimumab group (n=300)			Chemotherapy group (n=284)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Any	148 (49%)	79 (26%)	12 (4%)	141 (50%)	73 (26%)	18 (6%)
Diarrhoea	52 (17%)	10 (3%)	0	19 (7%)	2 (1%)	0
Pruritus	46 (15%)	3 (1%)	0	1 (<1%)	0	0
Rash	40 (13%)	3 (1%)	0	15 (5%)	0	0
Fatigue	38 (13%)	3 (1%)	0	50 (18%)	5 (2%)	0
Hypothyroidism	32 (11%)	0	0	0	0	0
Nausea	29 (10%)	1 (<1%)	0	97 (34%)	7 (2%)	0
Anaemia	5 (2%)	1 (<1%)	0	70 (25%)	32 (11%)	0
Decreased appetite	27 (9%)	2 (1%)	0	48 (17%)	2 (1%)	0
Constipation	12 (4%)	0	0	41 (14%)	1 (<1%)	0
Vomiting	8 (3%)	0	0	35 (12%)	6 (2%)	0
Asthenia	25 (8%)	0	0	32 (11%)	12 (4%)	0
Increased lipase	7 (2%)	11 (4%)	2 (1%)	0	1 (<1%)	0
Colitis	3 (1%)	7 (2%)	0	1 (<1%)	1 (<1%)	0
Increased amylase	10 (3%)	6 (2%)	1 (<1%)	1 (<1%)	0	0
Thrombocytopenia	0	2 (1%)	0	16 (6%)	4 (1%)	6 (2%)
Neutropenia	0	1 (<1%)	1 (<1%)	28 (10%)	31 (11%)	12 (4%)

Data are n (%). Safety was assessed in all patients who received at least one dose of study drug. Treatment-related adverse events with an incidence of ≥10% in any group or grade 3 or 4 severity with an incidence of ≥2% in any group are shown. All grade 3 and 4 events are listed in the appendix (pp 13–16). Treatment-related adverse events included those reported between the first dose of study drug and 30 days after the last dose of study drug. *Only events that led to death within 24 h were documented as grade 5 and reported as deaths. Events leading to death >24 h after onset are reported with the worst grade before death.

Table 3: **Summary of treatment-related adverse events in all treated patients***

events were reported in 46 (15%) patients treated with nivolumab plus ipilimumab versus 17 (6%) treated with chemotherapy (appendix pp 17–19). Any-grade treatment-related adverse events that led to discontinuation (due to either component of the regimen) were reported in 69 (23%) of 300 patients treated with nivolumab plus ipilimumab and 45 (16%) of 284 patients treated with chemotherapy, and 45 (15%) patients treated with nivolumab plus ipilimumab and 21 (7%) patients treated with chemotherapy had grade 3–4 events that led to discontinuation (appendix p 20).

The most frequent any-grade treatment-related adverse events were diarrhoea in the nivolumab plus ipilimumab group (62 [21%] of 300 patients) and nausea in the chemotherapy group (104 [37%] of 284 patients). The most frequently reported any-grade serious treatment-related adverse events were colitis in the nivolumab plus ipilimumab group (nine [3%]) and anaemia in the chemotherapy group (six [2%]; appendix pp 17–19). The median exposure time was 6·5 months (IQR 2·99–12·22) for nivolumab plus ipilimumab and 4·5 months (3·65–4·68) for chemotherapy. Treatment exposure was 220·3 person-years with nivolumab plus ipilimumab and 94·5 person-years with chemotherapy. The overall exposure-adjusted incidence of treatment-related adverse events was 502·1 per 100 person-years with nivolumab plus ipilimumab versus 1355·3 per 100 person-years with chemotherapy.

A summary of treatment-related select adverse events (those with a potential immunological cause), time to onset and resolution of treatment-related select adverse events, the proportion of patients requiring immune-modulating concomitant medication (mostly corticosteroids), and the duration of use of immune-modulating concomitant medication are shown in the appendix (p 21). The most commonly reported any-grade treatment-related select adverse events with nivolumab plus ipilimumab were skin (108 [36%] of 300 patients) and gastrointestinal (66 [22%]) events. Overall, 198 (66%) of 300 patients who were given nivolumab plus ipilimumab died, with 183 (61%) deaths due to disease progression. 212 (75%) of 284 patients given chemotherapy died, with 199 (70%) deaths due to disease progression. Three (1%) treatment-related deaths occurred in the nivolumab plus ipilimumab group, due to pneumonitis, encephalitis, and heart failure. One (<1%) treatment-related death occurred in the chemotherapy group due to myelosuppression.

Discussion

To our knowledge, CheckMate 743 is the first large, randomised, phase 3 study to show significant and clinically meaningful improvement in overall survival with immunotherapy versus standard-of-care platinum plus pemetrexed chemotherapy for first-line treatment of unresectable MPM. Based on these results, in October, 2020, the US Food and Drug Administration approved nivolumab plus ipilimumab for this patient population.[12] With a median follow-up of 29·7 months, nivolumab plus ipilimumab provided durable survival benefit versus chemotherapy, with a 50% improvement

in the 2-year overall survival rate (41% *vs* 27%). Furthermore, estimated rates of patients who still had a response at 2 years was 8% with chemotherapy versus 32% with nivolumab plus ipilimumab. The safety profile of nivolumab plus ipilimumab in this study was consistent with that seen previously in NSCLC at this dose and schedule[15] and no new safety signals were reported.

The frequencies of grade 3 or 4 serious treatment-related adverse events and those leading to discontinuation were higher with nivolumab plus ipilimumab than with chemotherapy; however, most were manageable and resolved with steroids or supportive treatment. Moreover, when treatment-related adverse events were adjusted for exposure, the overall incidence of treatment-related adverse events was lower with nivolumab plus ipilimumab than with chemotherapy.

Benefit with nivolumab plus ipilimumab was observed in most subgroups assessed, with the exception of patients aged 75 years or older. However, these subgroups were small and did not have statistical power. As such, results from these subgroup analyses should be interpreted with caution. Importantly, benefits were observed across histological groups, albeit at different magnitudes. For example, median overall survival with nivolumab plus ipilimumab was consistent between patients with epithelioid histology (18·7 months; HR 0·86 [95% CI 0·69–1·08]) and non-epithelioid histology (18·1 months; HR 0·46 [0·31–0·68]), showing clinically meaningful survival improvements across both groups; 1-year and 2-year overall survival rates were also similar between the two histological subgroups. Notably, in the epithelioid subgroup, nivolumab plus ipilimumab showed an improvement of 2 months in median overall survival compared with chemotherapy, with an HR favouring nivolumab plus ipilimumab despite the 95% CI overlapping 1. Furthermore, the 2-year overall survival rate in the epithelioid subgroup showed a long-term benefit of nivolumab plus ipilimumab with a 9% absolute difference versus chemotherapy. The larger magnitude of benefit observed in the non-epithelioid subgroup was primarily driven by the inferior effect of chemotherapy in the non-epithelioid subtype, as previously reported.[3] This difference in outcomes between the subgroups treated with chemotherapy could not be attributed to the type of chemotherapy received because exploratory data from CheckMate 743 suggest that patients derive a similar overall survival benefit regardless of platinum backbone; median overall survival was similar between pemetrexed plus cisplatin and pemetrexed plus carboplatin.

Median progression-free survival and objective response rates were each numerically similar for nivolumab plus ipilimumab and chemotherapy. Median progression-free survival was similar to results from previously reported clinical trials in recurrent MPM.[16,18] The progression-free survival Kaplan-Meier curves crossed at approximately 8 months, reflecting more rapid, although not durable, disease control with chemotherapy. However, radiographic assessments in MPM can be challenging because of the absence of distinguishable tumour margins over time and successive CT evaluations.[22] Thus, overall survival is considered to be a more objective and reliable endpoint in this tumour type. Notably, nivolumab plus ipilimumab provided long-term overall survival benefit, although the slight early survival benefit observed with chemotherapy was not durable.

The duration of response and durable survival benefit observed with nivolumab plus ipilimumab in patients with MPM in CheckMate 743 builds on the existing body of evidence that shows extended survival benefit with this dual immunotherapy regimen across a number of other tumour types, including NSCLC.[13–15,23] Ipilimumab is hypothesised to drive memory T-cell production leading to durable responses when combined with nivolumab.[11] Results of the current study also corroborate the promising activity seen with anti-PD-1 or anti-PD-L1, and anti-CTLA-4 combination therapies in phase 2 studies in second-line or later settings of MPM,[16,18,24] and support the use of dual immunotherapy over single-agent anti-PD-1 or anti-CTLA-4 inhibitors, which have shown little benefit over chemotherapy.[25,26]

Some treatment guidelines (eg, NCCN guidelines) include the optional addition of the anti-angiogenic agent bevacizumab to platinum plus pemetrexed chemotherapy for first-line treatment of MPM in select patients, based on the survival benefit seen in a phase 3 trial;[5,10] however, this regimen is not approved by regulators. Nonetheless, given the durable survival benefit seen in CheckMate 743, combining nivolumab plus ipilimumab with other therapies, including anti-angiogenic agents or, as approved for NSCLC in May, 2020, a short course of chemotherapy,[12] merits investigation to determine whether survival outcomes can be further enhanced. Similarly, future trials assessing the benefit of second-line targeted therapies (eg, bevacizumab and ramucirumab) after nivolumab plus ipilimumab treatment are warranted.

Reliable biomarkers to predict the benefit of dual-agent immunotherapy in the treatment of MPM have not yet been identified. Although PD-L1 expression is an established biomarker for single-agent immunotherapy in NSCLC,[27] its role in predicting treatment outcomes with dual immunotherapy regimens has not been established. More specifically, in MPM trials investigating immunotherapies, the association between PD-L1 expression and efficacy is inconsistent.[17,18,24] In CheckMate 743, overall survival outcomes with nivolumab plus ipilimumab were similar in the subgroups with less than 1% and with 1% or higher PD-L1 expressions and better outcomes were seen with nivolumab plus ipilimumab than with chemotherapy at 2 years in both subgroups. However, survival with chemotherapy was better in patients with tumour PD-L1 expression of less than 1% than those with expression of 1% or higher. These observations suggest that absence of PD-L1 expression might be indicative of better prognosis

with chemotherapy. However, these descriptive and exploratory data should be interpreted with caution given their potential limitations—ie, PD-L1 expression was not a stratification factor in the study and the sample size of the PD-L1 expression less than 1% group was small. As such, the potential for imbalances in known or unknown prognostic factors does not allow us to draw definitive conclusions. Better characterisation of this heterogeneous disease using transcriptomic and epigenetic profiling should guide future patient selection and therapeutic strategies, and aid in the identification of novel biomarkers.[28,29]

In summary, first-line nivolumab plus ipilimumab provided a significant and clinically meaningful improvement in overall survival versus platinum plus pemetrexed chemotherapy. Nivolumab plus ipilimumab has a favourable clinical benefit–risk profile that has led to approval in the USA and should be considered as a new standard of care for previously untreated patients with unresectable MPM, regardless of histological subtype.

Contributors

PB, AS, AKN, NF, SPe, AST, ASM, SPo, TJ, PA, AO, CB, and GZ provided substantial contributions to the conception and design of the study. PB, AS, AKN, NF, SPe, AST, ASM, SA, YO, YB, RC, LG, FG, DK, JR-C, and GZ enrolled and treated patients. CB wrote the study statistical analysis plan, did all statistical analyses, and generated data. PB, AKN, NF, SPe, AST, ASM, SPo, TJ, PA, AO, CB, and GZ analysed and interpreted the data. PA and CB verified the underlying data from the study. All authors reviewed the data, contributed to the development of the manuscript, and approved the final version for publication.

Declaration of interests

PB has received institutional grant funding from Bristol Myers Squibb and MSD and has a consultancy or advisory role for Bristol Myers Squibb, MSD, Roche, Beigene, Epizyme, Takeda, Trizell, and Daichii-Sankyo (all honoraria are paid to his institute). 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Data sharing

The Bristol Myers Squibb policy on data sharing is available online.

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ORIGINAL ARTICLE

Clinical Efficacy and Safety of Nivolumab in Japanese Patients With Malignant Pleural Mesothelioma: 3-Year Results of the MERIT Study

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ABSTRACT

Introduction: We examined the long-term efficacy and safety of nivolumab, a human monoclonal antibody that inhibits interactions between the programmed cell death protein-1 receptor and its ligands (programmed death-ligand 1 and programmed death-ligand 2), in Japanese patients with malignant pleural mesothelioma (MPM).

Methods: Japanese patients with previously treated MPM (one or two regimens) were enrolled in a single-arm, phase 2 study and received nivolumab intravenously 240 mg every 2 weeks until progressive disease or unacceptable toxicity. The primary end point was the centrally assessed objective response rate. Other end points included overall survival (OS), progression-free survival (PFS), treatment-related adverse events, and patient-reported outcomes (Lung Cancer Symptom Scale for mesothelioma and EuroQOL visual analog scale). Patient enrollment started on June 16, 2016. Here, we report 3-year follow-up data (cutoff date: November 12, 2019).

Results: Thirty-four patients were enrolled. The centrally assessed objective response rate was previously reported (29.4%). The 2- and 3-year OS rates were 35.3% and 23.5%, respectively, and the corresponding PFS rates were 17.0% and 12.7%. Median OS and PFS were 17.3 and 5.9 months, respectively. Eight patients were alive at 3 years of follow-up. Nivolumab was well tolerated and no new safety signals were found. The patient-reported outcomes were maintained without marked deteriorations during the study.

Conclusions: Our results reveal clinically relevant long-term efficacy and safety of nivolumab for the treatment of MPM.

Keywords: Malignant pleural mesothelioma; Nivolumab; Programmed death-1; Japan

Introduction

Malignant pleural mesothelioma (MPM) is a rare, highly aggressive malignancy that is mostly due to occupational exposure to asbestos and is more common in older males.[1-3] In previous Japanese studies, the median survival of patients with newly diagnosed MPM was just 7.9 months, generally because most patients are diagnosed at an advanced stage.[1,2] The U.S. National Comprehensive Cancer Network guidelines for MPM recommend pemetrexed plus cisplatin (or carboplatin) with or without bevacizumab as first-line chemotherapy.[4] However, most patients fail to respond to first-line chemotherapy, necessitating subsequent systemic therapy, which may now involve pemetrexed (if not administered as first-line chemotherapy or as rechallenge), nivolumab with or without ipilimumab, or pembrolizumab.[4]

Nivolumab, a human monoclonal antibody that inhibits interactions between the programmed cell death protein-1 receptor and its ligands (programmed death-ligand 1 [PD-L1] and PD-L2), was approved in Japan (August 2018) for patients with pemetrexed–platinum doublet-treated MPM on the basis of the results of the Multicenter, Open-label, Single-arm, Japanese Phase II study in Malignant Pleural Mesothelioma (MERIT) study,[5] which enrolled 34 Japanese patients. After a median follow-up of 16.8 months, 10 patients had an objective response and the median overall survival (OS) was 17.3 months.[5]

To our knowledge, there are no published studies reporting the 3-year OS after second-line treatment. Here, we report the results obtained at the 3-year follow-up of patients enrolled in the MERIT study, including the efficacy outcomes for all patients and according to PD-L1 expression and MPM subtype (epithelioid or non-epithelioid), changes in quality of life (QOL) (determined using the EuroQOL visual analog scale [EQ-VAS] and Lung Cancer Symptom Scale for mesothelioma [LCSS-Meso] average symptom burden index), and treatment-related adverse events (TRAEs).

Materials and Methods

MERIT was an open-label, single-arm, phase 2 study performed at 15 centers in Japan. Its design is described in more detail in our previous report.[5] This study adhered to the Declaration of Helsinki and Good Clinical Practice and was registered on clinicaltrials.jp (JapicCTI-163247).

Patients

The full eligibility criteria are described in our previous report.[5] Briefly, males and females aged at least 20 years were eligible if they had histologically confirmed MPM, unresectable advanced or metastatic MPM without surgery, MPM resistant or intolerable to one or two previous chemotherapeutic regimens (platinum and pemetrexed), and at least one measurable lesion defined according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST) for MPM.[6] Key exclusion criteria included history of severe hypersensitivity reactions to other drugs (including antibody products), concurrent or history of autoimmune disease, multiple primary cancers, brain or meningeal metastases, current or history of interstitial lung disease or pulmonary

fibrosis, and previous treatment with immune checkpoint inhibitors (ICIs), therapeutic antibodies, or drugs targeting T-cell regulation. All patients provided written informed consent for participation in the study.

Study Design

All patients were treated with nivolumab at a dose of 240 mg by intravenous infusion every 2 weeks (one cycle) on day 1 of each cycle. Its dose or administration mode could not be adjusted. As previously explained,[5] nivolumab was to be continued until the patient met one of the discontinuation criteria: documentation of progressive disease (PD); unequivocal clinical progression; grade 2 or higher interstitial lung disease, grade 2 or higher eye disorder that did not improve to grade 1 or less with topical treatment, and a causal relationship with nivolumab could not be excluded; grade 3 or higher bronchospasm, neurotoxicity, hypersensitivity reaction, infusion reaction, or uveitis for which a causal relationship with nivolumab could not be excluded; no administration of nivolumab for 6 weeks after the previous dose (unless nivolumab is withheld for at least 6 weeks for steroid tapering); or the investigator or subinvestigator deemed it necessary to discontinue treatment in consideration of the efficacy or safety of nivolumab. Immunosuppressants, corticosteroids at doses of at least 10 mg/day prednisone equivalents, antitumor therapies, concurrent radiotherapy, pleurodesis, and surgical therapies for malignant tumors were prohibited. Tumor imaging (computed tomography or magnetic resonance imaging) was performed every three cycles. Target lesions in the pleura were measured unidimensionally as the largest tumor thickness perpendicular to the chest wall or mediastinum according to mRECIST.[6] Nonpleural lesions were measured according to RECIST version 1.1. PD-L1 expression was assessed as previously described.[5] PD-L1–positive status was defined as membranous staining in at least 1% of tumor cells.

End Points

The primary end point was the objective response rate (ORR), with central assessment according to mRECIST, and was defined as the proportion of patients with a complete response or partial response (PR). Secondary end points included the investigator-assessed ORR, changes in tumor size, disease control rate, OS, progression-free survival (PFS), duration of response, time to response, and best overall response (BOR) assessed centrally. Tumor responses were assessed in all patients combined and in patients divided into subgroups by PD-L1 expression ($<1\%$ or $\geq 1\%$) and histologic subtype (epithelioid, sarcomatoid, or biphasic) in prespecified analyses. QOL was assessed using the EQ-VAS and the LCSS-Meso symptom burden index[7] at enrollment and at each study visit. Safety was evaluated in terms of laboratory tests, AEs, and TRAEs. AEs and TRAEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

Statistical Analyses

As previously noted, a sample size of at least 29 patients was sufficient to detect a significant ORR with a power of 80% and a one-sided significance level of 0.025, on the basis of an expected ORR of 19%.[5] We also performed a landmark analysis of OS according to the BOR at 3 months for patients who survived for at least 3 months. All analyses were performed using standard methods at 95% confidence levels. Wilson's method was used to determine the 95% confidence intervals (CIs) for the ORR, disease control rate, and BOR. All analyses were conducted using SAS version 9.3 (SAS Institute Inc., Cary, NC).

Role of the Funding Source

This work was funded by Ono Pharmaceutical Co., Ltd., Japan, and Bristol-Myers Squibb, United States. The sponsors contributed to the study design, data collection, data analysis, data interpretation, and writing of the clinical study report.

Results

Patients

Patient enrollment started on June 16, 2016, and patients were followed up to the data cutoff date, November 12, 2019. Forty-three patients were screened (provided consent), and nine were excluded because they did not meet the inclusion criteria or withdrew their consent. A total of 34 patients were enrolled and treated with nivolumab, including 29 males (85.3%) and five (14.7%) females. Their characteristics are described in Supplementary Table 1 and in our previous report.[5] The minimum follow-up was 36 months. The median follow-up was 17.3 (range: 1.8–39.9) months for all 34 patients and 38.0 (range: 37.0–39.9) months for seven censored patients included in the end-of-study analysis.

Overall Response Rate

The centrally assessed ORR was unchanged from our previous report at 29.4% (95% CI: 16.8%–46.2%; 10 of 34 patients), with PR in 10 patients (Table 1). In most patients with PR or stable disease, their responses were maintained for a long period of time (Supplementary Fig. 1), up to approximately 2 years. Table 1 reveals the ORR in subgroups of patients, including the previously reported ORR by histologic subtype and PD-L1

Table 1. Responses to Nivolumab (N = 34)

Outcome	n/N (%)[a]	95% CI
BOR		
CR	0/34 (0.0)	0.0-10.2
PR	10/34 (29.4)	16.8-46.2
Stable disease	13/34 (38.2)	23.9-55.0
PD	9/34 (26.5)	n/c
NA	2/34 (5.9)	n/c
Response rate by subgroup		
Sex		
Male	7/29 (24.1)	12.2-42.1
Female	3/5 (60.0)	23.1-88.2
Age (y)		
<65	3/11 (27.3)	9.7-56.6
≥65	7/23 (30.4)	15.6-50.9
ECOG PS		
0	4/13 (30.8)	12.7-57.6
1	6/21 (28.6)	13.8-50.0
Histologic subtype		
Epithelioid	7/27 (25.9)	13.2-44.7
Sarcomatoid	2/3 (66.7)	20.8-93.9
Biphasic	1/4 (25.0)	4.6-69.9
Number of prior treatment(s)		
1	9/24 (37.5)	21.2-57.3
2	1/10 (10.0)	1.8-40.4
PD-L1 status		
≥1%	8/20 (40.0)	21.9-61.3
<1%	1/12 (8.3)	1.5-35.4
NA	1/2 (50.0)	9.5-90.5

BOR, best overall response; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; NA, not assessable; n/c, not calculable; PD, progressive disease; PD-L1, programmed death ligand-1; PR, partial response.
[a]Percentages are calculated by the number (N) of patients within that subgroup.

status.[5] The present analyses newly revealed that the ORR was lower in patients with two previous treatments than in patients with one previous treatment.

OS and PFS

The 2- and 3-year OS rates were 35.3% and 23.5%, respectively, and the median OS was 17.3 months (95% CI: 11.5–26.6 months) (Fig. 1*A*). The 2- and 3-year PFS rates were 17.0% and 12.7%, respectively, and the median PFS was 5.9 months (Fig. 1*B*).

In PD-L1–positive patients, the 2- and 3-year OS rates were 35.0% and 15.0%, respectively, and the median OS was 19.1 months. The 2- and 3-year PFS rates were 18.9% and not calculable, respectively, and the median PFS was 7.2 months. In PD-L1–negative patients, the 2- and 3-year OS rates were both 33.3%, and the median OS was 11.6 months. The 2- and 3-year PFS rates were both 16.7%, and the median PFS in this subgroup was 2.9 months.

OS and PFS according to the histologic subtype of MPM are shown in Figure 2. Owing to the small numbers of patients with sarcomatoid or biphasic histologic subtypes, these patients were pooled together (as non-epithelioid subtype). In this subgroup, the median OS was 26.6 months, with 2- and 3-year OS rates of 57.1% and 42.9%, respectively (Fig. 2*A*). The median PFS was 18.2 months, whereas 2- and 3-year PFS rates were 42.9% and not calculable, respectively (Fig. 2*B*). In patients with the epithelioid histologic subtype, the median OS was 15.7 months and the 2- and 3-year OS rates were 29.6% and 18.5%, respectively (Fig. 2*A*). The median PFS, 2-year PFS, and 3-year PFS were 3.9 months, 9.6%, and 9.6%, respectively (Fig. 2*B*).

We also performed a landmark analysis of OS in patients with a best response of PR, stable disease, or PD (Supplementary Fig. 2). The median OS in these three subgroups was 20.9, 19.9, and 8.0 months, respectively.

Patient Status at 3 Years and Poststudy Treatments

Eight patients were alive at 3 years of follow-up, including seven at the database lock (Fig. 3). These seven patients were on a poststudy treatment at the cutoff date. They included four with epithelioid, two with biphasic, and one with sarcomatoid histologic subtypes. Four patients were treated with nivolumab for 2 years and one patient for 3 years. Eighteen patients received subsequent systemic treatments, as listed in Supplementary Table 2, including nivolumab in three patients. Nivolumab was not rechallenged as subsequent treatment in patients with PD, but one patient was switched to commercially available nivolumab after completing the clinical study, one patient started on commercially available nivolumab after the patient requested discontinuation of the clinical study upon approval of nivolumab in Japan, and one resumed nivolumab after discontinuation due to an AE.

Comparison of 3-Year Survivors and Nonsurvivors

In an exploratory analysis, we compared the characteristics and BOR between patients who survived for 3 years and nonsurvivors (Supplementary Table 3). Although there was an imbalance in the numbers of patients in these two groups, we observed no marked differences in their patient characteristics, except for the distribution of Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 and 1, with a significantly higher proportion of patients with ECOG PS of 0 among 3-year survivors ($p = 0.033$). The proportion of patients with a BOR of PR or stable disease was not significantly different between the two groups (75.0% in 3-year survivors and 65.4% in nonsurvivors, $p = 0.640$).

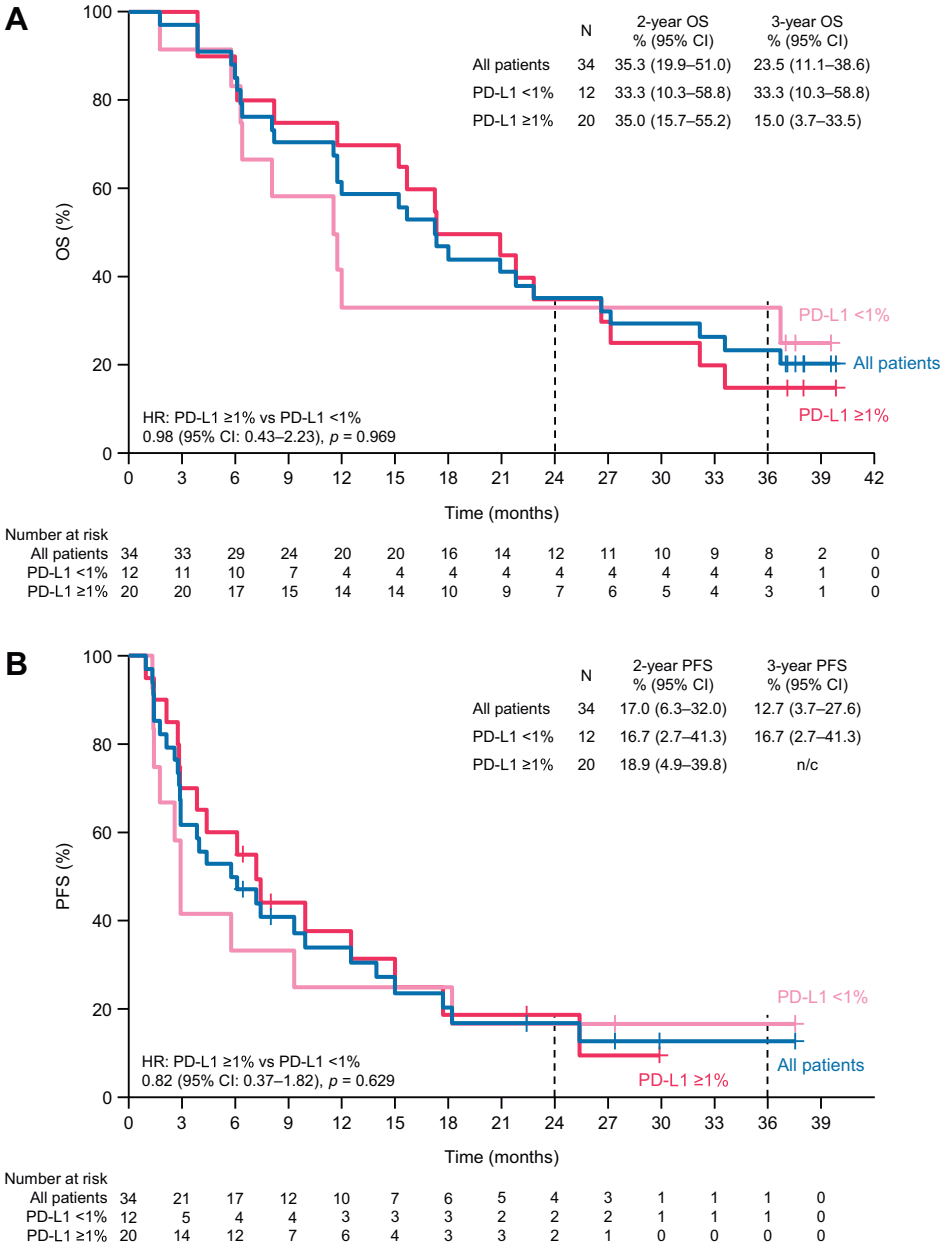

Figure 1. (*A*) OS and (*B*) PFS in all patients and in patients divided into subgroups by PD-L1 expression. CI, confidence interval; HR, hazard ratio; n/c, not calculable; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival.

Quality of Life

QOL was evaluated in terms of the EQ-VAS and LCSS-Meso symptom burden scale. Both outcomes were maintained over time among patients with available data (Fig. 4*A–D*).

Safety

We previously reported that TRAEs occurred in 26 patients (76.5%), including grade 3 to 4 TRAEs in 11 (32.4%) by the cutoff date of March 14, 2018,[5,8] and no additional TRAEs were observed thereafter until the cutoff date of November 12, 2019. There were no grade 5 TRAEs. The most common TRAEs were rash (six patients), lipase increased (five patients), and diarrhea and amylase increased (four patients each). Other TRAEs that occurred in at least two patients are listed in Table 2. Grade 3 or 4 TRAEs included lipase increased in four patients and diarrhea,

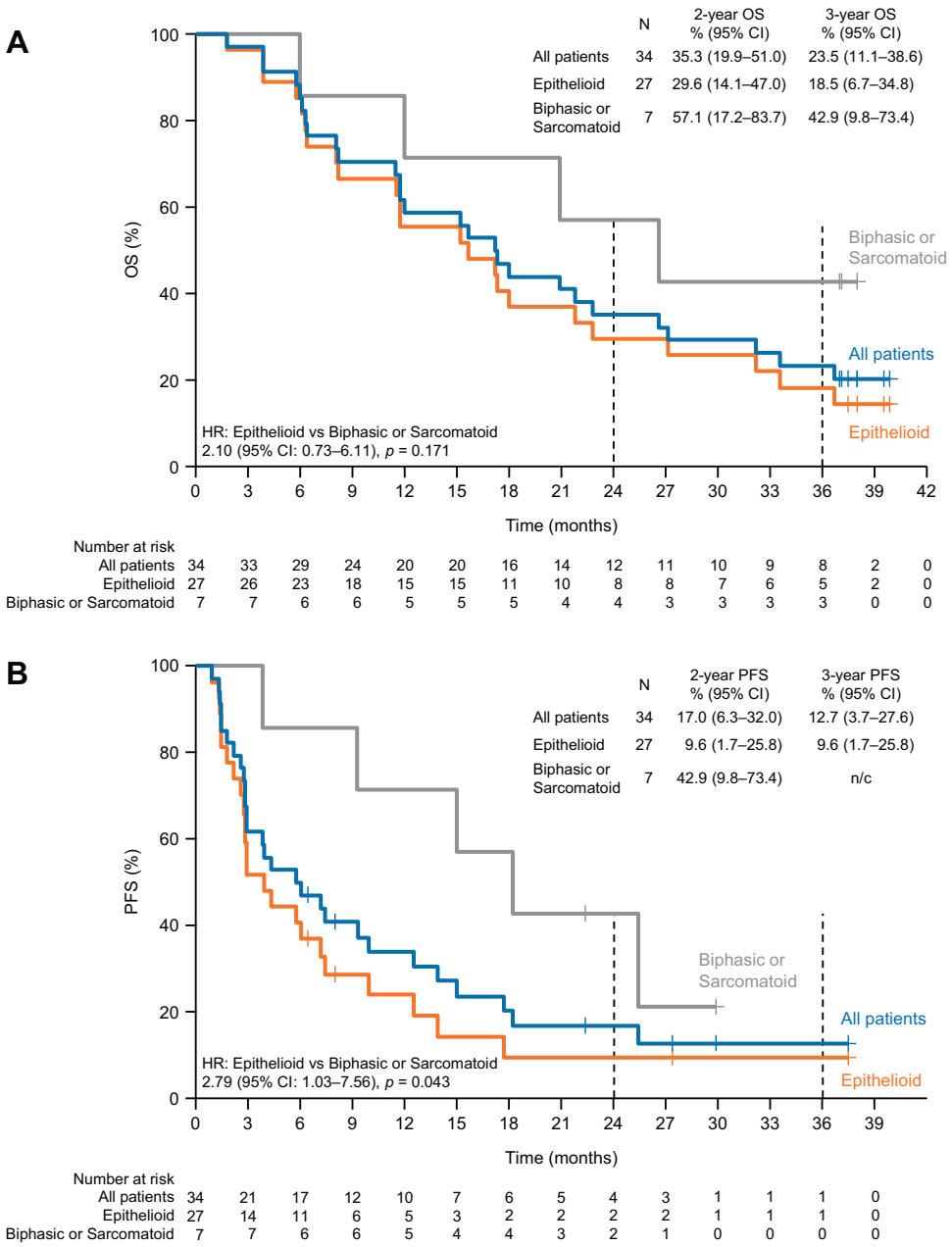

Figure 2. (*A*) OS and (*B*) PFS according to histologic subtype. Patients with biphasic or sarcomatoid histologic subtypes were pooled and compared with patients with the epithelioid histologic subtype. CI, confidence interval; HR, hazard ratio; n/c, not calculable; OS, overall survival; PFS, progression-free survival.

amylase increased, and pneumonitis in two patients each.

Discussion

The MERIT study evaluated the efficacy and safety of nivolumab in Japanese patients with MPM, and led to the approval of nivolumab for this indication in Japan. Until now, long-term survival rates of patients with MPM have remained poor, with limited benefit of chemotherapy. For example, second-line pemetrexed in combination with best supportive care (8.4 versus 9.7 months for best supportive care alone)[9] did not elicit marked improvements in OS. The introduction of ICIs has improved the prognosis of MPM. In the MAPS2 study, which enrolled patients with relapse after one or two lines of therapy, the median OS in nivolumab-treated patients was 11.9 months from the time of randomization (median follow-up of 20.1 months in the overall study population).[10] Therefore, we analyzed the OS and PFS at a 3-year follow-up in the MERIT study. We observed a

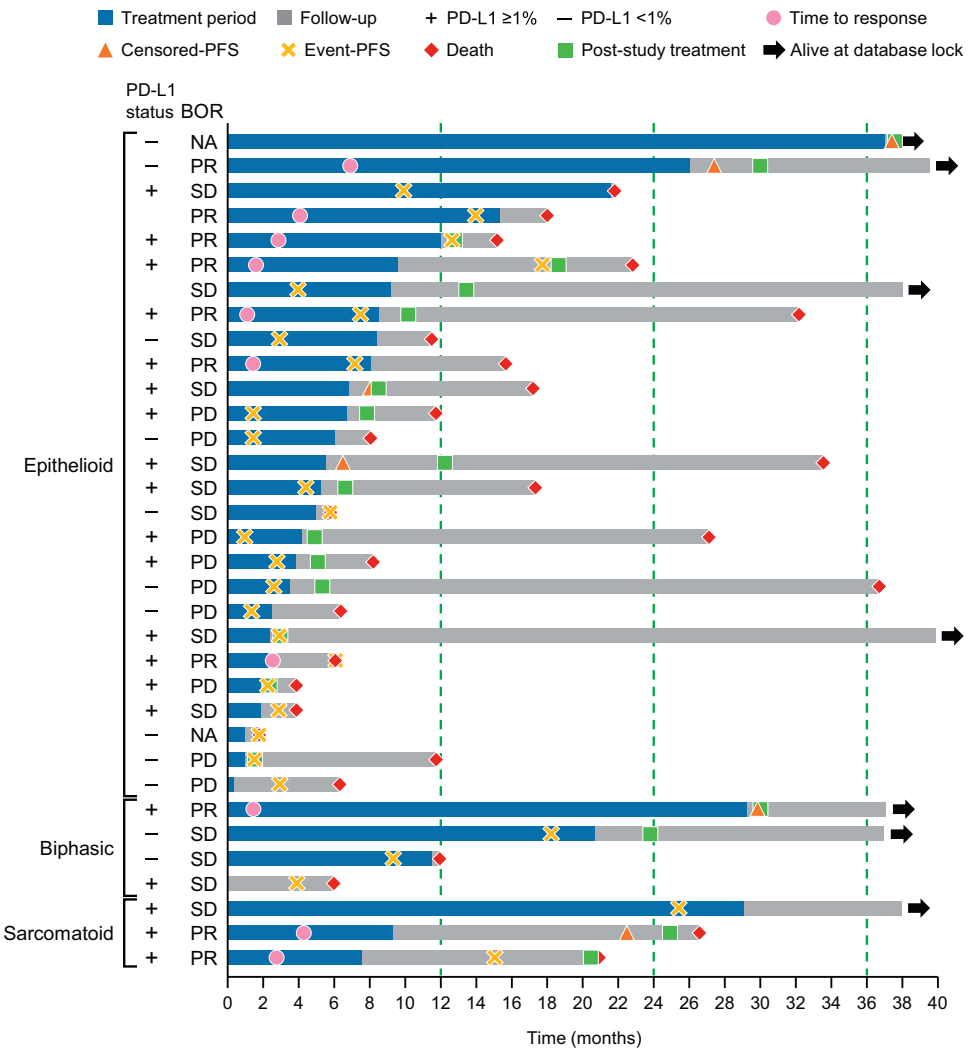

Figure 3. Swimmer plot of treatment duration, response to nivolumab, and follow-up period. BOR, best overall response; NA, not assessable; PD, progressive disease; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PR, partial response; SD, stable disease.

promising long-term survival of nivolumab-treated patients with a 3-year OS rate of 23.5%.

Although PD-L1 expression status was associated with the ORR, there were no significant differences in OS or PFS at 2 or 3 years between PD-L1–positive and PD-L1–negative patients. These results suggest that long-term survival in patients with nivolumab-treated MPM is not dependent on PD-L1 expression status. However, owing to the small number of patients, our findings may warrant confirmation in a future study with a larger number of patients or using a patient registry.

The histologic subtype of MPM is considered to be a prognostic factor for MPM, because patients with the biphasic or sarcomatoid histologic subtypes typically have worse prognosis after chemotherapy than patients with the epithelioid histologic subtype.[11,12] In the present analyses, the survival outcomes, especially PFS, were quite favorable in the patients with nonepithelioid subtypes. Furthermore, as in our previous report,[5] the ORR was also more favorable in patients with the nonepithelioid subtypes relative to that in patients with the epithelioid subtype. Thus, patients with nonepithelioid histologic subtypes tended to have better outcomes, although the reason for this is unknown. Further research is needed to investigate whether genomic alterations may explain the differences in survival with nivolumab between patients with nonepithelioid and epithelioid subtypes of MPM.

It is noteworthy that eight patients were alive at 3 years. There were no marked differences in patient characteristics between 3-year survivors and non-survivors except for ECOG PS at baseline.

Beyond assessing the efficacy of nivolumab in terms of tumor responses, we also examined its impact on QOL. We found that QOL, measured using the EQ-VAS and

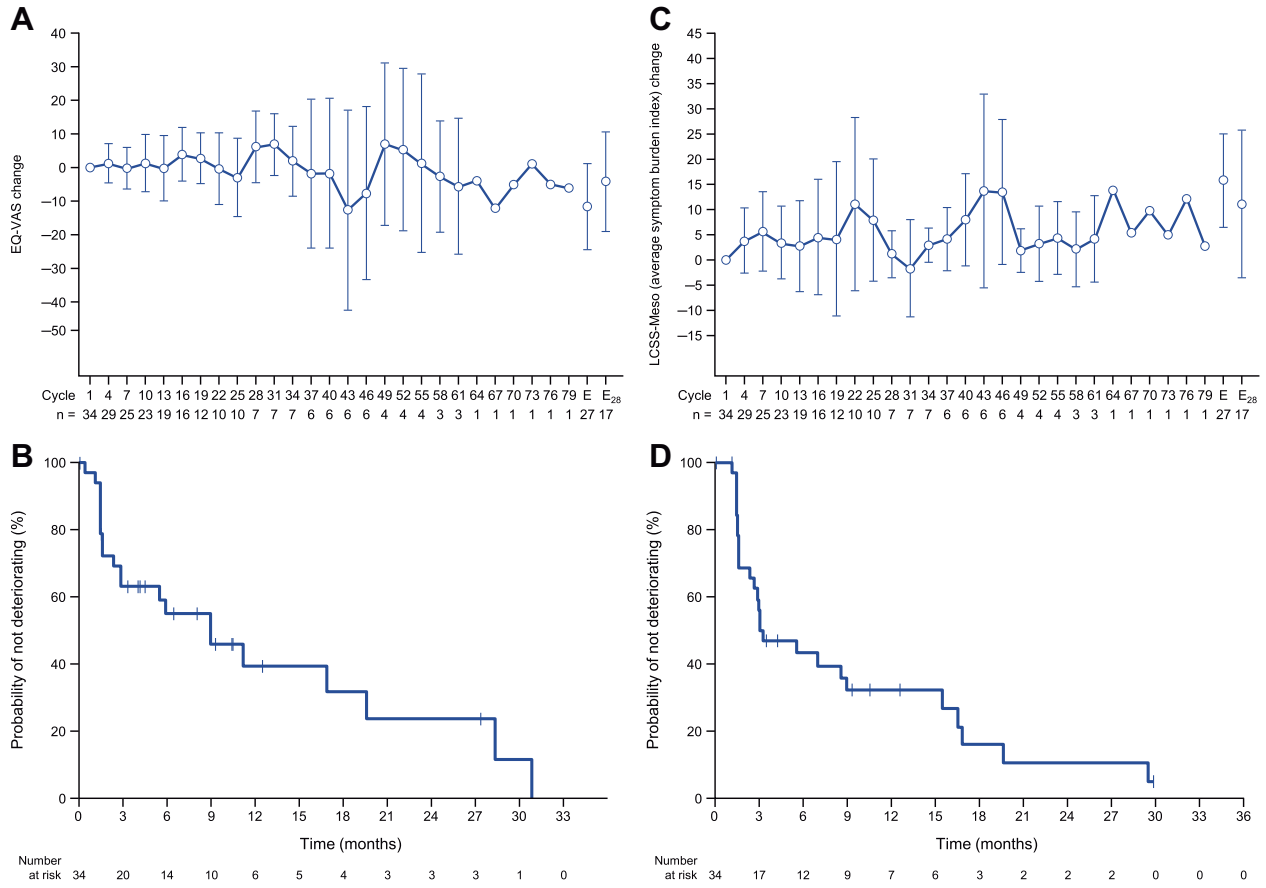

Figure 4. (*A*, *B*) Evolution of EQ-VAS and (*C*, *D*) LCSS-Meso average symptom burden index over time. Data are presented as means with 95% CIs. E, end of the treatment period (discontinuation); E_{28}, 28 days after the end of the treatment period; EQ-VAS, EuroQOL visual analog scale; LCSS-Meso, Lung Cancer Symptom Scale for mesothelioma.

LCSS-Meso symptom burden index, was maintained over time in this cohort of nivolumab-treated patients. The stability of QOL in nivolumab-treated patients observed here may reflect the potential clinical benefit of nivolumab in terms of long-term survival, especially in responders.

The MERIT study also monitored the safety of nivolumab in patients with MPM. Of note, despite the longer follow-up of patients in the present analyses, we detected no additional TRAEs (any grade or grades 3–4) since the previous cutoff date,[5,8] supporting the long-term safety of nivolumab in this patient population.

Another promising strategy for the treatment of MPM involves combining nivolumab with ipilimumab, a CTLA-4 antibody. This strategy was tested in the CheckMate 743 study, in which nivolumab plus ipilimumab significantly extended OS compared with chemotherapy (median: 18.1 versus 14.1 months, hazard ratio = 0.74, $p = 0.002$) with a median follow-up of 29.7 months.[13] Thus, this combination is expected to become a standard of care for MPM in the future. However, nivolumab monotherapy after second-line treatment may be useful for ICI-naive patients.

Our findings should be discussed in the context of the limitations of the study, notably the single-arm design and the sample size (34 patients). Furthermore, the subgroups included in the analyses of overall response and survival were small, which might introduce some bias because the study was not powered to detect differences among subgroups. Therefore, we must take care when generalizing the results to a broader population of patients treated with nivolumab in clinical practice, and our findings should be confirmed in future studies with more patients.

In conclusion, the 3-year follow-up of the MERIT study reveals the longer-term efficacy and safety of nivolumab with survival for more than 3 years in some patients and a clinical benefit as second- or third-line therapy for patients with MPM.

Data Availability

Qualified researchers may request Ono to disclose individual patient-level data from clinical studies through the following website: ClinicalStudyDataRequest.com. For more information on Ono's Policy for the Disclosure of

Table 2. TRAEs in Two or More Patients (N = 34)

AE	Any Grade	Grades 3-4
Any	26 (76.5)	11 (32.4)
Most common AEs by preferred term (in ≥2 patients)		
Rash	6 (17.6)	1 (2.9)
Lipase increased	5 (14.7)	4 (11.8)
Diarrhea	4 (11.8)	2 (5.9)
Amylase increased	4 (11.8)	2 (5.9)
Stomatitis	3 (8.8)	1 (2.9)
Weight decreased	3 (8.8)	1 (2.9)
Decreased appetite	3 (8.8)	1 (2.9)
Fatigue	3 (8.8)	0 (0.0)
Malaise	3 (8.8)	0 (0.0)
Arthralgia	3 (8.8)	0 (0.0)
Pneumonitis	2 (5.9)	2 (5.9)
Interstitial lung disease	2 (5.9)	1 (2.9)
Hypothyroidism	2 (5.9)	0 (0.0)
Nausea	2 (5.9)	0 (0.0)
Vomiting	2 (5.9)	0 (0.0)
Mucosal inflammation	2 (5.9)	0 (0.0)
Pyrexia	2 (5.9)	0 (0.0)
Lymphocyte count decreased	2 (5.9)	0 (0.0)
Rash maculopapular	2 (5.9)	0 (0.0)

Note: Data are presented as n (%).
AE, adverse event; TRAE, treatment-related AE.

Clinical Study Data, please see the following website: https://www.ono.co.jp/eng/rd/policy.html.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2020.100135.

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石綿関連胸膜疾患における個別化治療とケアの確立

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