

2012OCT16

@国立がん研究センター東病院

がん臨床試験のエンドポイントは PFSかOSか？



(財)パブリックヘルスリサーチ・臨床研究支援事業(CSP)担当
NPO日本臨床研究支援ユニット理事長
スタットコム(株)取締役会長
NPO日本メディカルライタ協会理事長
(社)日本臨床試験研究会代表理事
日本医薬情報コンソシウム理事長

東京大学医学系研究科 公共健康医学専攻 生物統計学

大橋靖雄

OSがもちろん絶対ではないが・・・

**本日は進行がんのPFSとOSとに話題を限定
(補助療法のDFSについてはあまり触れない)**

本日の発表内容は「癌と化学療法」誌に投稿予定です

**2012年臨床試験研究会ランチオンセミナーの講演をもとにし
ております。3月のSoCRAセミナーでも触れています**

がん臨床試験のエンドポイントと奏効判定

里見・吉村：誰も教えてくれなかった癌臨床試験の正しい解釈、中外医学社、2011

◆ エンドポイント

試験の目的にそって測定される評価項目だが、しばしば研究者から試験の目的そのものと混同され、またPMDAによって不適切なものに差し替えられる

◆ 奏効率

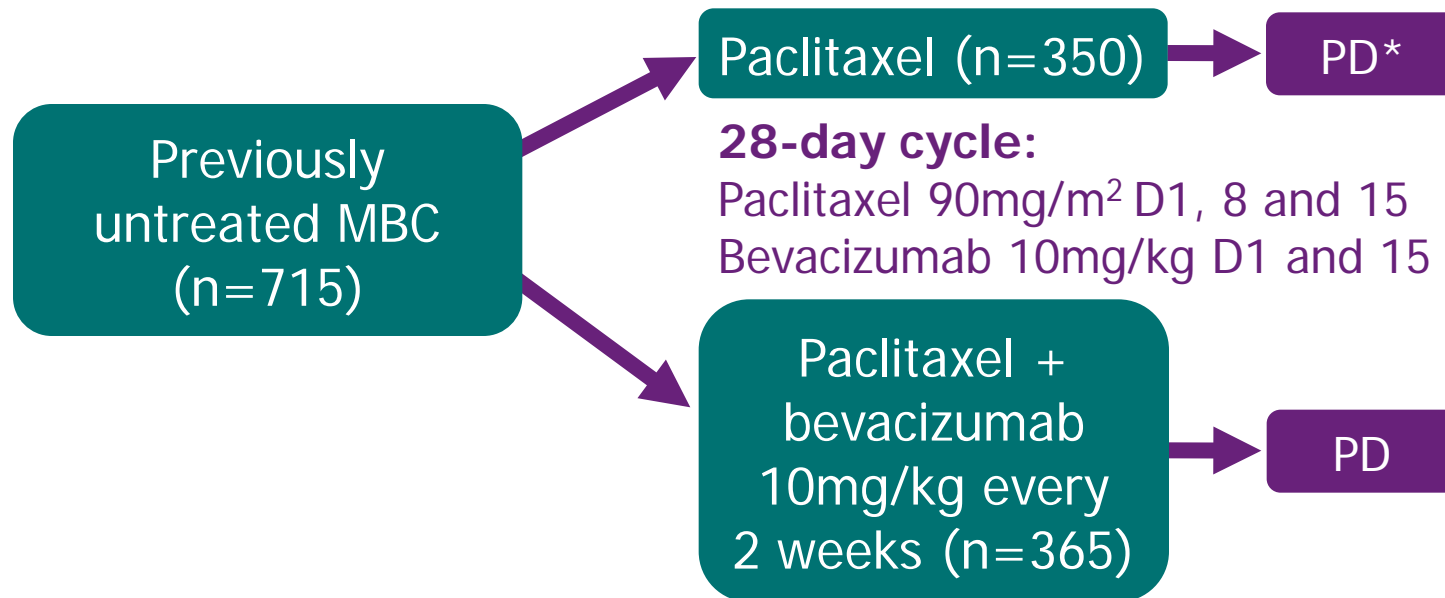
昔の二方向性の計測で45%とか、今のRECISTで25%とかいう微妙な縮小効果の時に、「もう一度きちんと測り直してみい」と上司に関西弁で言われて測定し直した結果、出る数値

PFS とOS

- ◆ Bevacizumab は特殊な例？ ますます混迷？
- ◆ 治験でも研究者主導研究でもPFSが採用される例が増加
- ◆ FDAがPFSに基づいて最近承認した事例
 - gemcitabine in ovarian cancer
 - sorafenib in advanced renal cancer
 - bevacizumab in metastatic breast cancer ?
 - rituximab in Non-Hodgkin's lymphoma
 -

Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, May 2007

Phase III trial of 1st-line bevacizumab in MBC (E2100)

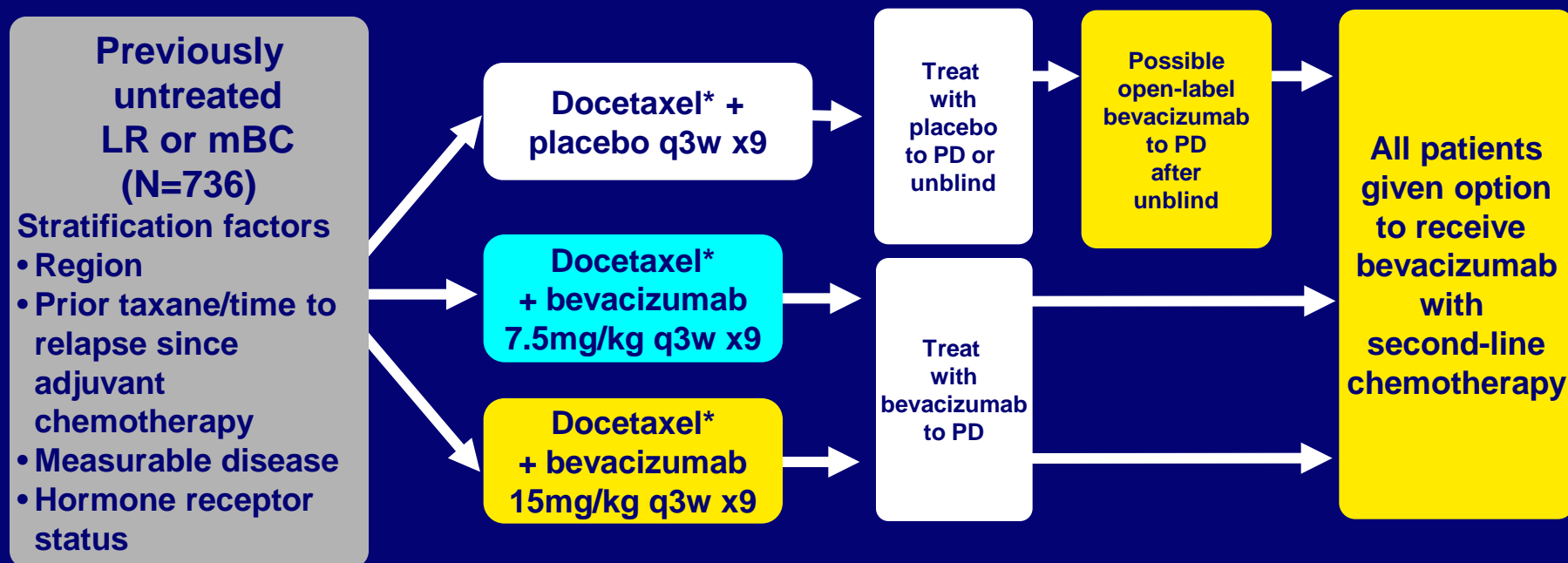


Stratify:

- Disease-free interval ≤ 24 vs > 24 months
- < 3 vs ≥ 3 metastatic sites
- Adjuvant chemotherapy yes vs no
- ER+ vs ER- vs ER unknown

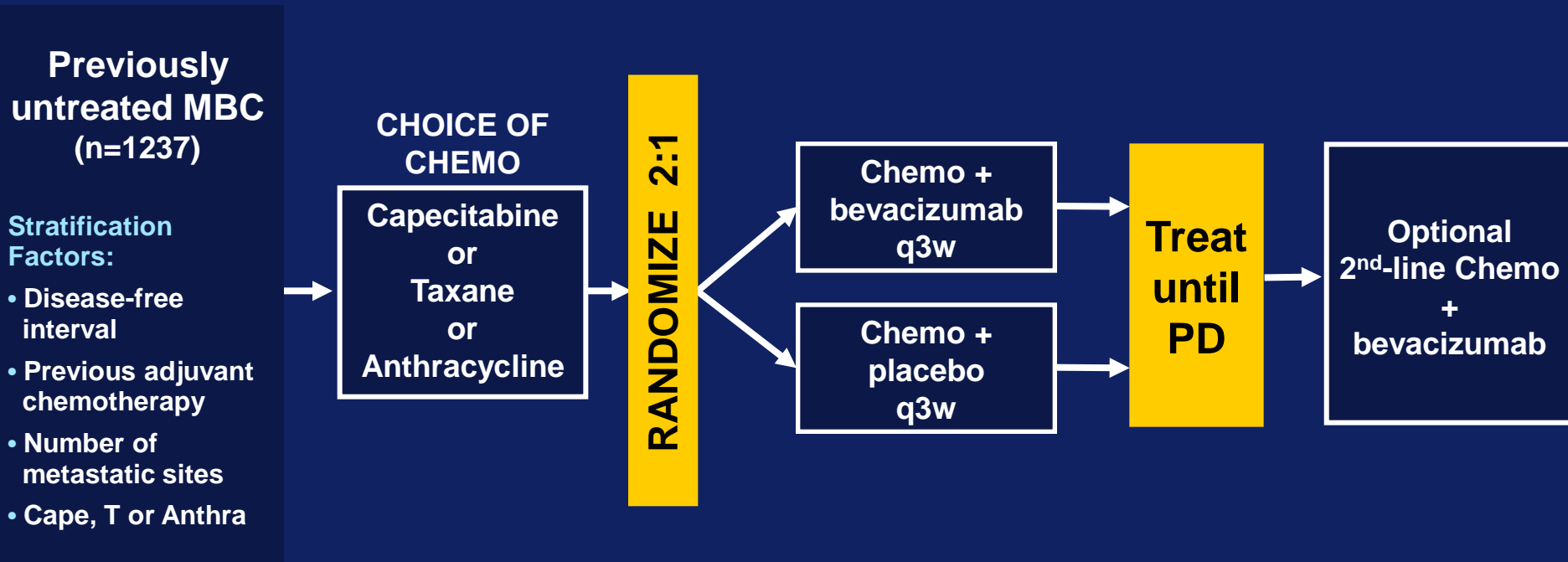
Miller et al ASCO 2005

AVADO: double-blind, placebo-controlled trial



- **Primary endpoint: PFS**
- **Secondary endpoints: ORR, 1-year survival, OS, TTF, duration of response, quality of life, safety**

RIBBON-1: Study Design



- Capecitabine (1000 mg/m² BID x 14d)
- Taxane (docetaxel q3w or protein-bound paclitaxel q3w)
- Anthracycline-based chemotherapy (AC, EC, FAC, FEC)
- Placebo or bevacizumab (15 mg/kg q3w)

Avastin in 1st line setting for MBC

Trial	E2100 ^{1,2} (n=722)	AVADO ³ (n=736)	RIBBON-1 ⁴ Cape cohort (n=615)	RIBBON-1 ⁴ A/T cohort (n=622)
Placebo controlled	No	Yes	Yes	Yes
Chemo	weekly Paclitaxel	Q3w Docetaxel	Capecitabine	Anthracycline or Taxane
Dose of Avastin	10mg/kg q2w	7.5 or 15mg/kg q3w	15mg/kg q3w	15mg/kg q3w
Primary Endpoint	PFS	PFS	PFS	PFS
IRF* review	Retrospective	Yes	Yes	Yes

*IRF:Independent Review Facility

¹ Robert Gray et al. J Clin Oncol 2009; 27:4966-4972. ²Kathy Miller et al. N Engl J Med 2007; 357:2666-76

³ Miles D et al. SABCS2009 abstr#41.

⁴N. J. Robert et al. ASCO2009 abstr#1005

Avastin in 1st line setting for MBC

<Efficacy>

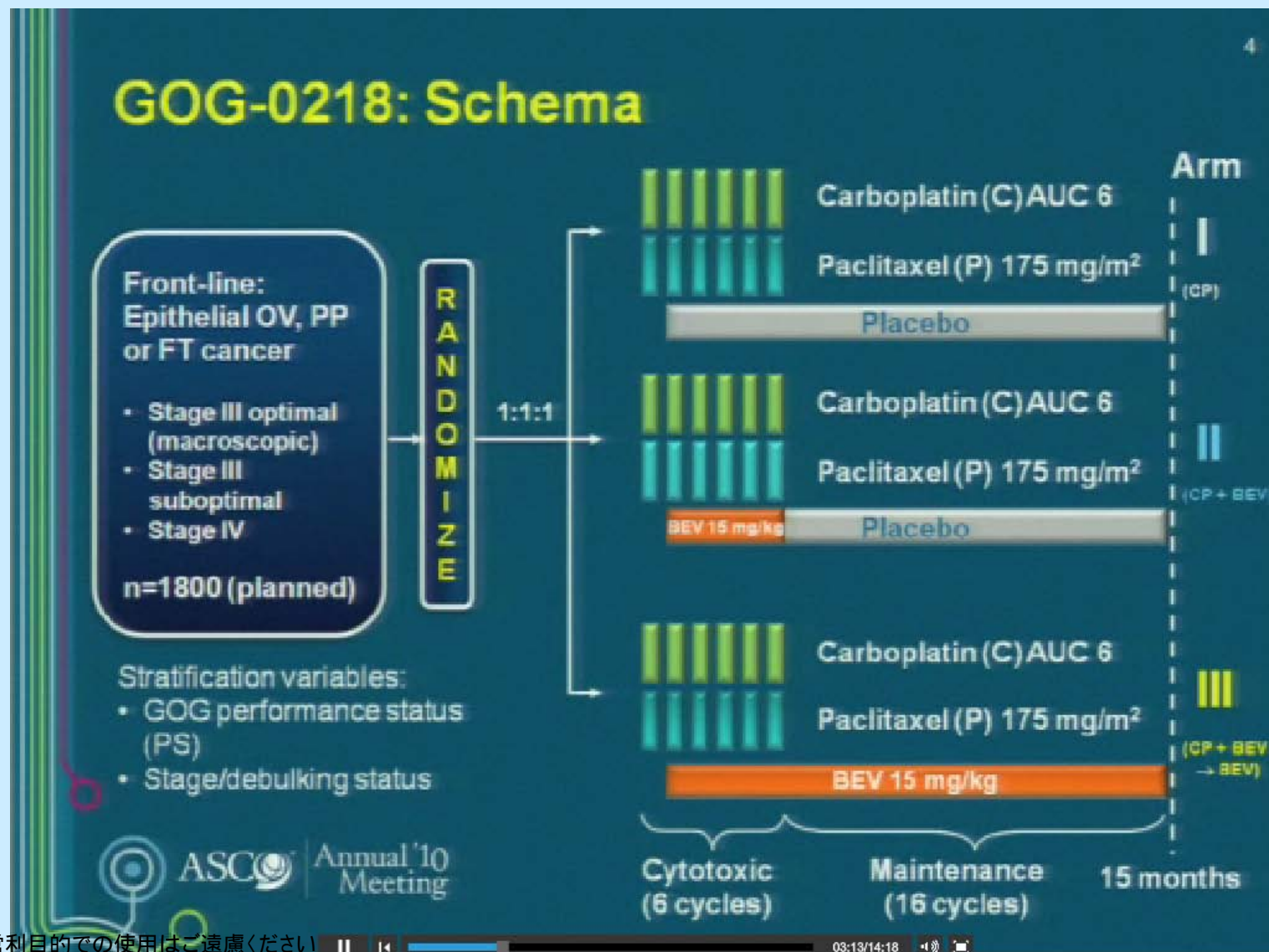
試験	E2100 ^{1,2} (n=722)		AVADO ³ (n=736)		RIBBON-1 ⁴ Cape cohort (n=615)		RIBBON-1 ⁴ A/Tcohort (n=622)	
arm	Paclitaxel	Paclitaxel + BV	Docetaxel + PL	Docetaxel + BV*	Cape + PL	Cape + BV	A/T + PL	A/T + BV
PFS (m)	5.8	11.3	8.2	10.1	5.7	8.6	8.0	9.2
HR	0.48 P<0.0001		0.77 P=0.0061		0.69 P=0.0002		0.64 P<0.0001	
RR	22%	49%	46%	64%	24%	35%	38%	51%
	P<0.0001		P=0.0003		P=0.0097		P=0.0054	
OS (m)	25.2	26.7	31.9	30.2	21.2	29.0	23.8	25.2
HR	0.88		1.03		0.85		1.03	

¹ Robert Gray et al. J Clin Oncol 2009; 27:4966-4972. ²Kathy Miller et al. N Engl J Med 2007; 357:2666-76

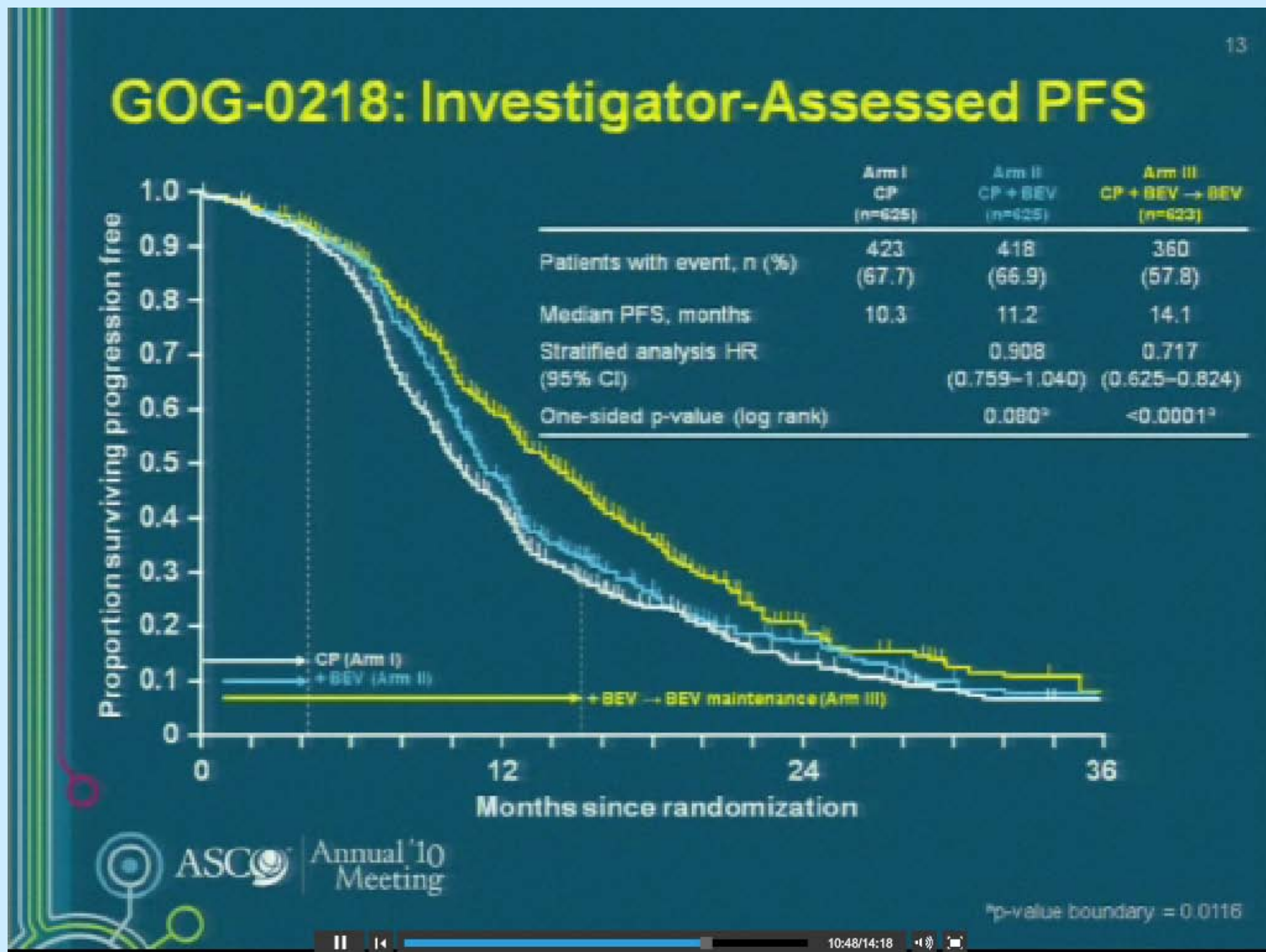
³ Miles D et al. SABCS2009 abstr#41.

⁴N. J. Robert et al. ASCO2009 abstr#1005.

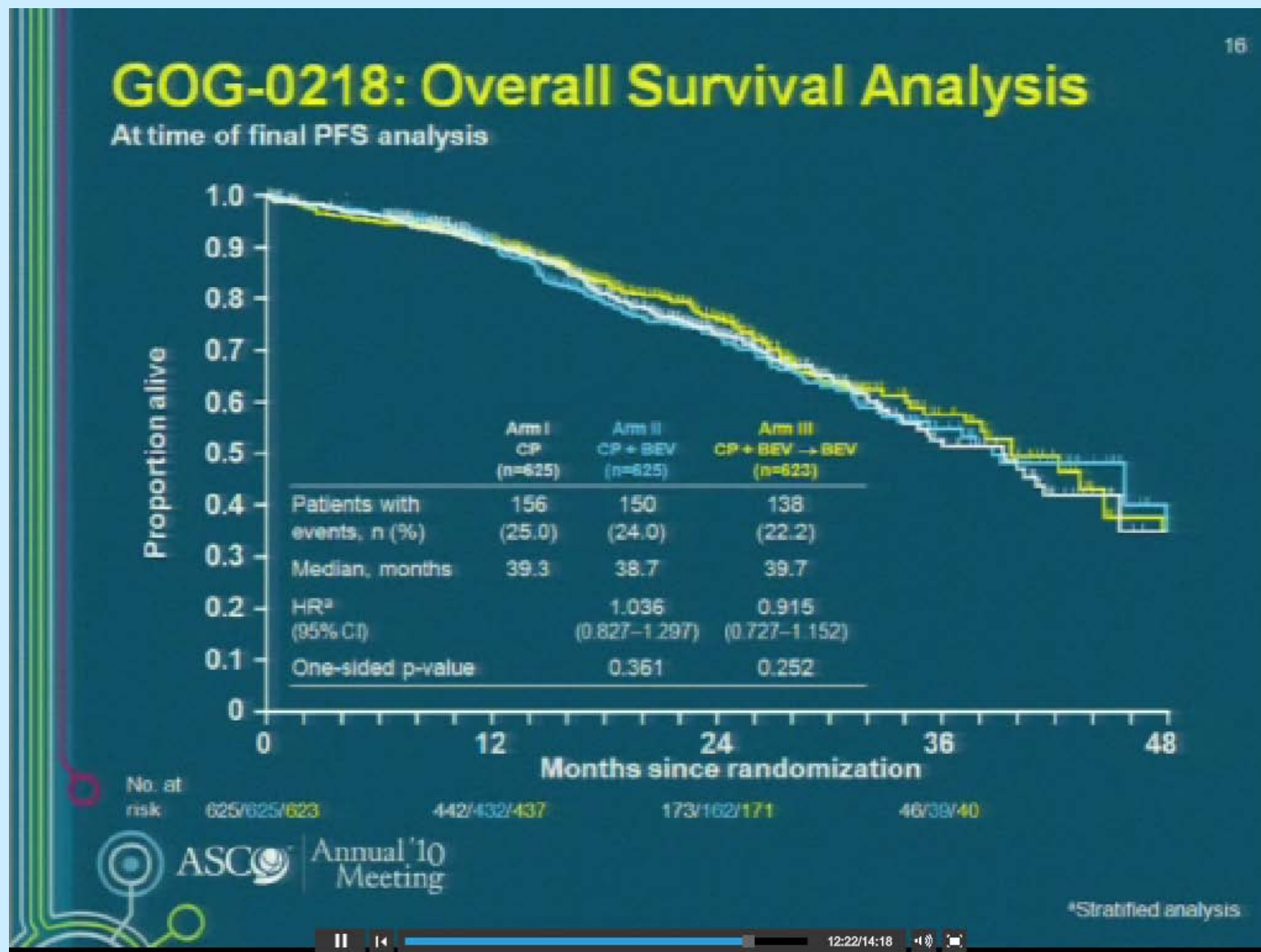
Phase III trial of bevacizumab (BEV) in the primary treatment of advanced epithelial ovarian cancer (EOC), primary peritoneal cancer (PPC), or fallopian tube cancer (FTC): A Gynecologic Oncology Group study.



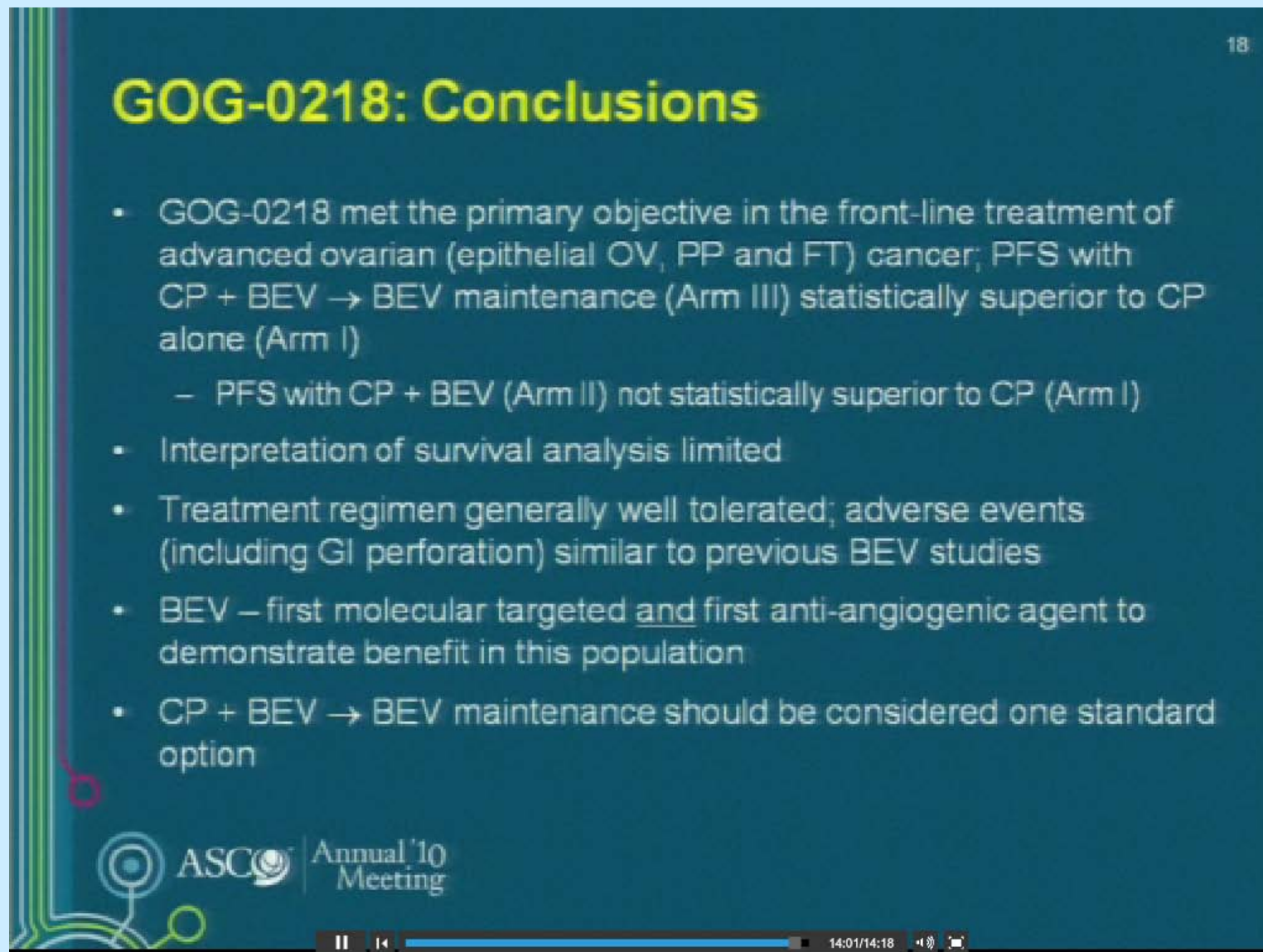
ASCO2010 LBA1 Burger et al.



ASCO2010 LBA1 Burger et al.



ASCO2010 LBA1 Burger et al.



18

GOG-0218: Conclusions

- GOG-0218 met the primary objective in the front-line treatment of advanced ovarian (epithelial OV, PP and FT) cancer; PFS with CP + BEV → BEV maintenance (Arm III) statistically superior to CP alone (Arm I)
 - PFS with CP + BEV (Arm II) not statistically superior to CP (Arm I)
- Interpretation of survival analysis limited
- Treatment regimen generally well tolerated; adverse events (including GI perforation) similar to previous BEV studies
- BEV – first molecular targeted and first anti-angiogenic agent to demonstrate benefit in this population
- CP + BEV → BEV maintenance should be considered one standard option

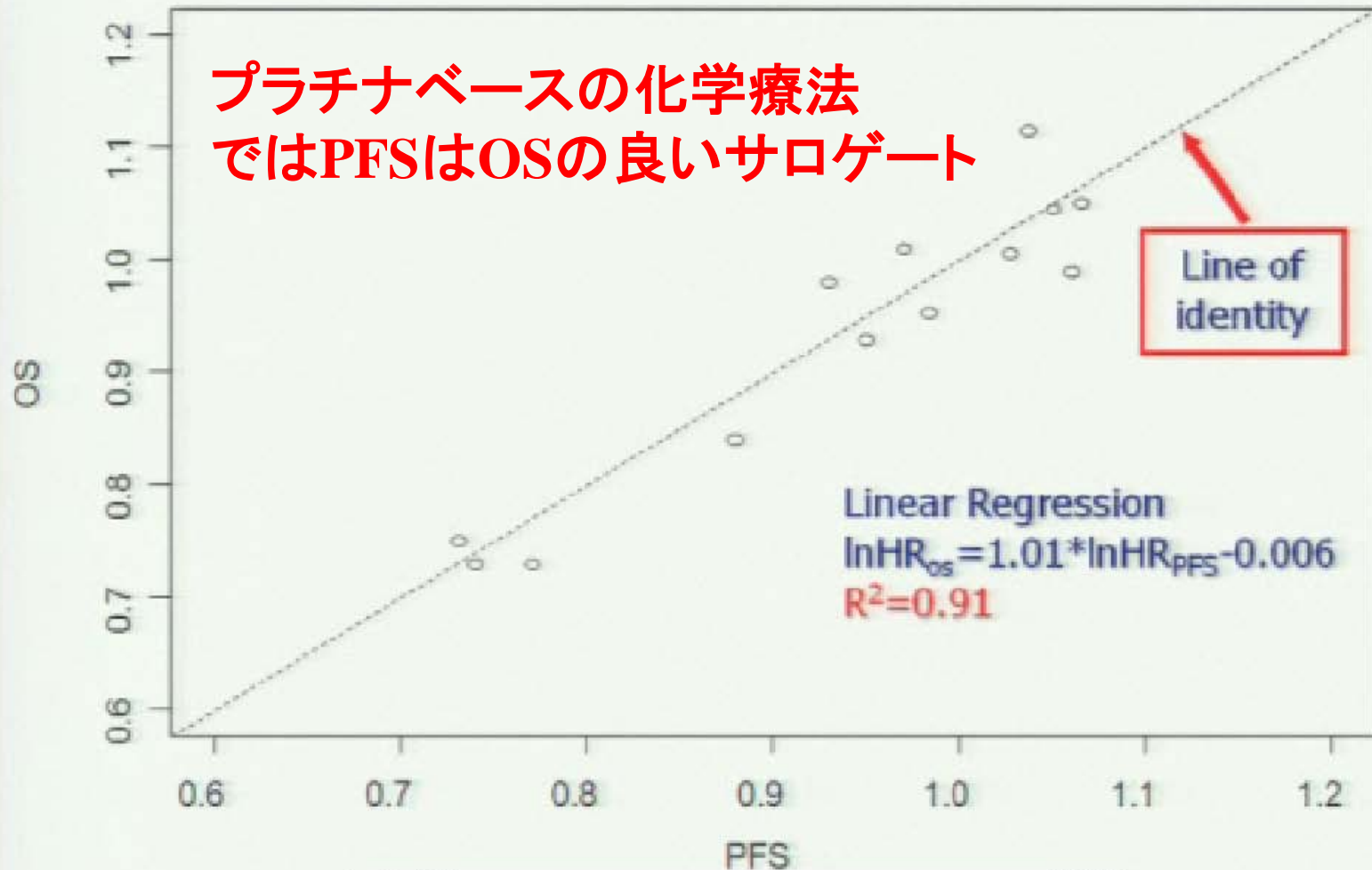
ASCO Annual '10 Meeting

14:01/14:18

ASCO2010 LBA1 Discussion to Burger et al.

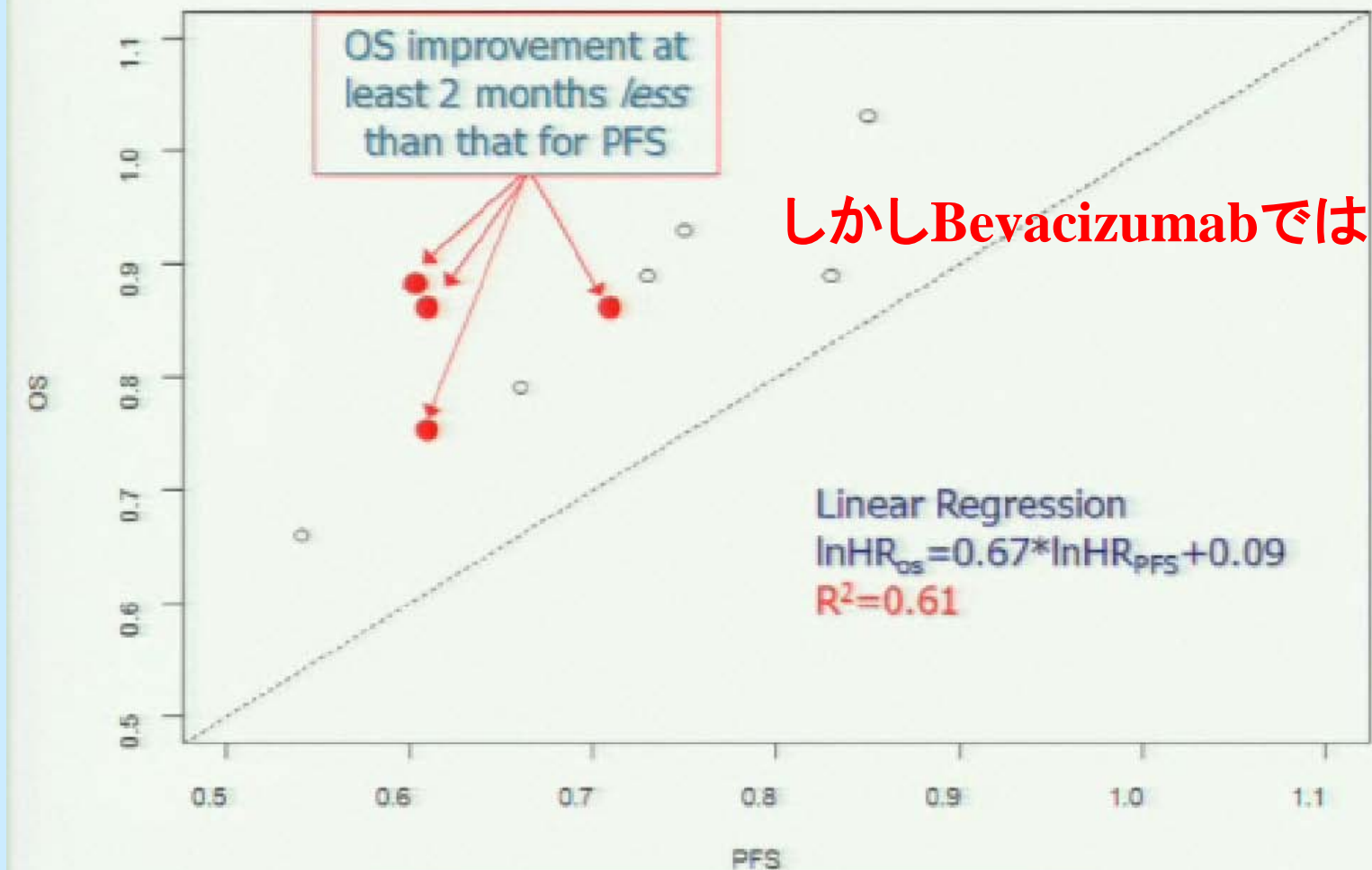
Hazard Ratios of PFS vs. OS:

Data from Platinum-based Chemotherapy Trials
in Advanced OVCA



ASCO2010 LBA1 Discussion to Burger et al.

Hazard Ratios of PFS vs. OS: Data from RCTs of Bevacizumab in Other Solid Tumors



ASCO2010 LBA1 Discussion to Burger et al.

Cost-Effectiveness: Focusing on Drug Only



- Drug costs major (~75%) contributor to overall incremental cost in recent analyses of colorectal cancer trials.
- “Back of Envelope” cost analysis
- Median Arm III bevacizumab cost \$5.76/mg
- Efficacy as of today: 3.8 mo med. PFS gain (unknown OS gain)
= US \$229,187 / yr of progression free survival gained
- Calculation sensitive to denominator (increase in PFS or OS)

コストの問題

Use of bevacizumab for *progression free survival* gain reported to date is unlikely to be considered cost-effective in many jurisdictions.

NCIC CTG
NCIC GEC

* 15 mg/kg per cycle, median 14 cycles, cost \$5.76/mg, assume average wt of 60 kg



13:15/15:41



**Burger et al.
NEJM 2011; 365:
2473-83.**

ORIGINAL ARTICLE

Incorporation of Bevacizumab in the Primary Treatment of Ovarian Cancer

Robert A. Burger, M.D., Mark F. Brady, Ph.D., Michael A. Bookman, M.D., Gini F. Fleming, M.D., Bradley J. Monk, M.D., Helen Huang, M.S., Robert S. Mannel, M.D., Howard D. Homesley, M.D., Jeffrey Fowler, M.D., Benjamin E. Greer, M.D., Matthew Boente, M.D., Michael J. Birrer, M.D., Ph.D., and Sharon X. Liang, M.D., for the Gynecologic Oncology Group*

**Perren et al.
NEJM 2011; 365:
2484-96.**

ORIGINAL ARTICLE

A Phase 3 Trial of Bevacizumab in Ovarian Cancer

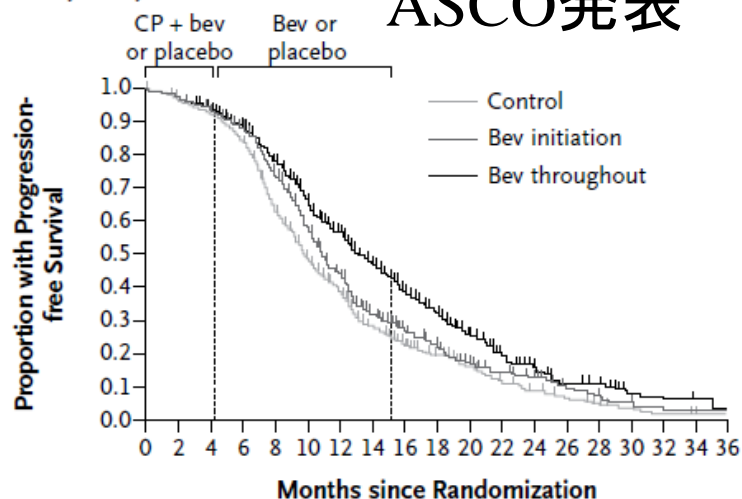
Timothy J. Perren, M.D., Ann Marie Swart, M.D., Jacobus Pfisterer, M.D., Jonathan A. Ledermann, M.D., Eric Pujade-Lauraine, M.D., Gunnar Kristensen, M.D., Mark S. Carey, M.D., Philip Beale, M.D., Andrés Cervantes, M.D., Christian Kurzeder, M.D., Andreas du Bois, M.D., Jalid Sehouli, M.D., Rainer Kimmig, M.D., Anne Stähle, M.D., Fiona Collinson, M.D., Sharadah Essapen, M.D., Charlie Gourley, M.D., Alain Lortholary, M.D., Frédéric Selle, M.D., Mansoor R. Mirza, M.D., Arto Leminen, M.D., Marie Plante, M.D., Dan Stark, M.D., Wendi Qian, Ph.D., Mahesh K.B. Parmar, Ph.D., and Amit M. Oza, M.D., for the ICON7 Investigators*

Burger et al. NEJM 2011; 365: 2473-83.

PFSの有意性は持続

A Primary Analysis

ASCO発表

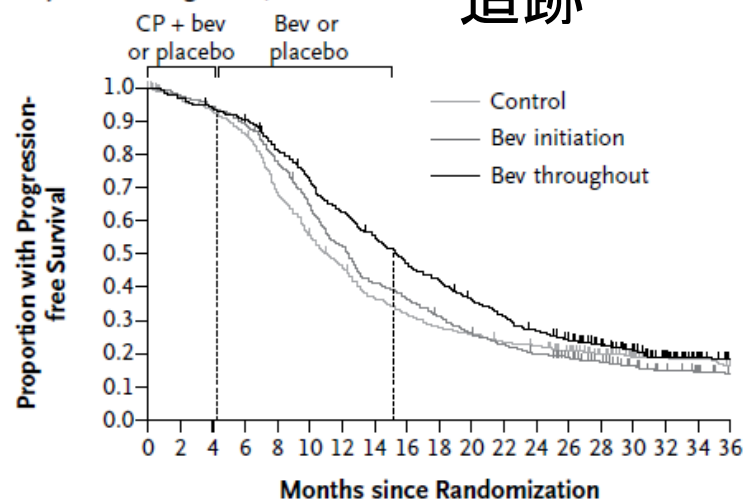


No. at Risk

Control	625	199	33	8
Bev initiation	625	219	29	6
Bev throughout	623	254	38	8

B Analysis as of August 26, 2011

追跡



No. at Risk

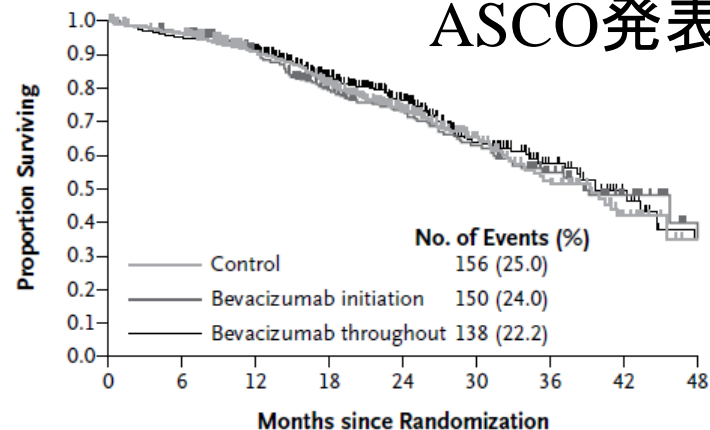
Control	625	535	283	169	133	78	49
Bev initiation	625	552	319	190	121	67	40
Bev throughout	623	559	386	256	162	97	56

**Burger et al.
NEJM 2011; 365:
2473-83.**

OSの「差なし」も持続

A Analysis at Time of Primary Analysis

ASCO発表

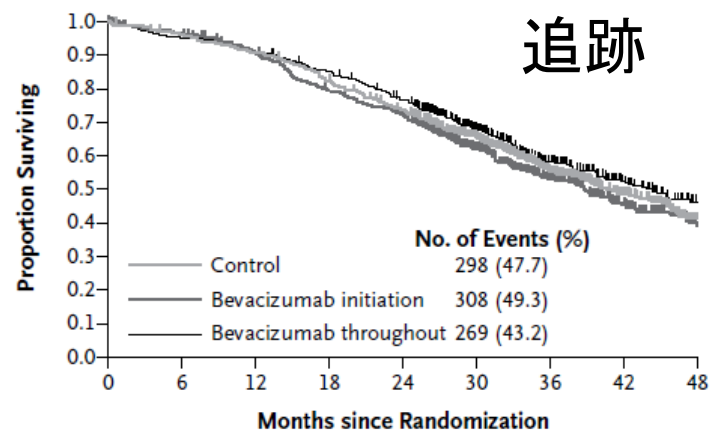


No. at Risk

Control	625	442	173	46
Bevacizumab initiation	625	432	162	39
Bevacizumab throughout	623	437	171	40

B Analysis as of August 26, 2011

追跡

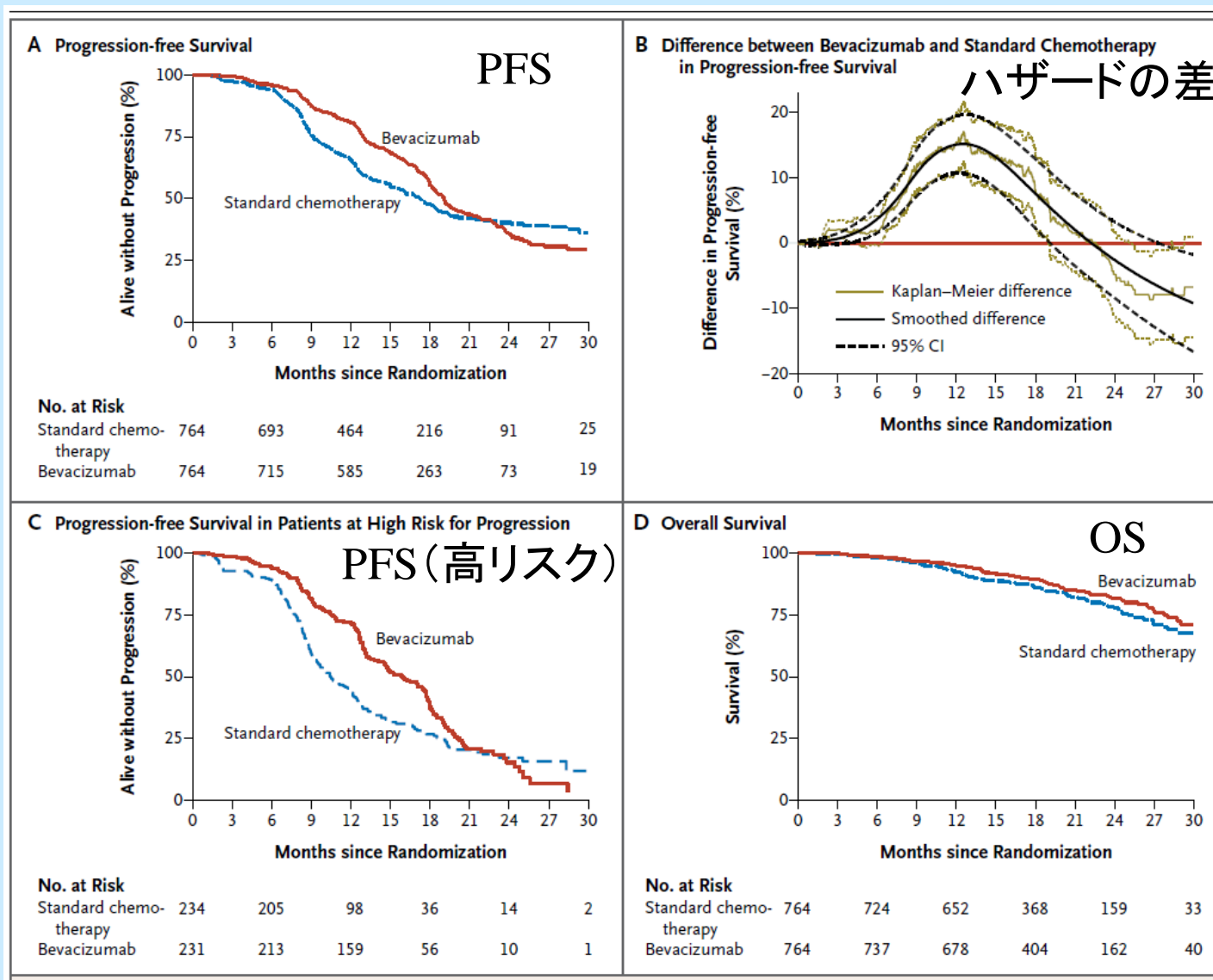


No. at Risk

Control	625	595	558	506	446	322	200	116	56
Bevacizumab initiation	625	598	557	486	440	304	191	108	54
Bevacizumab throughout	623	587	561	519	463	321	201	114	62

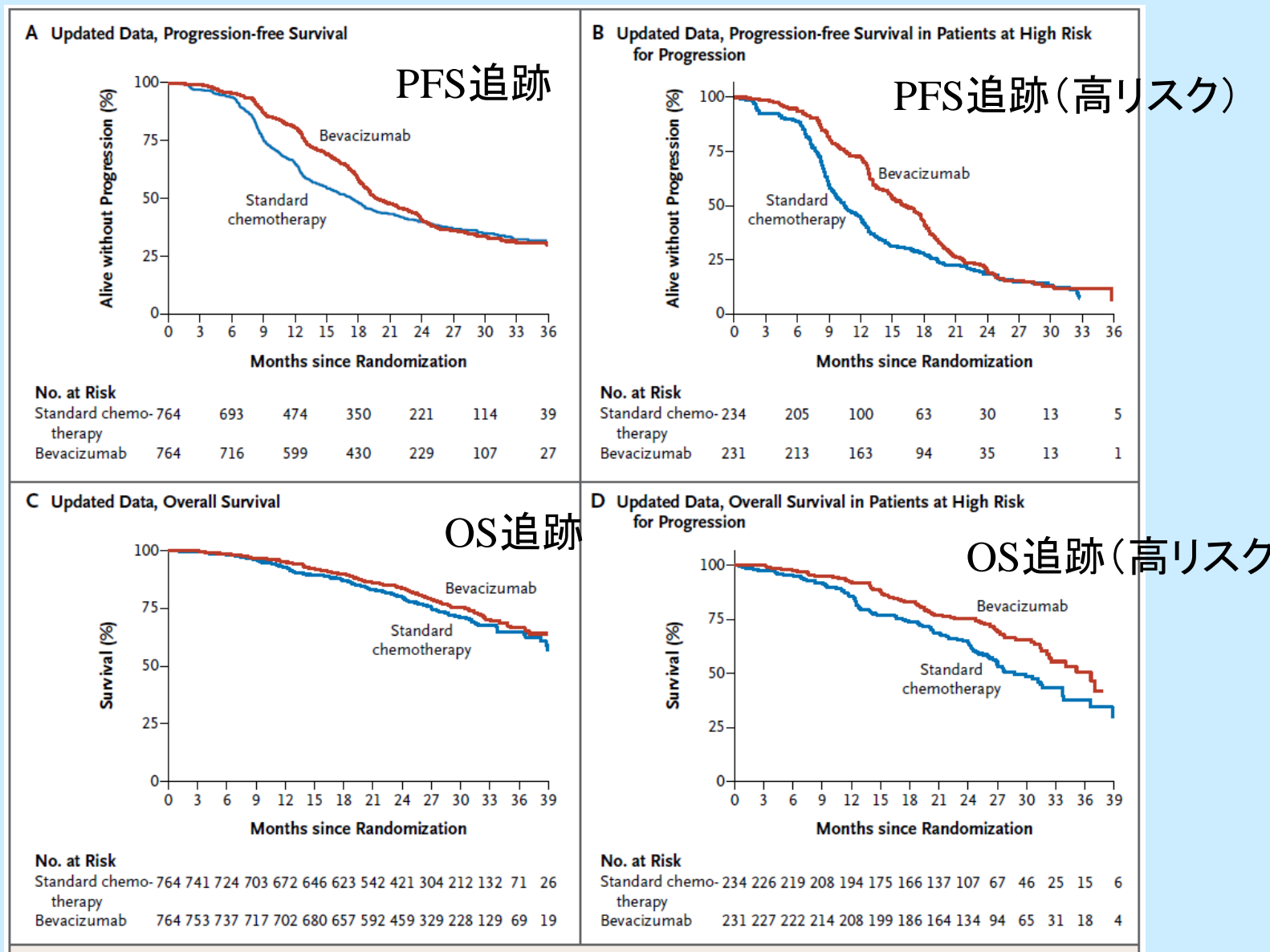
Perren et al.
NEJM 2011; 365:
2484-96.

比例ハザード性がPFSでも成立しない



Perren et al.
NEJM 2011; 365:
2484-96.

ハイリスクではOSにも差



Bevacizumab Beyond Progression? (BRiTE研究) Grothey A et al. JCO 2008; 26: 5326-34.

進行後でもBeverizumabを投与した群では予後が良い
Treatment by indication?

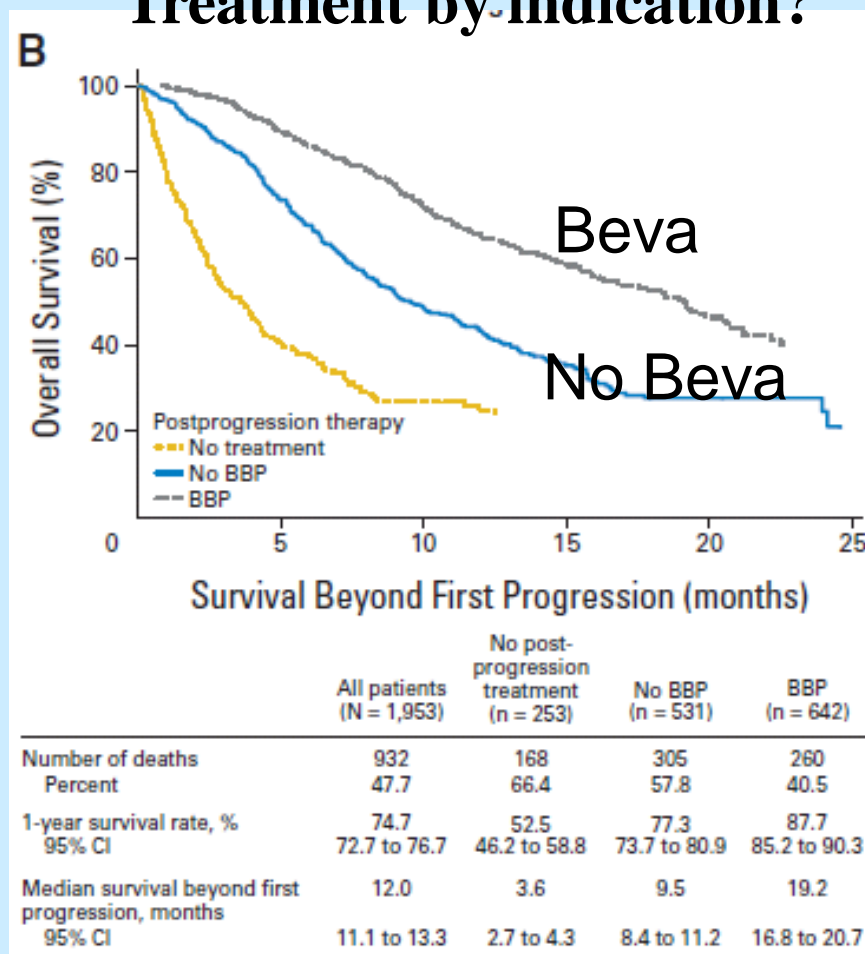


Fig2B

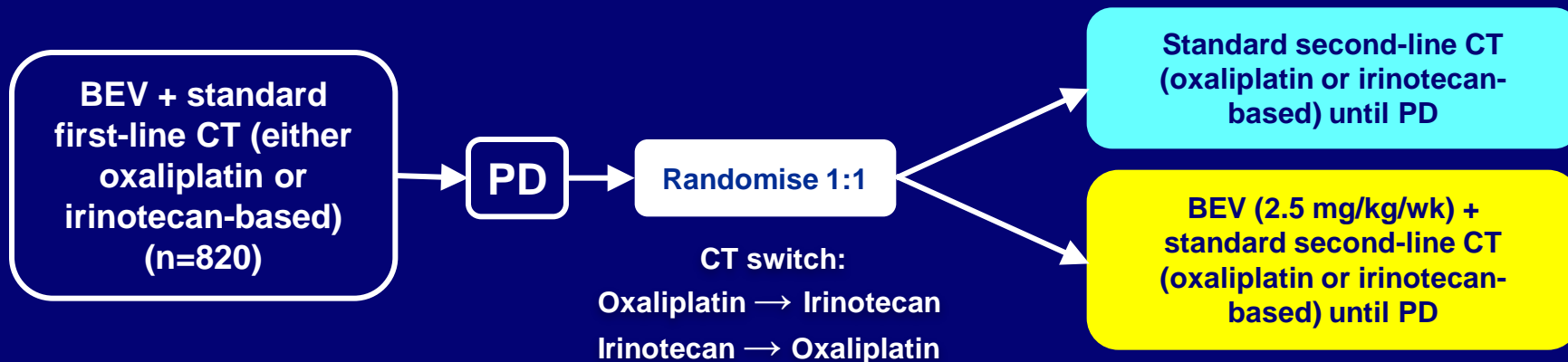
Bevacizumab (BEV) plus chemotherapy (CT) continued beyond first progression in patients with metastatic colorectal cancer (mCRC) previously treated with BEV + CT: Results of a randomised phase III intergroup study – TML (ML18147)

D Arnold¹, T Andre², J Bennouna³, J Sastre⁴, P Österlund⁵, R Greil⁶
E Van Cutsem⁷, R von Moos⁸, I Reyes-Rivera⁹, B Bendahmane¹⁰, S Kubicka¹¹

on behalf of the AIO, GERCOR, FFCD, UNICANCER GI, TTD, BGDO, GEMCAD and AGMT groups

¹Hamburg, Germany; ²Paris, France; ³Nantes, France; ⁴Madrid, Spain
⁵Helsinki, Finland; ⁶Salzburg, Austria; ⁷Leuven, Belgium; ⁸Chur, Switzerland ⁹South San Francisco, USA; ¹⁰Basel, Switzerland; ¹¹Reutlingen, Germany

ML18147 study design (phase III)



Primary endpoint

- Overall survival (OS) from randomisation

Secondary endpoints included

- Progression-free survival (PFS)
- Best overall response rate
- Safety

Stratification factors

- First-line CT (oxaliplatin-based, irinotecan-based)
- First-line PFS (≤ 9 months, > 9 months)
- Time from last BEV dose (≤ 42 days, > 42 days)
- ECOG PS at baseline (0/1, 2)

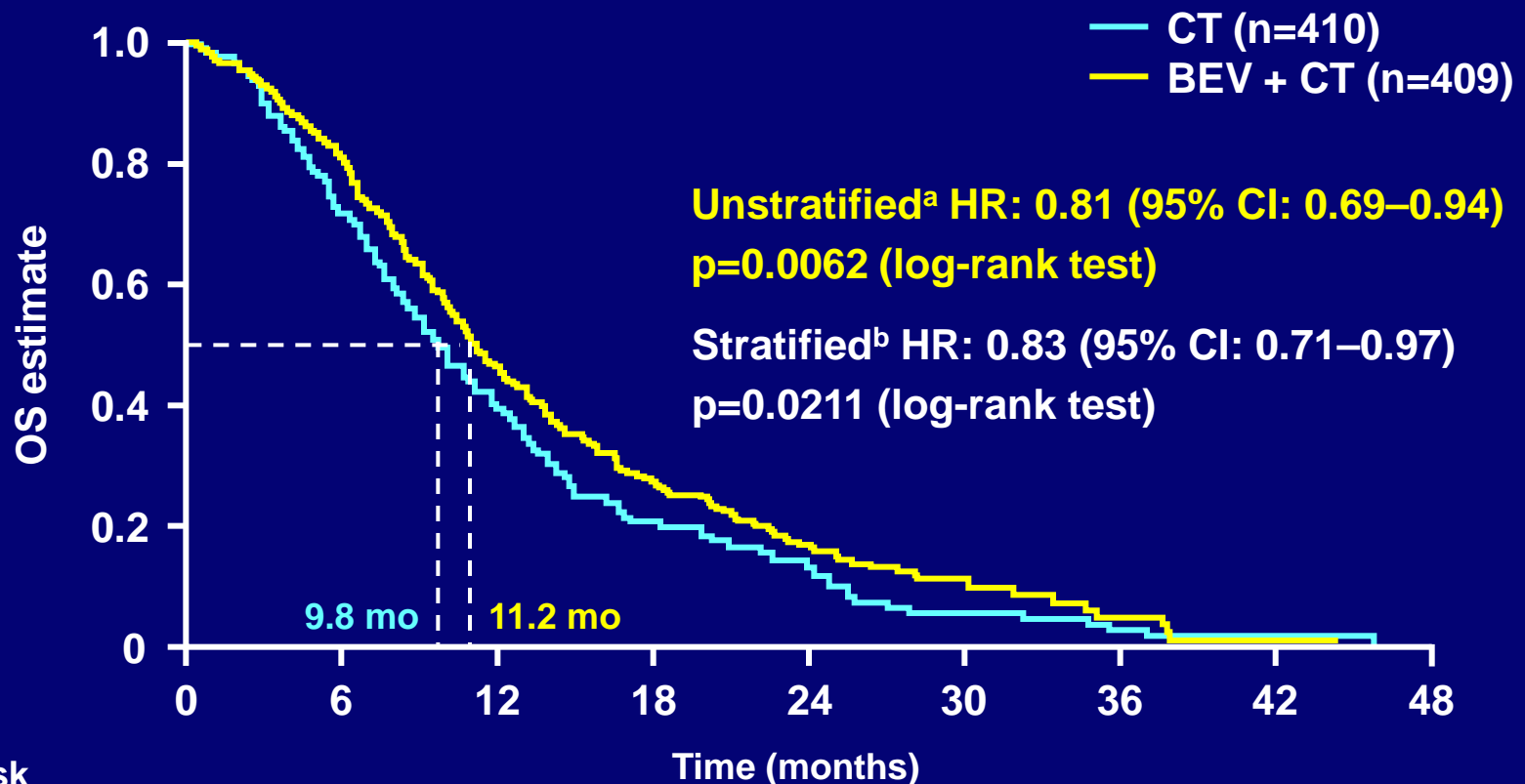
Study conducted in 220 centres in Europe and Saudi Arabia

営利目的での使用はご遠慮ください

Statistical considerations

- Study initiated as AIO KRK 0504 then transferred to Roche (after enrolment of 261 patients)
 - Primary endpoint changed from PFS to OS
 - Sample size increased from 572 to 810 patients
- Designed to detect 30% (HR 0.77) improvement in median OS (90% power, 2-sided 5%)
 - 613 events required for analysis
- OS curves estimated using Kaplan–Meier method, differences assessed using unstratified log-rank tests
 - Unstratified Cox regression model used to estimate HR for OS
 - Stratified log-rank tests and Cox regression analyses used as supportive analyses

OS: ITT population



No. at risk

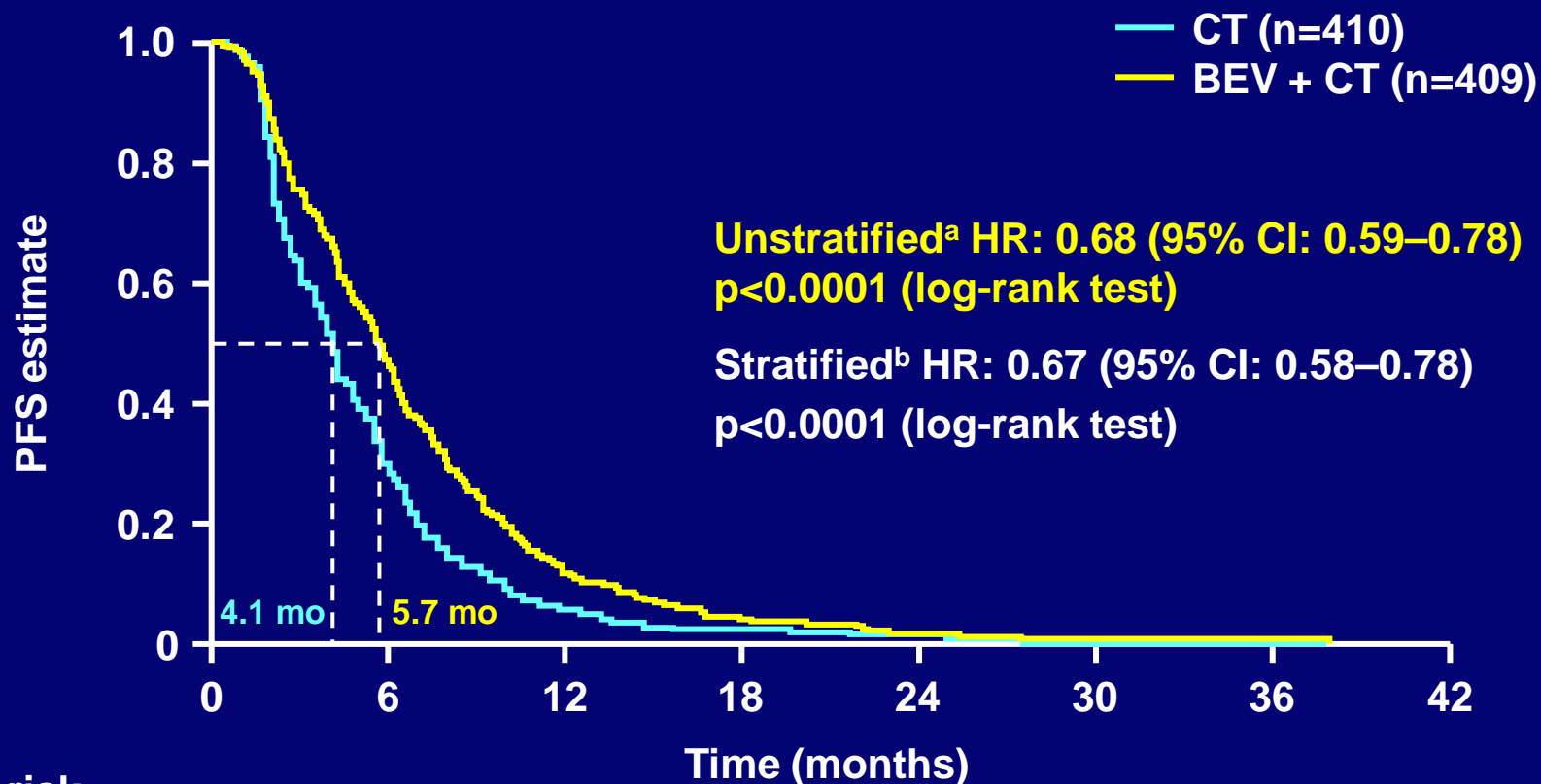
CT	410	293	162	51	24	7	3	2	0
BEV + CT	409	328	188	64	29	13	4	1	0

Median follow-up: CT, 9.6 months (range 0–45.5); BEV + CT, 11.1 months (range 0.3–44.0)

^aPrimary analysis method; ^bStratified by first-line CT (oxaliplatin-based, irinotecan-based), first-line PFS (≤ 9 months, >9 months), time from last dose of BEV (≤ 42 days, >42 days), ECOG performance status at baseline (0, ≥ 1)

営利目的での使用はご遠慮ください

PFS: ITT population



^aPrimary analysis method; ^bStratified by first-line CT (oxaliplatin-based, irinotecan-based), first-line PFS (≤ 9 months, > 9 months), time from last dose of BEV (≤ 42 days, > 42 days), ECOG performance status at baseline (0, ≥ 1)

Best overall response: Measurable disease population

Outcome	CT (n=406)	BEV + CT (n=404)
Responders ^a , n (%)	16 (3.9)	22 (5.4)
p-value (unstratified)		0.3113
p-value (stratified)		0.4315
Complete response, n (%)	2 (<1)	1 (<1)
Partial response, n (%)	14 (3)	21 (5)
Stable disease, n (%)	204 (50)	253 (63)
Disease control rate, n (%)	220 (54)	275 (68)
p-value ^b		<0.0001
PD, n (%)	142 (35)	87 (22)
Missing ^c , n (%)	44 (11)	42 (10)

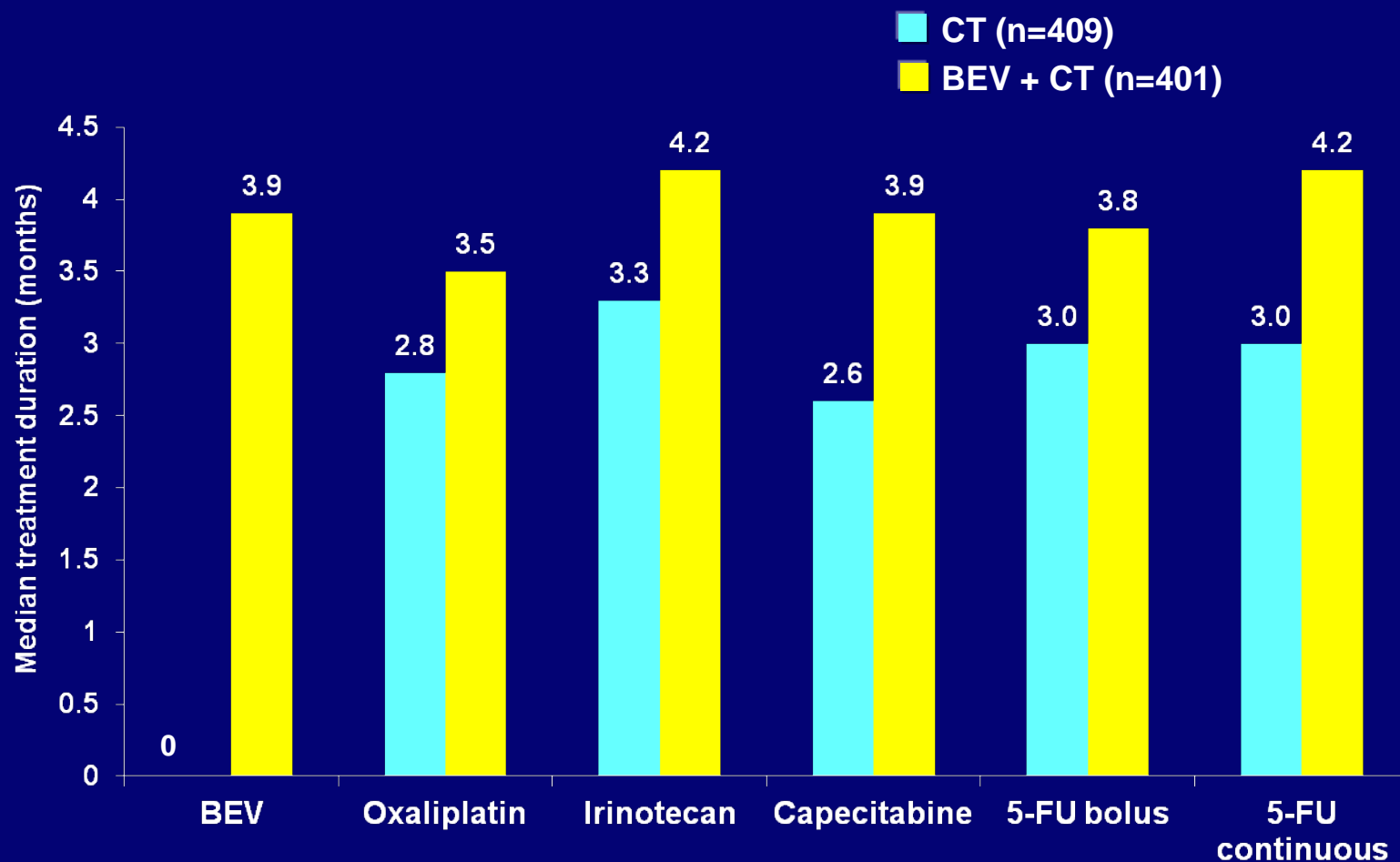
^aPatients with a best overall response of confirmed complete or partial response

^bThis analysis was not prespecified

^cIncludes 'not-evaluable' or 'no tumour assessment' following baseline visit

営利目的での使用はご遠慮ください

Treatment duration: Safety population



Duration from randomisation (ie first study drug) until discontinuation of all study drugs was 3.2 months for CT and 4.2 months for BEV + CT

Overview of adverse events: Safety population

Patients, %	CT (n=409)	BEV + CT (n=401)
Any AE	99	98
Serious AEs	34	32
Grade 3–5 AEs	58	64
Grade 5 AEs ^a	3	3
Discontinued any treatment due to AEs	9	16
Discontinued CT due to AE	9	13
Discontinued BEV only due to AE	N/A	2

^aPD leading to death captured for some patients as grade 5 AE; these events were excluded from this summary

AE: adverse event

営利目的での使用はご遠慮ください

Grade 3–5 adverse events (incidence $\geq 2\%$) in any arm: Safety population

Adverse event, %	CT (n=409)	BEV + CT (n=401)
Neutropenia	13	16
Leukopenia	3	4
Diarrhoea	8	10
Vomiting	3	4
Nausea	3	3
Abdominal pain	3	4
Subileus	<1	2
Asthenia	4	6
Fatigue	2	4
Mucosal inflammation	1	3
Dyspnoea	3	2
Pulmonary embolism	2	3
Polyneuropathy	2	3
Neuropathy peripheral	2	1
Hypokalaemia	2	2
Decreased appetite	2	1

Summary

- **BEV + standard second-line CT, crossed over from BEV + standard first-line CT, significantly prolongs OS and PFS**
 - **OS**
 - Median: BEV + CT 11.2 months, CT 9.8 months
 - HR: 0.81 (95% CI: 0.69–0.94), $p=0.0062^a$
 - **PFS**
 - Median: BEV + CT 5.7 months, CT 4.1 months
 - HR: 0.68 (95% CI: 0.59–0.78), $p\leq 0.0001^a$
- **Findings from subgroup analyses for OS generally consistent with overall population**
 - Treatment effect according to gender appeared to be different; however, treatment-gender interaction test was not statistically significant
- **Differences in best overall response rate not statistically significant; low response rate in both treatment groups**
- **AEs not increased when continuing BEV beyond PD; AE profile consistent with previous findings**

Conclusions

- First randomised clinical trial that prospectively investigated the impact of continued VEGF inhibition with BEV beyond first progression
- Study confirms that continuing BEV beyond first progression while modifying CT is beneficial for patients with mCRC and leads to a significant improvement in OS and PFS
- This provides a new second-line treatment option for patients who have been treated with BEV + standard CT in first line while maintaining an acceptable safety profile
- Findings indicate a potential new model for treatment approaches through multiple lines and this is currently being investigated in other tumour types

Discussion to #3504 (P. Vencok)



Other ASCO Meetings

Browse Tracks

Browse Sessions



2012 ASCO Annual Meeting > Gastrointestinal (Colorectal) Cancer Track > Gastrointestinal (Colorectal) Cancer

BRiTE Registry: Bevacizumab Regimens: Investigation Treatment Effects

Grothey et al, ASCO, 2007

	All Patients (N=1953)	No Post-PD Treatment (n=253)	No BBP (n=531)	BBP (n=642)
Number of Deaths, n (%)	932 (48%)	168 (66%)	306 (58%)	260 (41%)
Median OS, months (95% CI)	25.1 (23.4, 27.5)	12.6 (10.6, 15.7)	19.9 (18.0, 22.0)	31.8 (27.9, NE)
1-year survival rate, % (95% CI)	74.7 (72.7, 76.7)	52.5 (46.2, 58.8)	77.3 (73.7, 80.9)	87.7 (85.2, 90.3)
Median Survival beyond 1 st PD, months (95% CI)	12.0 (11.1, 13.3)	3.6 (2.7, 4.3)	9.5 (8.4, 11.2)	19.2 (16.8, 20.7)

Median OS: 19.9 v. 31.8 mos

OS Beyond PD: 9.5 v. 19.2 mos

7

PRESENTED AT: ASCO Annual '12 Meeting

II

0:03:50 0:24:36



The screenshot shows a presentation slide from the ASCO 2012 Annual Meeting. The slide is titled "What else does TML teach us?" in red. It contains a bulleted list in blue text stating that registry studies have limited utility regarding interventions and outcomes, with specific data from the BRiTE and TML trials. A red text block states that BRiTE findings were not replicated and could be cited as an example of registry data pitfalls. A footnote at the bottom right cites Grothey et al, JCO, 2008. The slide is presented by an individual (name obscured) at the ASCO Annual '12 Meeting. The video player interface at the bottom shows a progress bar at 0:06:33 of a 0:24:36 video.

ASCO

Other ASCO Meetings Browse Tracks Browse Sessions

2012 ASCO Annual Meeting > Gastrointestinal (Colorectal) Cancer Track > Gastrointestinal (Colorectal) Cancer

What else does TML teach us?

- Affirms the limited utility of Registry studies regarding interventions and outcomes:
 - BRiTE: 9.5 v. 19.2 OS beyond PD
 - TML: 9.8 v. 11.2

BRiTE findings not replicated; the publication* could be cited as an example of the pitfalls of Registry data

* Grothey et al, JCO, 2008

PRESENTED BY: [Name obscured]

PRESENTED AT: ASCO Annual '12 Meeting

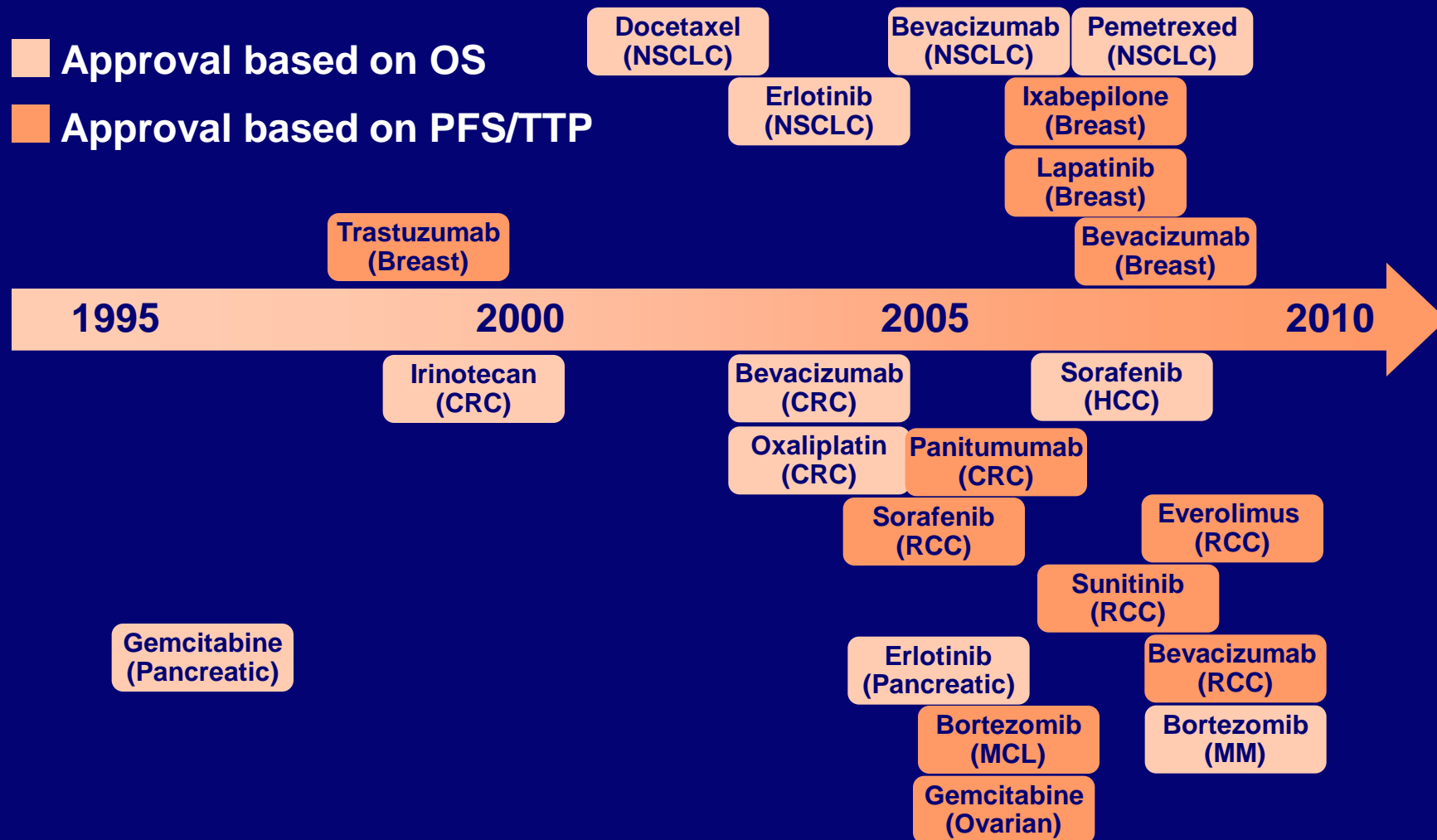
0:06:33 | 0:24:36

PFS とOS

- ◆ Bevacizumab は特殊な例？ ますます混迷？
- ◆ 治験でも研究者主導研究でもPFSが採用される例が増加
- ◆ FDAがPFSに基づいて最近承認した事例
 - gemcitabine in ovarian cancer
 - sorafenib in advanced renal cancer
 - bevacizumab in metastatic breast cancer
 - rituximab in Non-Hodgkin's lymphoma
 -

Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, May 2007

Increasing Acceptance of PFS as a Basis for FDA Approval



とりあえずの結論

- ◆ 2次治療以降に有効な治療が登場すれば
- ◆ SPP(survival post progression)が延長すれば
PFSのOSに対する代替性は薄まる(ハザードは希釈される)
- ◆ PFSの曖昧さとそれに対する対処の必要性
- ◆ 大きなPFSの改善と優れたrisk/benefit profileなら(さらに
経済的に許容できるなら)PFSによる承認は当然ありうる

ASCO2011 Targeting Angiogenesis in Breast Cancer: Where Do We Stand in 2011? Appropriate Endpoints for Clinical Trials and Source of U.S. Food and Drug Administration/Oncologic Drugs Advisory Committee Controversy Daniel J. Sargent, P もっともスマートな癌の生物統計家

ASCO

Other ASCO Meetings Browse Tracks Browse Sessions

2011 ASCO Annual Meeting > Breast Cancer Track > Targeting Angiogenesis in Breast Cancer: Where Do We Stand in 2011?

Phase III Trial Endpoints in Oncology: The PFS Controversy

Daniel Sargent, PhD
Professor of Biostatistics & Oncology
Mayo Clinic
June 7, 2011

MAYO CLINIC

0:00:12 0:24:15

ASCO2011: Targeting Angiogenesis in Breast Cancer: Where Do We Stand in 2011?

Appropriate Endpoints for Clinical Trials and Source of U.S. Food and Drug Administration/Oncologic Drugs Advisory Committee Controversy

Daniel J. Sargent, P 代替性の評価: 唯一の標準はない

The screenshot shows a presentation slide from the ASCO 2011 Annual Meeting. The slide is titled "Validation of Surrogate Endpoints" in large yellow text on a blue background. Below the title, it lists "Statistical" and "Clinical" considerations for surrogate endpoints. The "Statistical" section mentions "Meta-analyses of clinical trials data". The "Clinical" section mentions "Comprehensive understanding of the" followed by two bullet points: "Causal pathways of the disease process" and "Intervention's intended and unintended mechanisms of action". At the bottom, it states "No single gold standard approach". The slide is part of a video player, with a progress bar at the bottom showing 0:03:06 / 0:24:15. The ASCO logo is in the top left corner of the slide frame, and the Mayo Clinic logo is in the bottom left corner of the slide content.

ASCO

Other ASCO Meetings Browse Tracks Browse Sessions

2011 ASCO Annual Meeting > Breast Cancer Track > Targeting Angiogenesis in Breast Cancer: Where Do We Stand in 2011?

Validation of Surrogate Endpoints

Statistical

- Meta-analyses of clinical trials data

Clinical

- Comprehensive understanding of the
 - ~ Causal pathways of the disease process
 - ~ Intervention's intended and unintended mechanisms of action

No single gold standard approach

MAYO CLINIC

0:03:06 0:24:15

ASCO2011: Targeting Angiogenesis in Breast Cancer: Where Do We Stand in 2011?

Appropriate Endpoints for Clinical Trials and Source of U.S. Food and Drug Administration/Oncologic Drugs Advisory Committee Controversy

Daniel J. Sargent, P **PFSの問題**

The screenshot shows a presentation slide from the ASCO 2011 Annual Meeting. The slide is titled "Progression free survival" in yellow text on a blue background. It lists two main points: "Typical definition: Time to the first of disease progression or death" and "Challenges". Under "Challenges", there are four sub-points: "Subjective – subject to bias", "Measurement error", "Non-radiographic worsening", and "Stopping treatment for reasons other than progression". The slide is part of a video presentation, as indicated by the ASCO logo and navigation buttons at the top, and a video player interface at the bottom showing a progress bar and time (0:04:27 / 0:24:15).

ASCO

Other ASCO Meetings Browse Tracks Browse Sessions

2011 ASCO Annual Meeting > Breast Cancer Track > Targeting Angiogenesis in Breast Cancer: Where Do We Stand in 2011?

Progression free survival

- Typical definition: Time to the first of disease progression or death
- Challenges
 - Subjective – subject to bias
 - Measurement error
 - Non-radiographic worsening
 - Stopping treatment for reasons other than progression

MAYO CLINIC

0:04:27 0:24:15

ASCO2011: Targeting Angiogenesis in Breast Cancer: Where Do We Stand in 2011?

Appropriate Endpoints for Clinical Trials and Source of U.S. Food and Drug Administration/Oncologic Drugs Advisory Committee Controversy

Daniel J. Sargent, P

オンコロジストはPFS向上の意義を過大評価しがち

The image shows a screenshot of a presentation slide from the ASCO 2011 Annual Meeting. The slide is titled "Is PFS a Clinical Benefit Endpoint? Opinion: Con" and features a bulleted point stating: "We believe the oncology community may be over-interpreting the value of improvements in PFS; such improvements, particularly if related to asymptomatic imaging changes, do not necessarily provide evidence for a gain in important outcomes to patients". The slide is attributed to "Ocaña et al JCO 2011" and includes the Mayo Clinic logo in the bottom left corner. The presentation interface includes navigation buttons at the top and a video player control bar at the bottom.

ASCO

Other ASCO Meetings Browse Tracks Browse Sessions

2011 ASCO Annual Meeting > Breast Cancer Track > Targeting Angiogenesis in Breast Cancer: Where Do We Stand in 2011?

Is PFS a Clinical Benefit Endpoint?

Opinion: Con

- 'We believe the oncology community may be over-interpreting the value of improvements in PFS; such improvements, particularly if related to asymptomatic imaging changes, do not necessarily provide evidence for a gain in important outcomes to patients'

Ocaña et al JCO 2011

MAYO CLINIC

0:06:01 0:24:15

ASCO2011: Targeting Angiogenesis in Breast Cancer: Where Do We Stand in 2011?

Appropriate Endpoints for Clinical Trials and Source of U.S. Food and Drug Administration/Oncologic Drugs Advisory Committee Controversy

Daniel J. Sargent, 致死的疾患において便益が充分で副作用受容可能なら、PFS向上を受け入れない理由は無い

ASCO

Other ASCO Meetings Browse Tracks Browse Sessions

2011 ASCO Annual Meeting > Breast Cancer Track > Targeting Angiogenesis in Breast Cancer: Where Do We Stand in 2011?

Is PFS a Clinical Benefit Endpoint? Opinion: Pro

- "I have no problem accepting that, in a lethal disease such as metastatic cancer, delaying progression is a clinical benefit in itself, provided that the magnitude of the benefit is sufficient and the side-effect profile acceptable."

R Pazdur, NCI Cancer Bulletin May 13, 2008
http://www.cancer.gov/ncicancerbulletin/NCI_Cancer_Bulletin_051308/page7

MAYO CLINIC

10

01:06:16 01:24:15

ASCO2011: Targeting Angiogenesis in Breast Cancer: Where Do We Stand in 2011?

Appropriate Endpoints for Clinical Trials and Source of U.S. Food and Drug Administration/Oncologic Drugs Advisory Committee Controversy

Daniel J. Sargent, P PFSの長所と代替性

The screenshot shows a video player interface for an ASCO 2011 presentation. The top navigation bar includes the ASCO logo and buttons for 'Other ASCO Meetings', 'Browse Tracks', and 'Browse Sessions'. The breadcrumb trail reads: '2011 ASCO Annual Meeting > Breast Cancer Track > Targeting Angiogenesis in Breast Cancer: Where Do We Stand in 2011?'. The main content area displays a blue slide with the title 'Merits of PFS as an endpoint' in yellow. The slide lists three main points: 'Un-encumbered by cross-over', 'Available more quickly than OS', and 'Variable demonstration of surrogacy for OS'. The third point is further detailed with three sub-points: 'Colon – Yes – Buyse JCO 2007', 'Breast – No – Burzykowski, JCO 2008', and 'Lung – Unclear – Buyse ASCO 2008'. The slide footer includes the Mayo Clinic logo and the number '12'. The video player controls at the bottom show a progress bar, a timestamp of 0:08:35, and a total duration of 0:24:15.

ASCO

Other ASCO Meetings Browse Tracks Browse Sessions

2011 ASCO Annual Meeting > Breast Cancer Track > Targeting Angiogenesis in Breast Cancer: Where Do We Stand in 2011?

Merits of PFS as an endpoint

- Un-encumbered by cross-over
- Available more quickly than OS
- Variable demonstration of surrogacy for OS
 - Colon – Yes – Buyse JCO 2007
 - Breast – No – Burzykowski, JCO 2008
 - Lung – Unclear – Buyse ASCO 2008

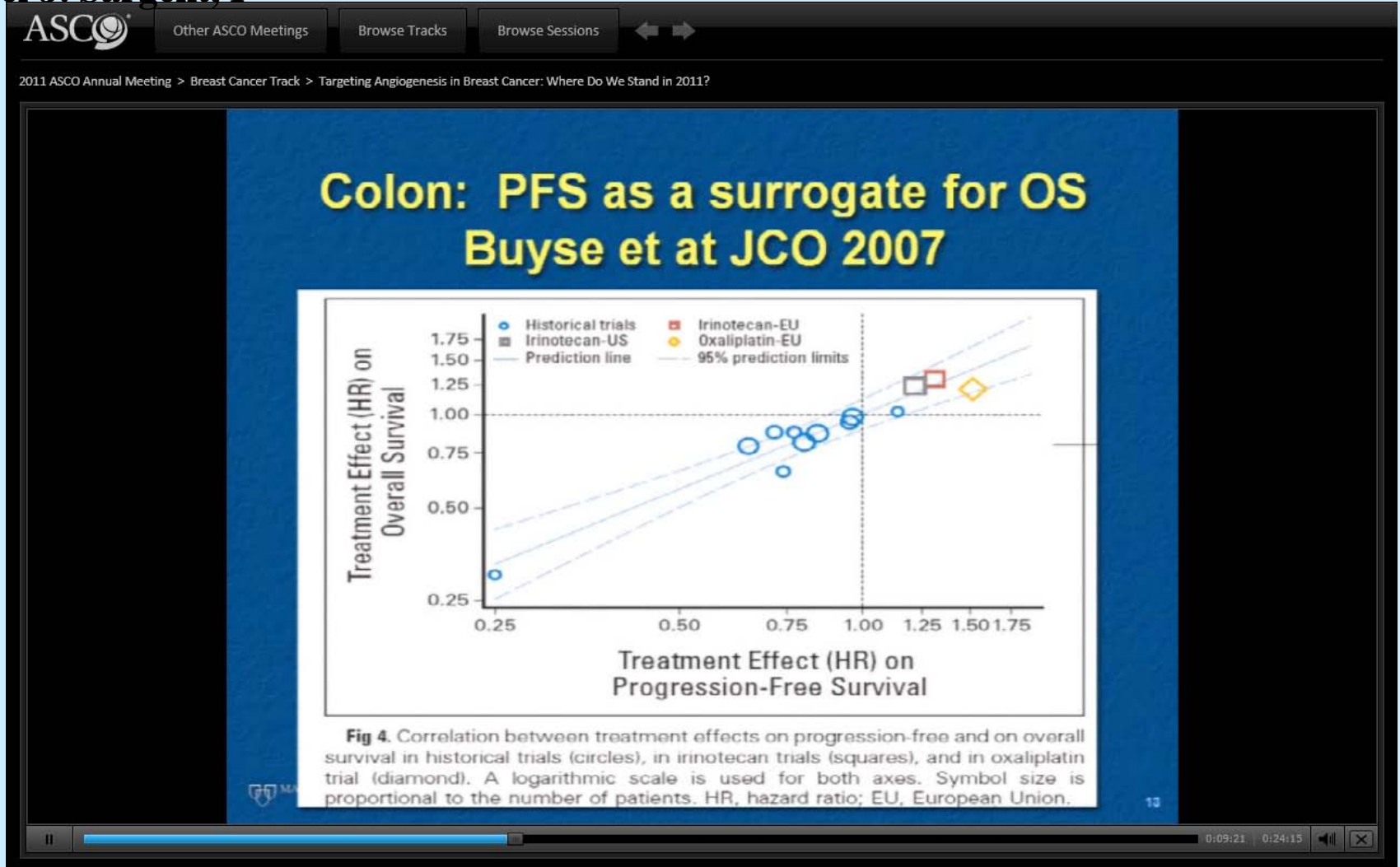
MAYO CLINIC 12

0:08:35 0:24:15

ASCO2011: Targeting Angiogenesis in Breast Cancer: Where Do We Stand in 2011?

Appropriate Endpoints for Clinical Trials and Source of U.S. Food and Drug Administration/Oncologic Drugs Advisory Committee Controversy

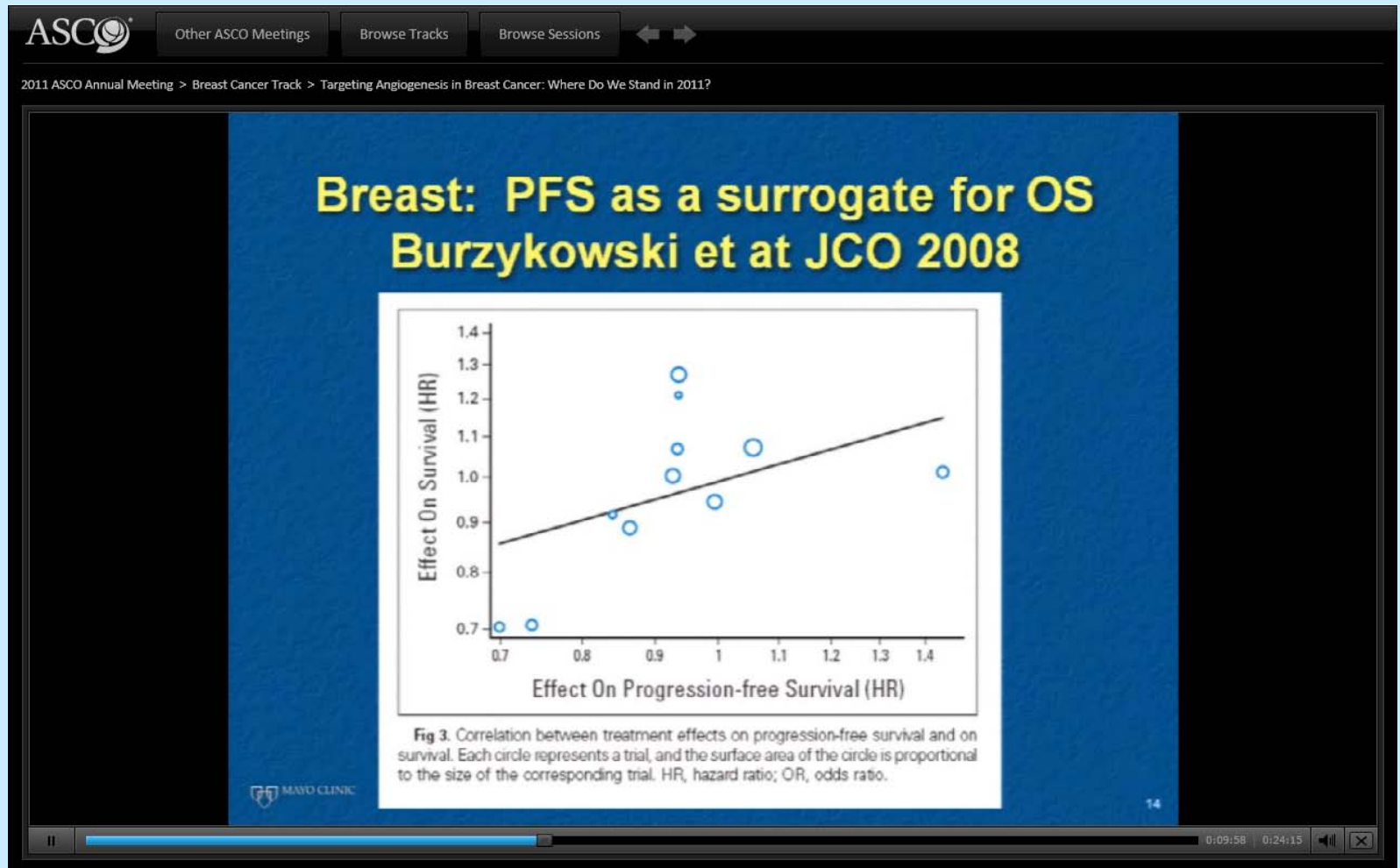
Daniel J. Sargent, P



ASCO2011: Targeting Angiogenesis in Breast Cancer: Where Do We Stand in 2011?

Appropriate Endpoints for Clinical Trials and Source of U.S. Food and Drug Administration/Oncologic Drugs Advisory Committee Controversy

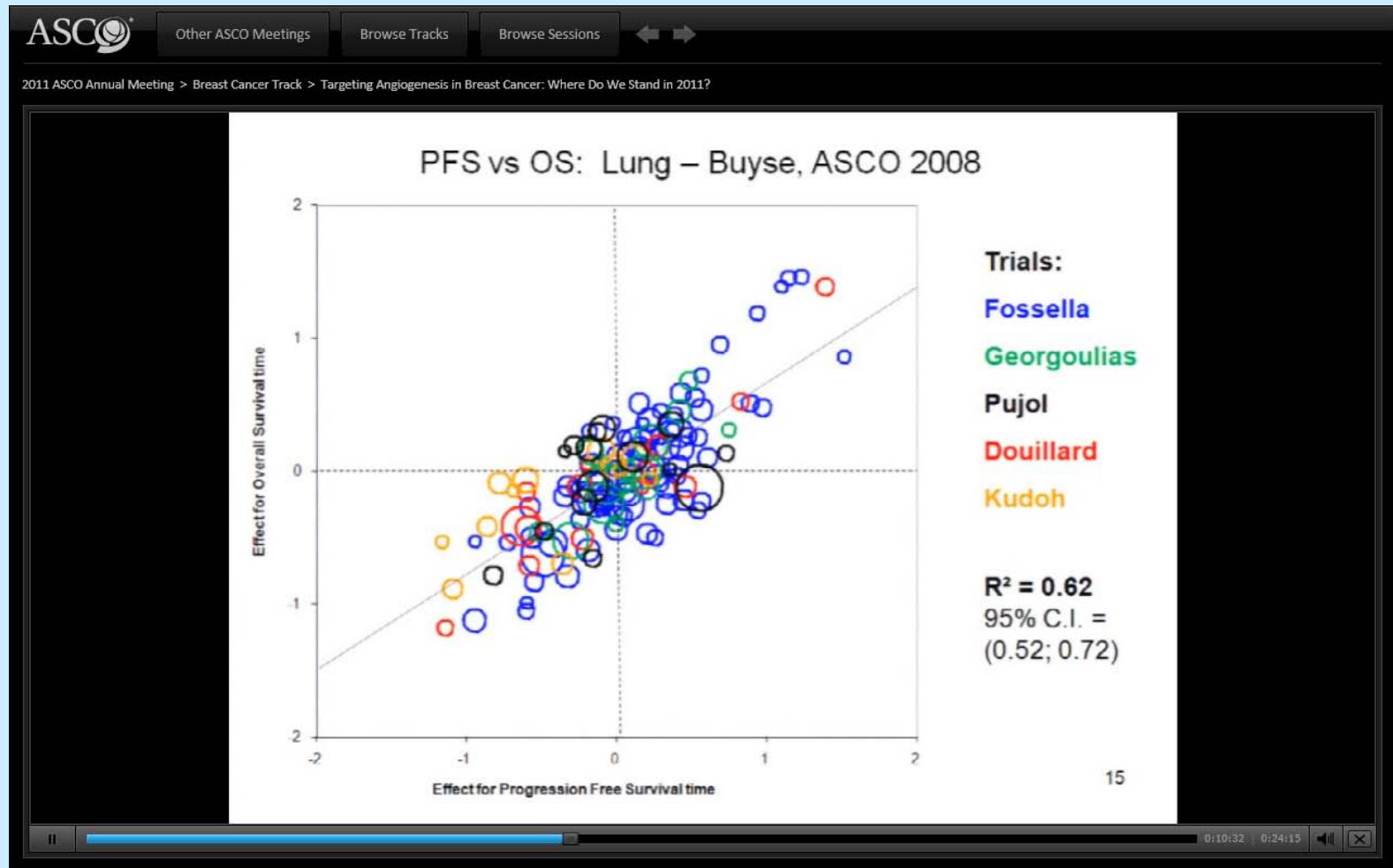
Daniel J. Sargent, P



ASCO2011: Targeting Angiogenesis in Breast Cancer: Where Do We Stand in 2011?

Appropriate Endpoints for Clinical Trials and Source of U.S. Food and Drug Administration/Oncologic Drugs Advisory Committee Controversy

Daniel J. Sargent, P



ASCO2011: Targeting Angiogenesis in Breast Cancer: Where Do We Stand in 2011?

Appropriate Endpoints for Clinical Trials and Source of U.S. Food and Drug Administration/Oncologic Drugs Advisory Committee Controversy

Daniel J. Sargent, P

ASCO

Other ASCO Meetings Browse Tracks Browse Sessions

2011 ASCO Annual Meeting > Breast Cancer Track > Targeting Angiogenesis in Breast Cancer: Where Do We Stand in 2011?

PFS Surrogacy Summary: Meta-Analyses

Disease	Treatment comparisons	Trials	Units	Patients
Advanced breast	taxanes vs. anthracyclines	11	11 trials	3953
Advanced colorectal	5-FU+LV vs. 5FU / tomudex	10	10 trials	3089
Advanced lung	docetaxel vs. vinca alkaloids	7	401 centers	2838

Disease	R ² between PFS and OS	R ² between treatment effects	Surrogate threshold effect (HR)
Advanced breast	0.47 (0.47 – 0.48)	0.23 (0.12 – 1.69)	Not estimable
Advanced colorectal	0.82 (0.82 – 0.83)	0.98 (0.88 – 1.08)	0.86
Advanced lung	0.61 (0.61 – 0.61)	0.72 (0.63 – 0.79)	0.70

Refs: Burzykowski et al, J Clin Oncol 2008; 26: 1987
Buyse et al, J Clin Oncol 2007; 25: 5218
Buyse et al, ASCO 2008

16

0:10:47 0:24:15

ASCO2011: Targeting Angiogenesis in Breast Cancer: Where Do We Stand in 2011?

Appropriate Endpoints for Clinical Trials and Source of U.S. Food and Drug Administration/Oncologic Drugs Advisory Committee Controversy

Daniel J. Sargent, P

ASCO

Other ASCO Meetings Browse Tracks Browse Sessions

2011 ASCO Annual Meeting > Breast Cancer Track > Targeting Angiogenesis in Breast Cancer: Where Do We Stand in 2011?

Conclusions: PFS as a surrogate endpoint

- Is PFS a surrogate for OS in cancer?
 - When no effective 2nd line rx: Yes
 - When effective 2nd and later lines rx: likely no
- As survival beyond progression lengthens, surrogacy becomes difficult
 - Attenuated HR
 - Additional noise
- Need further modeling to understand when surrogacy even possible

MAVO CLINIC

28

0:20:20 0:24:15

ASCO2011: Targeting Angiogenesis in Breast Cancer: Where Do We Stand in 2011?

Appropriate Endpoints for Clinical Trials and Source of U.S. Food and Drug Administration/Oncologic Drugs Advisory Committee Controversy

Daniel J. Sargent, P

ASCO

Other ASCO Meetings Browse Tracks Browse Sessions

2011 ASCO Annual Meeting > Breast Cancer Track > Targeting Angiogenesis in Breast Cancer: Where Do We Stand in 2011?

Final thoughts: Beyond statistics

- Requirement of OS benefit from one of many lines a very high bar
- PFS benefits must be clinically relevant with acceptable risk/benefit ratio
- Failure of PFS advantage to translate into OS must be plausible

MAYO CLINIC

33

0:22:33 0:24:15

ASCO2011- 4095 GASTRICの胃癌メタアナリシスグループ (投稿準備中)

The screenshot displays the ASCO 2011 Slide Viewer interface. At the top, the ASCO logo is on the left, and navigation buttons for 'Other ASCO Meetings', 'Browse Tracks', and 'Browse Sessions' are on the right. Below these is a breadcrumb trail: '2011 ASCO Annual Meeting > Gastrointestinal (Noncolorectal) Cancer Track > Gastrointestinal (Noncolorectal) Cancer'. The main area is a slide titled 'Progression-free Survival as Surrogate Endpoint of Overall Survival in Patients with Advanced/Recurrent Gastric Cancer: Individual Patient Data Analysis on 4,102 patients from 20 Randomized Trials'. The authors are 'Kohei Shitara and Tomasz Burzykowski', and the text continues 'on behalf of the Global Advanced/Adjuvant Stomach Tumor Research through International Collaboration (GASTRIC)'. The slide has a blue gradient background. At the bottom, there is a navigation bar with arrows and a progress indicator showing '1 / 15'.

ASCO

Other ASCO Meetings Browse Tracks Browse Sessions

2011 ASCO Annual Meeting > Gastrointestinal (Noncolorectal) Cancer Track > Gastrointestinal (Noncolorectal) Cancer

SLIDE VIEWER Use arrows below to navigate

Progression-free Survival as Surrogate
Endpoint of Overall Survival in Patients with
Advanced/Recurrent Gastric Cancer:
Individual Patient Data Analysis on 4,102
patients from 20 Randomized Trials

Kohei Shitara and Tomasz Burzykowski
on behalf of the Global Advanced/Adjuvant Stomach Tumor
Research through International Collaboration (GASTRIC)

1 / 15

4095 試験内のOSとPFSの相関は高いものの、試験間は中間



Other ASCO Meetings

Browse Tracks

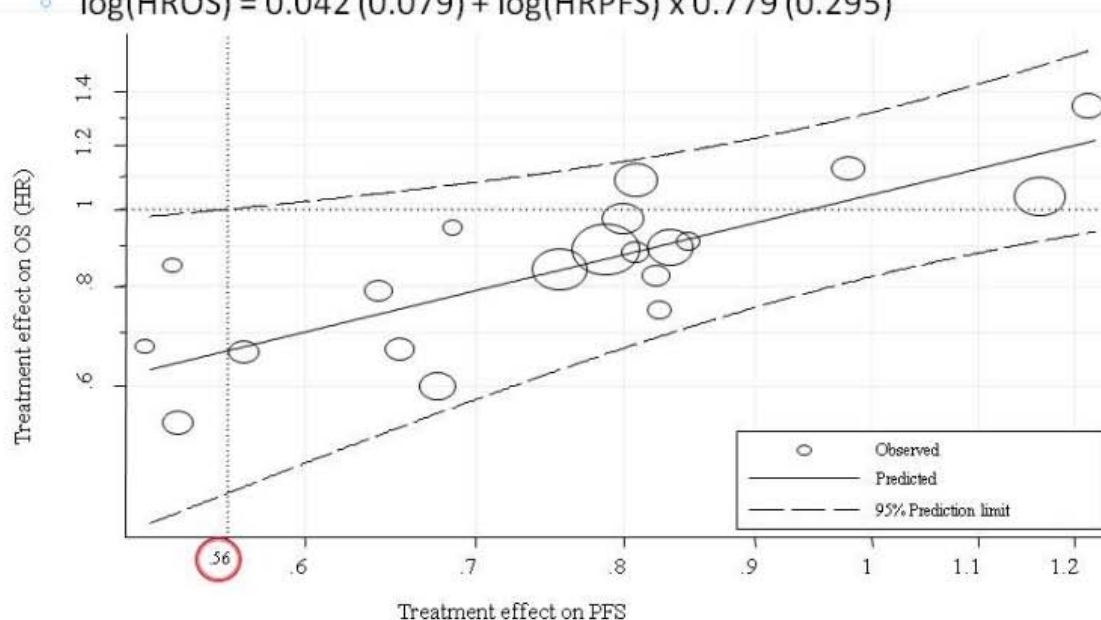
Browse Sessions



2011 ASCO Annual Meeting > Gastrointestinal (Noncolorectal) Cancer Track > Gastrointestinal (Noncolorectal) Cancer

Treatment effects on OS and PFS

- Trial-level R^2 adjusted for the estimation errors, present in the observed treatment effects, was estimated to be equal to 0.61 (95% CI 0.04-1.17)
- $\log(\text{HROS}) = 0.042 (0.079) + \log(\text{HRPFS}) \times 0.779 (0.295)$



12



ASC02011- 1035

FDA申請データの乳癌データの解析。FDAではこれができる

The screenshot shows the ASCO 2011 Slide Viewer interface. At the top, there is a navigation bar with the ASCO logo and buttons for "Other ASCO Meetings", "Browse Tracks", and "Browse Sessions". Below this, a breadcrumb trail reads "2011 ASCO Annual Meeting > Breast Cancer Track > Breast Cancer - Triple-negative/Cytotoxics/Local Therapy". The main content area is a slide viewer with a blue background. The slide title is "Relationship between OS and PFS in metastatic breast cancer: review of FDA submission data" in large yellow text. Below the title, the authors are listed: "P. Cortazar, J. Zhang, R. Sridhara, R. Justice, R. Pazdur". At the bottom of the slide, there is a word cloud and the text "Presented at the 2011 ASCO Annual Meeting. Presented data is the property of the author." followed by the ASCO logo and "Annual '11 Meeting". The slide viewer interface includes a "SLIDE VIEWER" label, navigation arrows, and a progress bar at the bottom.

ASCO

Other ASCO Meetings Browse Tracks Browse Sessions

2011 ASCO Annual Meeting > Breast Cancer Track > Breast Cancer - Triple-negative/Cytotoxics/Local Therapy

SLIDE VIEWER Use arrows below to navigate

Relationship between OS and PFS in metastatic breast cancer: review of FDA submission data

P. Cortazar, J. Zhang, R. Sridhara,
R. Justice, R. Pazdur

Presented at the 2011 ASCO Annual Meeting. Presented data is the property of the author. ASCO Annual '11 Meeting



Other ASCO Meetings

Browse Tracks

Browse Sessions



2011 ASCO Annual Meeting > Breast Cancer Track > Breast Cancer - Triple-negative/Cytotoxics/Local Therapy

Study (N)	Treatment Arm/Control Arm	Therapy Line
SO14999 (511)	capecitabine + docetaxel/ docetaxel	2 nd /3 rd
EGF1000151 (399)	lapatinib + capecitabine/ capecitabine	2 nd /3 rd
CA163046 (752)	ixabepilone + capecitabine/ capecitabine	2 nd /3 rd
BCA3001 (751)	Doxorubicin (liposomal)+docetaxel/ docetaxel	2 nd /3 rd
AVF2119g (462)	bevacizumab + capecitabine/ capecitabine	2 nd /3 rd
RIBBON2 (684)	bevacizumab + chemo/ chemo	2 nd /3 rd
EMBRACE (762)	Eribulin/ physician's choice	2 nd /3 rd
H0648g (469)	Trastuzumab + paclitaxel/ paclitaxel	1 st
JHQG (529)	gemcitabine + paclitaxel/ paclitaxel	1 st
E2100 (722)	bevacizumab + paclitaxel/ paclitaxel	1 st
AVADO (736)	bevacizumab + docetaxel/ docetaxel	1 st
RIBBON1 (1237)	bevacizumab+chemo/ chemo	1 st
EGF30008 (1286)	lapatinib + letrozole/ letrozole	1 st
EFC11486 (519)	iniparib + gem-carboplatin/ gem-carboplatin	1 st /2 nd /3 rd

Presented at the 2011 ASCO Annual Meeting. Presented data is the property of the author.

Annual '11
Meeting

1035 TNでは相関高い



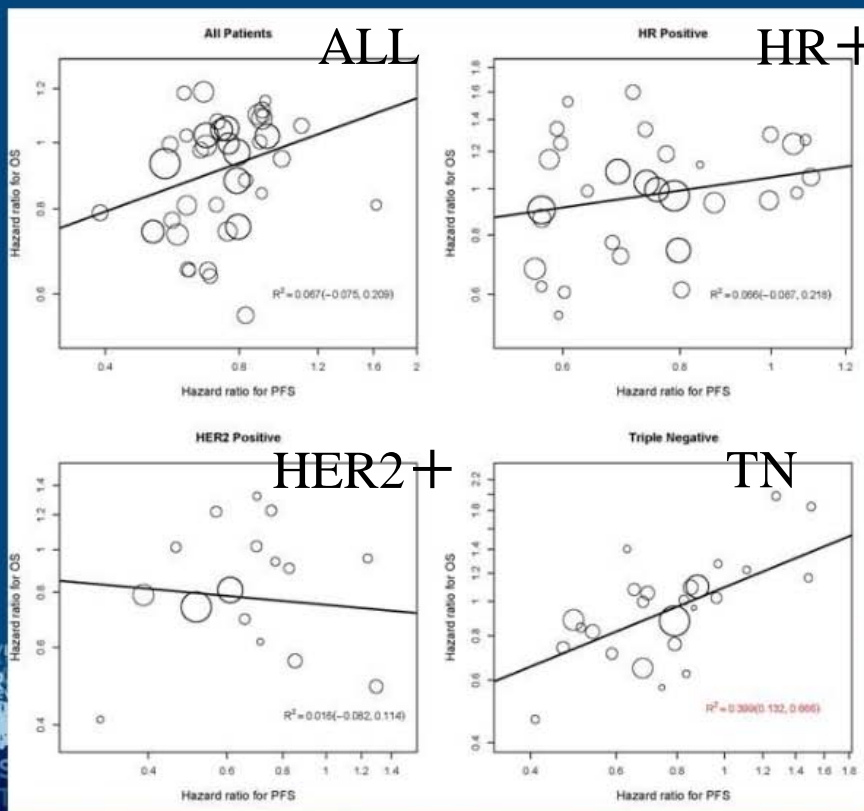
Other ASCO Meetings

Browse Tracks

Browse Sessions



2011 ASCO Annual Meeting > Breast Cancer Track > Breast Cancer - Triple-negative/Cytotoxics/Local Therapy




Presented at the 2011 ASCO Annual Meeting. Presented data is the property of the author.



Annual '11 Meeting


1035 TNは有効な2次治療が存在しない


[Other ASCO Meetings](#)
[Browse Tracks](#)
[Browse Sessions](#)

2011 ASCO Annual Meeting > Breast Cancer Track > Breast Cancer - Triple-negative/Cytotoxics/Local Therapy

Subgroup	N (%)	R ² (95% CI)
All patients	9819 (100%)	0.067 (-0.075, 0.209)
HR positive	5594 (57.0%)	0.066 (-0.087, 0.218)
HR negative	2086 (21.2%)	0.100 (-0.089, 0.289)
HER2 positive	1449 (14.8%)	0.016 (-0.082, 0.114)
HER2 negative	5821 (59.3%)	0.063 (-0.095, 0.221)
Triple negative	1918 (19.5%)	0.399 (0.132, 0.666)
1 st line	5276 (56.7%)	0.162 (-0.087, 0.410)
2 nd /3 rd line	4543 (48.8%)	0.100 (-0.117, 0.316)

Presented at the 2011 ASCO Annual Meeting. Presented data is the property of the author.

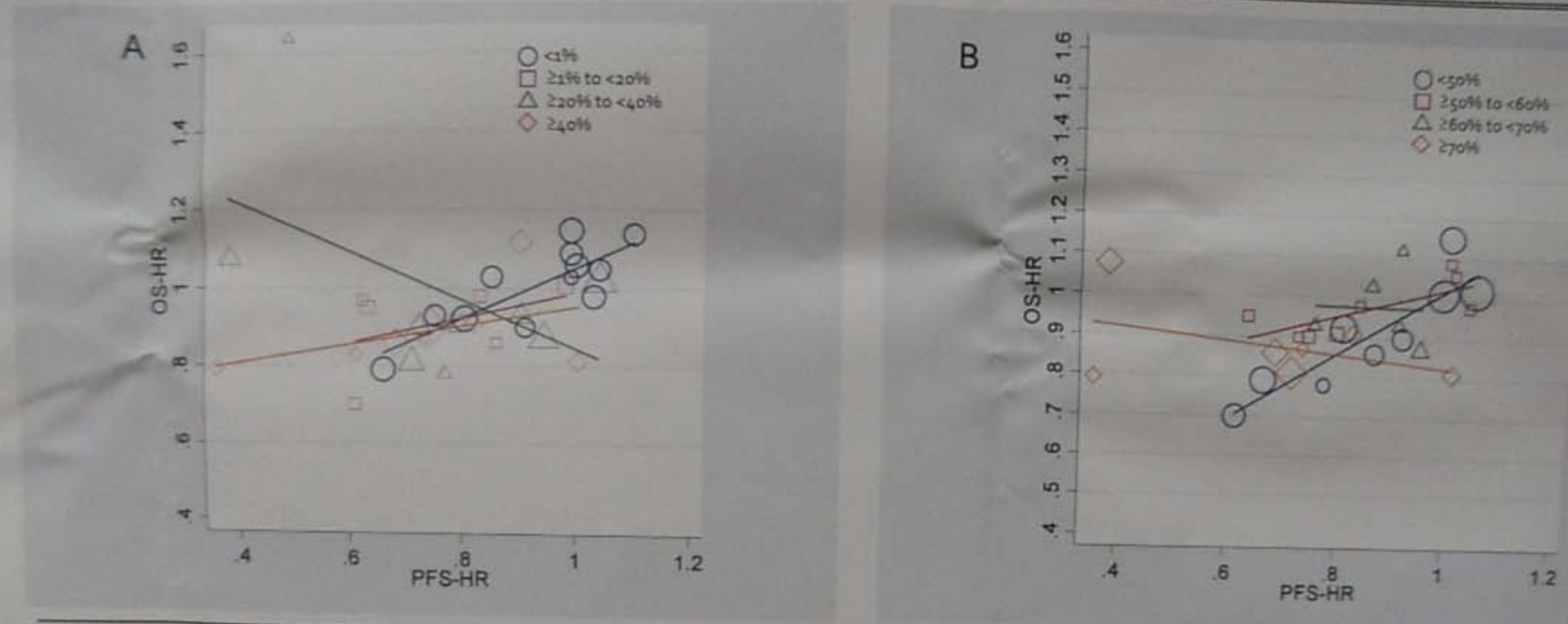

Annual '11 Meeting

ASCO2011-7540 Hotta et al.

肺癌の事例：クロスオーバーと2次治療の影響

2次治療へのクロスオーバーによりPFS代替性失われる

Fig. 3 Associations between PFS- and OS-HR stratified by the proportion of crossover therapy (A) and by the proportion of any post-study chemotherapy



OSかPFSか？

- ◆ **Survival Post Progression (SPP) が長くなる (たとえば12ヶ月以上) と、PFSのOSに対する代替性は弱くなる**

乳癌から、大腸癌そしてNSCLCへ

Broglio and Berry, *JNCI* 2009; 101: 1642-9.

Detecting an Overall Survival Benefit that Is Derived From Progression-Free Survival

Kristine R. Broglio, Donald A. Berry

Background	Whether progression-free survival (PFS) or overall survival (OS) is the more appropriate endpoint in clinical trials of metastatic cancer is controversial. In some disease and treatment settings, an improvement in PFS does not result in an improved OS.
Methods	We partitioned OS into two parts and expressed it as the sum of PFS and survival postprogression (SPP). We simulated randomized clinical trials with two arms that had respective medians for PFS of 6 and 9 months. We assumed no treatment difference in median SPP. We found the probability of a statistically significant benefit in OS for various median SPP and observed <i>P</i> values for PFS. We compared the sample sizes required for PFS vs OS for various median SPP. We compare our results with the literature regarding surrogacy of PFS for OS by use of the correlation between hazard ratios for PFS and OS. All statistical tests were two-sided.
Results	For a trial with observed <i>P</i> value for improvement in PFS of .001, there was a greater than 90% probability for statistical significance in OS if median SPP was 2 months but less than 20% if median SPP was 24 months. For a trial requiring 280 patients to detect a 3-month difference in PFS, 350 and 2440 patients, respectively, were required to have the same power for detecting a real difference in OS that is carried over from the 3-month benefit in PFS when the median SPP was 2 and 24 months.
Conclusions	Addressing SPP is important in understanding treatment effects. For clinical trials with a PFS benefit, lack of statistical significance in OS does not imply lack of improvement in OS, especially for diseases with long median SPP. Although there may be no treatment effect on SPP, its variability so dilutes the OS comparison that statistical significance is likely lost. OS is a reasonable primary endpoint when median SPP is short but is too high a bar when median SPP is long, such as longer than 12 months.

J Natl Cancer Inst 2009;101:1642-1649

PFSのOSに対する代替性

Broglio and Berry, JNCI 2009; 101: 1642-9

CONTEXT AND CAVEATS

Prior knowledge

It is still controversial as to whether progression-free survival (PFS) or overall survival (OS) is the most appropriate endpoint in clinical trials of metastatic cancer.

まだまだ議論の余地あり

Study design

Clinical trials with two arms having respective medians for PFS of 6 and 9 months were simulated. OS was the sum of PFS and **survival postprogression (SPP)**.

Probabilities of a benefit in OS were determined for various median SPP, by assuming no treatment related difference in SPP, and for observed *P* values for PFS. Sample sizes required for various PFS and OS values were determined.

進行後の生存(SPP)

PFSのOSに対する代替性

Broglio and Berry, JNCI 2009; 101: 1642-9

CONTEXT AND CAVEATS

Contribution

OS was a reasonable primary endpoint when median SPP was short but was too high a bar when median SPP was long (eg, longer than 12 months).

Implications

As therapies for metastatic cancer improve, SPP would be expected to increase, which may decrease the utility of OS as a clinical endpoint.

Limitations

Simulations considered a specific difference in median PFS, accrual rate, and follow-up time. PFS and SPP were assumed to follow exponential distributions. The assumption that there was no difference in SPP may not be correct in a particular circumstance.

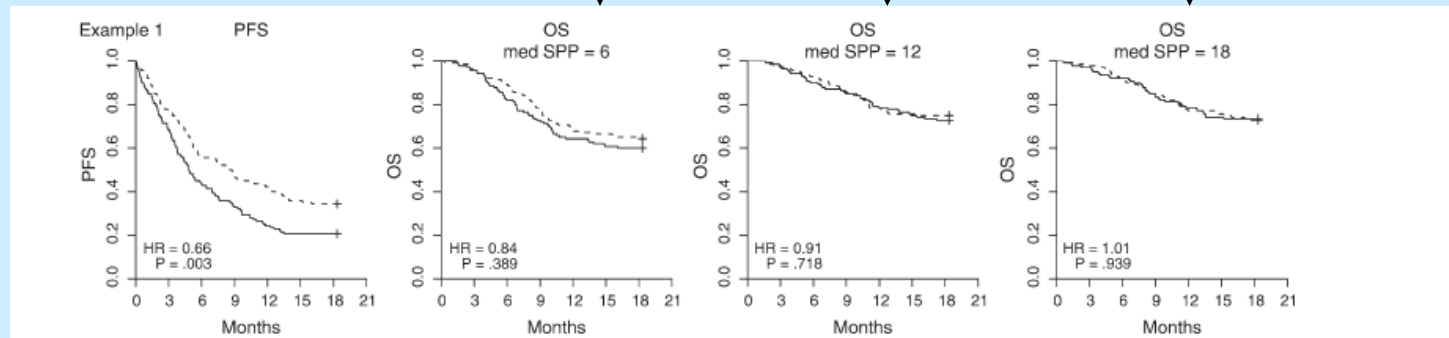
SPPが短い場合にはOSは妥当なエンドポイント、しかしこれが長くなると(メディア
ンで12月以上)ハードルが高くなりすぎる

進行癌に対する治療が改善するほどSPPは長くなり、エンドポイントとしてのOSの
有効性は減少するだろう

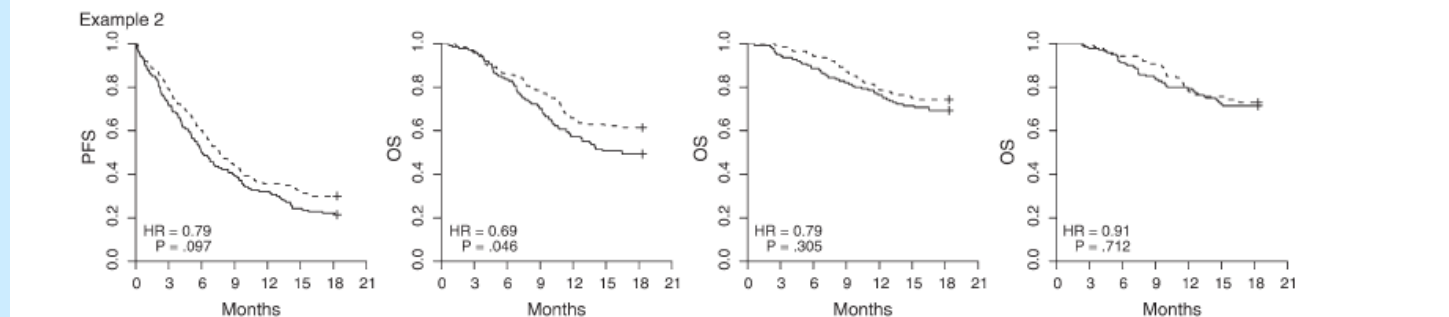
$SPP(\text{survival postprogression})=0$ median PFS= 2:3 OS=PFS+SPP

↓ 6months ↓ 12months ↓ 18months

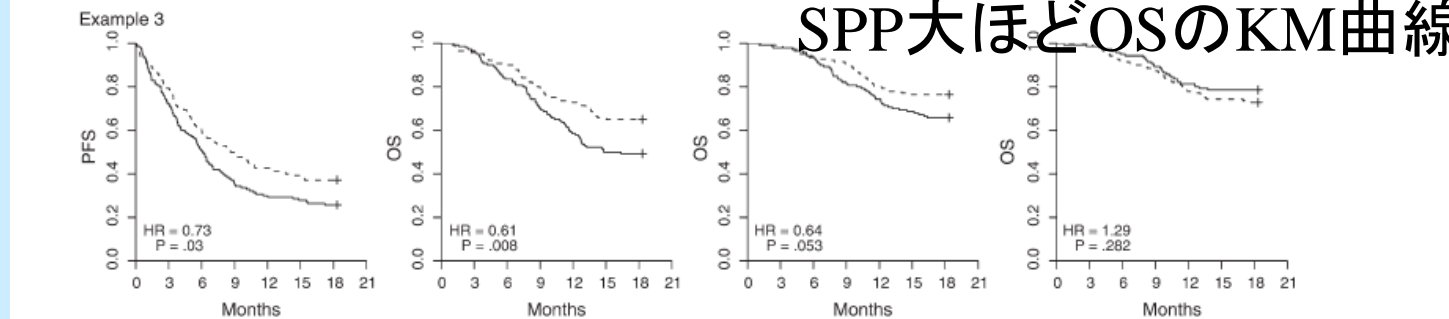
Ex.1



Ex.2



Ex.3



SPP大ほどOSのKM曲線重なる

Figure 1. Three typical examples of Kaplan-Meier progression-free survival (PFS) curves and associated overall survival (OS) curves from the simulations. Each row of plots is an example of a single simulated trial. The leftmost plot shows PFS, simulated to have median PFS of 6 months (control) and 9 months (experimental). The other three plots in each row show OS and differ only in median SPP

(6, 12, and 18 months). The hazard ratios and P values shown are those observed for the single simulated example. These three examples were typical of the simulations carried out. PFS and OS were compared by the log-rank test, and all statistical tests were two-sided. HR = hazard ratio; med = median. Solid line = control arm; dashed line = experimental arm.

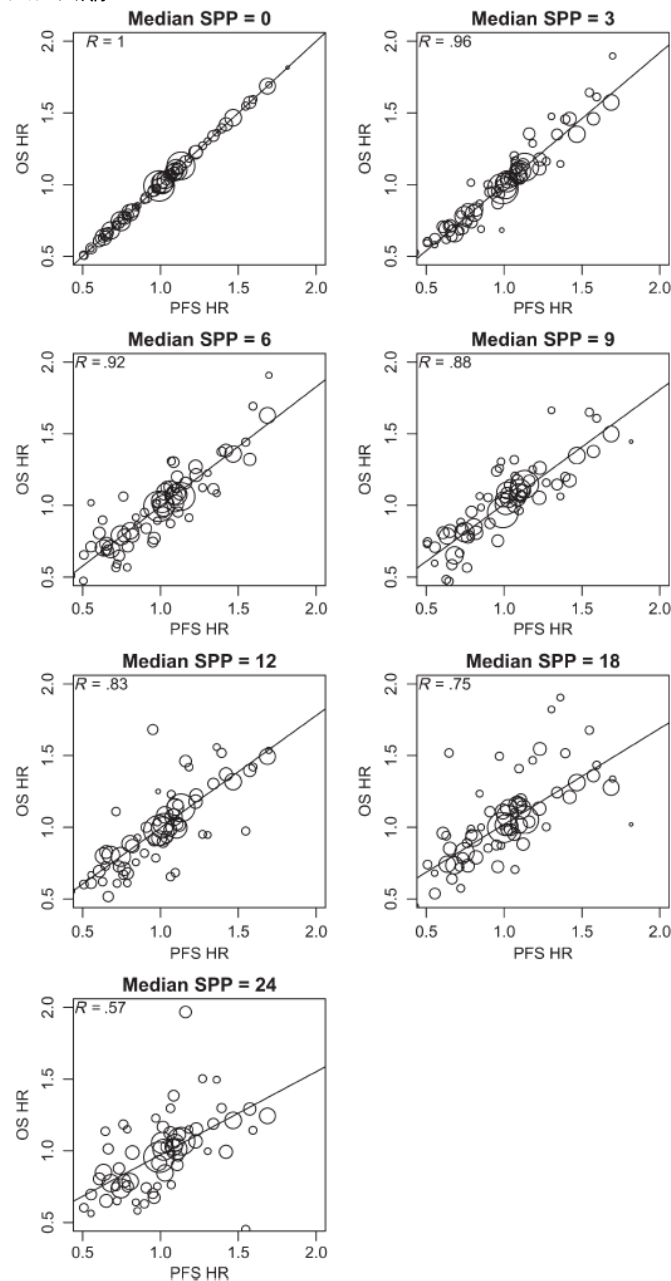


Figure 4. Association between progression-free survival (PFS) and overall survival (OS) for a single simulation of 67 trials. Each study had a randomly selected sample size and PFS hazard ratio, which remains fixed across progression-free survival postprogression (SPP) times (0, 3, 6, 9, 12, 18, and 24 months). Hazard

ratios (HRs) for PFS and OS were estimated with a proportional hazards model, and the correlation was estimated from a linear regression model weighted by the number of patients in each trial. The size of the circle is relative to the total sample size of the study. The diagonal line is the fitted weighted linear regression line.

シミュレーションによる 仮想的試験での PFSとOS

SPP(survival
postprogression) が大き
くなるとPFSのハザード
比とOSのハザード比の
相関低下

$$\text{median PFS} = 2:3 \text{ OS} = \text{PFS} + \text{SPP}$$

Table 1. Summary of hazard ratios for overall survival (OS)*

Median SPP, mo	Median OS, HR (95% interval)
2	0.687 (0.514–0.909)
4	0.710 (0.517–0.966)
6	0.727 (0.511–1.023)
8	0.736 (0.502–1.068)
10	0.746 (0.491–1.100)
12	0.749 (0.479–1.140)
14	0.752 (0.470–1.174)
16	0.758 (0.462–1.207)
18	0.759 (0.448–1.241)
20	0.762 (0.440–1.277)
22	0.763 (0.428–1.304)
24	0.763 (0.416–1.333)

* The 95% interval of the OS hazard ratio values extends from the 2.5 percentile to the 97.5 percentile for 50000 simulations. HR = hazard ratio; SPP = survival postprogression.

OSのハザード比メディアンは0.75前後、しかし信頼区間が広がり
有意でない確率が上昇する

$$\text{median PFS} = 2:3 \quad \text{OS} = \text{PFS} + \text{SPP}$$

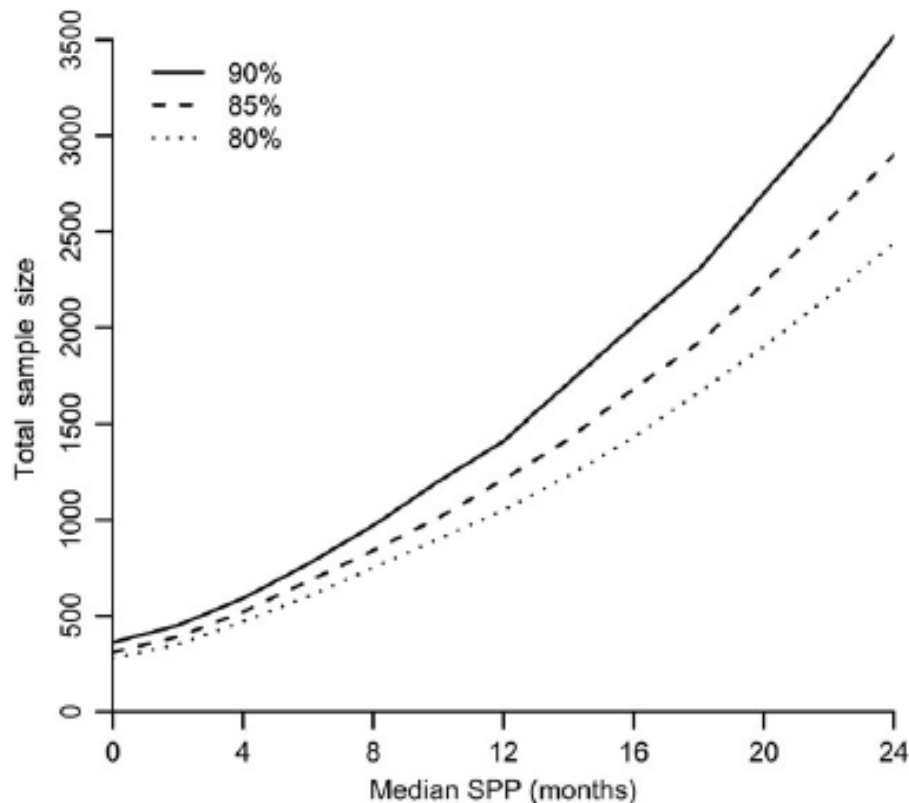


Figure 3. Sample sizes required for detecting a statistically significant difference in overall survival by median survival postprogression (SPP). The three curves were indexed by the power for overall survival (ie, powers of 90%, 85%, and 80%).

SPP(survival postprogression)が
大きくなると必要サンプルサイズが
増加

N=280 (検出力80%)

→

N=350(SPP=2), 2440(SPP=24)

OSかPFSか？

- ◆ Survival Post Progression (SPP) が長くなる (たとえば12ヶ月以上) と、PFSのOSに対する代替性は弱くなる

乳癌から、大腸癌そしてNSCLCへ

Broglia and Berry, *JNCI* 2009; 101: 1642-9.

- ◆ PFSには曖昧さ

測定間隔・測定手段、予定していない検査の扱い

主治医評価と中央評価の食い違い、QC

盲検下できない場合の報告バイアスと脱落バイアス

感度解析の必要性

Freidlin et al. *JCO* 2007; 25: 2122-6.

Bhattacharya et al. *JCO* 2009; 27: 5958-64.

Dodd et al. *JCO* 2008; 3791-6.

- ◆ FDAの曖昧な態度も批判されている。十分なPFSの差とQOL向上が示されれば問題ないのであろうが基準設定は困難

盲検化されていない場合のPFS測定の問題と提案

Freidlin et al. *JCO* 2007; 25: 2122-6

◆ 報告バイアス

評価を行う医師が患者を試験治療にスイッチしたいと思う気持ちから、画像評価を過大に行い、対照群でより早くPFSを宣言してしまう(主観による評価バイアス)

試験治療を受けたいと思う患者が対照治療群でより早く症状の進行を医師に報告し、その確認のための画像評価が早めになされてしまい、その結果早めにPFSが報告されることもありうる(評価時期のバイアス)。逆に毒性の強い試験治療で来院と画像評価が早めになり、試験治療群で早めにPFSが報告されることも起こりうる

◆ 患者脱落attritionバイアス

対照治療に割り付けられた患者に、新しい治療を受けたいという希望から脱落が多くなり、これがバイアスを引き起こす

◆ 正式の評価時点を2回に!

対照(標準)治療でのメディアンPFSとその2倍

途中でのPD判定はその後の**正式**な時点で

検出力はすべての時点を用いる方法と比べそれほど低下しない

負担の軽減とバイアスの軽減

PFSのブラインド下での中央判定は必要か？

Dodd et al. JCO 2008; 3791-6

VOLUME 26 · NUMBER 22 · AUGUST 1 2008

JOURNAL OF CLINICAL ONCOLOGY

STATISTICS IN ONCOLOGY

Blinded Independent Central Review of Progression-Free Survival in Phase III Clinical Trials: Important Design Element or Unnecessary Expense?

Lori E. Dodd, Edward L. Korn, Boris Freidlin, C. Carl Jaffe, Lawrence V. Rubinstein, Janet Dancey, and Margaret M. Mooney

A B S T R A C T

Progression-free survival is an important end point in advanced disease settings. Blinded independent central review (BICR) of progression in randomized clinical trials has been advocated to control bias that might result from errors in progression assessments. However, although BICR lessens some potential biases, it does not remove all biases from evaluations of treatment effectiveness. In fact, as typically conducted, BICRs may introduce bias because of informative censoring, which results from having to censor unconfirmed locally determined progressions. In this article, we discuss the rationale for BICR and different ways of implementing independent review. We discuss the limitations of these approaches and review published trials that report implementing BICR. We demonstrate the existence of informative censoring using data from a randomized phase II trial. We conclude that double-blinded trials with consistent application of measurement criteria are the best means of ensuring unbiased trial results. When such designs are not practical, BICR is not recommended as a general strategy for reducing bias. However, BICR may be useful as an auditing tool to assess the reliability of marginally positive results.

J Clin Oncol 26:3791-3796. Published by the American Society of Clinical Oncology

From the Branches of Biometric Research, Investigational Drug, Cancer Investigations, and Diagnostic Imaging, Division of Cancer Treatment and Diagnosis, National Cancer Institute, Rockville, MD.

Submitted January 14, 2008; accepted May 21, 2008.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Corresponding author: Lori Dodd, PhD, National Cancer Institute, 6130 Executive Blvd, MSC 743, EPN Rm 8140, Rockville, MD 20892; e-mail: doddli@mail.nih.gov.

Published by the American Society of Clinical Oncology

0732-183X/08/2622-3791/\$20.00

PFSのブラインド下での中央判定は必要か？

結論

- ◆ PFSが望ましいエンドポイントである場合、2重盲検試験がバイアス最小化のための最良の方法
- ◆ これが不可能な場合、バイアス軽減の一般的な戦略としてはブラインド中央判定を推奨できない
- ◆ 施設での進行判定後の追加画像撮影はinformative censoringの問題を軽減する点で推奨できるが、実装は難しいであろう。BICRを測定バラツキ軽減の手段とすることも考えられるが、informative censoringバイアスとのバランスを考慮すべき
- ◆ BICRを最終的な解析手法として推奨しないものの、施設判定のバイアスをチェック(audit)する仕組みとしては有効であり、臨床的有効性の観点からはぎりぎりの試験結果の信憑性を高めることにはつながる
- ◆ そもそもPFSをエンドポイントとする臨床試験は、臨床的にも重要な意義のある、大きな治療効果を目指すべきである。このような状況下では、本稿で議論したようなバイアスに対し結論は頑健であろう

Informative censoring: ローカルで進行と判断され中央で進行せずとされた例を打ち切り扱いにすると、生存率を上げる方にバイアス

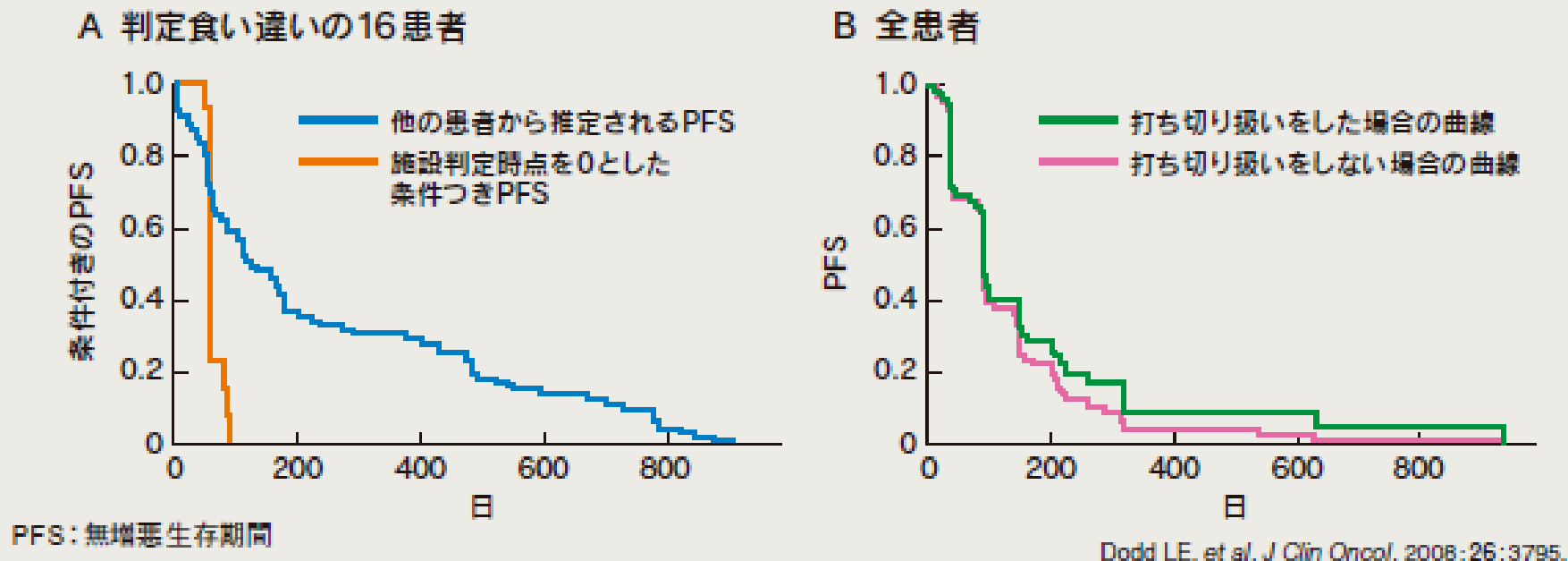
Informative censoring

- ◆ 中央判定で進行とする前に施設で進行を判定
- ◆ 施設で進行が判定されれば治療法も変更され、それ以降の画像評価も行われないことが多い。つまり中央判定が不能となる。(わが国においても同様の状況)
- ◆ このような場合にFDAのガイドラインは打ち切り判定を推奨
- ◆ しかし、この種の打ち切りはinformativeであり評価にバイアス、みかけの成績を上げる効果
- ◆ もし対照治療群にこの打ち切りが多く発生すれば、治療効果が薄まる方向のバイアスが生ずる

Bias due to informative censoring

- ◆ 16患者においてBICR判定に先立って施設で進行が判定
- ◆ 16患者を打ち切り扱いすることにより上側のバイアス

図1 無増悪曲線の対比



Sensitivity analysis 感度解析

Bhattacharya et al. JCO 2009; 27: 5958-64

Role of Sensitivity Analyses in Assessing Progression-Free Survival in Late-Stage Oncology Trials

Suman Bhattacharya, Gwen Fyfe, Robert J. Gray, and Daniel J. Sargent

A B S T R A C T

Sensitivity analysis is an important statistical technique that assesses whether the results of phase III trials are robust and likely to be generalizable. Until recently, sensitivity analyses were rarely included in phase III trials, and they remain poorly understood by many oncologists. Sensitivity analyses are critical to understanding the strength of conclusions made in the primary analysis of a late-stage clinical trial. They examine the influence of protocol design errors, unintended biases, deviations from assumptions underlying statistical models, and any unanticipated treatment delivery or practice patterns on trial results. In trials with complex or subjective end points, they also allow an understanding of the extent to which a positive outcome is driven by a single, possibly subjective, and therefore biased, element of an end point. The purposes of this article are to explain how sensitivity analyses are performed, to discuss areas of a clinical trial where sensitivity analyses should focus, and to illuminate the importance of this technique in the rigorous evaluation of late-stage clinical trial data, using specific examples. This article focuses on late-stage trials that use progression-free survival or time to progression as their primary end point, because sensitivity analyses are particularly important in these cases for which the end point is potentially subject to bias. Three sources of potential bias are explored: assessment time, symptomatic (ie, nonradiologic) disease progression, and missing data. For each source of potential bias, case studies are presented to highlight the role that sensitivity analyses play in determining whether the trial's conclusions are robust.

J Clin Oncol 27:5958-5964. © 2009 by American Society of Clinical Oncology

PFSに対する感度解析Sensitivity analysis

Bhattacharya et al. JCO 2009; 27: 5958-64

- ◆ PFSに曖昧さが伴うことは避けられない
- ◆ データの取り扱いを何通りかに変更し結論のrobustnessを検討
- ◆ 解析方法についてはプロトコルあるいは解析計画書に規定
- ◆ PFSに差がないという仮定のもとで判定時期の違いがどう影響するかシミュレーションを行う
- ◆ 両群を対等に扱う
- ◆ 試験群は保守的に、対照群はliberalに扱う
 - 予定していない判定時期、不完全情報なら遡らせる
 - 臨床情報に基づくPD判定を除く
 - 中央委員会で確認されなかったPD判定を打ち切り扱い

Sensitivity analysis (Example of E2100)

robustness of the results is confirmed

Table 4. Sensitivity Analyses for Missing Data Bias				
Type of Analysis	Experimental Arm	Control Arm	HR	(95% CI)
	Median PFS (months)			
	Bevacizumab + Paclitaxel (n = 368)	Paclitaxel (n = 354)		
Study E2100 (bevacizumab in metastatic breast cancer) ^a				
Primary analysis of PFS	11.3	5.8	0.48	0.39 to 0.61
PFS analysis of the patients (N = 649) with at least one scan submitted for the IRF review	11.3	6.0	0.50	0.40 to 0.63
The PD date was backdated to the date of the first missed tumor assessment if one or more tumor assessments were missing immediately preceding PD	11.2	5.6	0.48	0.38 to 0.61
The PD date for patients whose investigator-reported PD was not confirmed by the IRF was set to the last tumor assessment + 1 day	9.2	5.0	0.46	0.37 to 0.56
Worst-case analysis: PD date was set to the last tumor assessment + 1 day in the bevacizumab arm and was censored in the paclitaxel-only arm for cases in which the investigator-reported PD was not confirmed by the IRF	9.2	5.8	0.60	0.48 to 0.74
Worst-case analysis: Censoring because of nonprotocol cancer therapy and early discontinuation were considered PD events in bevacizumab arm and censored in the paclitaxel-only arm	8.2	5.8	0.78	0.64 to 0.95

オリジナル解析

両群を同様に保守的に扱う

試験群を保守的に対照群をliberalに扱う

進行・再発(肺)がん1次治療 OSに替わる評価？

- ◆ 2次治療以降は無視して大きなPFSの違いをめざす
- ◆ 治療戦略としての評価

PFS、OS

そしてQOL評価 (Quality Adjusted Life Year) と
経済評価

例: SELECT-BC

進行・再発乳癌1次治療 600例の登録完了

Taxane VS TS1

2次以降の治療は主治医選択

OSでのTS1の非劣性試験、ただしQALYを死亡まで評価

QOL ?

測れるはずがないのに測れると一部の人信じ、現実的な研究者を辟易させるもので、富山県などで出現すると蜚語楼とも呼ばれる

(里見・吉村:誰も教えてくれなかった癌臨床試験の正しい解釈、中外医学社、2011)

◆ 患者の立場にたった評価という点では一致

◆ 認識の違い

客観的な評価・症状

PS、副作用、体重変化、感染、入院日数、(痛みと)鎮痛剤



患者自身による計量心理的特性の主観的評価

(Patient Reported Outcome)

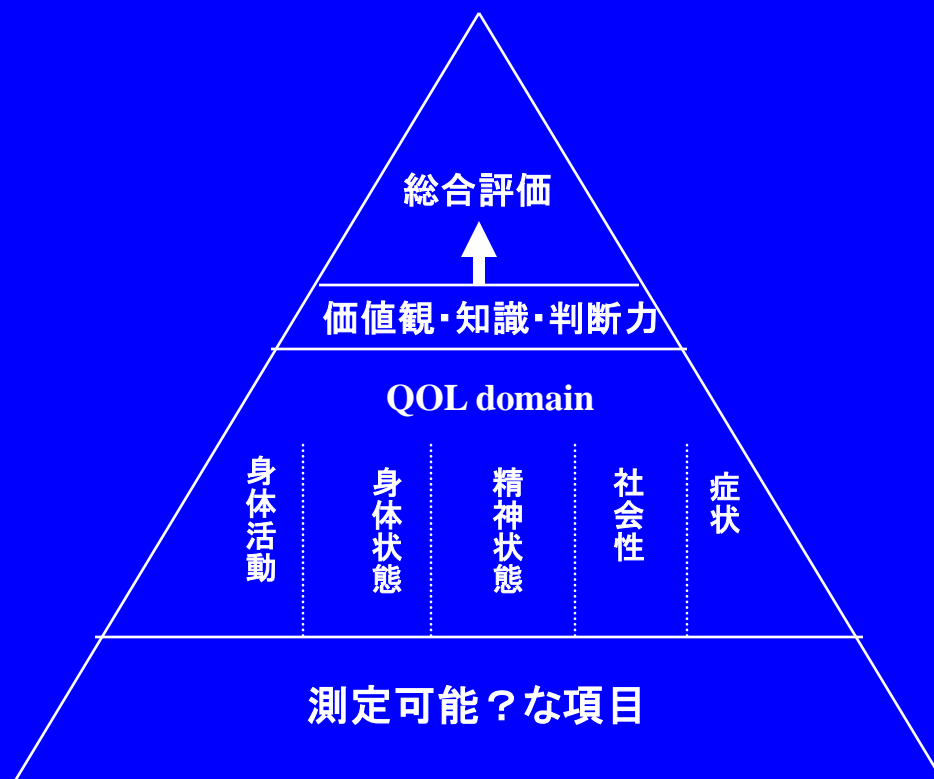
構成概念constructとしてのQOL

患者自身のフィルターを通した認識

多次元

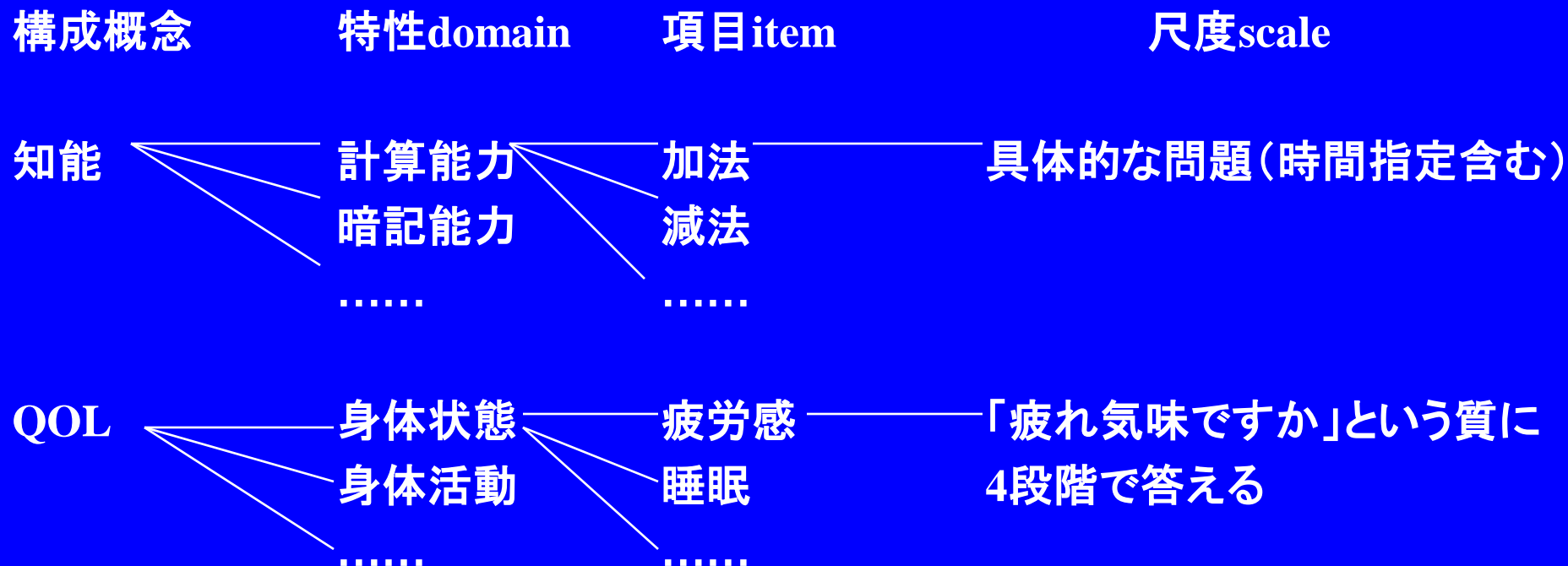
尺度(調査票)開発

構成概念constructとしてのQOL



QOL評価の水準

構成概念constructとしてのQOL



抗がん剤評価におけるQOL調査

- ◆ 日本の医師研究者の態度
新しい領域としての期待
うさんくささ

‘主観的で曖昧なQOL測定にどんな意義があるのか?’

- ◆ 既存調査票の翻訳・導入
EORTC, FACT

- ◆ 日本独自の調査票の開発

QOL-ACD (Kurihara et al.(1999、実質的には1990頃))

- ◆ 第III相試験での利用(1995-肺癌、乳癌)
- ◆ PRO (Patient Reported Outcome) の概念
- ◆ QALY測定と経済評価(?) (GEST研究、CSPOR-SELECT)

Health related QOL ?

**“Does subjective and vague measurement
of QOL have any significance?”**

“It is much more reliable and clinically significant than measuring natural killer”

D. Cella (Tutorial of Japan Stat. Assoc., 1996)

“It is relatively uncommon that studies of new drugs in oncology provide unambiguous evidence of a survival benefit. So in trying to assess clinical benefit for patients who are enrolled in oncology drug studies, QOL is becoming an increasingly important component of those types of applications and as a means of assessing clinical benefit for patients who are receiving one kind of therapy or another”

R. Shilsky (ODAC subcommittee, 2000 Feb 10)

Guidance for Industry

Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

December 2009
Clinical/Medical

経緯

2005, 7

ヨーロッパ医薬品機構評価機構(EMA)
医薬品評価における健康関連QOL使用
に関するガイダンス(ドラフト版)を公表
→内容は柔軟, 概要について言及
<http://www.ema.europa.eu/>

2006, *Fed Register* 71

FDA

医薬品・機器の開発における
患者主観的アウトカムの使用ガイダンス
(ドラフト版)を公開
→より詳細な言及, 推奨形式“should”

2009, FDA

医薬品・機器の開発における
患者主観的アウトカムの使用ガイダンス
を公開

FDA PROガイダンス

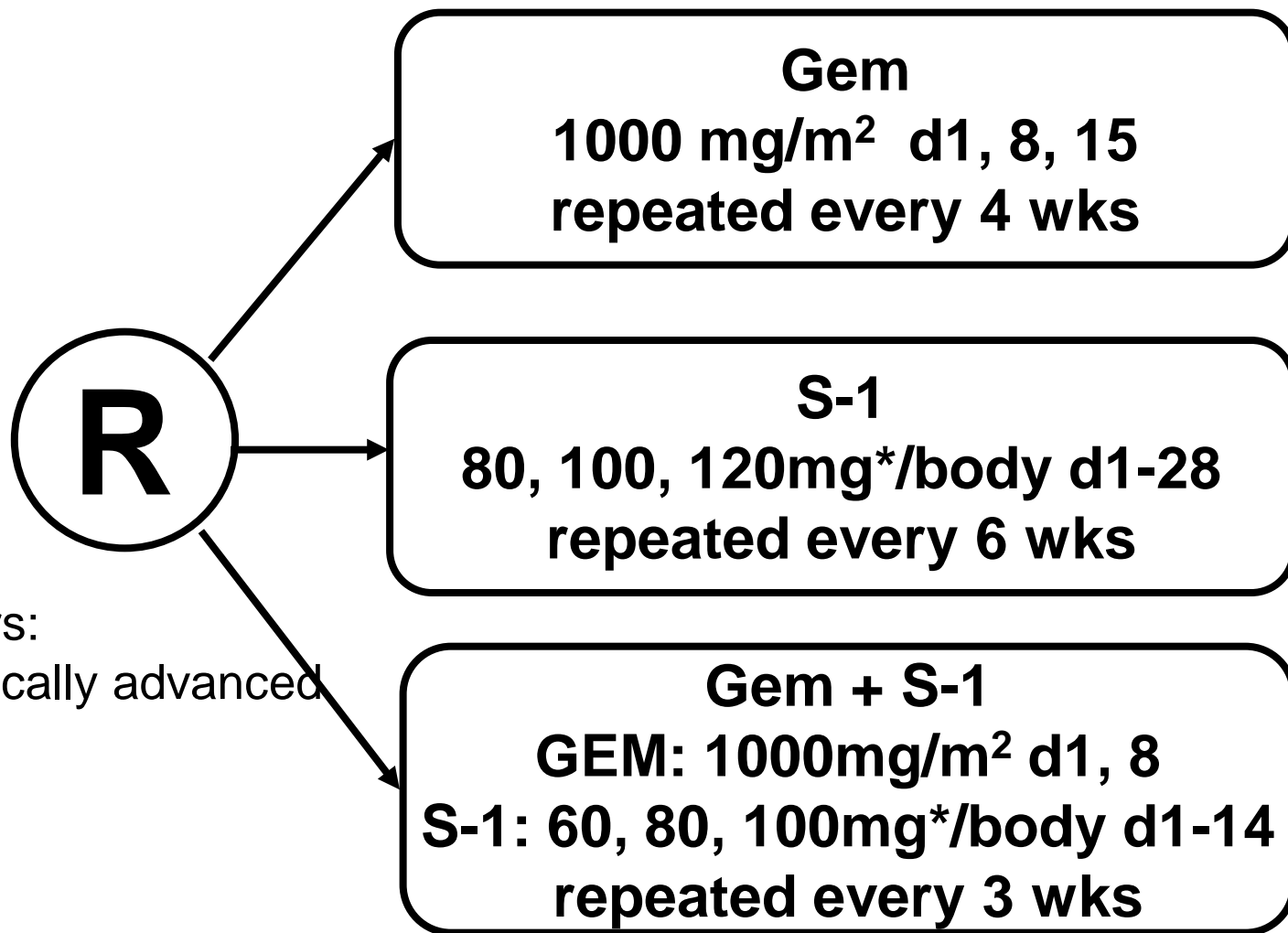
- ◆ 適切に定義され (well-defined)、信頼性の高い尺度で測定された結果は、医薬品の効能表示の裏付け根拠として使用可能である
- ◆ 患者自身が最も良く認識しているか、患者の視点からの測定が最も適切な概念については、**PROの使用を推奨**する

Quality of life (QOL) evaluation within a randomized phase III study of gemcitabine plus S-1 (GS) versus S-1 versus gemcitabine (Gem) in unresectable advanced pancreatic cancer (PC) in Japan and Taiwan: GEST study

Y. Ohashi, M. Tanaka, N. Boku, H. Ueno, T. Okusaka on behalf of the GEST study group

ASCO2011—9070

GEST study design

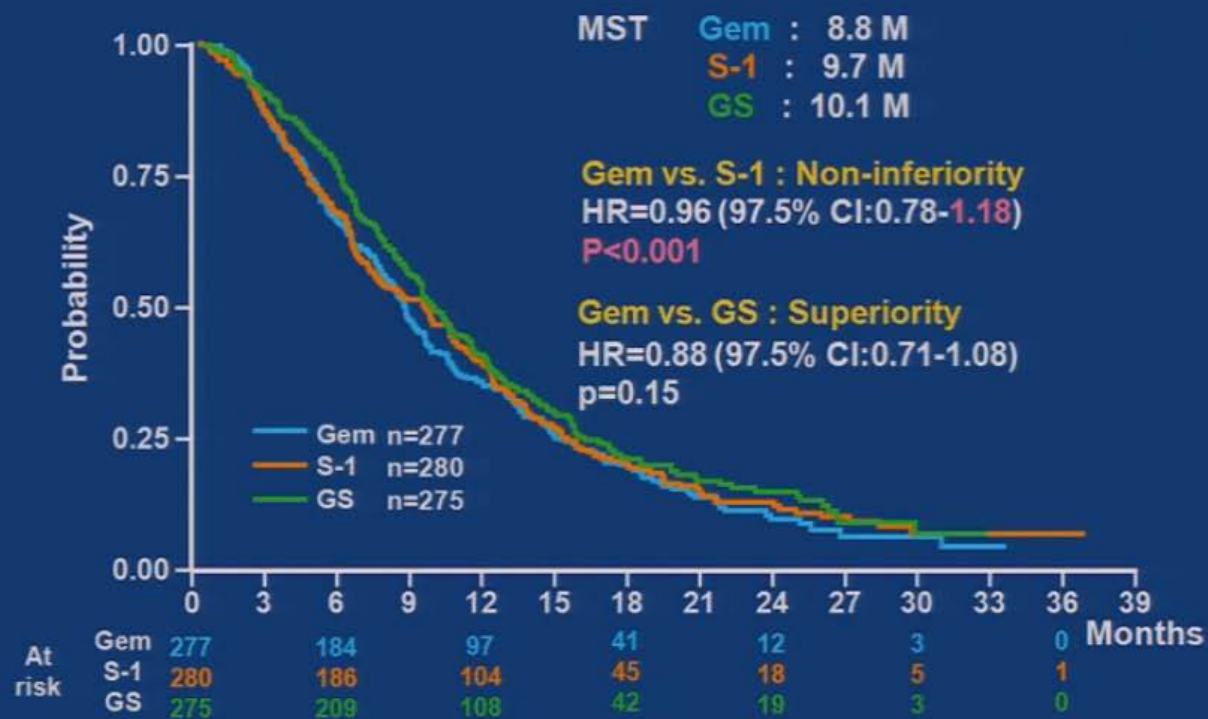


Stratification factors:

- Metastatic vs. Locally advanced
- Institution

*According to body surface area,
BSA < 1.25 m², 1.25 ≤ BSA < 1.5, BSA ≥ 1.5

Overall Survival (3 arms)



Primary objectives of the QOL analysis

To assess differences between the treatment groups

- EQ-5D utility index
- QALY (Quality Adjusted Life Years)

EQ-5D

- Standardized measure of health status developed by the EuroQol Group
- The EQ-5D descriptive system comprises the following 5 dimensions, and each dimension has 3 levels

Dimension	Level
Mobility	
Self-Care	1: no problems
Usual activities	2: some problems
Pain / Discomfort	3: severe problems
Anxiety / Depression	

- EQ-5D health status converted to a single summary index score (**EQ-5D utility index**) using the Japan value-set, ranging from 0 (death) to 1 (perfect health)

EQ-5D

【5項目法】 以下のそれぞれの項目の1つに印をつけて、あなた自身の今日の健康状態を最もよく表している記述を示してください。

移動の程度

1. 私は歩き回るのに問題はない
2. 私は歩き回るのにいくつかの問題がある
3. 私はベッド(床)に寝たきりである

身の回りの管理

1. 私は身の回りの管理に問題はない
2. 私は洗面や着替えを自分でするのに
いくらか問題がある
3. 私は洗面や着替えを自分でできない

ふだんの活動(例:仕事、勉強、家族・余暇活動)

1. 私はふだんの活動を行うのに問題はない
2. 私はふだんの活動を行うのにいくつか問題がある
3. 私はふだんの活動を行うことができない

痛み/不快感

1. 私は痛みや不快感はない
2. 私は中程度の痛みや不快感がある
3. 私はひどい痛みや不快感がある

不安/ふさぎ込み

1. 私は不安でもふさぎ込んでもいない
2. 私は中程度に不安あるいはふさぎ込んでいる
3. 私はひどく不安あるいはふさぎ込んでいる

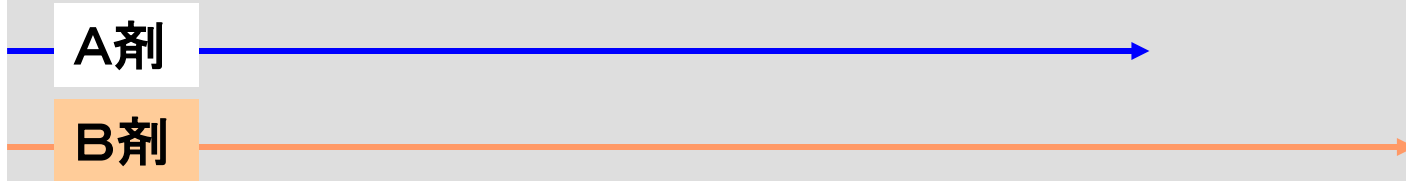
A part of EQ-5D value set

Mobility	Self-Care	Usual Activities	Pain/ Discomfort	Anxiety/ Depression	utility index
2	2	1	1	1	0.720
2	2	1	1	2	0.657
2	2	1	1	3	0.608
2	2	1	2	1	0.640
2	2	1	2	2	0.577
2	2	1	2	3	0.527
2	2	1	3	1	0.526
2	2	1	3	2	0.463
2	2	1	3	3	0.414
2	2	2	1	1	0.676
2	2	2	1	2	0.613
2	2	2	1	3	0.564
2	2	2	2	1	0.596
2	2	2	2	2	0.533

生存年数 と QALY (Quality Adjusted Life Years)

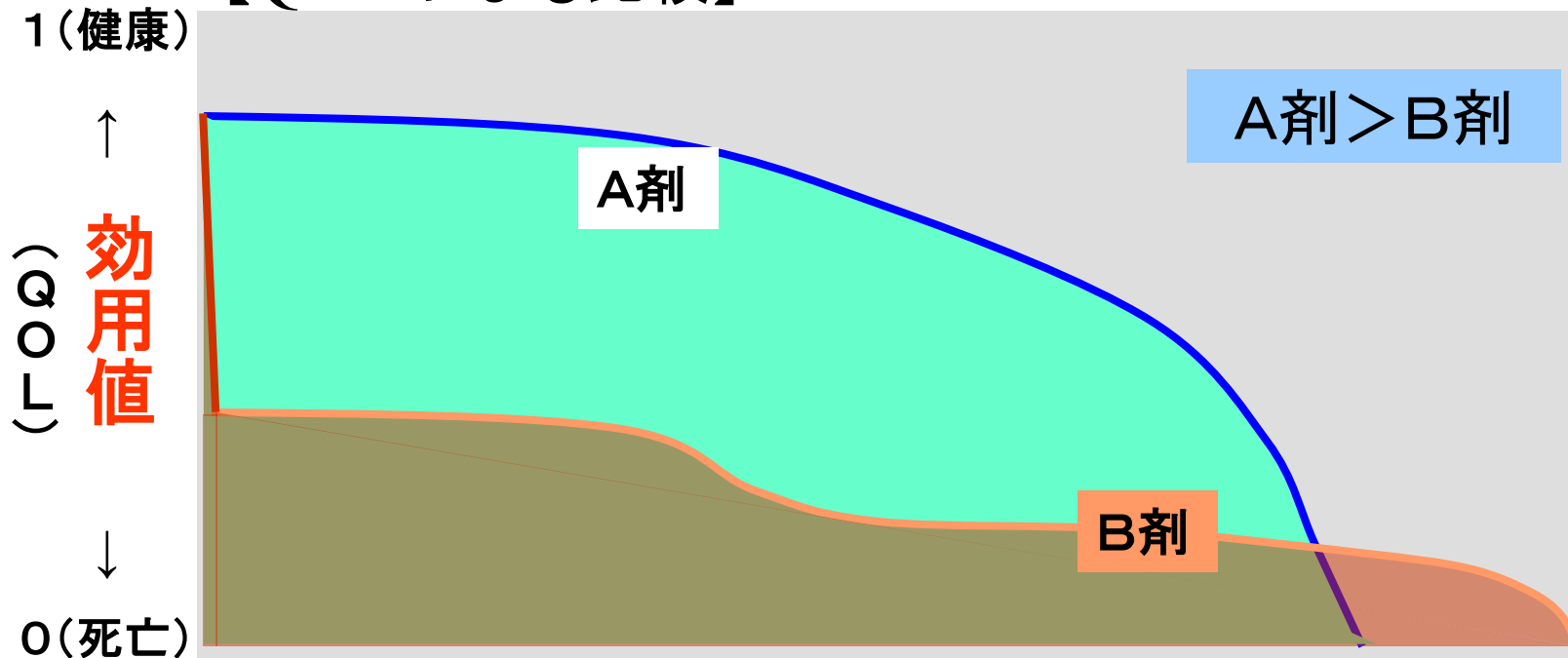
【生存年数による比較】

B剤 > A剤



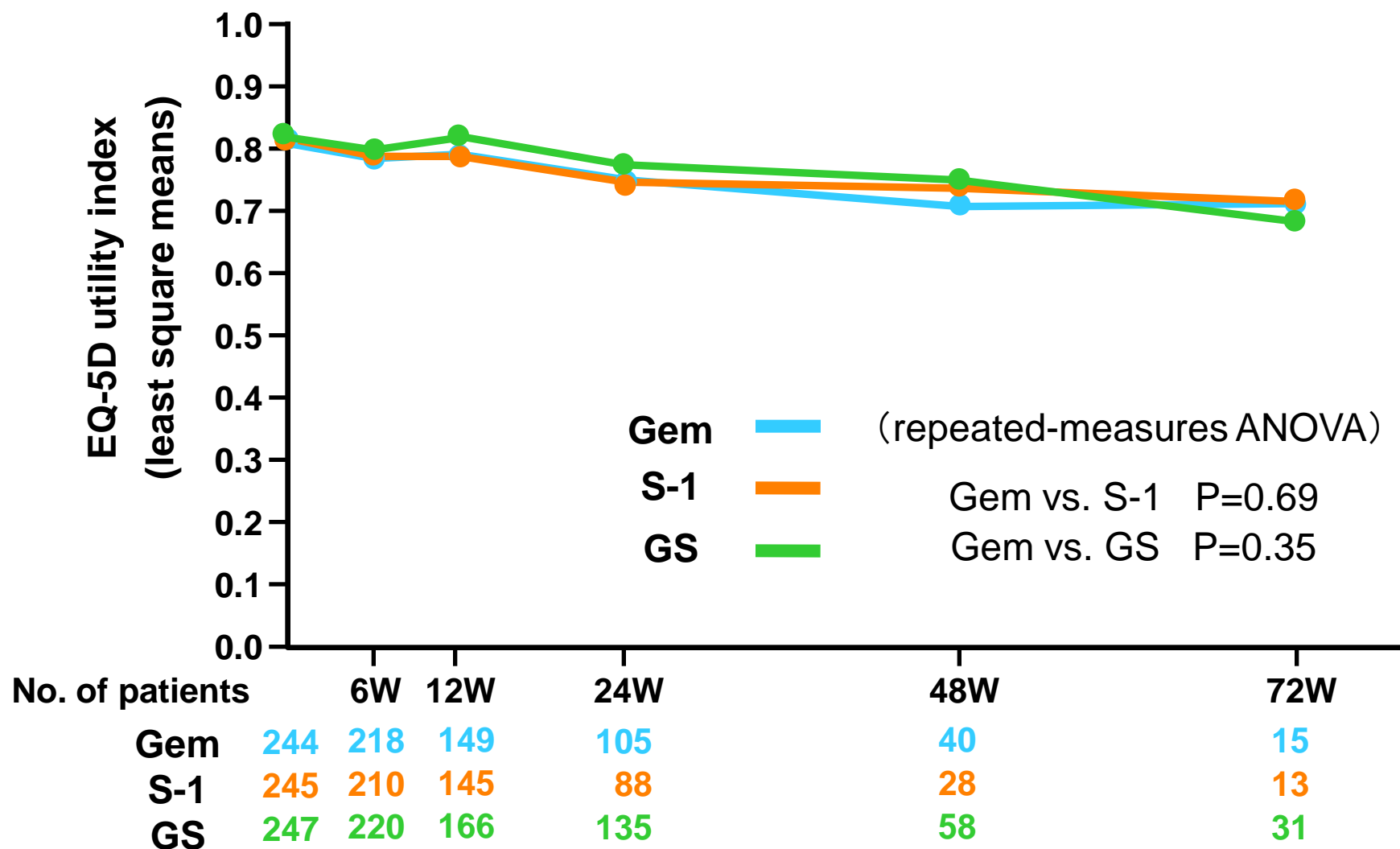
【QALYによる比較】

A剤 > B剤



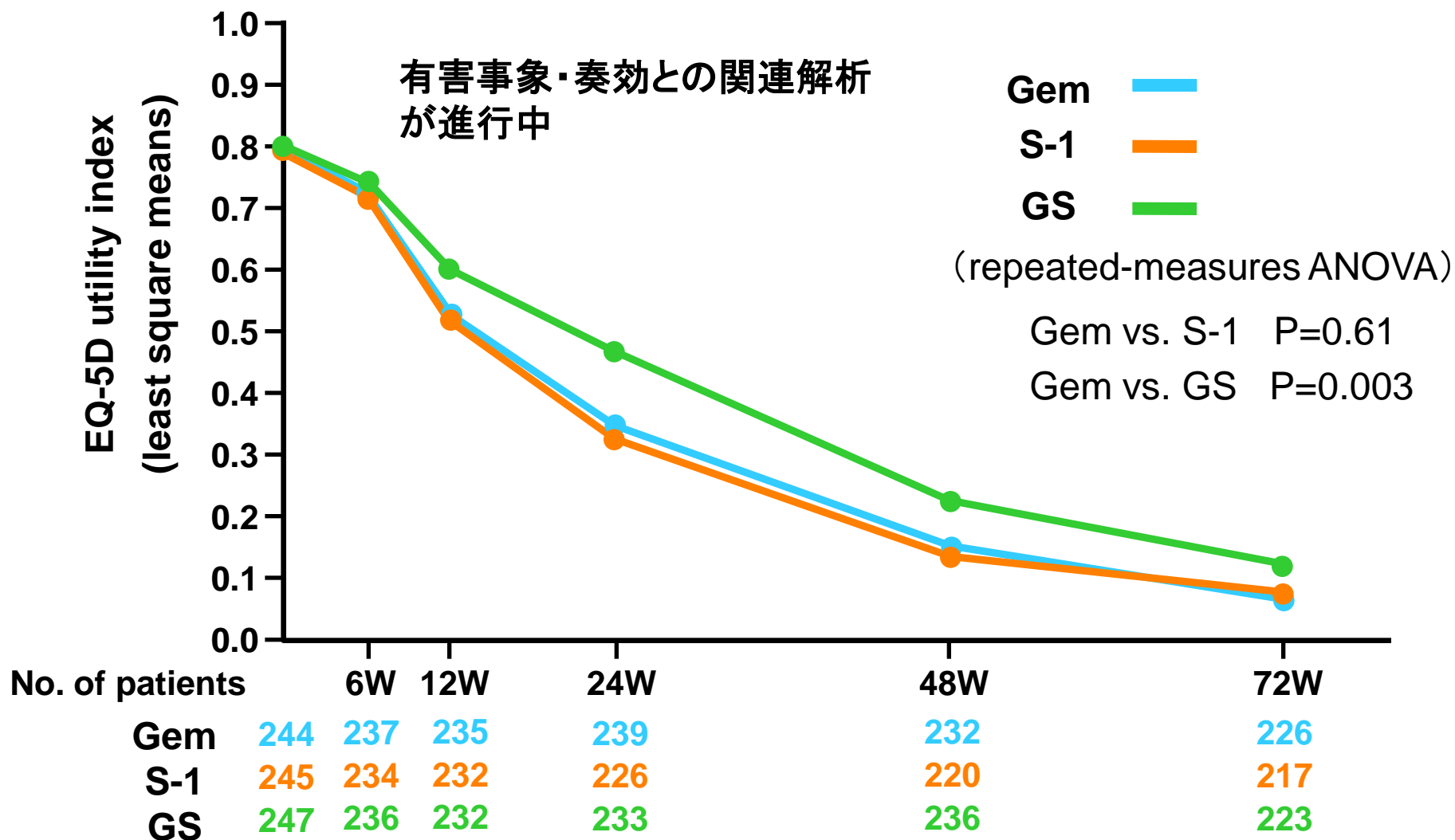
EQ-5D utility index

* Death : Not included



EQ-5D utility index

* Death : Treated as index 0



QALY

* Death : Treated as index 0

	n	QALY* median	P-value†
Gem	244	0.424	GEM vs. S-1 P=0.56 GEM vs. GS P=0.0008
S-1	245	0.410	
GS	247	0.536	

* adjusted for baseline EQ-5D utility index

† generalized Wilcoxon test

Relationship between QALY and PS

* Death : Treated as index 0

PS0

PS1

PS0				PS1		
	n	QALY* media n	P-value†	n	QALY* media n	P-value†
Gem	156	0.484	Gem vs. S-1 P=0.64	88	0.265	Gem vs. S-1 P=0.90
S-1	148	0.486		97	0.317	
GS	154	0.566	P=0.16	92	0.492	P<0.0001

* adjusted for baseline EQ-5D utility index

† generalized Wilcoxon test

結論+ α

- ◆ 2次治療以降に有効な治療が登場すれば
- ◆ SPP(survival post progression)が延長すれば
PFSのOSに対する代替性は薄まる(ハザードは希釈される)
- ◆ PFSの曖昧さとそれに対する対処の必要性
- ◆ 大きなPFSの改善と優れたrisk/benefit profileなら(さらに
経済的に許容できるなら)PFSによる承認は当然ありうる

PFS so what?

QOL (Patient Reported Outcome)と経済評価の必要性

Improving Drug Safety: From Toxicity Assessment to Post-marketing Surveillance

PRO

Education Session Chair(s): David Cella, PhD

ASCO

Other ASCO Meetings Browse Tracks Browse Sessions

2011 ASCO Annual Meeting > Health Services Research Track > Improving Drug Safety: From Toxicity Assessment to Post-marketing Surveillance

Improving Drug Safety: From Toxicity Assessment to Post-marketing Surveillance

David Cella, PhD
Richard Pazdur, MD
Julia Bohlius, MD, MScPH

TRUST DISCOVERIES PREVENTION PRACTICE PARTNERSHIP COMMUNITY THERAPY ADVOCACY COMMISSION QUALITY DISCOVERY
PATIENT CARE TRANSFORM CURE TRUST KNOWLEDGE PREVENTION TREATMENT DISCOVER
VOCACY COMMUNITY MULTIDISCIPLINARY CLINICAL TRIALS PRACTICE TRANSFORM QUALITY SCIENTIFIC DISCOVER

Presented at the 2011 ASCO Annual Meeting. Presented data is the property of the author.

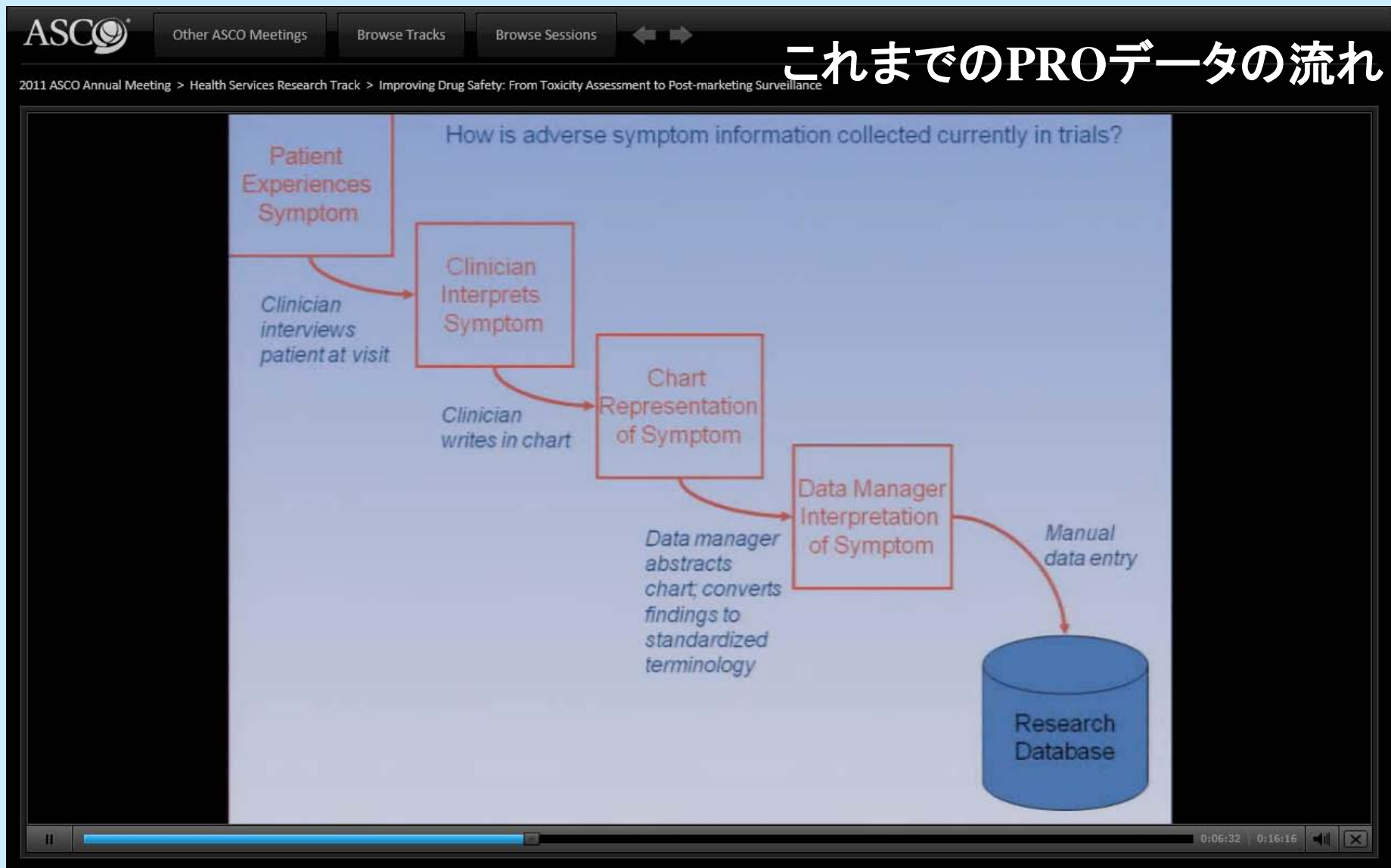
ASCO Annual '11 Meeting

0:00:17 0:16:16

CellaはFACTの開発者

Improving Drug Safety: From Toxicity Assessment to Post-marketing Surveillance PRO

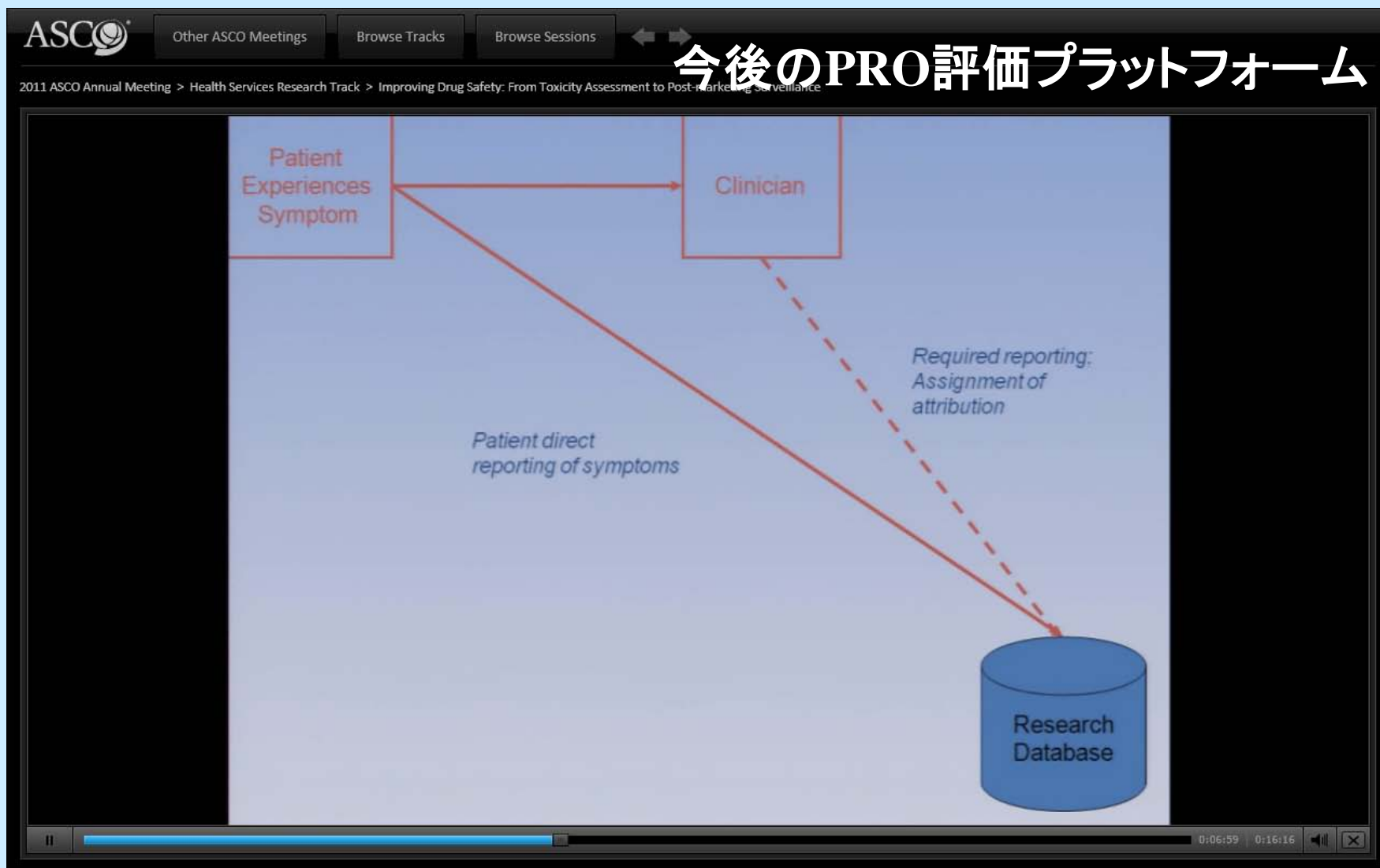
Education Session Chair(s): David Cella, PhD



Improving Drug Safety: From Toxicity Assessment to Post-marketing Surveillance PRO

Education Session Chair(s): David Cella, PhD

今後のPRO評価プラットフォーム



Improving Drug Safety: From Toxicity Assessment to Post-marketing Surveillance

PRO Education Session Chair(s): David Cella, PhD

ASCO

Other ASCO Meetings Browse Tracks Browse Sessions

2011 ASCO Annual Meeting > Health Services Research Track > Improving Drug Safety: From Toxicity Assessment to Post-marketing Surveillance

National Cancer Institute Initiative

PRO-CTCAE

*Patient-Reported Outcomes version of the
Common Terminology Criteria for Adverse Events*

Initiated in 2008

0:13:21 0:16:16

6000 Comparative Effectiveness ResearchにおけるPROガイダンス案

The screenshot shows a presentation slide from the ASCO 2011 Annual Meeting. The slide is titled "Effectiveness Guidance Document (EGD)" and discusses the development of guidance for including patient-reported outcomes (PROs) in post-approval clinical trials of oncology drugs for comparative effectiveness research (CER). The slide is presented in a "SLIDE VIEWER" window with navigation arrows. The ASCO logo is visible in the top left corner of the viewer. The slide content includes the title, a subtitle, and the names of the presenters: Ethan Basch MD, Amy Abernethy MD, Daniel Mullins PhD, Merianne Tiglao, and Sean Tunis, MD. The CMTP logo (Center for Medical Technology Policy) is in the bottom right corner of the slide.

ASCO

Other ASCO Meetings Browse Tracks Browse Sessions

2011 ASCO Annual Meeting > Health Services Research Track > Emerging Issues in Comparative Effectiveness Research

SLIDE VIEWER Use arrows below to navigate

Effectiveness Guidance Document (EGD)

Development of a guidance for including patient-reported outcomes (PROs) in post-approval clinical trials of oncology drugs for comparative effectiveness research (CER)

Ethan Basch MD; Amy Abernethy MD;
Daniel Mullins PhD, Merianne Tiglao, Sean Tunis, MD

CMTP
Center for Medical Technology Policy

Comparative Effectiveness Researchにおける Patient Reported Outcomeの測定 ASCO2011 #6000のガイドライン案

- ◆ PROを測定せよ
- ◆ 重要な13症状と、対象・治療介入によって意味のある症状を追加評価せよ
- ◆ 全体評価を含めよ。経済評価を可能とする指標の測定を推奨する
- ◆ 妥当性、信頼性、感度が保証された指標を用いよ
- ◆ 可能ならePROを採用せよ。収集方法が混合するなら同等性を検証せよ
- ◆ 必要時間は10分以内とせよ
- ◆ 欠損防止と重篤な症状に即対応できる警告システムを備えよ
- ◆ 適切な時点で測定を行え



Other ASCO Meetings

Browse Tracks

Browse Sessions



2012 ASCO Annual Meeting > Clinical Trials Track > Endpoints for Cancer Trials in 2012: Statistical, Regulatory, and Clinical Perspectives (eQ&A)

THE "PROS" FOR USE OF PROs IN CLINICAL TRIALS


	CTC AE	PROs
Primary use	Toxicity reporting	Health status reporting
Most useful for	Objective assessment (e.g. Diagnostic test, imaging, overt sign like bleeding)	Subjective assessment (e.g. Cannot be seen, felt, heard, observed or clinically tested by clinician)
Best captures	Severity, need for clinician intervention	Severity, Function, Impact on QOL and Treatment Adherence
Valid	Not tested	Yes*
Reliable	NO	Yes*
Data capture method	Through layers of interpretation	Directly from the patient
Time of data capture	As it occurs/as clinician picks it up	At designated timepoints

*Legacy instruments psychometrically tested to varying degrees; for current FDA use must conform to stringent guidelines



0:05:51 0:27:57




Other ASCO Meetings
Browse Tracks
Browse Sessions

2012 ASCO Annual Meeting > Clinical Trials Track > Endpoints for Cancer Trials in 2012: Statistical, Regulatory, and Clinical Perspectives (eQ&A)

CTC HAVE RARELY UNDERGONE *RELIABILITY* TESTING AND RESULTS ARE MODEST TO POOR (HAVE NOT UNDERGONE *VALIDITY* TESTING)

Japanese study evaluated the reliability of CTC v 2.0

- △ 5 experienced CRAs independently reviewed med. records from 17 pts and graded toxicities
- △ Agreement among raters:
 - nausea; 0.47 (0.23-0.71)
 - diarrhea; 0.59 (95%CI 0.35-0.82)
 - stomatitis/pharyngitis; 0.59 (0.35-0.82)
 - sensory neuropathy; 0.65 (0.42-0.87).
 - vomiting; 0.71 (0.49-0.92)
 - infection; 0.82 (0.64-1)
 - febrile neutropenia; 0.88 (0.73-1)

Kaba et al 31(8):1187-92:2004

Canadian NCIC-CTG expanded toxicity scale

- △ 7 experienced data managers rated scripted patient simulations
 - Lab-based toxicities (range,0.50-1.00)
 - Clinically (symptom based toxicities) (range, -0.04-0.82)
 - 17/49 (35%) Grade 4 toxicities correctly scored
 - 15/70 (21%) Grade 3 toxicities scored as Grade 4

Brundage et al;85(14):1138-48: 1993

0:08:38
0:27:57

Gan To Kagaku Ryoho. 2004 Aug;31(8):1187-92.

[Reliability at the National Cancer Institute-Common Toxicity Criteria version 2.0].

[Article in Japanese]

Kaba H, Fukuda H, Yamamoto S, Ohashi Y.

Statistics and Cancer Control Division, Research Center for Cancer Prevention and Screening, National Cancer Center Research Institute.

We evaluated the reliability of CTC v 2.0 based on source documents and also studied the degree of inconsistency in toxicity grading. Five clinical research coordinators from the National Cancer Center Hospital independently reviewed

environment, variability exists in the toxicity assessment and grading. Good training and education on toxicity assessment using common criteria and development of translated manual, including the interpretation of criteria assessment, may help reduce variability.



Other ASCO Meetings

Browse Tracks

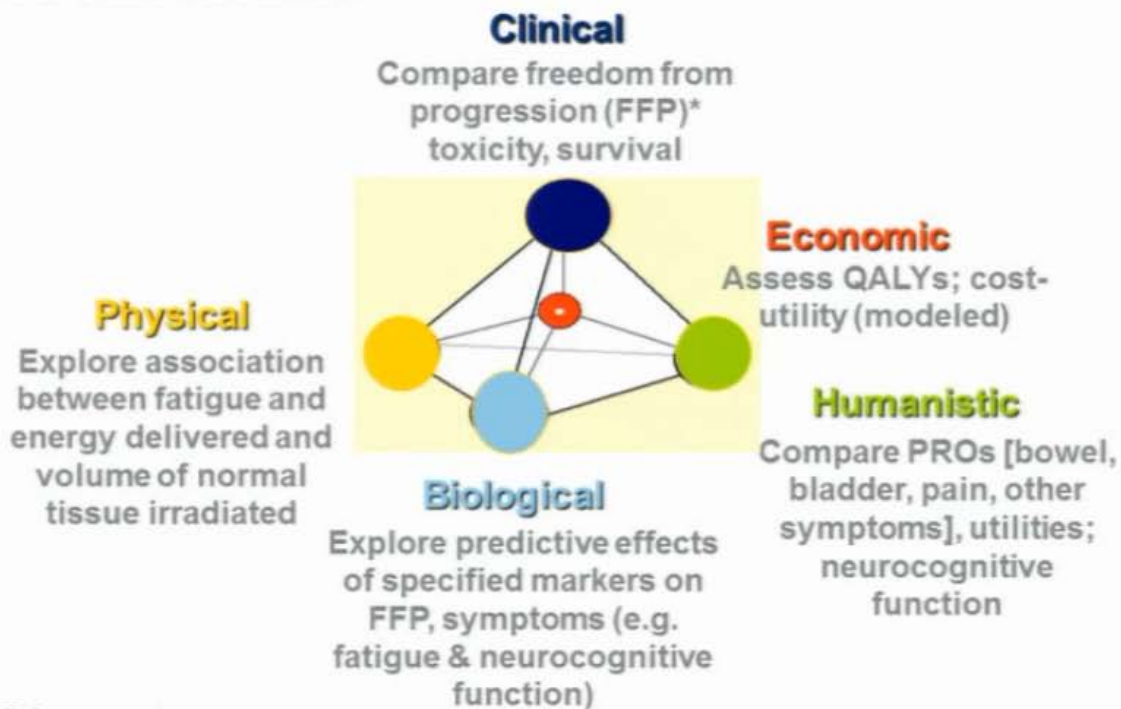
Browse Sessions




2012 ASCO Annual Meeting > Clinical Trials Track > Endpoints for Cancer Trials in 2012: Statistical, Regulatory, and Clinical Perspectives (eQ&A)

RTOG 0534: Short Term Androgen Deprivation with Pelvic Lymph Node or Prostate Bed Only RT in Prostate Cancer Patients with a Rising PSA After Radical Prostatectomy (n=1764) (Phase III)

RTOG Outcomes Model





Other ASCO Meetings Browse Tracks Browse Sessions

2012 ASCO Annual Meeting > Clinical Trials Track > Endpoints for Cancer Trials in 2012: Statistical, Regulatory, and Clinical Perspectives (eQ&A)

WHAT WE STAND TO GAIN BY INCLUDING PROs in CLINICAL TRIALS

We give VOICE to the PATIENT:

- △ More comprehensive reporting of prevalence of symptoms
- △ Improved accuracy in reporting of levels of severity
- △ Increased prognostic specificity
- △ Greater understanding of patient adherence
- △ Better information for patient and clinical decision making
- △ Additional targets for labeling claims
- △ Significant information for comparative effectiveness


0:27:06 0:27:57

2012ASCO Educational Session ‘Endpoints’ (D.Bruner)

ASCO®

Other ASCO Meetings Browse Tracks Browse Sessions

2012 ASCO Annual Meeting > Clinical Trials Track > Endpoints for Cancer Trials in 2012: Statistical, Regulatory, and Clinical Perspectives (eQ&A)



0:27:23 0:27:57



PALM(PDA)

iPHONE



Android



iPAD

Basch et al. JNCI 2011; 24: 1808-10.

EDITORIALS

Use of Patient-Reported Outcomes to Improve the Predictive Accuracy of Clinician-Reported Adverse Events

Ethan Basch, Antonia Bennett, M. Catherine Pietanza

Correspondence to: Ethan Basch, MD, MSc, Department of Medicine, Health Outcomes Research Group, and Center for Health Policy and Outcomes, Memorial Sloan-Kettering Cancer Center, 307 East 63 St, New York, NY 10065 (e-mail: ebasch@mskcc.org).

Abundant research has now demonstrated that patient and clinician reports of symptoms—and particularly symptomatic toxicities (ie, adverse events) during cancer treatment—provide discrepant yet complementary data (1–3).

How can this be? Can't only the patient *or* the clinician be “right”? The more patient-centered among us might state that the patient is always right by definition because nobody (not even the most sensitive clinician) can truly know another person's subjective experience. But the more traditional among us might assert that clinicians should be considered right because they have an “objective” perspective based on experience and training, which prevents them from exaggerating or understating what they observe.

In fact, it appears that both the patient and clinician provide information of value, which when combined provides a more accurate understanding of the patient's symptoms. This finding is good news for those of us who are interested in improving the measurement of symptoms in clinical trials and practice. The optimistic

NCI intergroup trial N9741 (7), in which an abundance of life-threatening gastrointestinal serious adverse events was ultimately detected (8). Therefore, availability of PRO data not only enhances the accuracy of clinician CTCAE reports but also may improve safety.

So, operationally how might this work? There are three potential approaches:

- 1) “Independent reporting,” in which patient and clinician toxicity data are collected, analyzed, and reported completely separately from each other;
- 2) “Merged reporting,” in which patient and clinician data are collected separately and then merged analytically into a single metric; and
- 3) “Collaborative reporting,” in which patients directly report symptomatic toxicity information, which is then provided to clinicians to inform their CTCAE reporting.

個々の主観的経験を報告するのに最適であるのは患者、これを疾患の観点から説明するのに最適なのは医師。両者は相補的・・・、時期のCTCAEv5は症状の正確性を向上させるためPROを組み込む予定

「OSかPFSか」 論争を受けての感想とまとめ

最近のがん臨床試験のデザイン(SoCRA講演から)

- ◆ がん領域の特徴とその試験デザインへの反映
- ◆ 新しいアプローチの必要性
- ◆ Time-to-eventをめぐる問題(OSかPFSか)
- ◆ より効率的・患者視点の臨床試験に向けて

分子標的を意識した新薬の開発ががん領域では盛んである。試験方法論の提案とその応用例も増えている。奏効率・PFSの見直しなど、これまで常識とされていた方法論の見直しさえ行なわれている。

全ての試験関係者にとって、「何のために、なぜ」という本質的な問いを常に心がけることがますます重要となろう。

何が必要か？ 具体的には・・・

- ◆ ヒストリカルデータの活用（症例の登録・追跡、これを可能とする施設の体制、検定バンクと標準化された手法によるマーカー測定、データ利用規定とデータ管理・解析を行う組織、病理医の協力、適切な倫理審査が必要となるが、わが国ではこのようなインフラストラクチャが脆弱である）
- ◆ 患者による毒性・QOLのPROによる評価（とくに第III相試験あるいは市販後の試験）
- ◆ 大規模試験あるいは市販後試験において試験実施の負担を軽減するための、毒性・併用治療に関するデータ収集適正化
- ◆ 新薬の承認や適応拡大・標準治療確立のために必要なデータは何か、そのためにどのような臨床試験（かつ市販後の監視）が必要かつ可能か、に関する当局あるいは統計家との協議。それを可能にする当局・統計家の能力とレギュラタリーサイエンスの発展