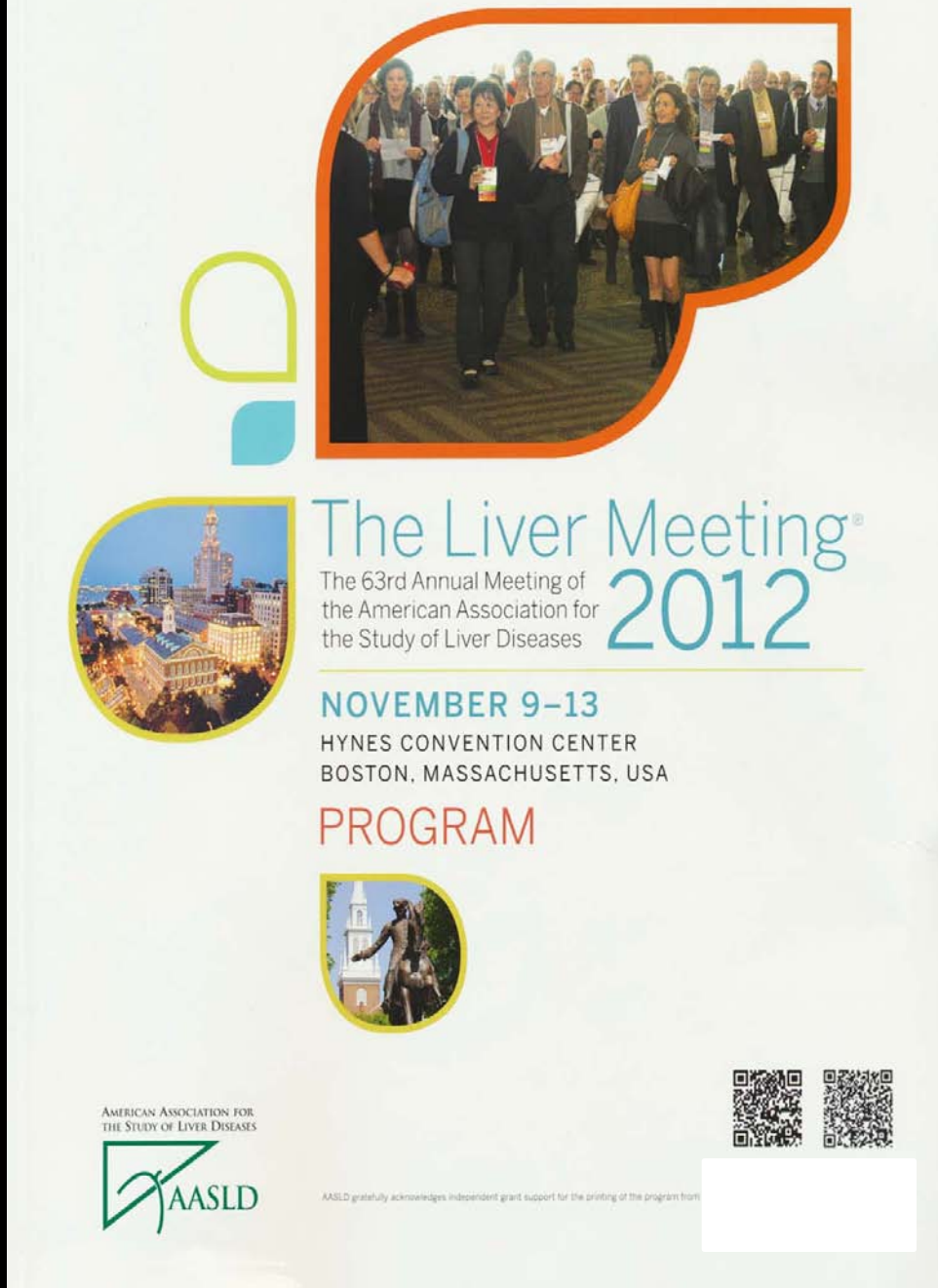
米国肝臓学会2012の最新の報告（B型肝炎）

国立病院機構長崎医療センター
八橋　弘



AASLD 2012 HBVまとめ

◆Sequential, Add on療法

- 216 ：*Q Ning. et al.*
- 19 ：*Sonneveld M. J. et al.*
- 430 ： *Zhongwen* Wu . et al.
- 465 ： *Ouzan D. et al. Abstract*
- 1857(T-cell)： *Sprinzl M. F. et al.*

◆核酸アナログ投与中の発癌

- 357(虎の門) ： *Tetsuya Hosaka et al.*
- 416(大阪大学)：*Ryoko Yamada et al.*
- 438(川崎病院)：*Miwa Kawanaka et al.*

◆New Compounds

- *LB-14* ：*Chan H. L.-Y. et al.*
- *424* : *Mamun A Mahtab.et al*

エンテカビル-PegIFNα2a Sequential療法

216：*Q Ning. et al.*

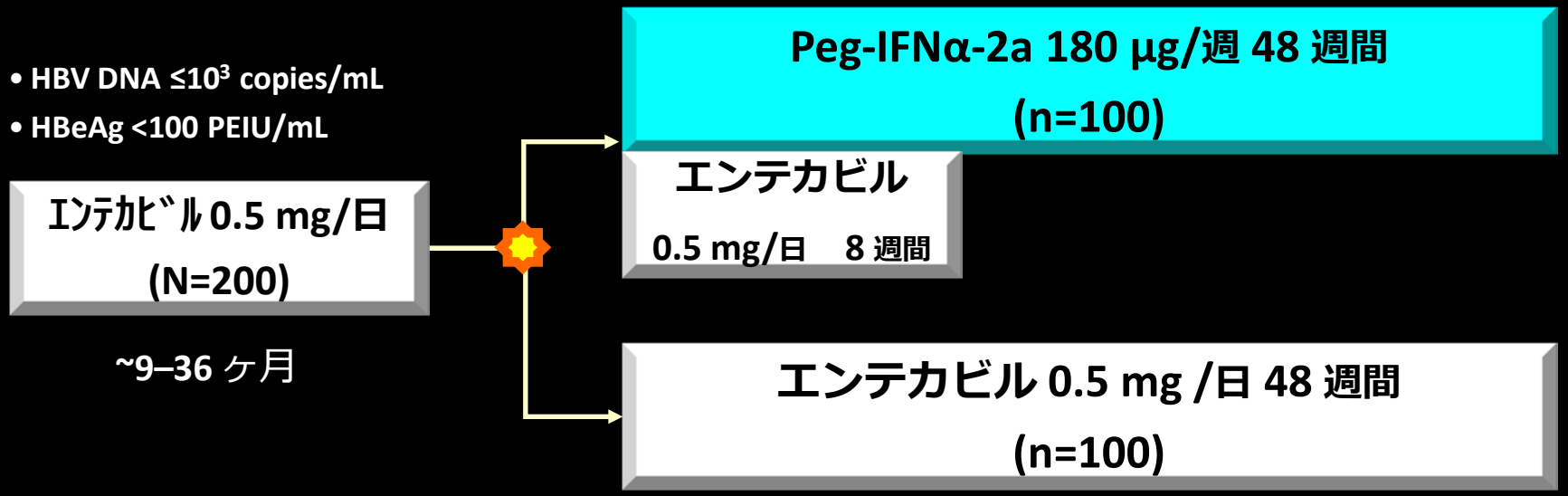
Presidential Plenary:Viral Hepatitis

New treatment strategy: switching from long-term entecavir to peginterferon alfa-2a induces HBeAg seroconversion/HBsAg clearance in patients with HBeAg-positive chronic hepatitis B

(The OSST study)

The OSST study デザイン
(エンテカビル-PegIFNα2a Sequential療法)

- 多施設無作為化オープン試験
- 主要評価項目: eセロコンバージョン (48週治療終了時)
- 副次的評価項目: S抗原消失(48週治療終了時)



ETV = エンテカビル; Peg-IFNα-2a = ペグインターフェロン アルファ2a
PEIU = validated with in-house reference standards obtained from Paul Ehrlich Institute.

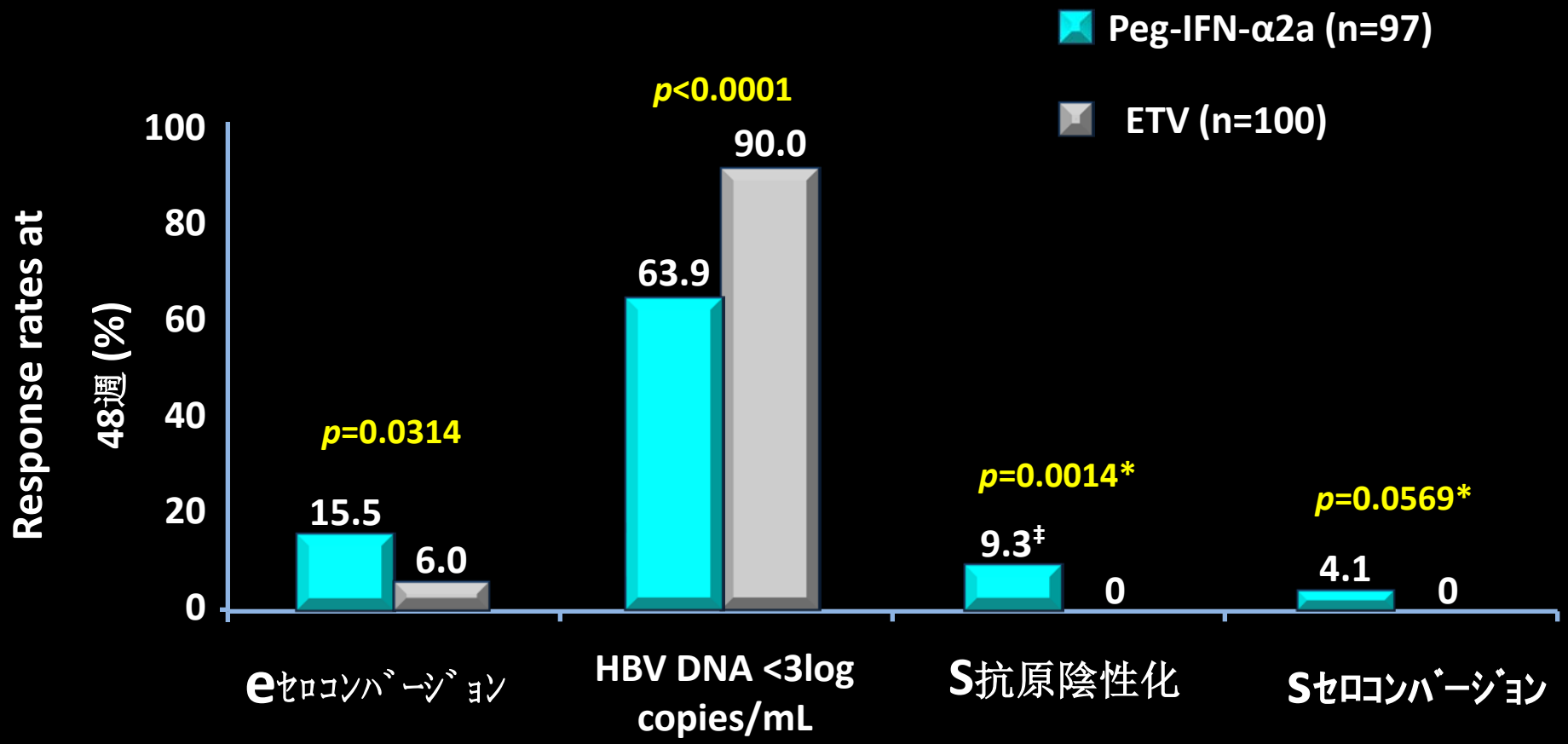
AASLD 2012 o-216：Q Ning. et al.

患者背景

		PegIFNα2aα2a (n=97)	ETV (n=100)
性別（男性）	n(%)	78(80.4)	87(87.0)
年齢（歳）	平均値(SD)	33.2(8.2)	33.2(8.9)
人種（アジア人）	n(%)	97(100)	100(100)
BMI（kg/m^2）	平均値(SD)	22.9(2.7)	22.9(2.9)
EVT事前投与期間（月）	平均値(SD)	19.7(8.2)	20.4(8.4)
HBsAg量（log_{10} copies/mL）	平均値(SD)	3.3(0.5)	3.3(0.5)
HBV DNA量（log_{10} copies/mL）PCR	平均値(SD)	3.0(0.1)	3.0(0.0)
ALT（U/L）	平均値(SD)	27.5(21.3)	24.2(13.6)
HBeAg（PEIU/mL）	平均値(SD)	15.6(48.0)	7.5(19.9)
HBe抗原陰性化	n(%)	54(55.7)	52(52.0)

AASLD 2012 o-216：Q Ning. et al.

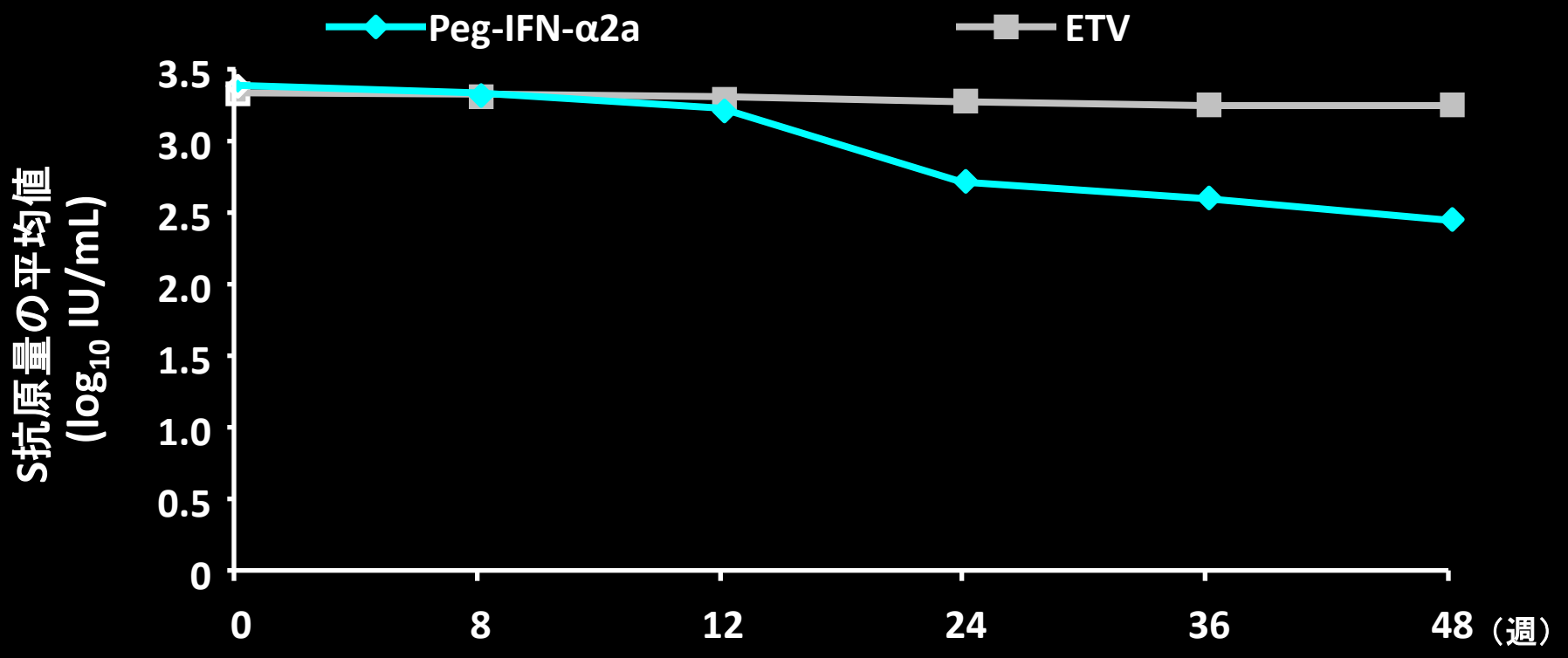
48週時の治療効果
(ITT解析集団)



*Fisher Exact test, other p-values are using Chi-Squared Test
‡Updated data from time of abstract submission
ITT = intention-to-treat

AASLD 2012 o-216：*Q Ning. et al.*

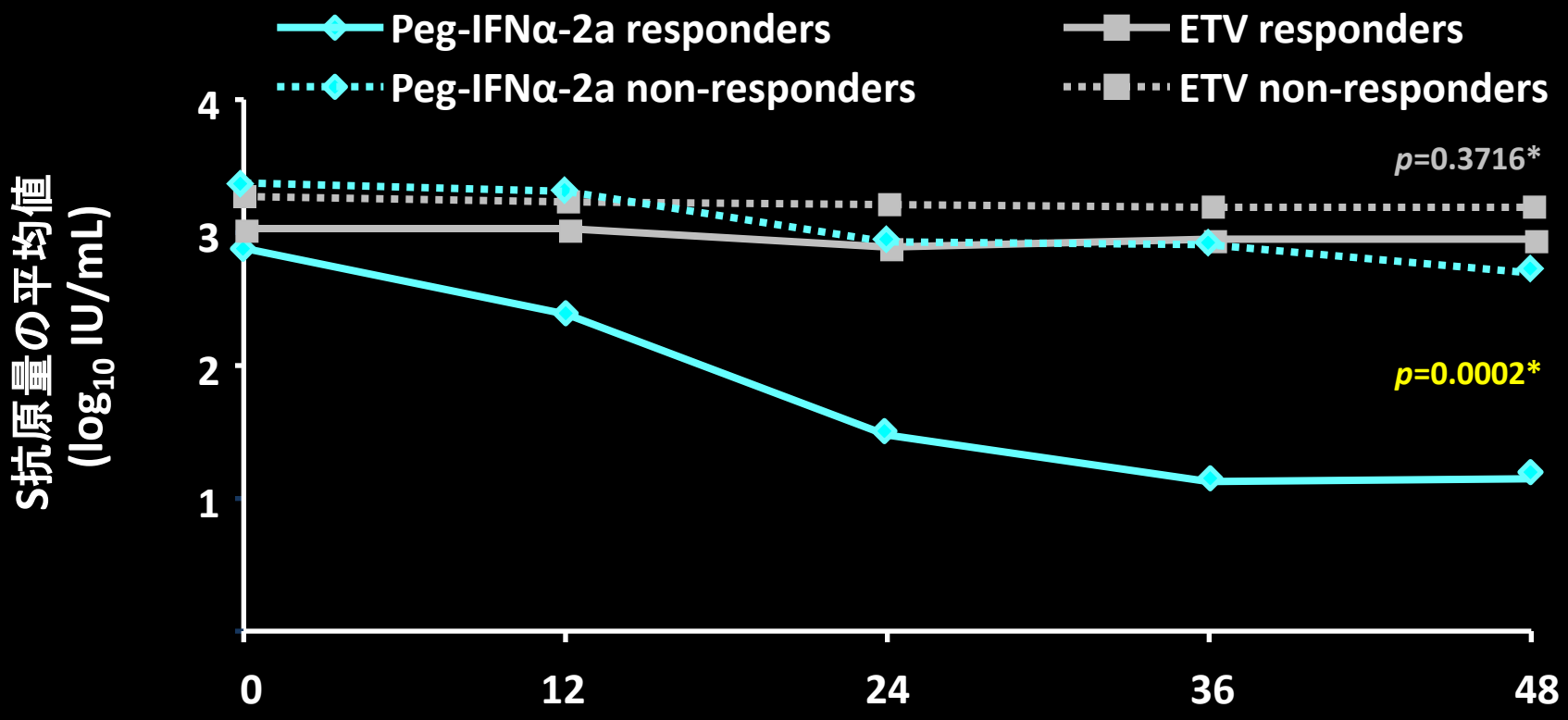
S抗原量（中央値）の推移



No. of patients						
Peg-IFNα2a	93	93	94	91	88	85
ETV	95	97	97	97	94	92

AASLD 2012 o-216：Q Ning. et al.

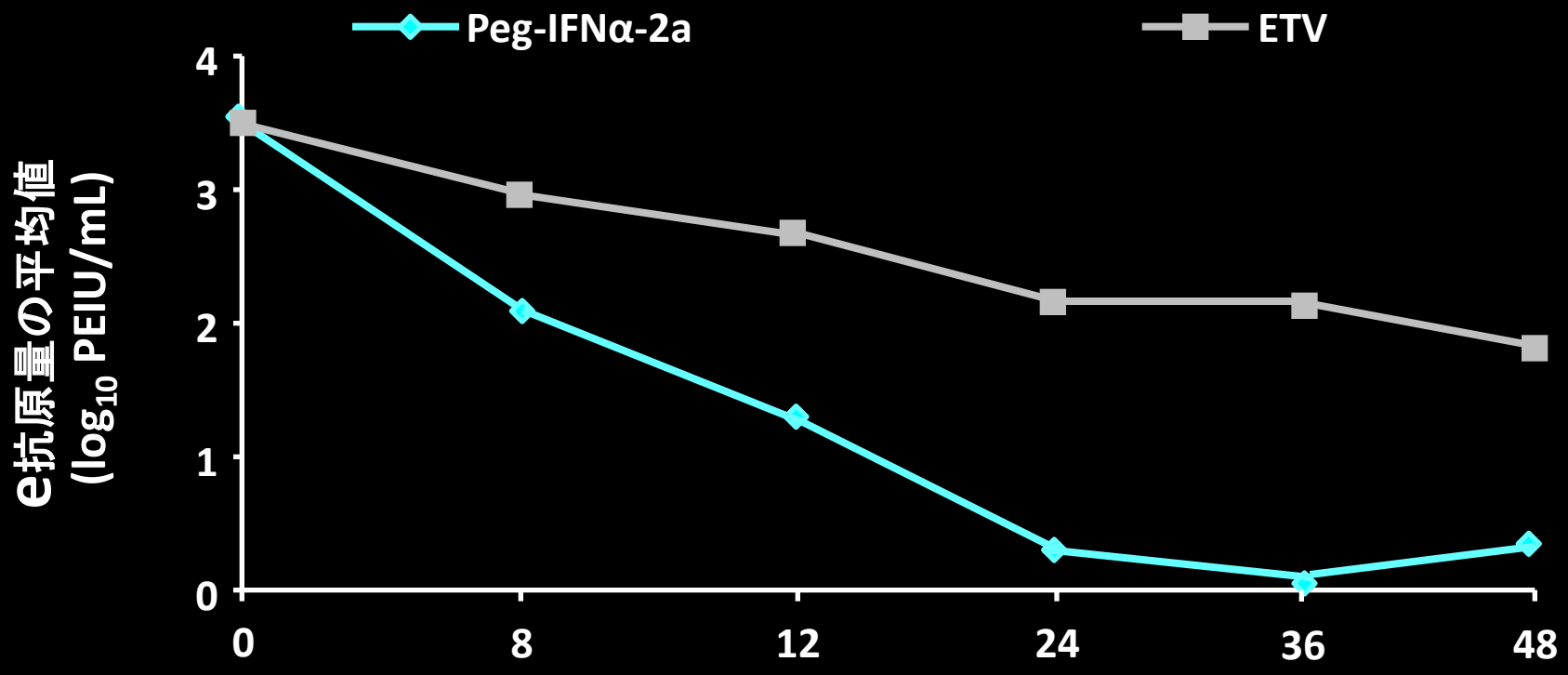
eセロコンバージョン反応別S抗原量推移



患者数(eセロコンバ-ジョン達成/未達成)					
Peg-IFNα-2a	13/80	15/79	15/76	15/72	13/70
ETV	6/89	6/91	6/91	6/88	6/86

AASLD 2012 o-216：*Q Ning. et al.*

e抗原量（平均値）の推移



患者数						
Peg-IFNα-2a	93	93	94	91	88	85
ETV	95	97	97	97	94	92

*p-value at week 48
*p-value for responders versus non-responders at week 48

AASLD 2012 o-216：*Q Ning. et al.*

重篤な有害事象用量変更・中止

	PegIFNα2a (n=97)	ETV (n=100)
中止,n(%)		
安全性による中止	8(8.3)	0
その他の理由による中止	7(7.2)	7(7.0)
用量変更,n(%)		
合計	14(14.4)	0
有害事象	3(3.1)	0
臨床検査値異常	13(13.4)	0
1つ以上の有害事象発生,n(%)	67(69.1)	5(5.0)
1つ以上の重篤有害事象発生,n(%)	6(6.2)	0
死亡	0	0
ALT flare	10(10.3)	0
ALTの最大値		
<1×ULN	15(15.5)	73(73.0)
1-5×ULN	72(74.2)	27(27.0)
5-10×ULN	10(10.3)	0
>10-×ULN	0	0

AASLD 2012 o-216：Q Ning. et al.

エンテカビル-PegIFNα2a Sequential療法

216：*Q Ning. et al.*

Presidential Plenary:Viral Hepatitis

New treatment strategy: switching from long-term entecavir to peginterferon alfa-2a induces HBeAg seroconversion/HBsAg clearance in patients with HBeAg-positive chronic hepatitis B

(The OSST study)

Conclusion:

Patients with maintained virological response on ETV who switch to a fine course ofPegIFNα-2a achieve significantly higher rates of HBeAg seroconversion /HBs Ag clearance than continuing on ETV. HBeAg loss + HBsAg<3000 IU/mL at baseline resulted in high rate Of HBsAg clearance(19%)

Hepatology 300A 2012

エンテカビル-PegIFNα2a Add on療法

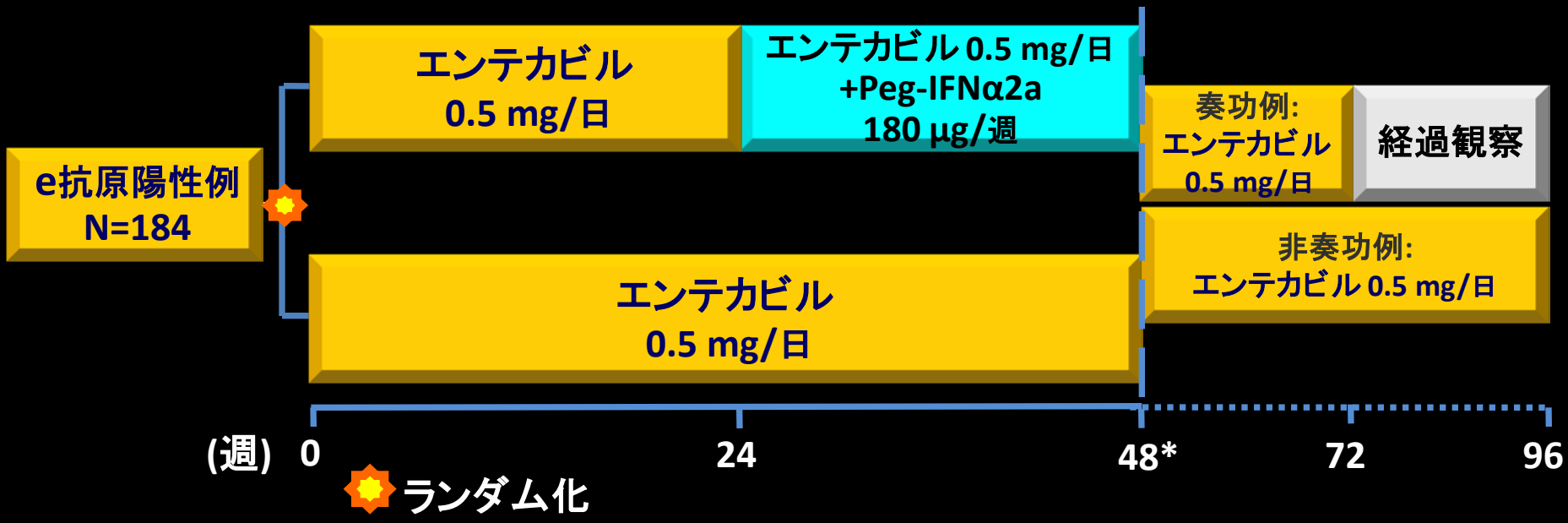
19 : *Sonneveld M. J. et al.*

Parallel 2 : HBV treatment and Clinical Trials

- Adding peginterferon alfa-2a to entecavir increases HBsAg decline and HBeAg clearance - first results from a global randomized trial (ARES study)

AASLD 2012 o-19 : Sonneveld M J et al,

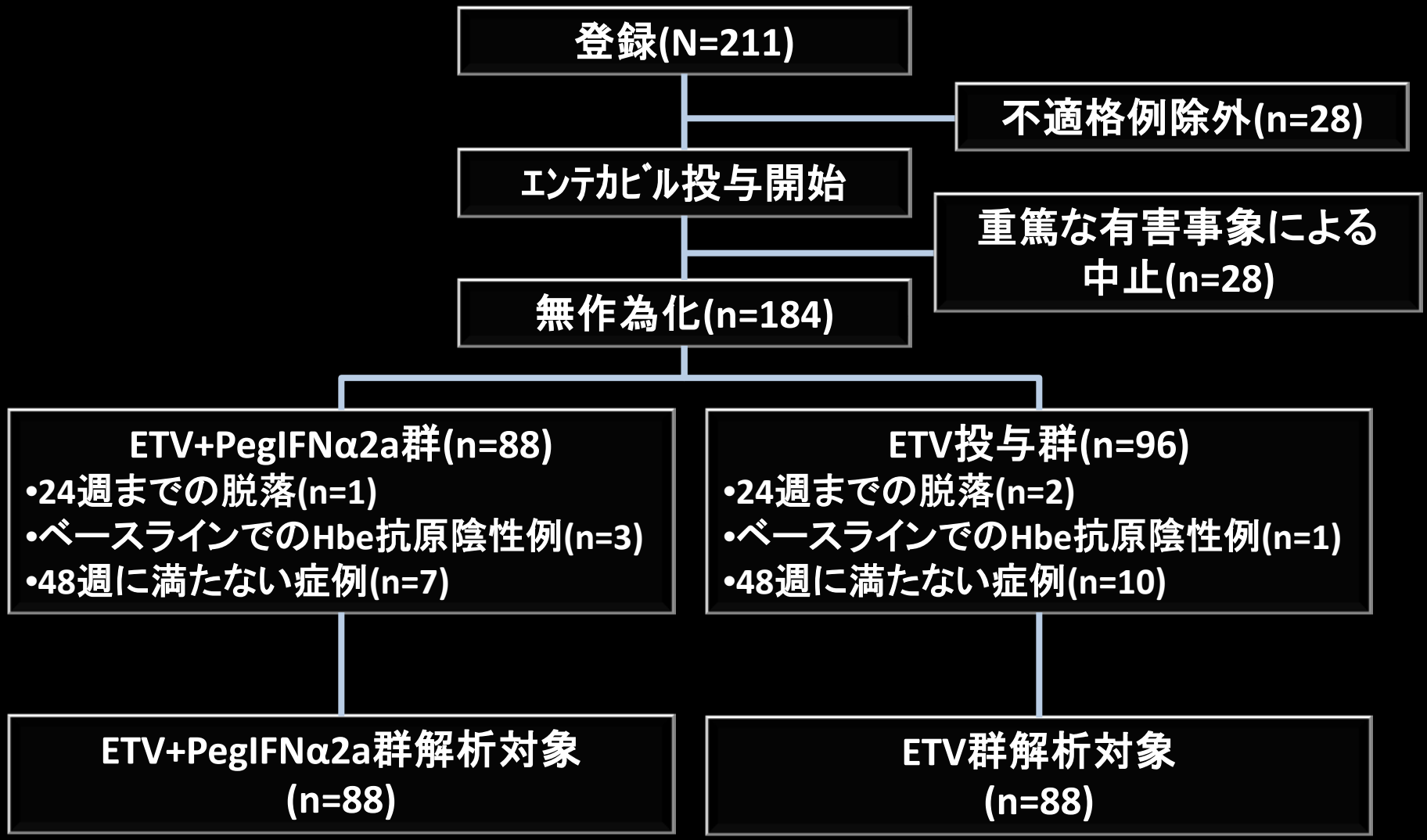
ARES study デザイン
(エンテカビル-PegIFNα2a Add on療法)



- 医師主導多施設無作為化比較試験(15 施設: ヨーロッパと中国)
- *48週時奏功例は72週以降エンテカビルを中断
  (奏功例:e抗原消失かつ HBV DNA <200 IU/mL)

AASLD 2012 o-19：*Sonneveld M J et al,*

方法



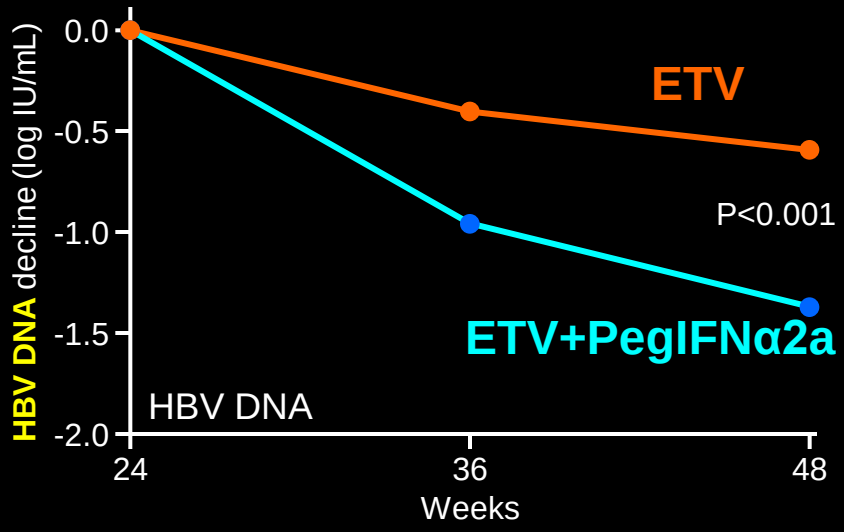
AASLD 2012 o-19：Sonneveld M J et al,

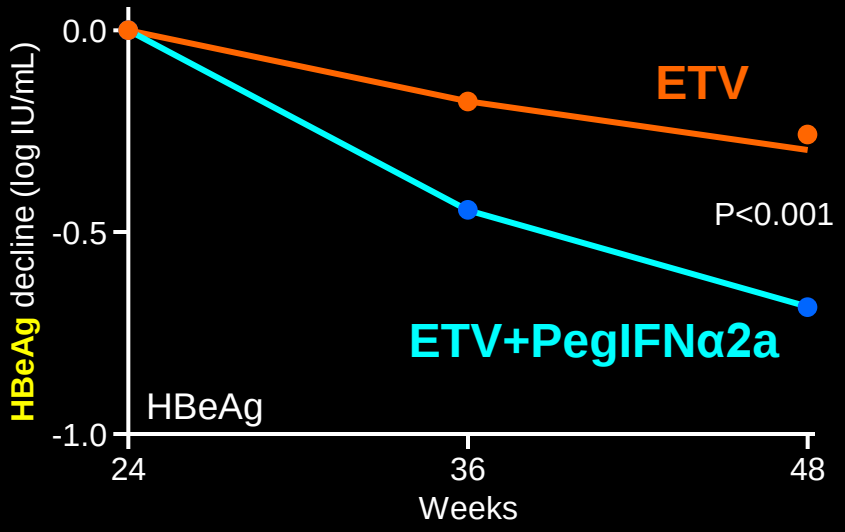
患者背景

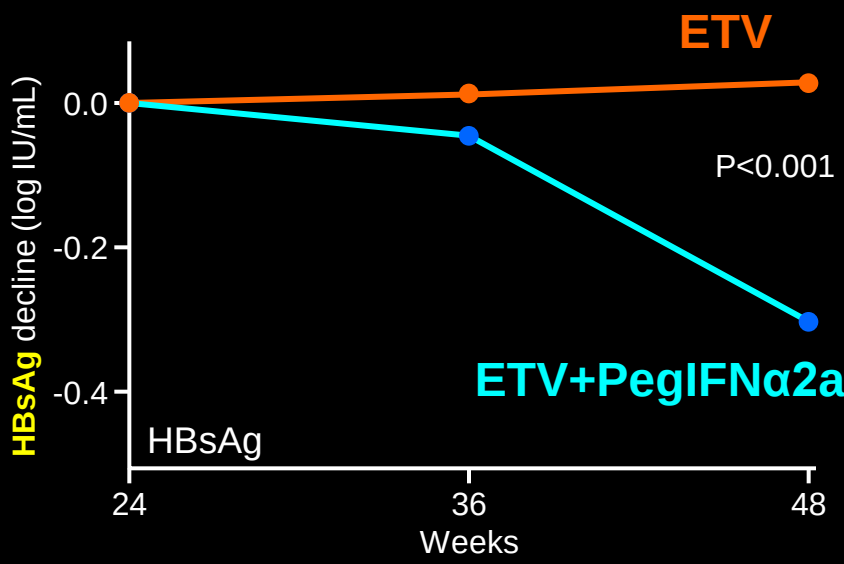
		ETV+PegIFNα2a群 (n=77)	ETV群 (n=83)
人口統計	男性,n(%)	58(76)	55(66)
	平均年齢(SD),歳	32.9(10)	31.9(9.3)
人種	アジア人,n(%)	47(61)	50(60)
	白人,n(%)	28(36)	32(39)
	その他,n(%)	2(3)	1(1)
臨床検査値	平均ALT×ULN(SD)	3.2(3.4)	2.7(2.0)
	平均HBVDNA量(SD)	7.7(1.4)	7.6(1.3)
	平均HBe抗原量(SD)	2.4(1.0)	2.2(1.0)
	平均HBs抗原量(SD)	4.3(0.7)	4.0(0.9)
HBV genotype	A,n(%)	4(5)	9(11)
	B,n(%)	17(22)	11(13)
	C,n(%)	30(39)	39(47)
	D,n(%)	26(34)	24(29)

AASLD 2012 o-19：Sonneveld M J et al,

無作為化後の HBV DNA量, HBe抗原量 , HBs抗原量の推移

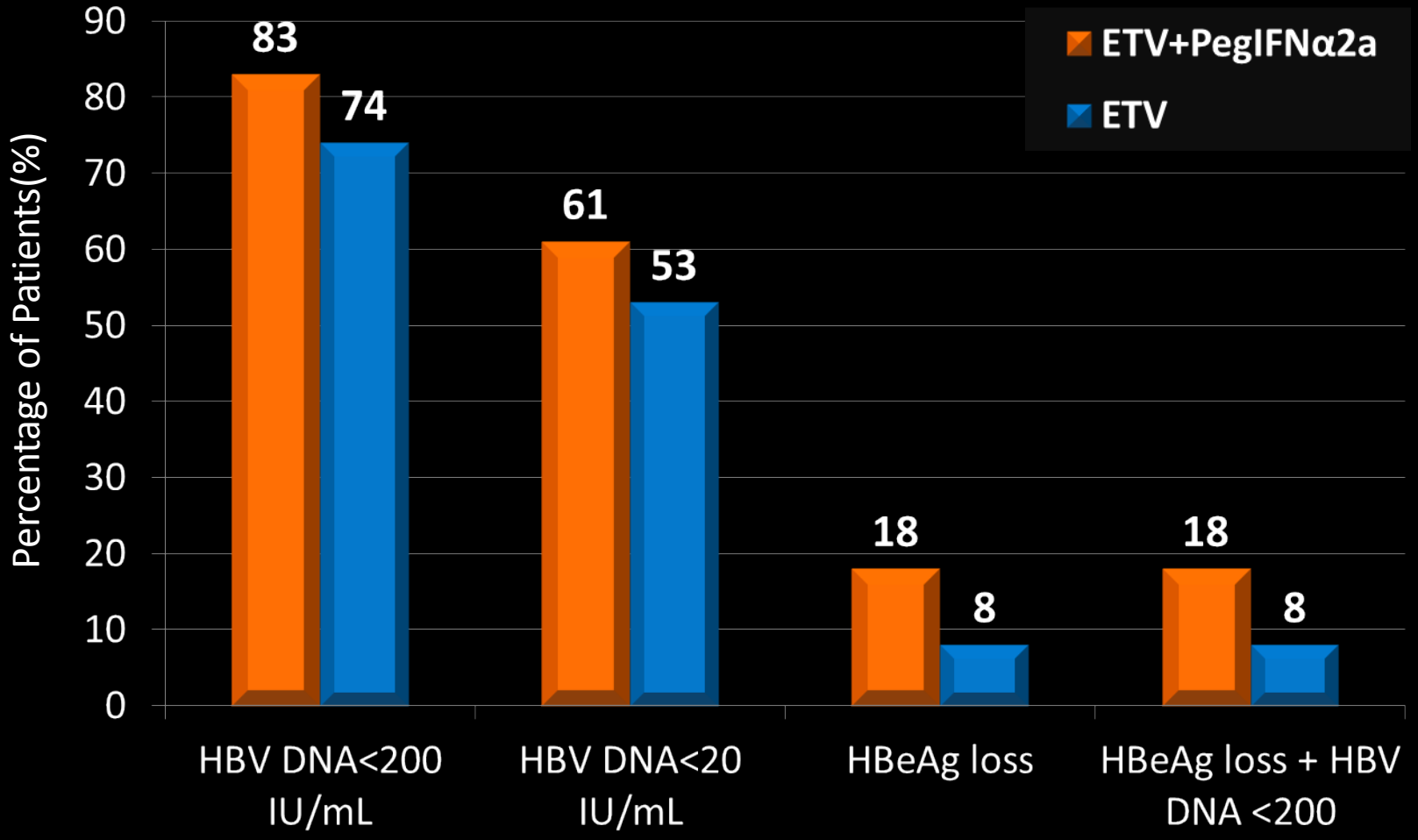






AASLD 2012 o-19：Sonneveld M J et al,

ウイルス学的効果（48週）



AASLD 2012 o-19：Sonneveld M J et al,

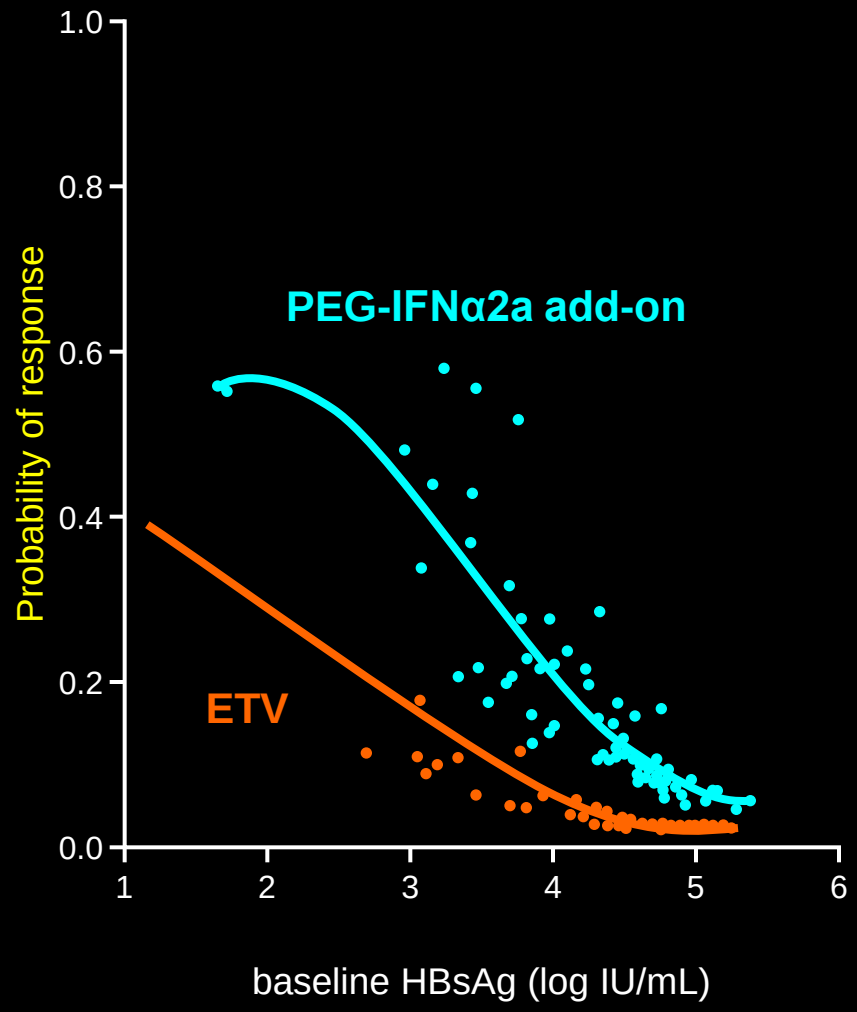
奏功に関連する因子

		OR(95% CI)	P
HBV genotype	(A/B vs C/D)	1.98(0.75-5.18)	0.166
性別	(男性 vs女性)	0.96(0.35-2.64)	0.931
人種	(アジア人 vs その他)	1.35(0.51-3.55)	0.544
0週時ALT	(×ULN)	1.04(0.90-1.21)	0.567
0週時HBV DNA	(log IU/ml)	0.69(0.51-0.93)	0.016
0週時HBe抗原量	(log IU/ml)	0.57(0.37-0.86)	0.008
0週時HBs抗原量	(log IU/ml)	0.46(0.28-0.76)	0.003
治療	(PegIFNα2a add-on vs ETV)	2.41(0.92-6.34)	0.068

AASLD 2012 o-19：Sonneveld M J et al,

PEG-IFN alfa-2a add-on therapy and lower HBsAg are independently associated with response

Variable	OR (95% CI)	p
HBV DNA week 0	1.10 (0.66-1.84)	0.708
qHBeAg week 0	0.59 (0.32-1.08)	0.084
qHBsAg week 0	0.42 (0.22-0.80)	0.009
PEG-IFN add-on	3.78 (1.27-11.2)	0.012



AASLD 2012 o-19 : Sonneveld M J et al,

エンテカビル-PegIFNα2a Add on療法

19 : *Sonneveld M. J. et al.*

Parallel 2 : HBV treatment and Clinical Trials

- Adding peginterferon alfa-2a to entecavir increases HBsAg decline and HBeAg clearance - first results from a global randomized trial (ARES study)

Conclusion:

A 24 week add-on PEG-IFN treatment increases HBsAg decline And clearance of HBeAg and may therefore improve the chances of finite treatment in HBeAg positive CHB patients treated with ETV.

Hepatology 199A 2012

AASLD 2012 o-19 : Sonneveld M J et al,

エンテカビル投与中の発癌

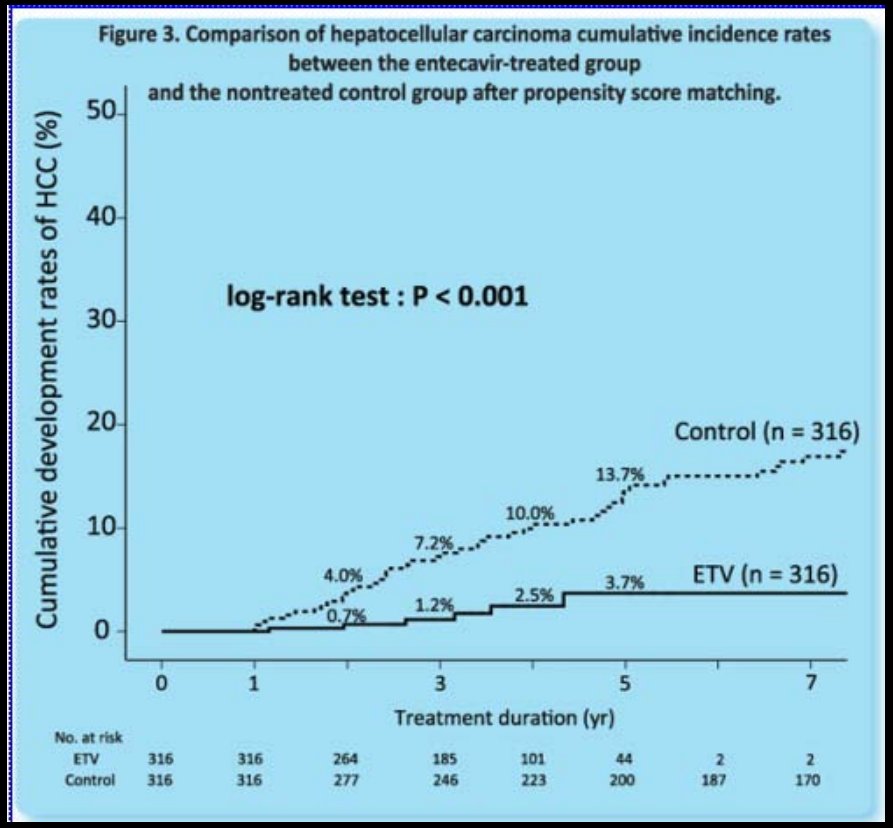
357(虎の門病院) ： *Tetsuya Hosaka et al.*

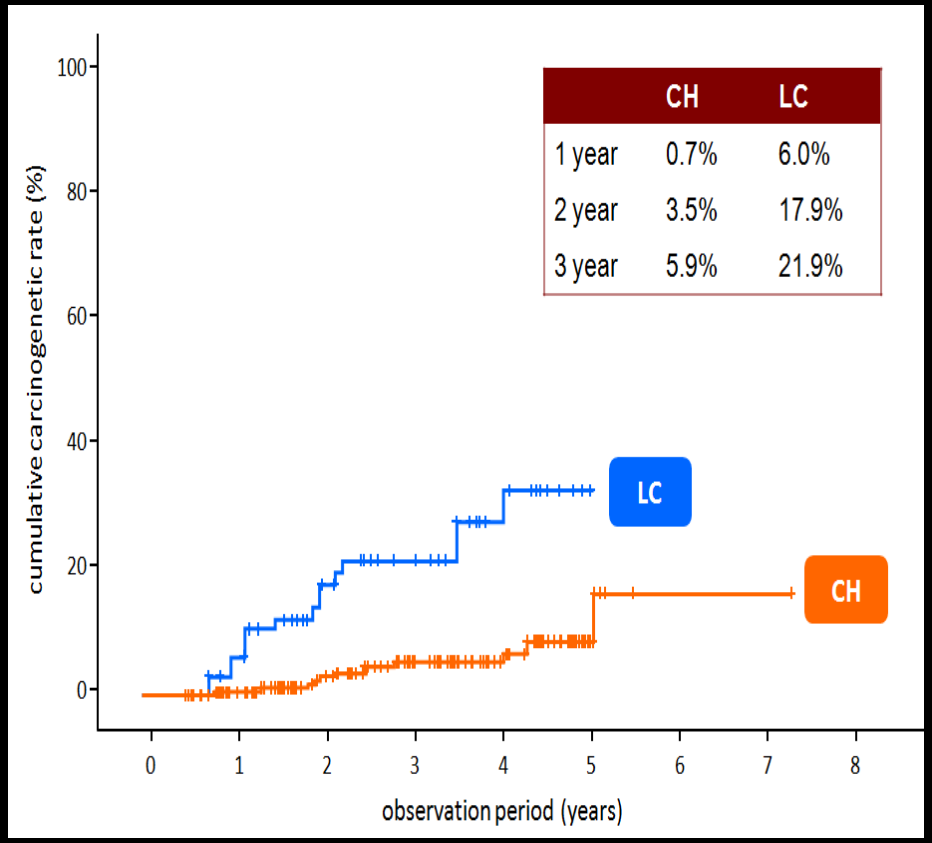
Long-term entecavir treatment reduces hepatocellular carcinoma incidence in patients with chronic hepatitis B

416(大阪大学)：*Ryoko Yamada et al.*

Suppressive effect of Entecavir therapy on incidence of hepatocelllular carcinoma in nucleotide analogue naïve patients with chronic hepatitis B

エンテカビル投与中の発癌

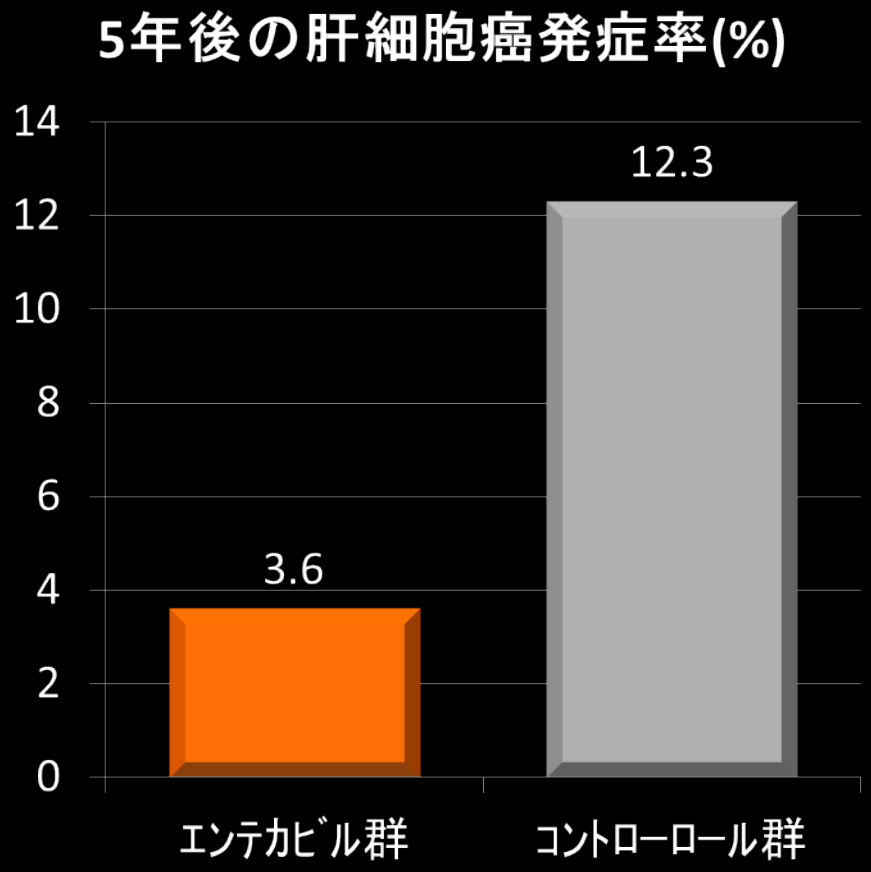




357(虎の門病院)： *Tetsuya Hosaka et al.*

416(大阪大学)：*Ryoko Yamada et al.*

エンテカビル投与中の発癌



・発癌に影響を及ぼす因子について調整後、多変量解析を行った結果 エンテカビル群はHCCの発症がコントロール群に比べ少ないことが示された。
(hazard ratio: 0.40; 95% CI: 0.21 to 0.76; P = 0.005).
HCC発症のリスクが高い集団ほどエンテカビルによるHCC発症のRiskの低下がみられた。

AASLD 2012 357 abstract： *Tetsuya Hosaka et*

Long-term ETV treatment reduces HCC incidence in patients with HBV infection

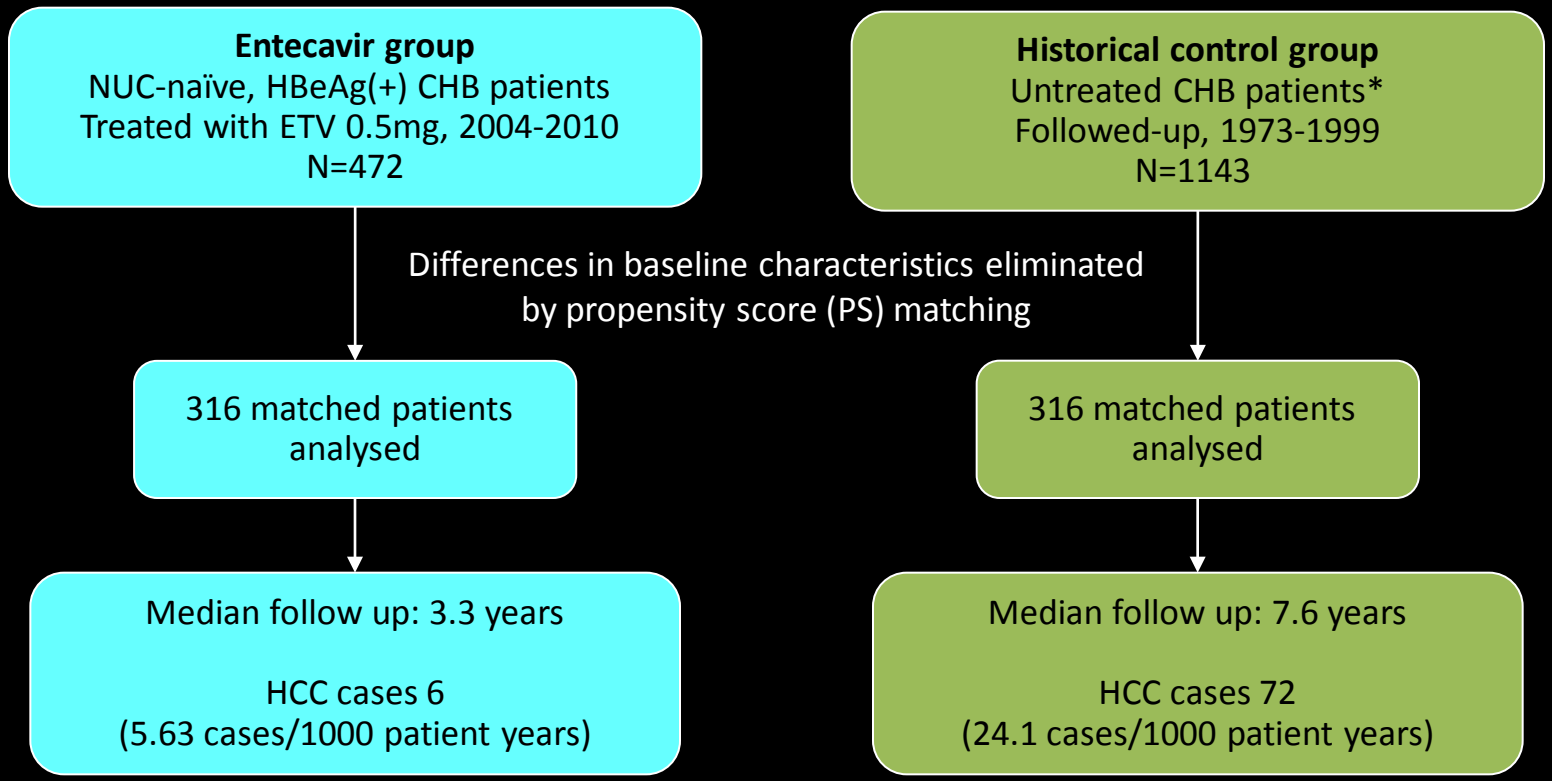
Hosaka, T, Suzuki F, Kobayashi M, Seko Y, Kawamura Y, Sezaki H, Akuta N, Suzuki Y, Saitoh S, Arase Y, Ikeda K, Kobayashi M, Kumada H

AASLD 2012, poster 357

Toranomon Hospital, Tokyo, Japan

Toranomon Hospital cohort: effect of ETV on HCC development

- Retrospective cohort study from Toranomon Hospital, Tokyo, Japan
- Aim: to compare HCC outcomes with ETV vs no NUC therapy



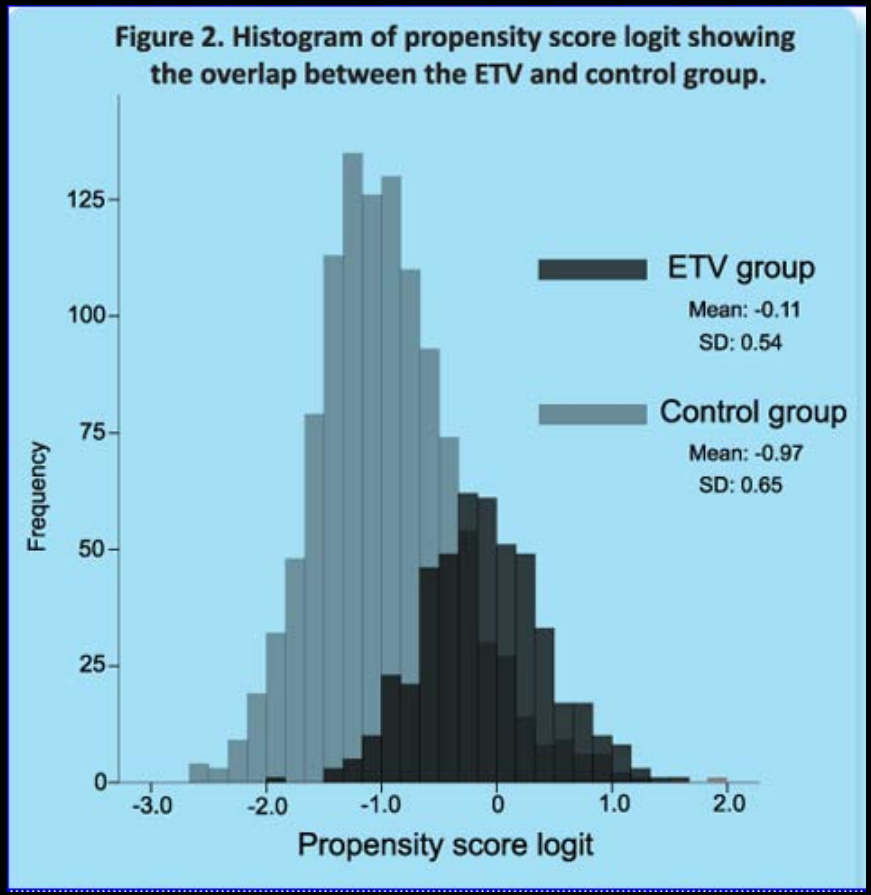
*Nucleos(t)ide analoges not available at this time in Japan

Hosaka T, et al. AASLD 2012; abstract 357.

Toranomon Hospital cohort: propensity score matched control group

Propensity score (PS) matching

- Multiple logistic regression
- Variables
  - Age, Sex, Pre-existing cirrhosis, HBeAg, HBV DNA, AST, ALT, γGTP, Bilirubin, Albumin, Platelet counts
- Pairs on PS logit matched to within 0.2 SD



Hosaka T, et al. AASLD 2012; abstract 357.

Toranomon Hospital cohort: selected baseline characteristics

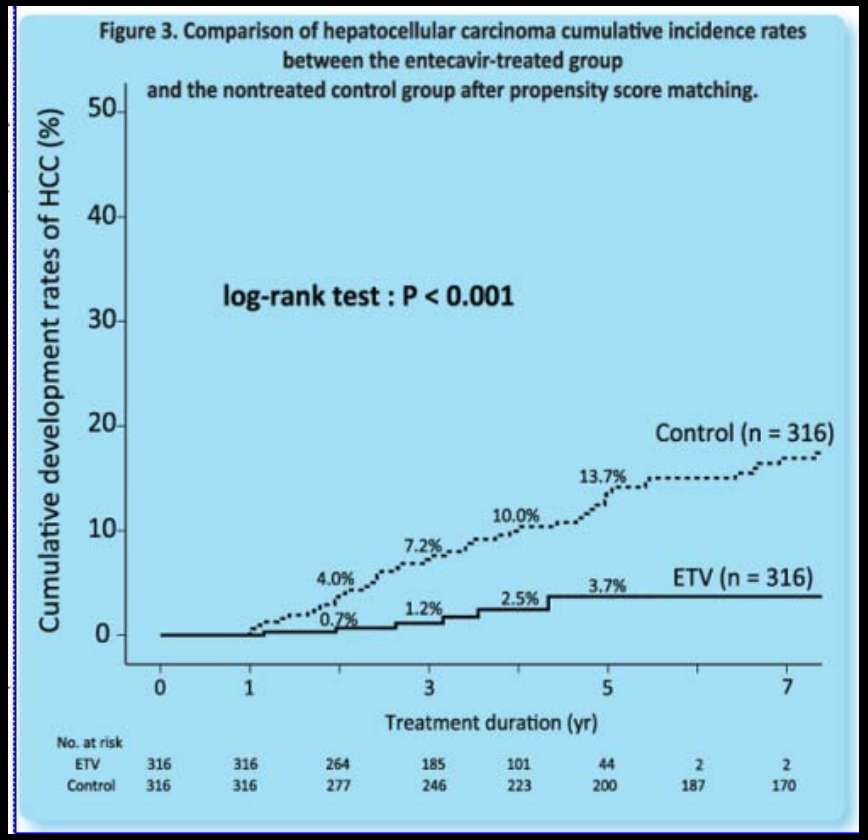
	Entire cohort			PS matched cohort*		
	ETV (N=472)	Control (N=1143)	P	ETV (N=316)	Control (N=316)	P
Age (mean, years)	47	39	<0.001	46	46	0.907
Male (n)	315	720	0.171	210	210	1.000
Cirrhosis (n/%)	116 (25)	311 (19)	0.001	79 (25)	85 (29)	1.000
HBV genotype (n/%)	-	-	<0.001	-	-	0.843
A	12 (3)	41 (4)	-	8 (2.5)	9 (2.8)	-
B	66 (14)	188 (16)	-	49 (15.5)	50 (15.8)	-
C	344 (73)	791 (69)	-	225 (71.2)	226 (71.5)	-
D	0 (0)	1 (1)	-	0	0	-
Other/missing	50 (11)	122 (10)	-	34 (10.7)	31 (9.8)	-
HBeAg(+)	219 (46)	398 (35)	<0.001	135 (43)	133 (42)	0.936
HBV DNA (log_{10} copies/mL)	6.7	5.8	<0.001	6.3	6.6	0.795
ALT (IU/L)	70	33	<0.001	61	60	0.101

*Differences in baseline characteristics were eliminated by Propensity Score matching on age, sex, presence of cirrhosis, HBeAg status, HBV DNA, AST, ALT, γGTP, bilirubin, albumin, platelet count

ALT, alanine aminotranferease; AST, aspartate aminotransferase.

Hosaka T, et al. Hepatology, 2012, manuscript accepted.

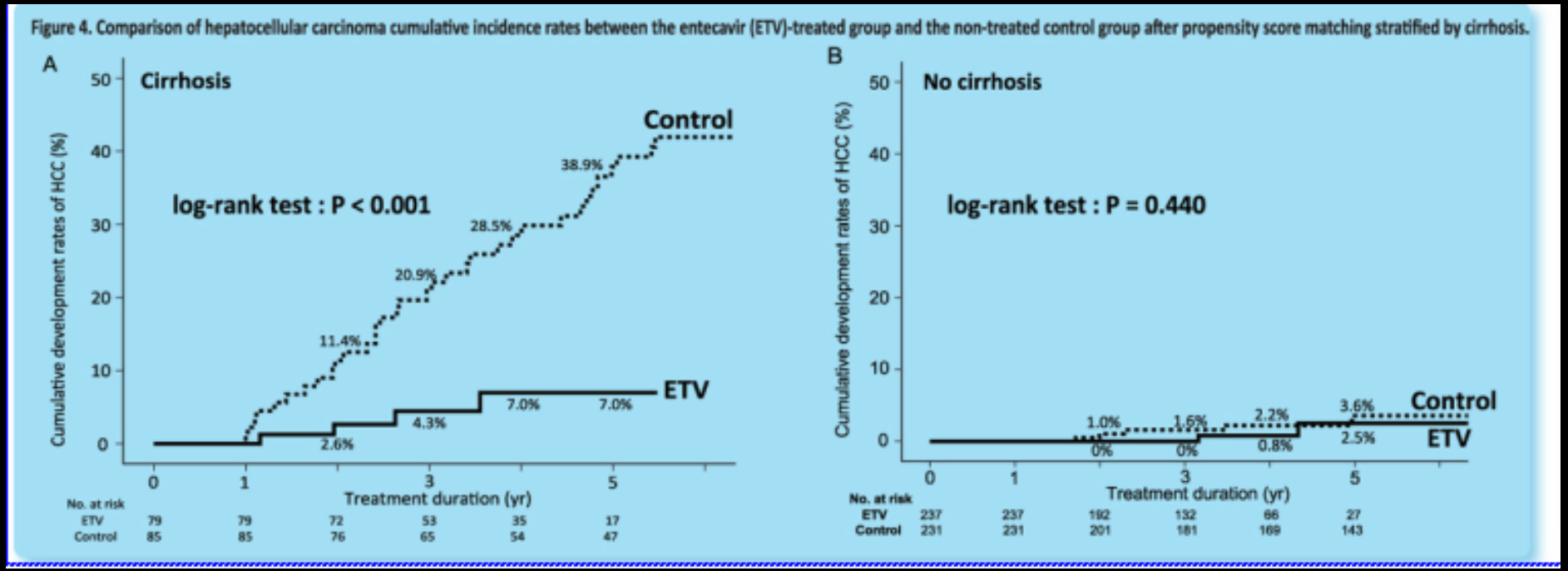
Toranomon Hospital cohort: ETV reduced HCC risk compared with control



- ETV therapy reduced the 5-year HCC risk by >60% compared with control group
- Multivariate cox regression analysis:*
  HR 0.37
  95% CI 0.15–0.91
  P=0.030

*Adjusted for age, sex, alcohol, smoking, cirrhosis, HBV genotype, HBeAg status, HBV DNA, ALT, albumin, γGTP, total bilirubin and platelet count.
CI, confidence interval; HR, hazard ratio.
Hosaka T, et al. AASLD 2012, abstract 357.

Toranomon Hospital cohort: reduction in HCC incidence with ETV greater among cirrhotic patients



Hosaka T, et al. AASLD 2012, abstract 357.

Toranomon Hospital cohort: reduction in HCC incidence with ETV was greatest among high-risk patients

			Cumulative 5-year incidence of HCC (%)[1]		
Risk score	**Risk**	**n**	**ETV**	**Control**	**P***
Yang HI 2011[2]	Low High	1272 342	1.1 8.3	2.4 23.9	0.313 0.006
Yuen MF 2009[3]	Low High	1110 505	0.7 7.2	0.5 21.0	0.914 0.002
Wong VWS 2010[4]	Low Medium High	1054 339 222	0.5 4.3 8.0	1.5 10.6 33.3	0.246 0.062 <0.001

*Log-rank test

1. Hosaka T, et al. AASLD 2012, abstract 357. 2. Yang HI, et al. Lancet Oncol 2011; 12:568-574.
3. Yuen MF, et al. J Hepatol 2009; 50:80-88. 4. Wong VWS, et al. J Clin Oncol 2010; 28:1660-1665.

Toranomon Hospital cohort: conclusions

- ETV therapy did not completely eliminate HCC risk, but significantly reduced the incidence of HCC compared with un-treated, matched historical controls
- The reduction in the incidence of HCC with ETV treatment was greatest among patients at high risk of HCC
  - Among low-risk patients HCC development is rare; a longer follow-up might be needed to assess the potential impact of ETV therapy on the development of HCC
- The authors propose the development of a scoring system to predict treatment effects in patients with different levels of HCC risk

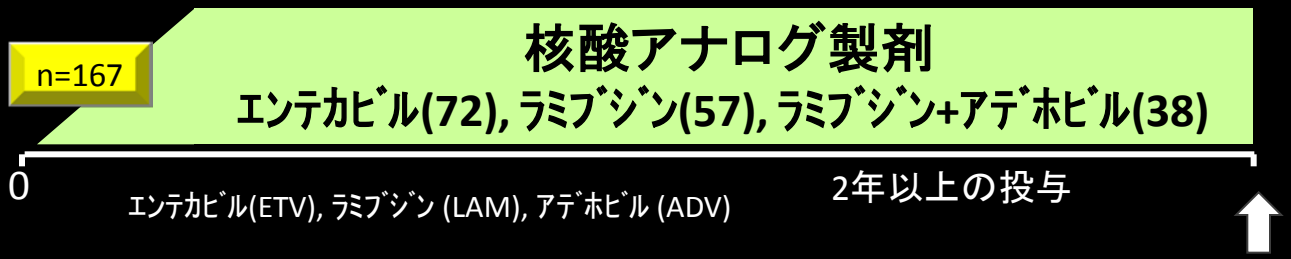
Hosaka T, et al. AASLD 2012, abstract 357.

核酸アナログ投与中の発癌とHBs抗原量

438(川崎病院)：*Miwa Kawanaka et al.*

Quantitative levels of hepatitis B virus DNA and surface antigen and risk of Hepatocellular carcinoma in chronic HBV patients with long-term Nuclotide analogue therapy.

試験デザインと患者背景

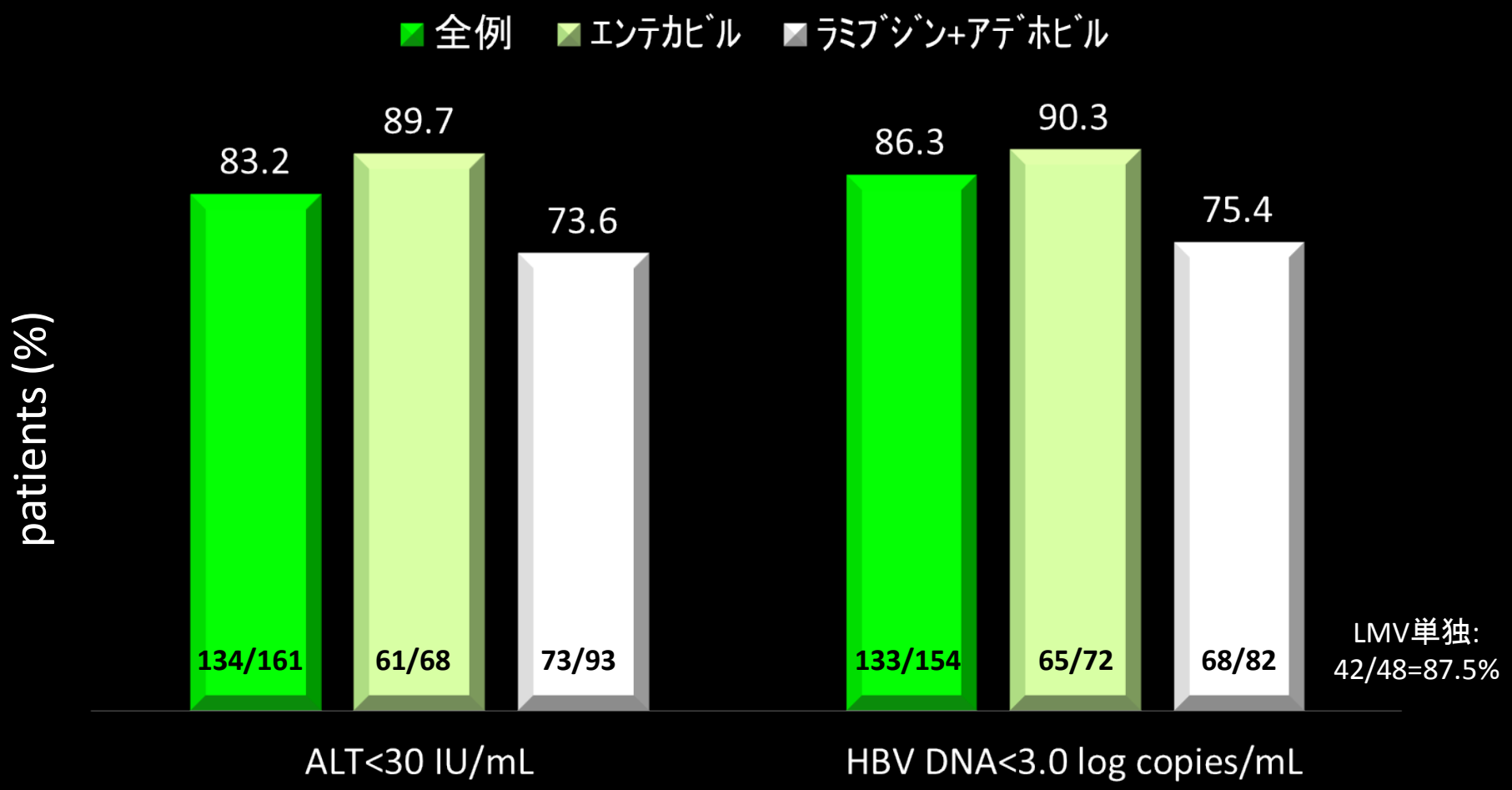


- Nucleotide Analogues(NA) treatment
  - Entecavir　0.5mg/day, n=72　: median 4.4±1.9 years
  - Lamivudine 100mg/day, n=57　: median 6.5±3.1 years
  - Lamivudine 100mg/day＋Adefovir dipivoxil 10mg/day, n=38 :median7.3 ±2.8 years
  - Treatment duration: median 5.8 (range 2-13.1) years

	Before treatment	After treatment
Age, years	49.2 ±12.7	56.7±25.4
Male/ Female ,n	112/55	
Chronic hepatitis/ Liver cirrhosis, n	126/41	
HBV DNA, Log copies/mL	6.8±1.3	1.6±1.5
HBV genotype: A/B/C/ND, n	3/4/144/16	
HBeAg positive , n(%)	81(50.9%)	42(25.6%)
HBsAg, cut off index, <2000/>2000 COI ,n	8/159	28/139

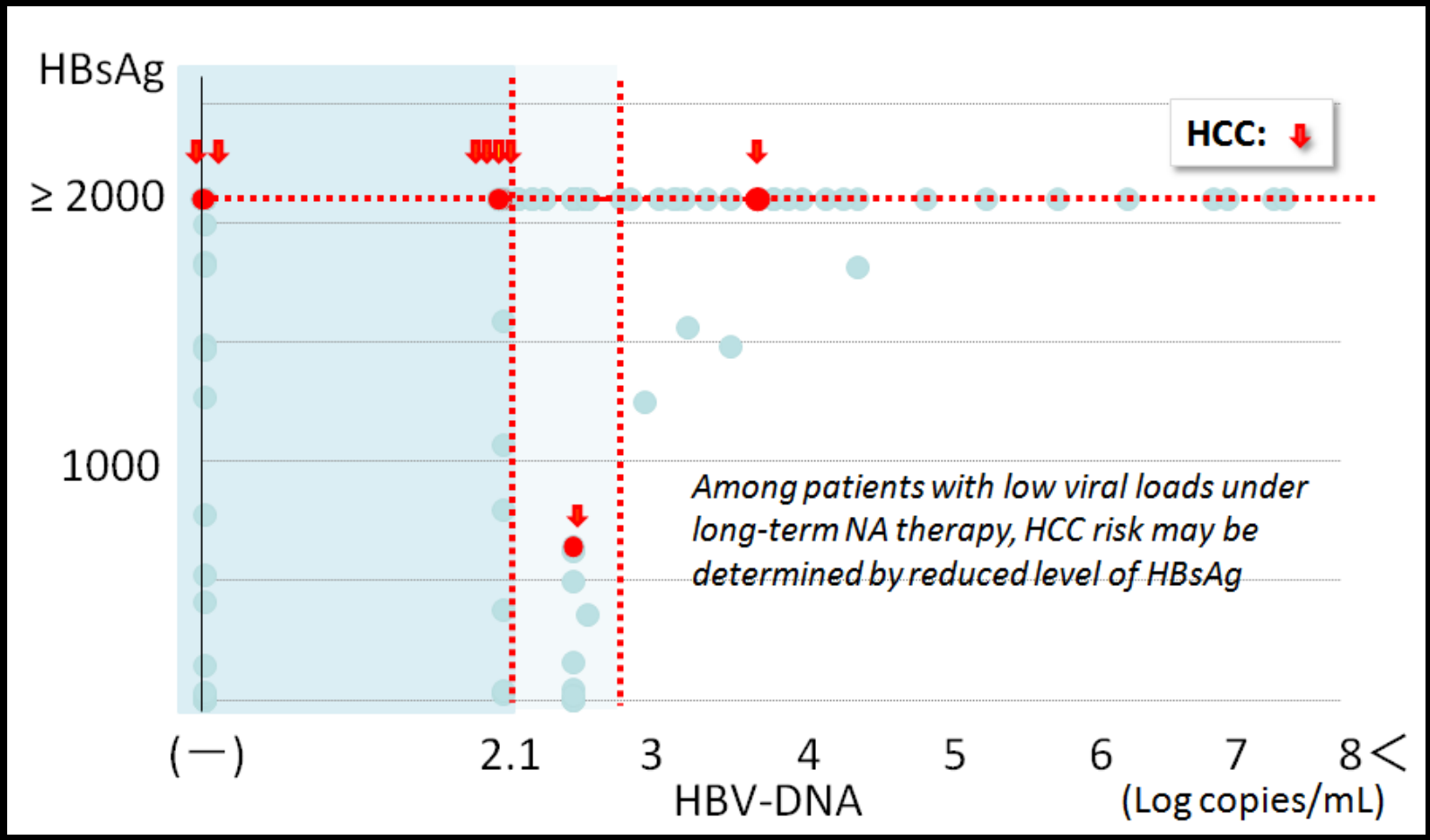
AASLD 2012 438： Miwa Kawanaka et al.

長期核酸アナログ投与の ALT正常化率及びHBV DNA陰性化率



AASLD 2012 438： Miwa Kawanaka et al.

核酸アナログ長期投与例での HBV DNA量/HBsAg量と発癌リスク

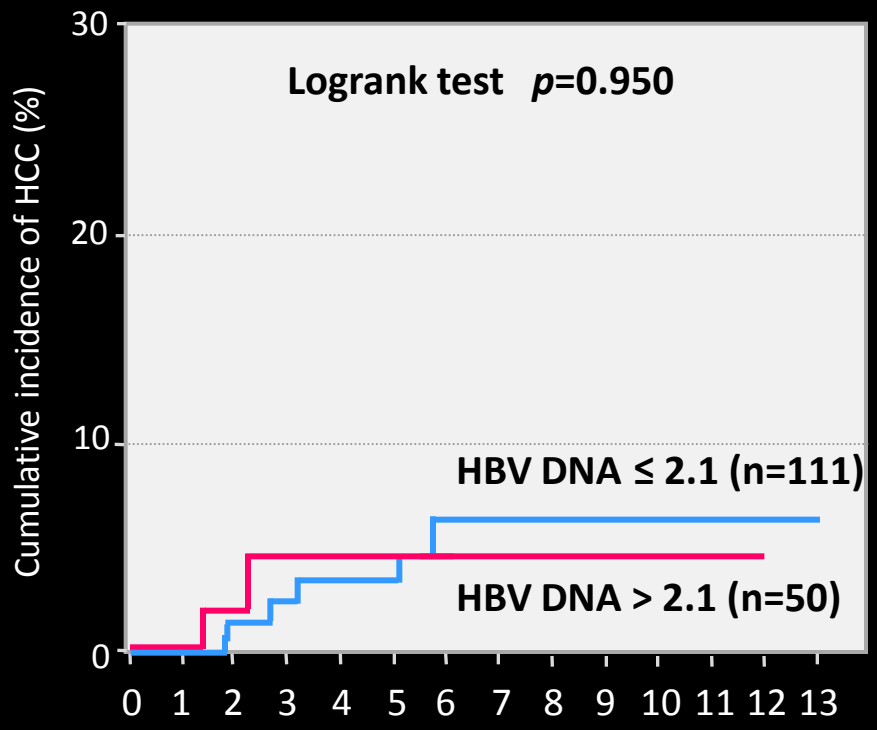


AASLD 2012 438： Miwa Kawanaka et al.

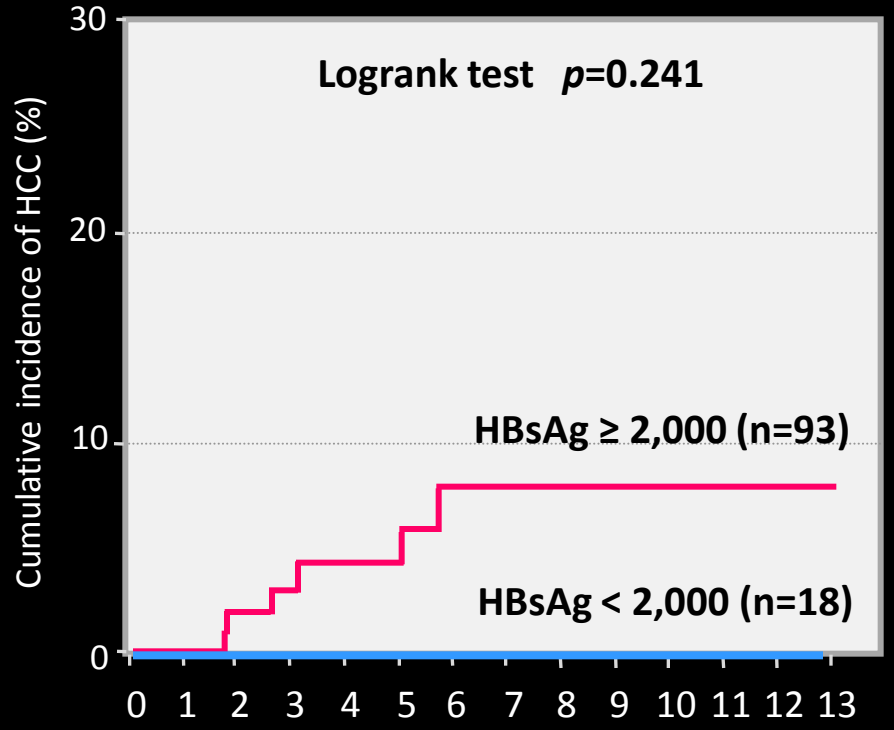
核酸アナログ投与中の発癌率

（HBV DNA量別、HBs抗原量別）

HBV DNA量別発癌率

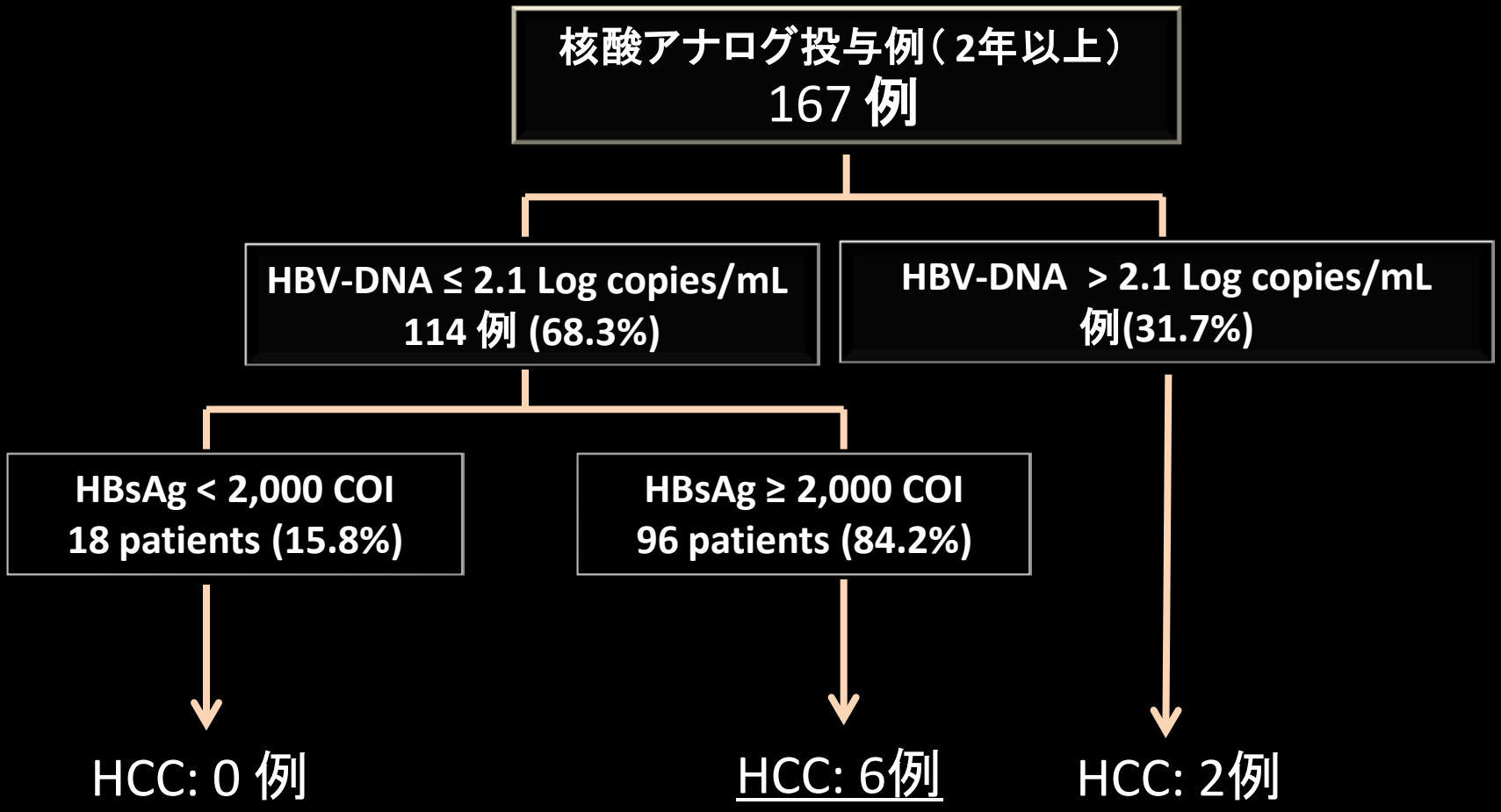


HBs抗原量別発癌率



AASLD 2012 438： Miwa Kawanaka et al.

HCC risk of HBV DNA and HBsAg level after long-term NA therapy



AASLD 2012 438： Miwa Kawanaka et al.

核酸アナログ投与中の発癌とHBs抗原量

438(川崎病院)：*Miwa Kawanaka et al.*

Quantitative levels of hepatitis B virus DNA and surface antigen and risk of Hepatocellular carcinoma in chronic HBV patients with long-term Nuclotide analogue therapy.

Conclusion:

No previous history of HBV maternal transmission , continued treatment with NA and <3 log/ml of HBVDNA or loss of HBeAg during first 24 weeks of treatment increased proportion with reduced level of HBsAg.

Among patients with low viral loads under long-term NA therapy ,HCC risk may be determined by reduced level of HBsAg.

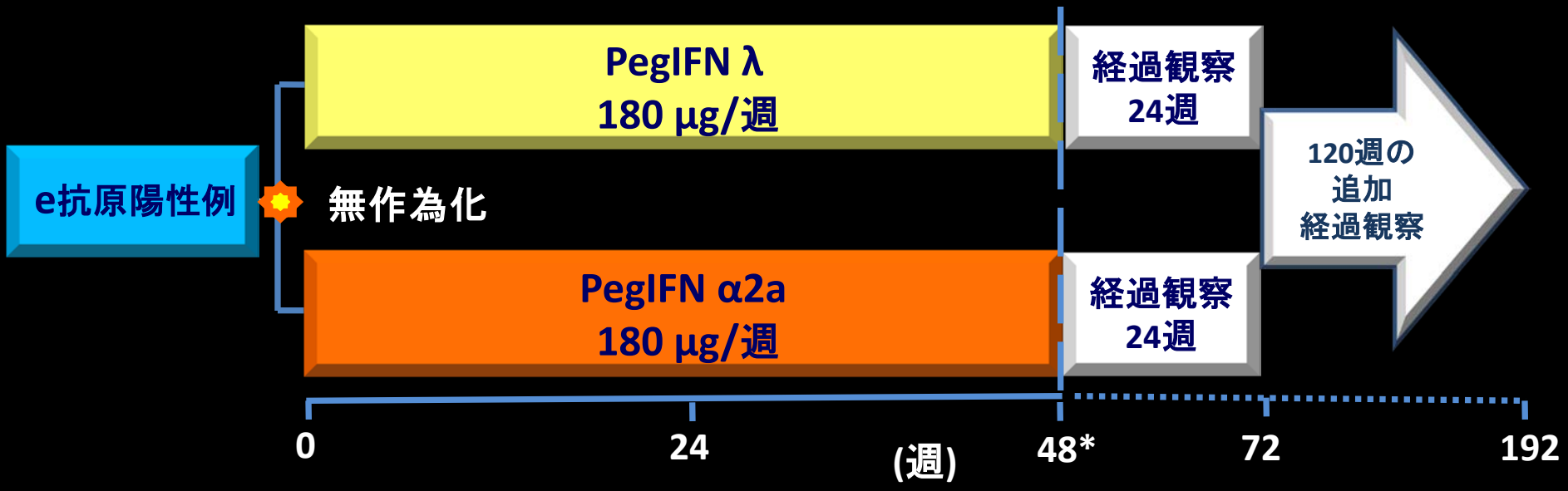
Hepatology 408A 2012

PegIFN λ

LB-14：*Henry LY Chan et al.*

Peginterferon Lambda, a New Potential Therapeutic Option for the Treatment of Chronic Hepatitis B: A Phase 2B Comparison with Peginterferon Alfa in Patients with HBeAg-Positive Disease

試験デザイン



主要評価項目：投与終了後24週時点のeセロコンバージョン率

AASLD 2012 LB-14： Henry LY Chan et al.

結果

N(%)		Lambda	Alfa
HBe抗原陰性化	12週	6(8)	6(7)
	24週	7(9)	7(8)
HBeｾﾛｺﾝﾊﾞｰｼﾞｮﾝ	12週	5(6)	5(6)
	24週	5(6)	7(8)
HBs抗原陰性化	24週	2(3)	0

AASLD 2012 LB-14： Henry LY Chan et al.

有害事象

N(%)	Lambda	Alfa
全有害事象	72(90)	75(90)
重篤な有害事象	4(5)	6(7)
有害事象による中止	4(5)	7(8)
有害事象による減量	6(8)	21(25)
好中球減少による減量	0	12(15)
血小板減少による減量	0	1(1)
ALT上昇による減量	4(5)	2(2)
ALT flares (ALT >10 x ULN and >2 x BL)	12(15)	6(7)
ALT flares (ALT > 5 x ULN and >2 x BL)	27(34)	13(16)

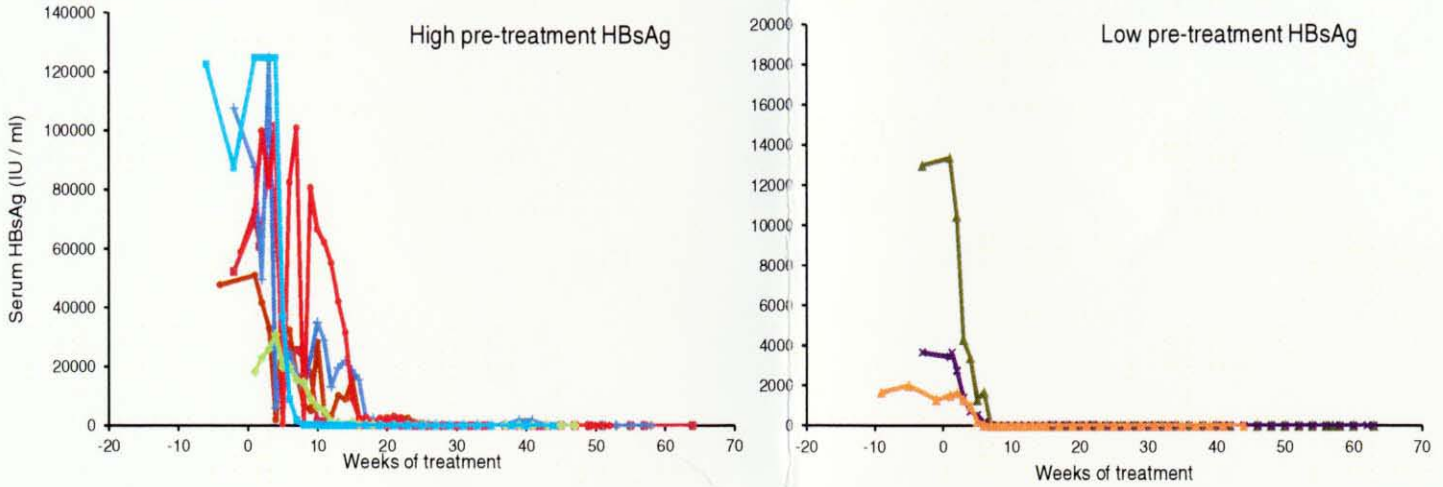
AASLD 2012 LB-14： Henry LY Chan et al.

REP 9AC’

A second generation HBsAg release inhibitor with improved tolerability

REP 9AC’ PROOF OF CONCEPT CLINICAL TRIAL

REP 9AC’ is currently undergoing testing in human patients with chronic HBeAg+ HBV in a proof of concept clinical trial where patients were treated with REP 9AC’. Typical dosing was 500mg once a week via intravenous infusion. Virologic monitoring included HBV DNA (Roche Cobas™), HBsAg, anti-HBs, HBeAg and anti-HBe (all by Abbott Architect™). The effects of REP 9AC’ treatment on reduction of HBsAg in the blood of infected patients is shown below.



AASLD 2012 424:Mamun A Mahtab.et al

REP 9AC’

A second generation HBsAg release inhibitor with improved tolerability

COMPARISON OF ON-TREATMENT ANTIVIRAL RESPONSE WITH IMMUNOTHERAPY ALONE VERSUS IMMUNOTHERAPY IN COMBINATION WITH REP 9AC’

Regimen	HBV DNA < 2000 IU (< 12,000 CPM)	HBsAg		HBeAg	
		seroclearance	seroconversion	seroclearance	seroconversion
interferon-based therapy (48 weeks)	36.5%[6]	8.25 – 10%[7, 8]	7%[7]	34%[7]	26 – 26.9%[6,7]
REP 9AC’ (19-34 weeks) ↓ REP REP 9AC’ + immunotherapy* (13 weeks)	**100%**	**100%**	**100%**	**67%**	**78%**

AASLD 2012 424:Mamun A Mahtab.et al