資料No. 5

アストラゼネカ社が行ったINTACT　1試験、INTACT　2試験について

（これらの試験は日本で申請された効能と異なる効能の取得を目的として、アストラゼネカ社が海外で実施したものであり、ゲフィチニブを既存の非小細胞肺がんに用いられている抗がん剤と併用し、非小細胞肺がんの一次治療としての有効性等を確認しようとしたもので、試験結果の要旨は承認後に提出されたものである。）

1．INTACT　1

①　対象患者：化学療法未治療非小細胞肺がん患者

②　投与群

プラセボ群：ゲムシタビン、シスプラチン、プラセボ

２５０ｍｇ群：ゲムシタビン、シスプラチン、ゲフィチニブ 250mg/日

５００ｍｇ群：ゲムシタビン、シスプラチン、ゲフィチニブ 500mg/日

③　結果

生存期間中央値はプラセボ群：１１．１月、２５０ｍｇ群：９．９月、５００ｍｇ：９．９月で有意差は見られなかった。

2．INTACT　2

①　対象患者：化学療法未治療非小細胞肺がん患者

②　投与群

プラセボ群：パクリタキセル、カルボプラチン、プラセボ

２５０ｍｇ群：パクリタキセル、カルボプラチン、ゲフィチニブ 250mg/日

５００ｍｇ群：パクリタキセル、カルボプラチン、ゲフィチニブ 500mg/日

③　結果

生存期間中央値はプラセボ群：９．９月、２５０ｍｇ群：９．８月、５００ｍｇ群：８．７月で有意差は見られなかった。

注）INTACT 1、INTACT 2から得られる副作用等の情報は、承認審査の中で評価・検討している。

(参考)

10月21日の欧州臨床腫瘍学会発表要旨

A Phase III clinical trial of ZD1839 ('Iressa') in combination with gemcitabine and cisplatin in chemotherapy-naive patients with advanced non-small-cell lung cancer (INTACT 1)

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The orally administered EGFR-TKI (epidermal growth factor receptor tyrosine kinase inhibitor) ZD1839 ('Iressa'), which blocks signal transduction pathways implicated in proliferation and survival of cancer cells, has a mode of action distinct from cytotoxic agents. A phase I, feasibility study showed ZD1839 in combination with gemcitabine and cisplatin to have an acceptable tolerability profile and high activity (Giaccone et al. Eur J Cancer 2001; 37 Suppl 6; S30,102A). This combination was assessed in a randomized, double-blind, placebo-controlled, multicenter trial: 'Iressa' NSCLC Trial Assessing Combination Treatment 1 (INTACT 1). Chemo-naive patients with stage III/IV disease, performance status (PS) 0-2, age ≥18 years, were randomized to CT + placebo, CT + 250 mg/d or CT + 500 mg/d ZD1839. CT consisted of 6 cycles gemcitabine 1250 mg/m^2 on days 1 and 8, plus cisplatin 80 mg/m^2 on day 1. Treatment with ZD1839 or placebo could be continued until disease progression. The primary endpoint was overall survival, with the study powered to detect a 33% increase (equivalent to an absolute increase of 2.3 months). Secondary endpoints were progression-free survival and time to worsening of symptoms per LCS (Lung Cancer Subscale of the FACT-L). Other endpoints included symptom improvement, objective tumor response and disease control rate (CR + PR + SD), quality of life, and safety. A total of 1093 pts (M/F 805/288; median [range] age 61 [31-85] years, PS 0/1/2/unknown: 364/620/105/4, disease stage III(A)/III(B)/IV/unknown: 24/306/757/6, histology adeno/squamous/NOS: 512/328/253) were recruited from 165 sites worldwide. The three treatment groups were well balanced across all disease and demographic characteristics. **Results:** There were no statistically significant differences in overall survival (median [CI] 11.1 [10.1-11.9], 9.9 [8.7-10.8] and 9.9 [8.8-11.4] months for

placebo, 250 mg and 500 mg arms respectively), progression-free survival and time to worsening of symptoms across the three arms. The comparative hazard ratios (HR) between the treatment arms for overall survival were: placebo:250 mg, HR=0.91, (p=0.30); placebo:500 mg, HR=0.93, (p=0.44); 250 mg:500 mg, HR=1.02 (p=0.82). The toxicity profile of ZD1839 combined with CT was comparable to CT alone, with exception of additive, dose dependant diarrhea and skin rash. **Conclusions:** ZD1839 in combination with this two-agent chemotherapy regimen for advanced NSCLC did not improve treatment outcomes. However, the combination exhibited an acceptable toxicity profile without worsening of CT-associated toxicities, and, based on the results of monotherapy ZD1839 in refractory NSCLC, further study of ZD1839 is warranted in other settings.

'Iressa' is a trademark of the AstraZeneca group of companies

ZD1839 ('Iressa') in combination with paclitaxel & carboplatin in chemotherapy-naive patients with advanced non-small-cell lung cancer (NSCLC): results from a Phase III clinical trial (INTACT 2)

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ZD1839 ('Iressa') inhibits EGFR tyrosine kinase (TK) thereby interfering with signal transduction pathways implicated in proliferation and survival of cancer cells. The INTACT 2 (Iressa NSCLC Trial Assessing Combination Treatment) study is a randomized, double-blind, placebo-controlled trial of chemotherapy (CT) ± ZD1839 in patients (pts) with advanced NSCLC. Eligibility criteria included: unresectable stages III or IV disease; no prior therapy; age ≥18 years; PS 0-2. Pts were randomized to CT + placebo, CT + 250 mg/d or CT + 500 mg/d of ZD1839. CT consisted of carboplatin (AUC=6) + paclitaxel (225 mg/m^2) every 3 wks for 6 cycles after which pts were continued on ZD1839 or placebo until disease progression (PD). The primary objective was overall survival (OS), with the study powered to detect a 33% increase (equivalent to an absolute increase of 2.3 months). Secondary endpoints included: progression-free survival (PFS) & time to worsening of disease-related symptoms (assessed using the lung cancer subscale [LCS] of FACT-L). Additional endpoints of interest included symptom improvement (per LCS), objective response rate, disease control rate (SD + responders), quality of life, & adverse event profiling. A total of 1037 pts were enrolled from 200 sites worldwide but predominantly in the USA. Study participants had the following characteristics: M/F = 619/418; median age = 62 yrs (range: 26-86); WHO PS 0/1/2/unk = 367/554/114/2; stage IIIA/IIIB/IV/unk = 30/168/834/5; & histology adeno/squamous/NOS = 602/195/240. The demographic & disease characteristics were well balanced across the three treatment groups. **Results:** Overal survival (median [CI] = 9.9 [8.9-11.1], 9.8 [8.4-10.6] and 8.7 [8.0-10.3] months for placebo, 250 mg and 500 mg arms respectively), PFS & time to worsening of symptoms were not statistically significantly increased in the ZD1839 arms compared to placebo. Hazard ratios (HR) for overall survival

comparing treatment arms were as follows: placebo:250 mg, HR= 1.04 (p=0.67); placebo:500 mg, HR= 0.96 (p=0.64); 250 mg:500 mg, HR=0.93 (p=0.43). **Conclusions:** As employed in this trial, ZD1839 + CT failed to effect a survival improvement in advanced NSCLC. However, the combination of ZD1839 + CT exhibited an acceptable toxicity profile without worsening of common CT-associated toxicities. Only diarrhea & skin rash were seen at a higher rate in ZD1839 treated pts. These toxicities were dose dependent. Based on the results of monotherapy ZD1839 in refractory NSCLC, further study of ZD1839 is warranted using alternative strategies.