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？

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NPO日本臨床研究支援ユニット理事長
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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ョ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

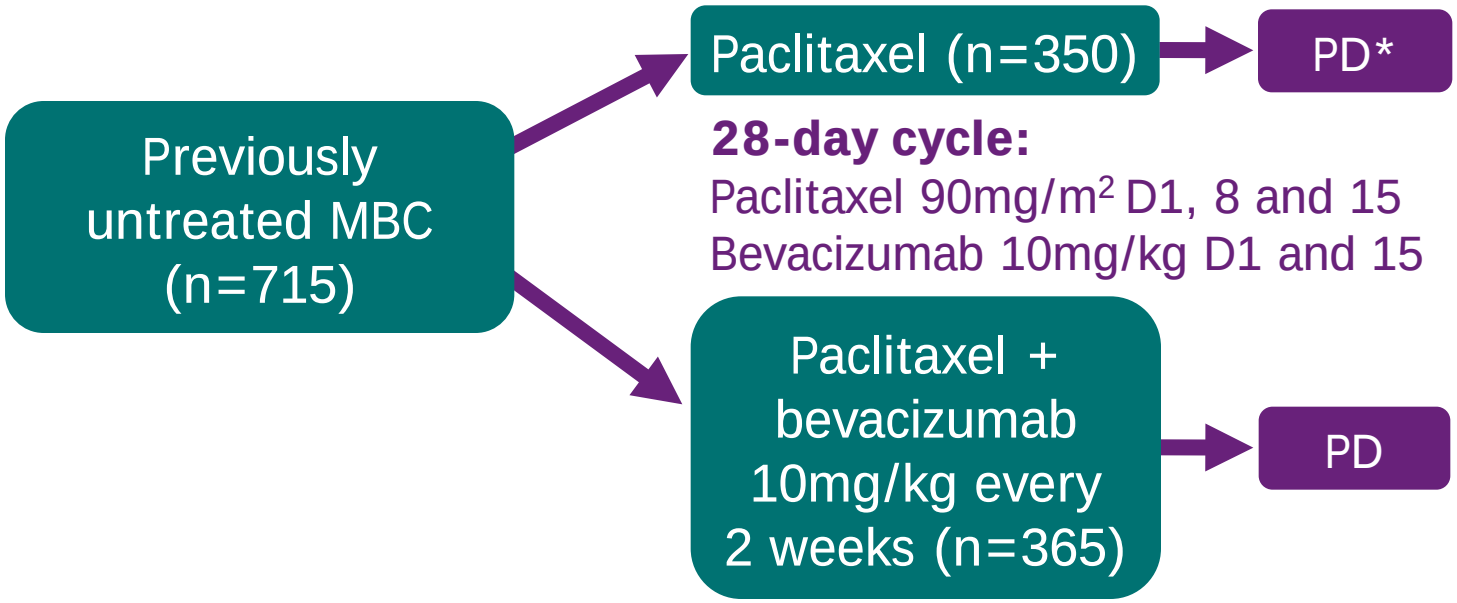
  bevacizumab in metastatic breast cancer　　？

  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)

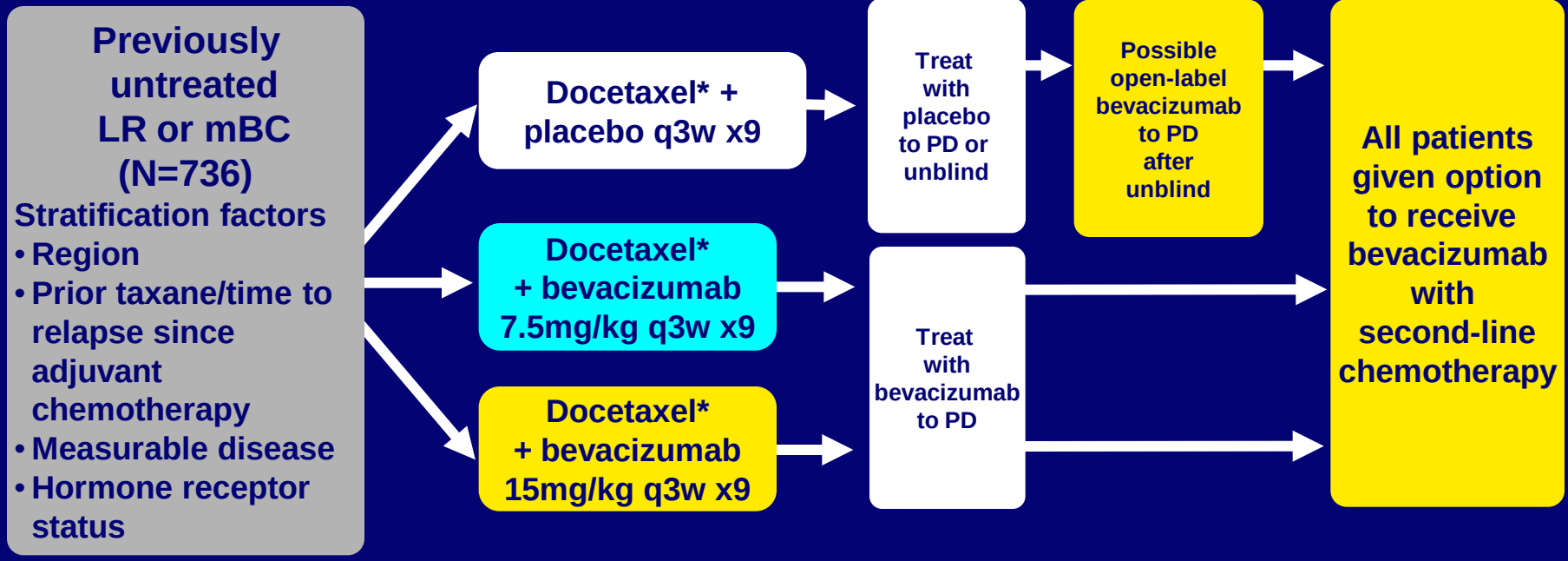


Stratify:

- 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

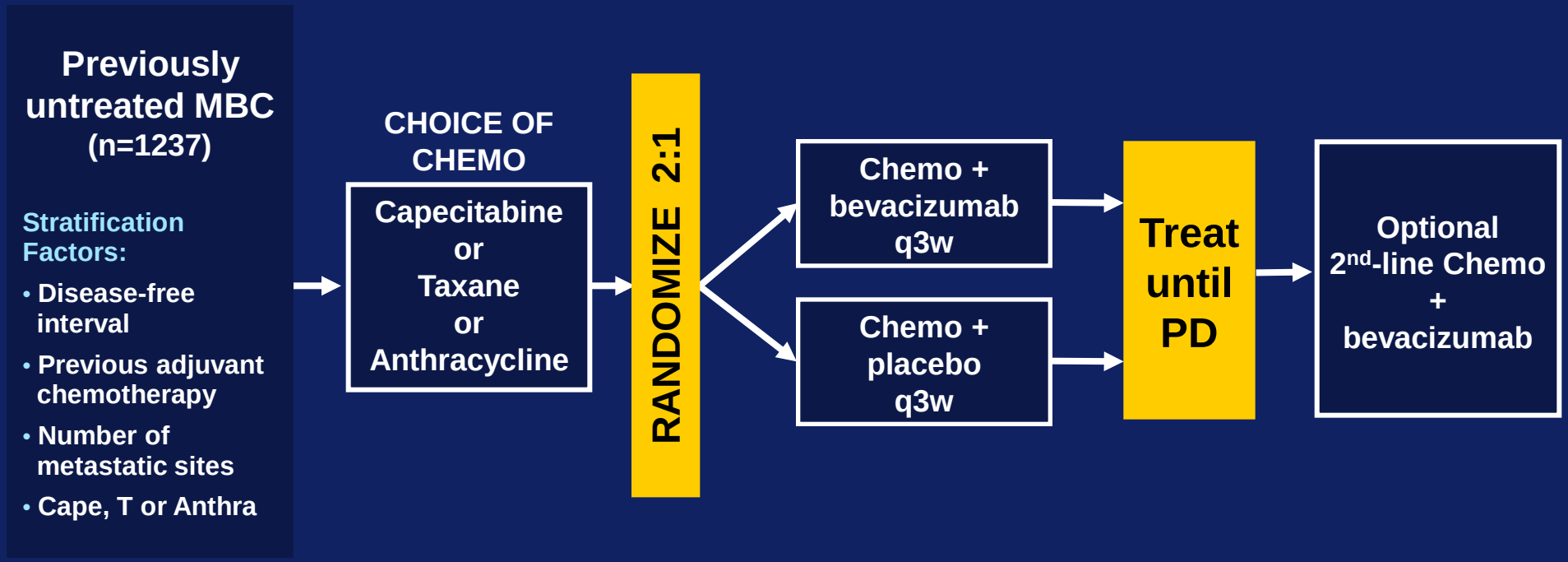


- Primary endpoint: PFS
- Secondary endpoints: ORR, 1-year survival, OS, TTF, duration of response, quality of life, safety

*Docetaxel: 100mg/m² q3w

Miles DW, et al. ASCO 2008

RIBBON-1: Study Design



- Capecitabine (1000 mg/m^2 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. [2]Kathy Miller et al. N Engl J Med 2007; 357:2666-76
[3] Miles D et al. SABCS2009 abstr#41.
[4]N. J. Robert et al. ASCO2009 abstr#1005

Avastin in 1st line setting for MBC <Efficacy>

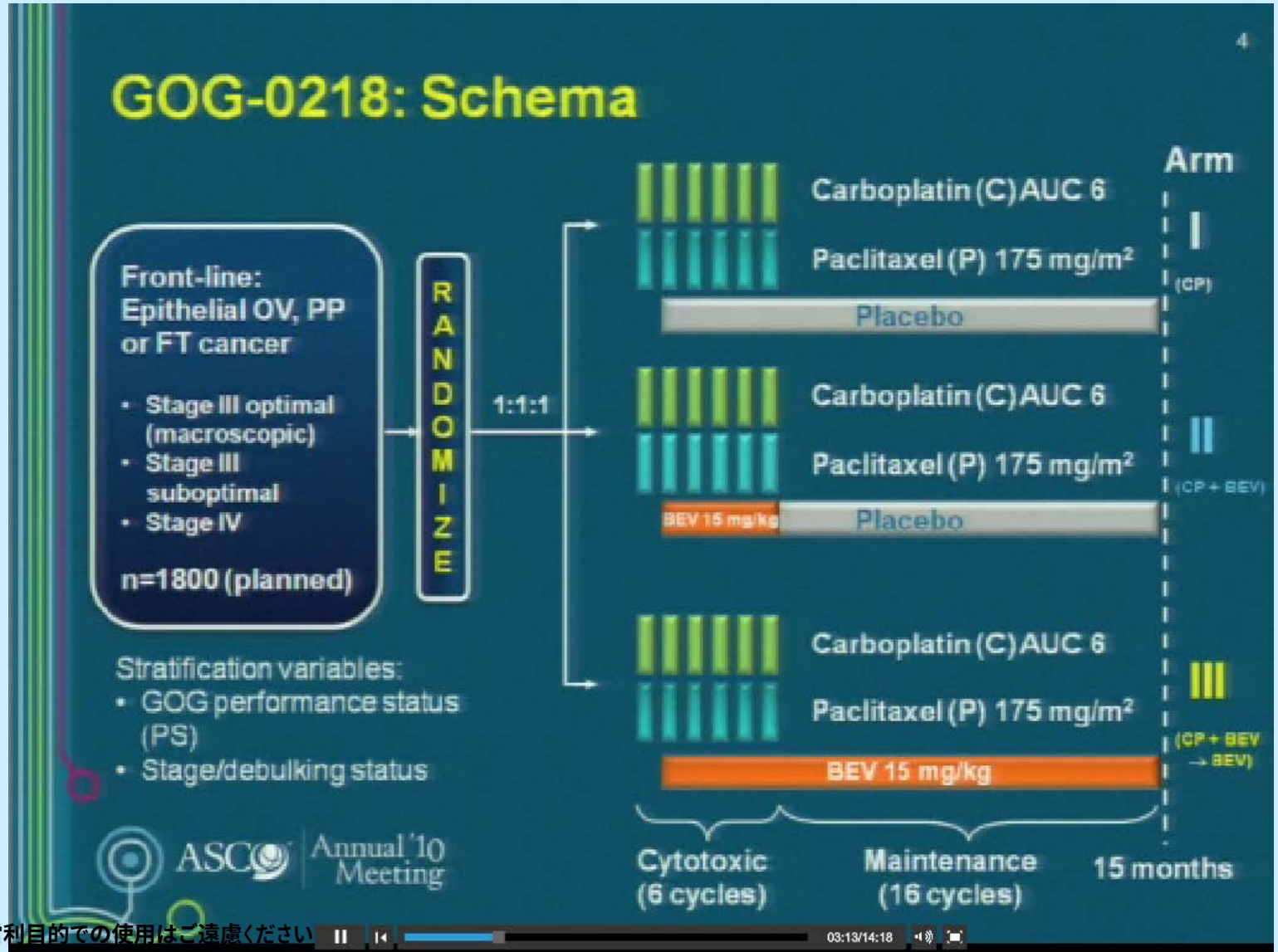
試験	E2100[1,2] (n=722)		AVADO[3] (n=736)		RIBBON-1[4] Cape cohort (n=615)		RIBBON-1[4] A/Tcohort (n=622)	
arm	Paclitaxel	Paclitaxel + BV	Docetaxel + PL	Docetaxel + BV*	Cape + PL	Cape + BV	A/T + PL	A/T + BV
PFS (m)	5.8	11.3	8.2	10.1	5.7	8.6	8.0	9.2
HR	0.48 P<0.0001		0.77 P=0.0061		0.69 P=0.0002		0.64 P<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. [2]Kathy Miller et al. N Engl J Med 2007; 357:2666-76
[3] Miles D et al. SABCS2009 abstr#41.
[4]N. J. Robert et al. ASCO2009 abstr#1005

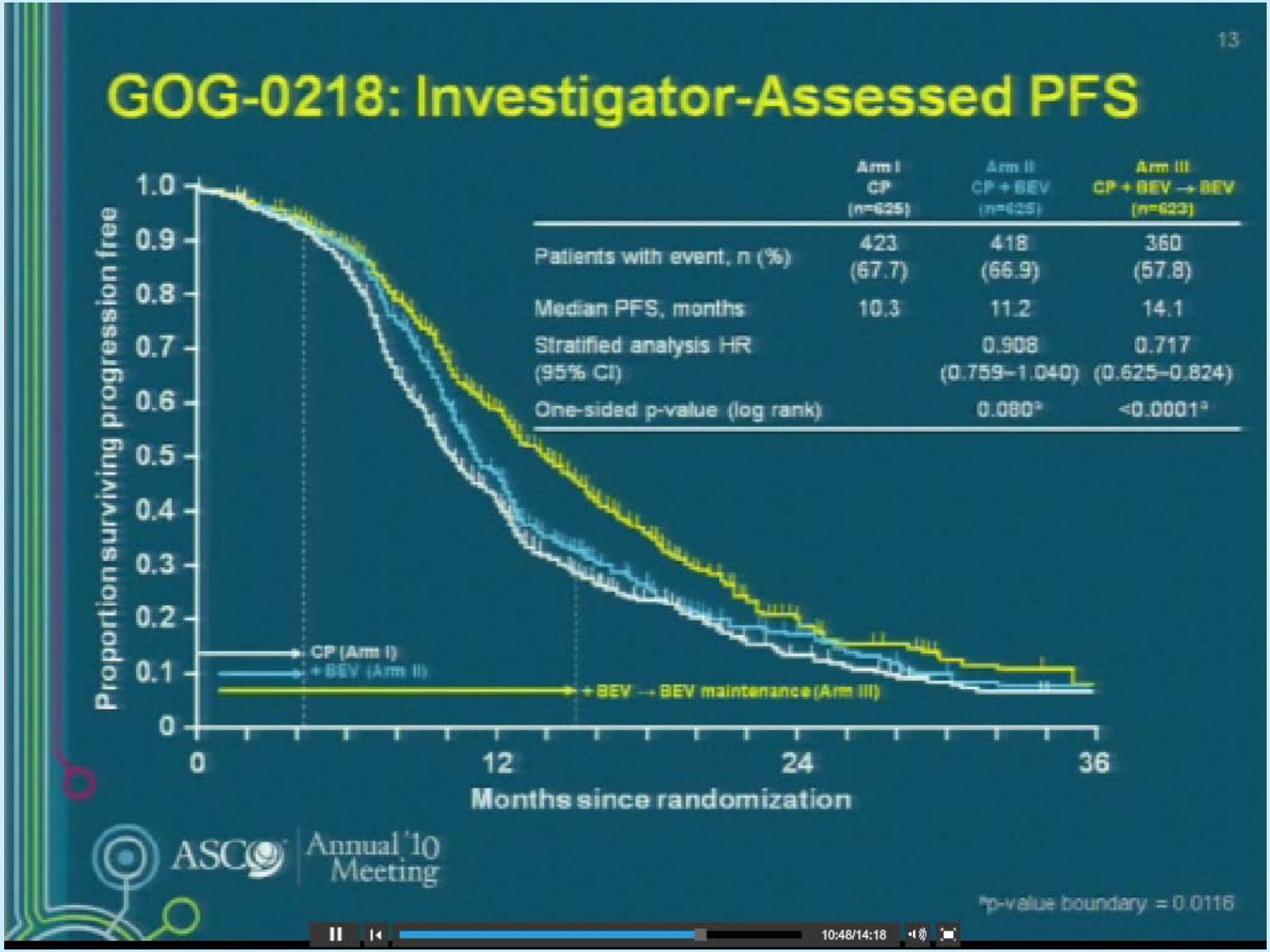
*Bevacizumab15mg/kg q3w

ASCO2010 LBA1 Burger et al.

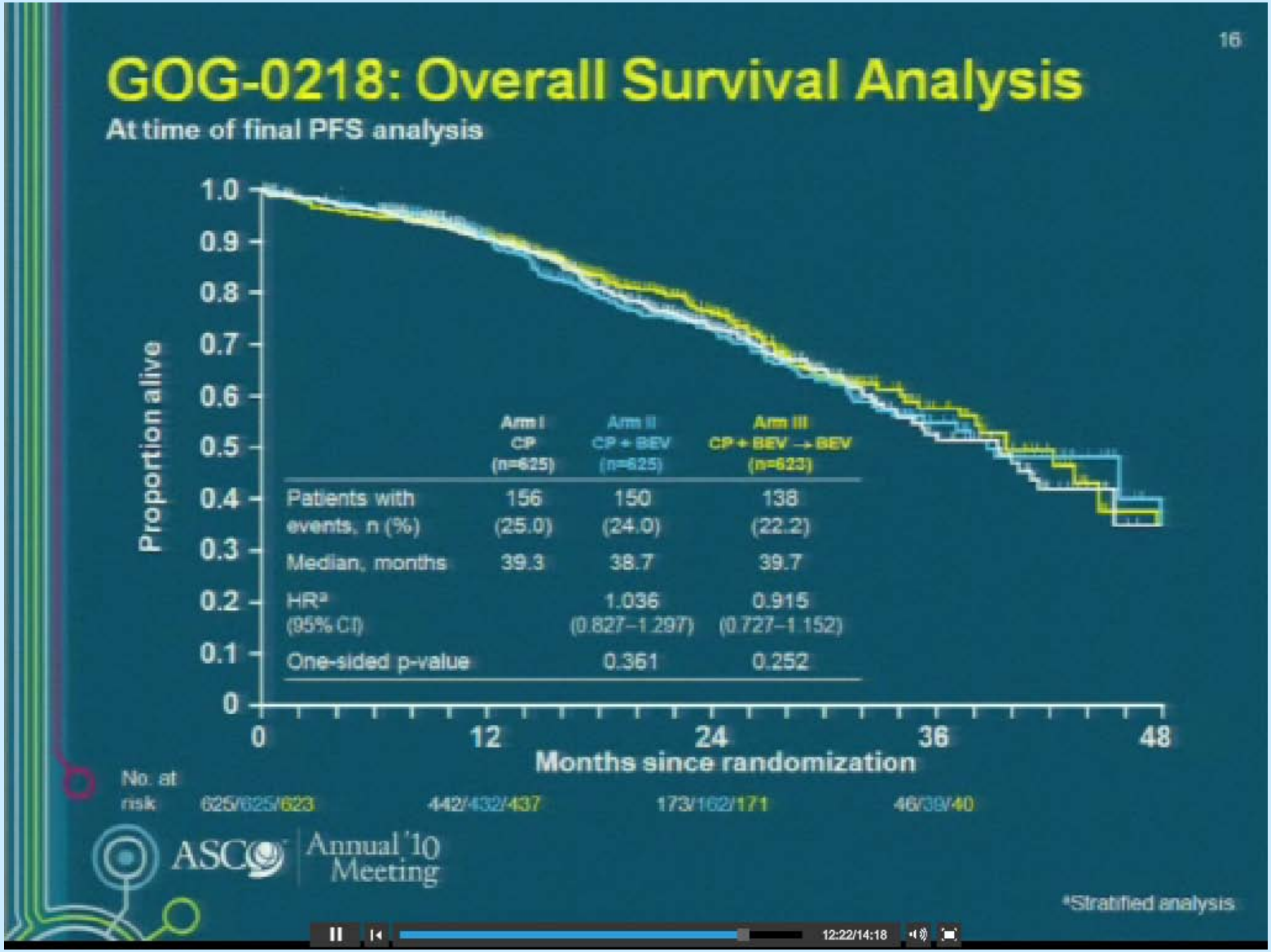
Phase III trial of bevacizumab (BEV) in the primary treatment of advanced epithelial ovarian cancer (EOC), primary peritoneal cancer (PPC), or fallopian tube cancer (FTC): A Gynecologic Oncology Group study.



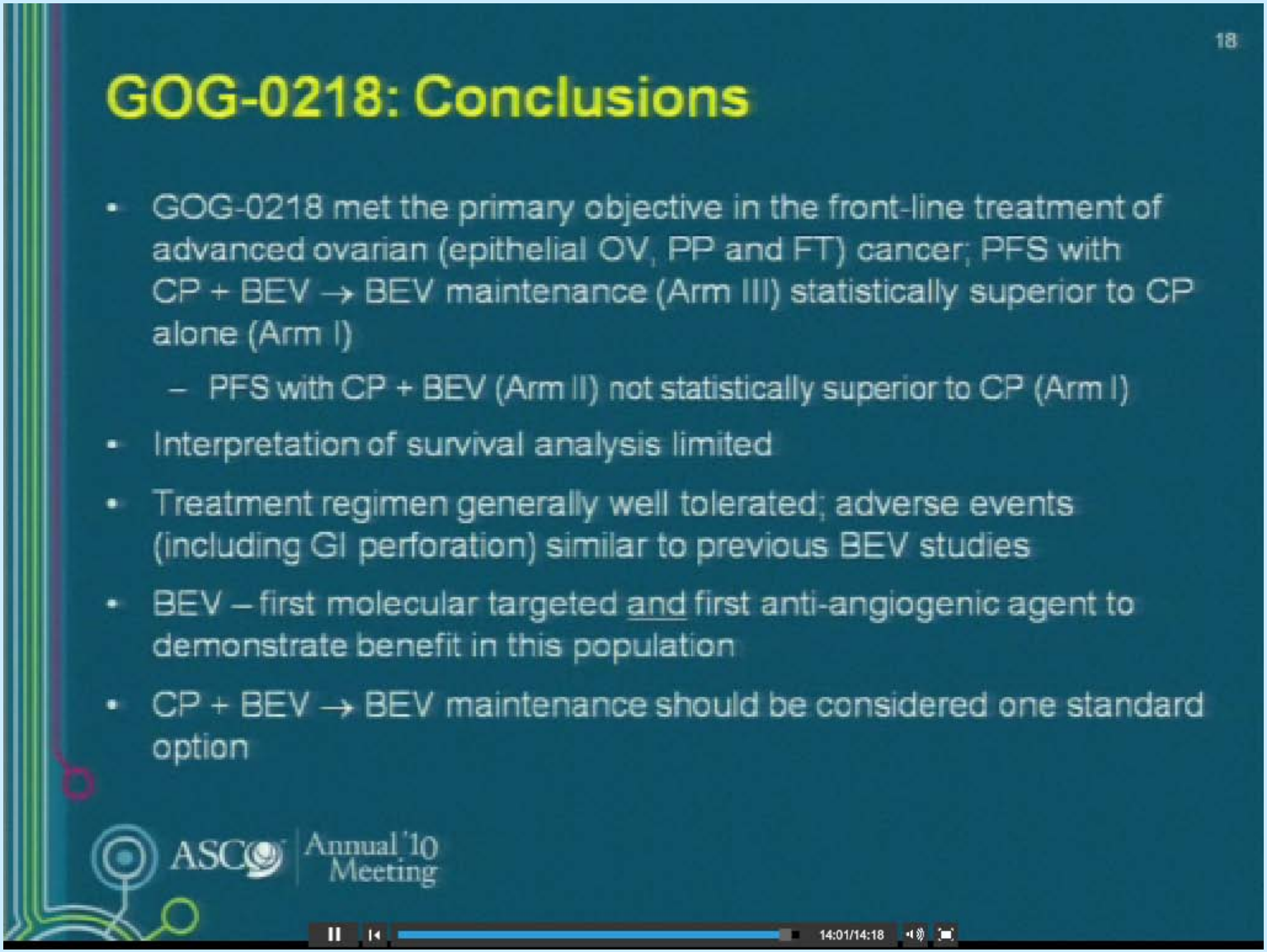
ASCO2010　LBA1　Burger et al.



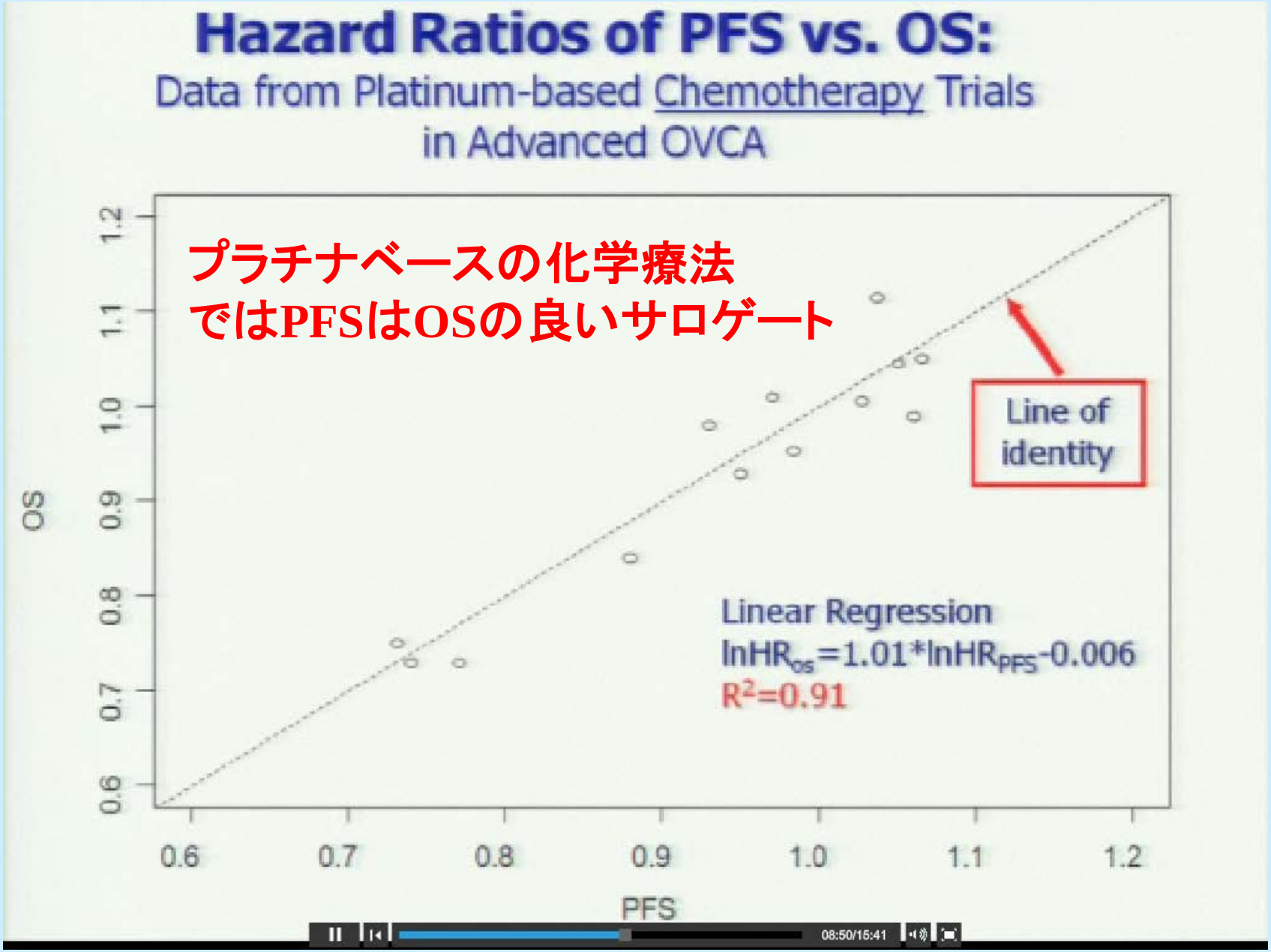
ASCO2010　LBA1　Burger et al.



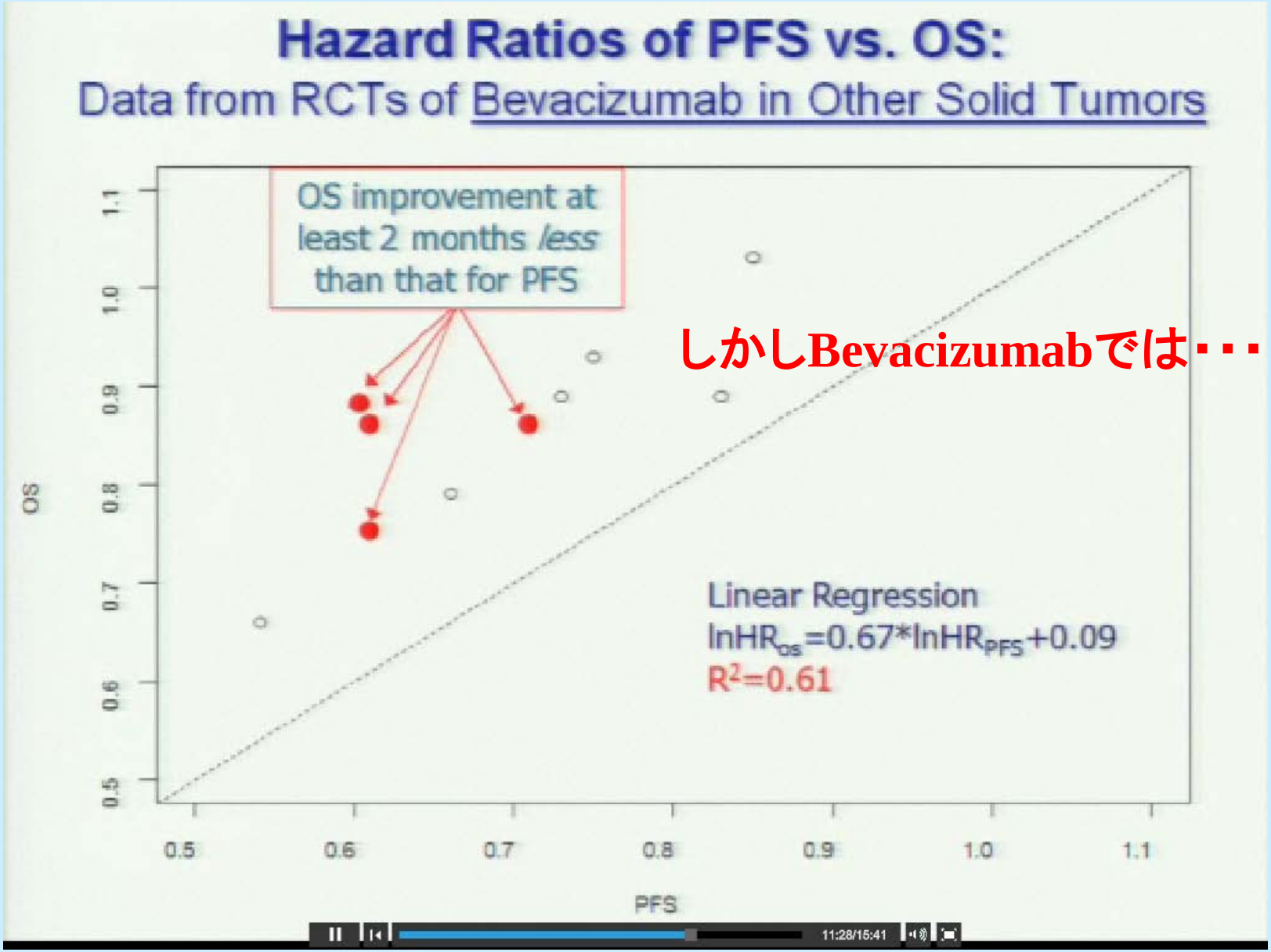
ASCO2010　LBA1　Burger et al.



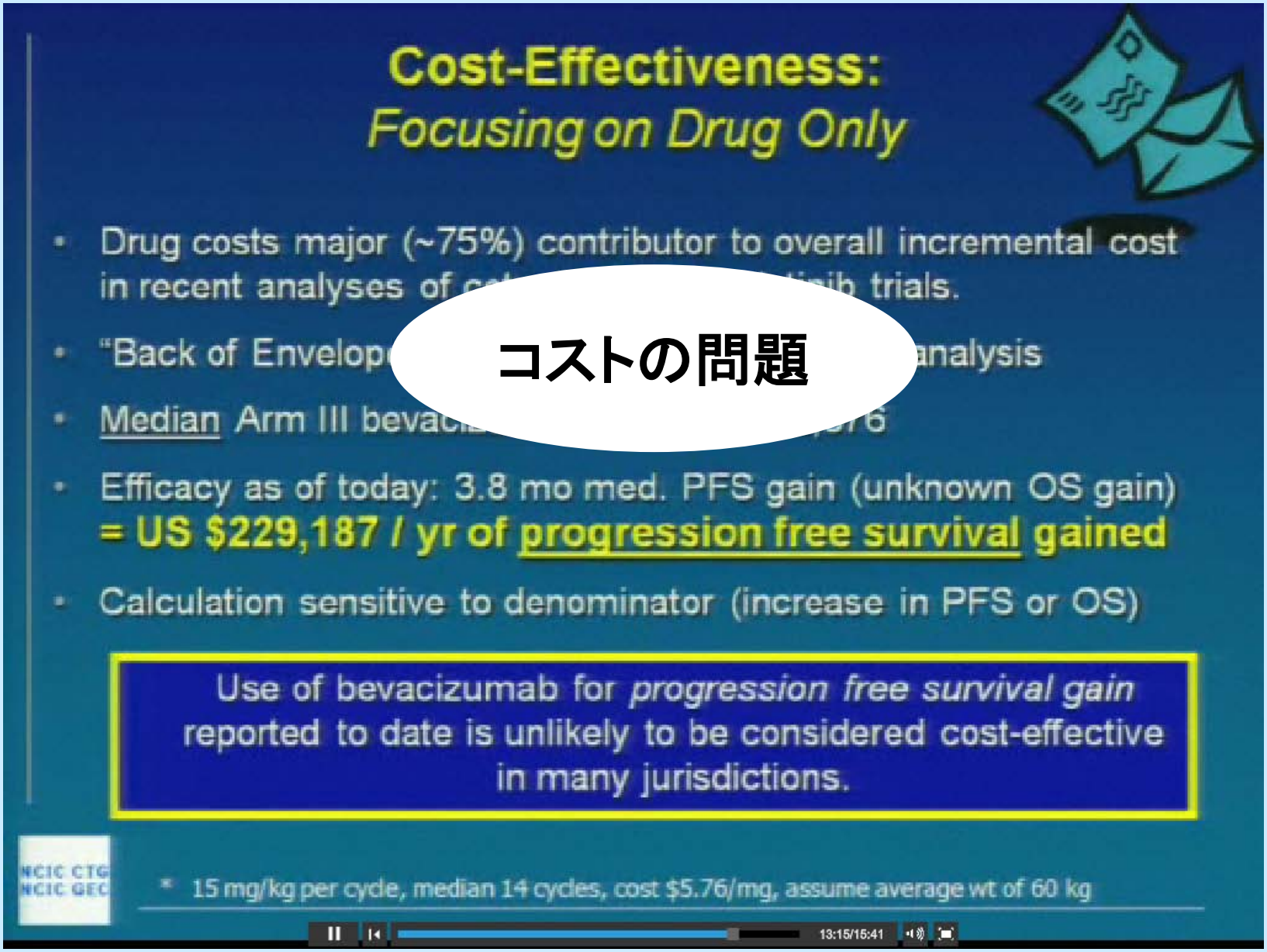
ASCO2010 LBA1 Discussion to Burger et al.



ASCO2010　LBA1　Discussion to Burger et al.



ASCO2010　LBA1　Discussion to Burger et al.



コストの問題

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.

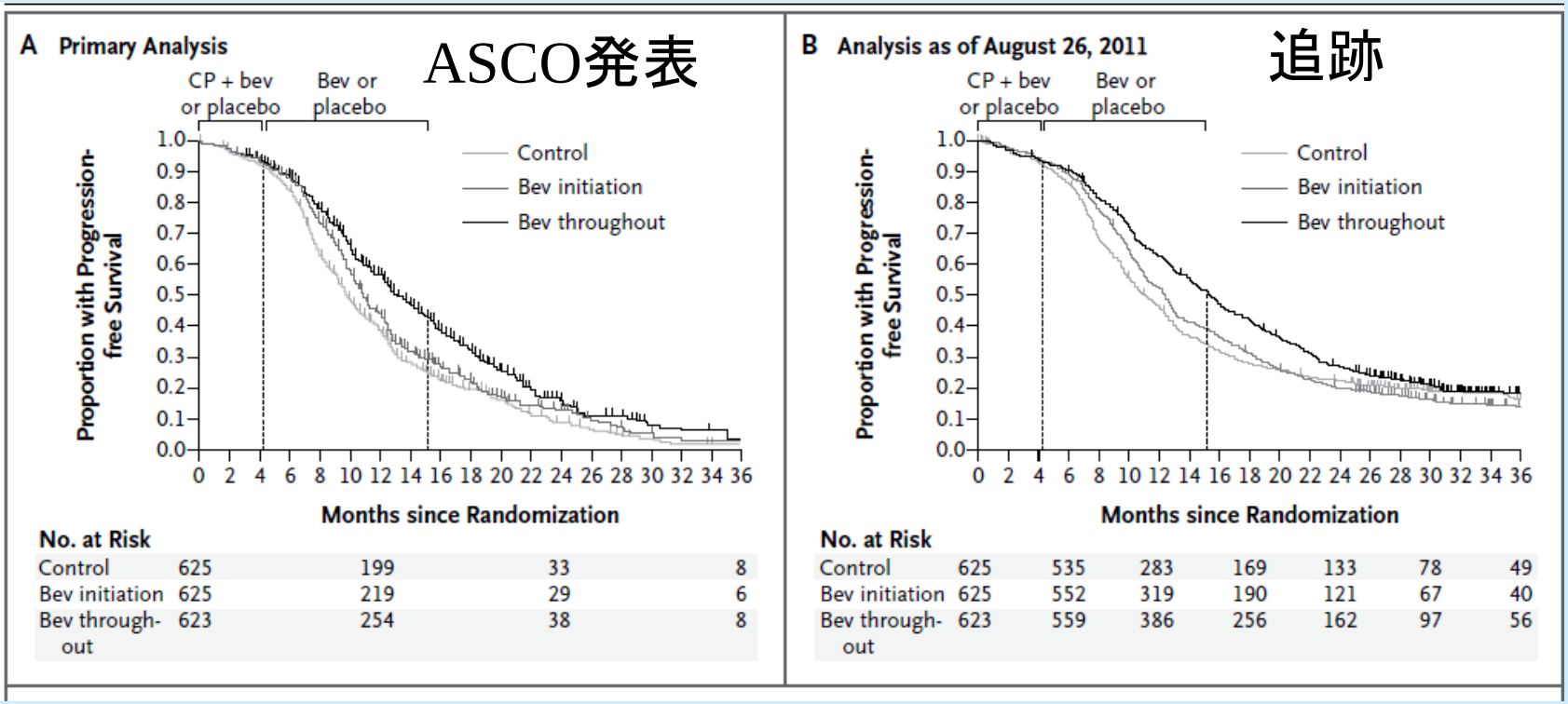
ORIGINAL ARTICLE

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*

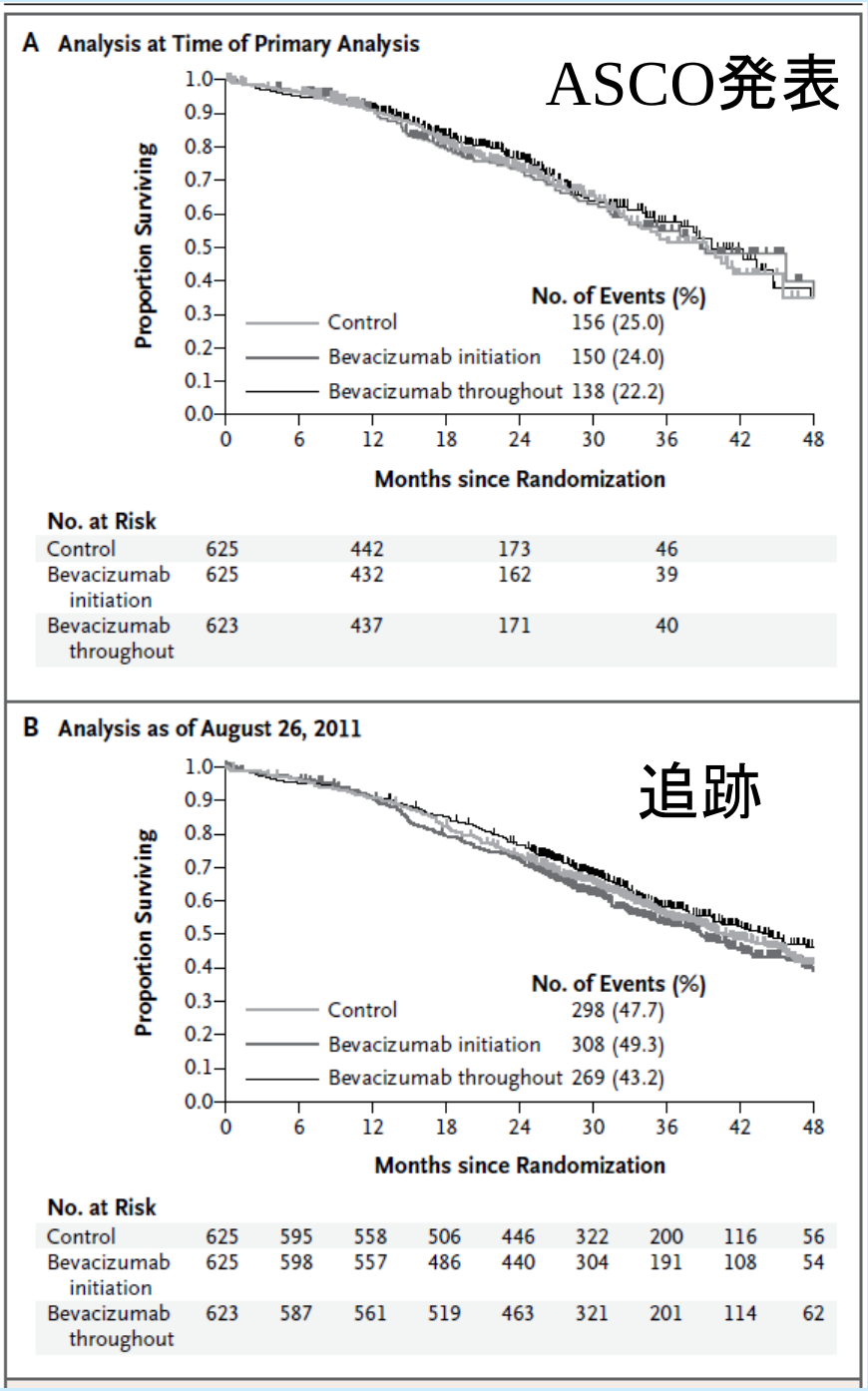
Burger et al. NEJM 2011; 365: 2473-83.

PFSの有意性は持続



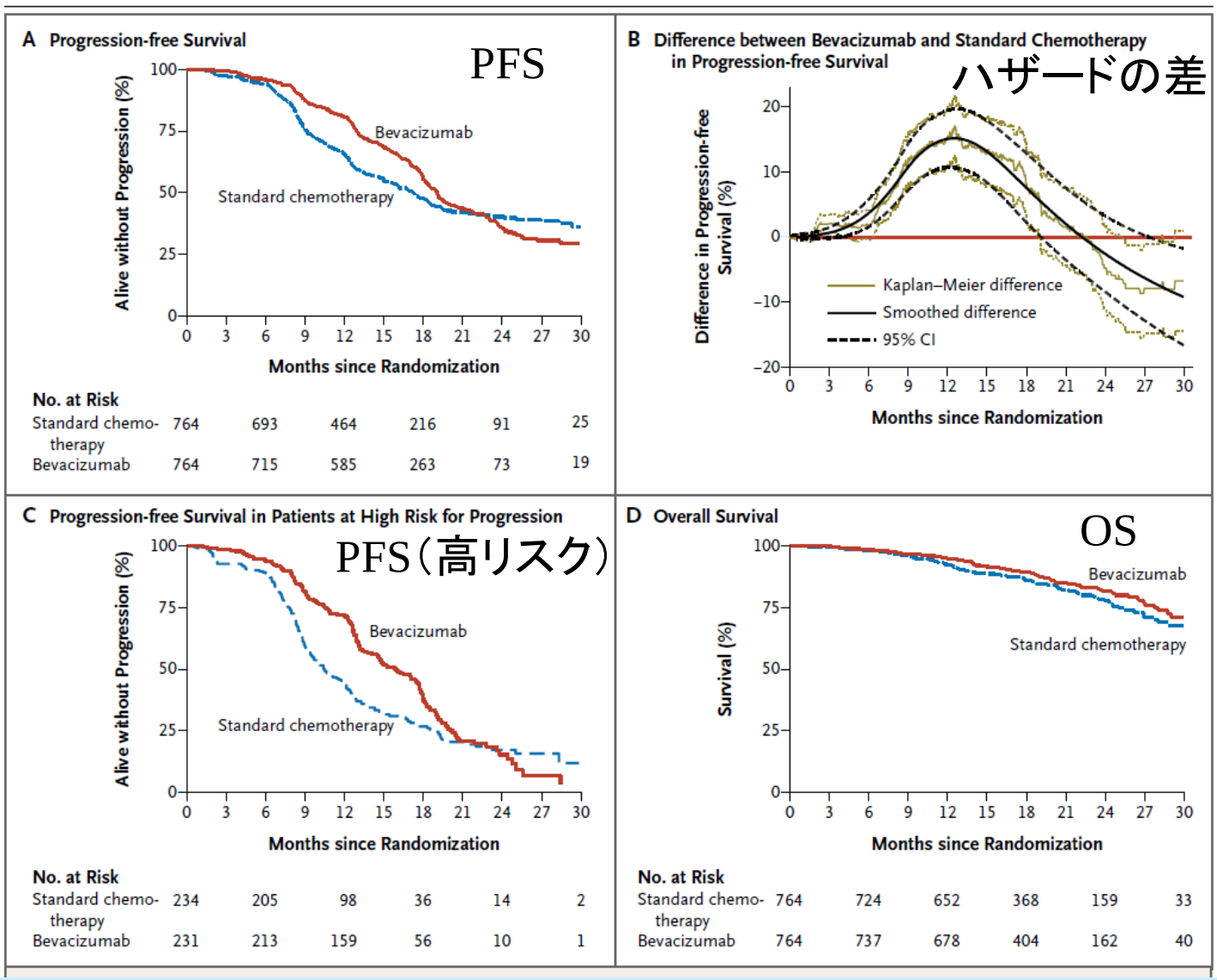
Burger et al. NEJM 2011; 365: 2473-83.

OSの「差なし」も持続



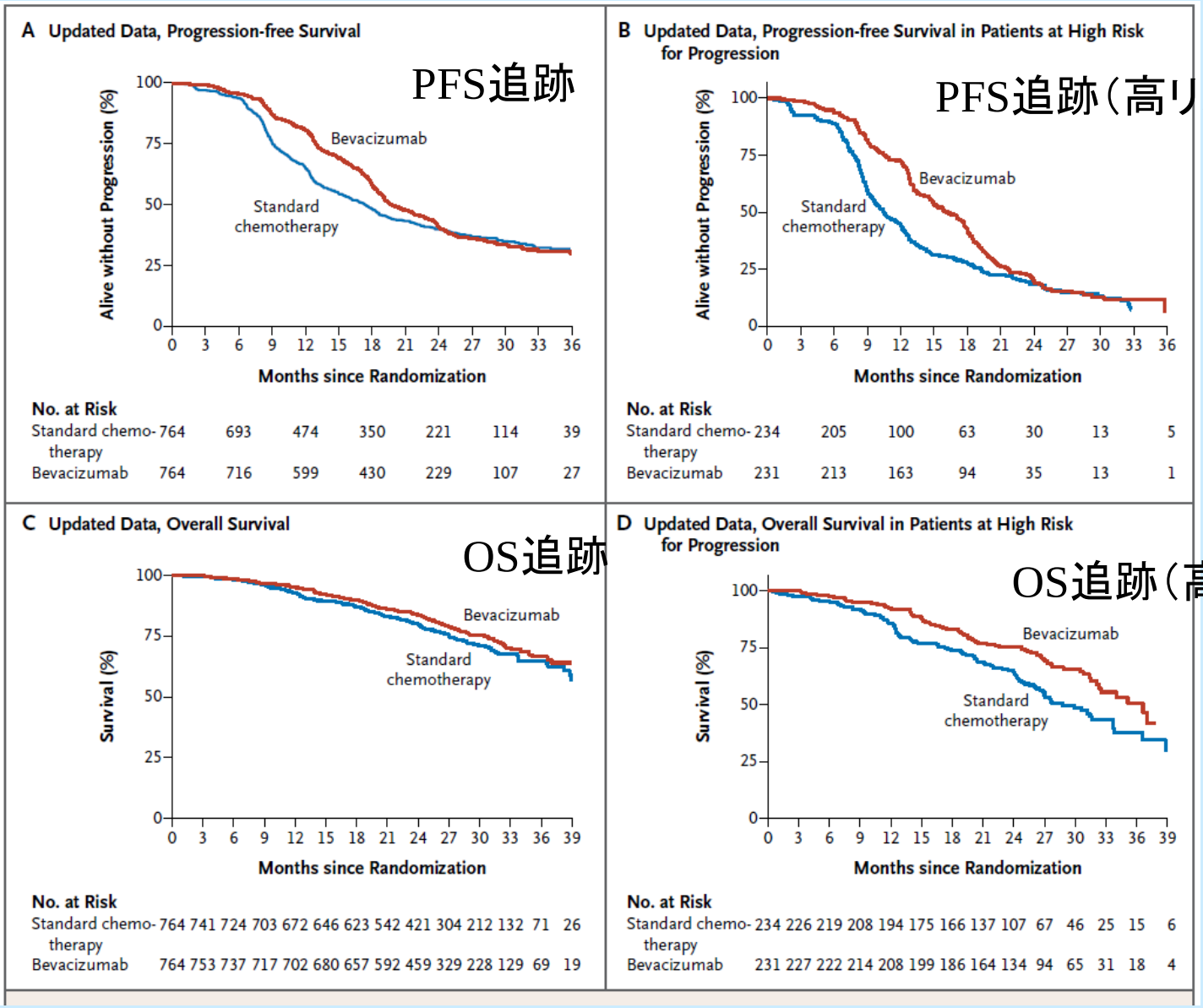
Perren et al. NEJM 2011; 365: 2484-96.

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

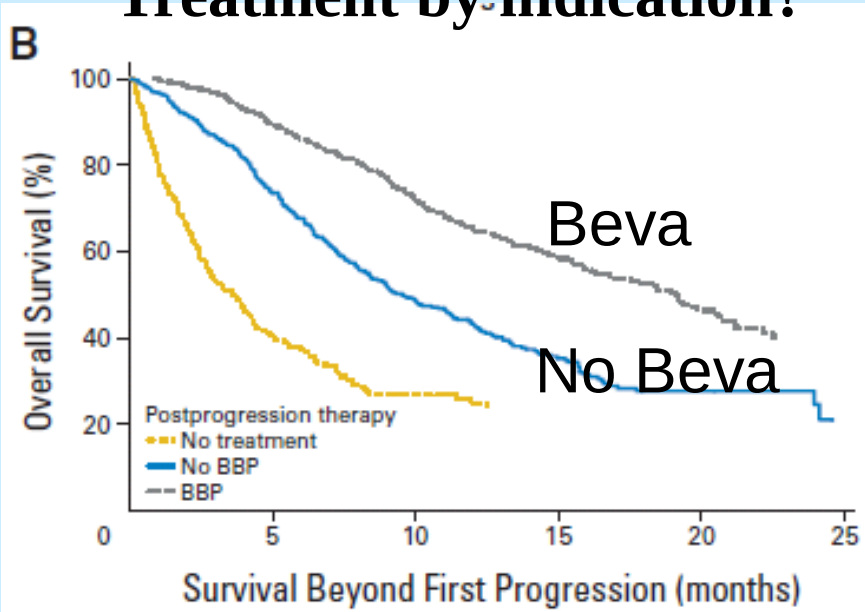


Bevacizumab Beyond Progression？ (BRiTE研究）

Grothey A et al. JCO 2008; 26: 5326-34.

進行後でもBevacizumabを投与した群では予後が良い

Treatment by indication?



	All patients (N = 1,953)	No post-progression treatment (n = 253)	No BBP (n = 531)	BBP (n = 642)
Number of deaths	932	168	305	260
Percent	47.7	66.4	57.8	40.5
1-year survival rate, %	74.7	52.5	77.3	87.7
95% CI	72.7 to 76.7	46.2 to 58.8	73.7 to 80.9	85.2 to 90.3
Median survival beyond first progression, months	12.0	3.6	9.5	19.2
95% CI	11.1 to 13.3	2.7 to 4.3	8.4 to 11.2	16.8 to 20.7

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)

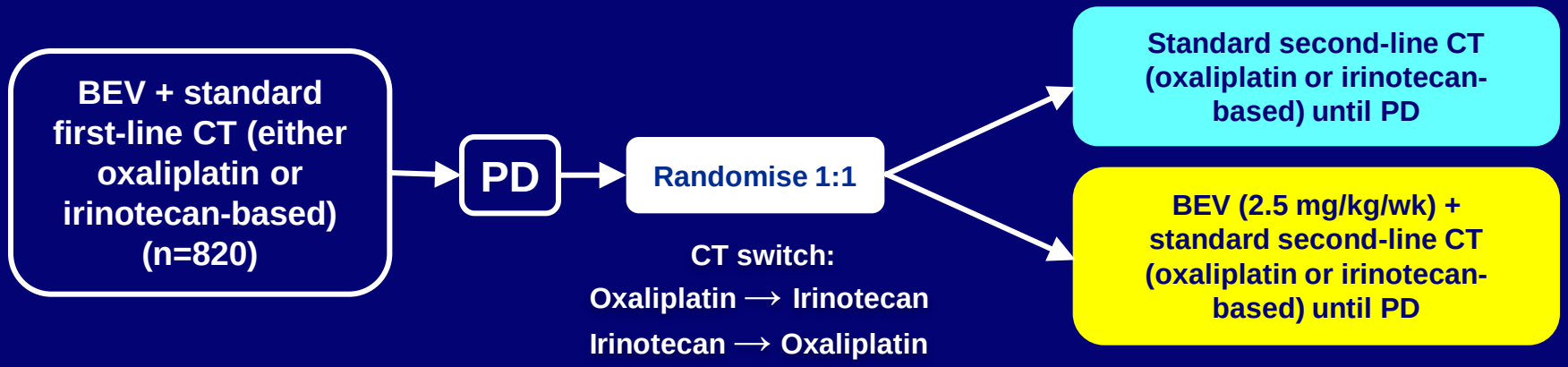
D Arnold[1], T Andre[2], J Bennouna[3], J Sastre[4], P Österlund[5], R Greil[6]
E Van Cutsem[7], R von Moos[8], I Reyes-Rivera[9], B Bendahmane[10], S Kubicka[11]

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

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

ASCO2012#3504

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

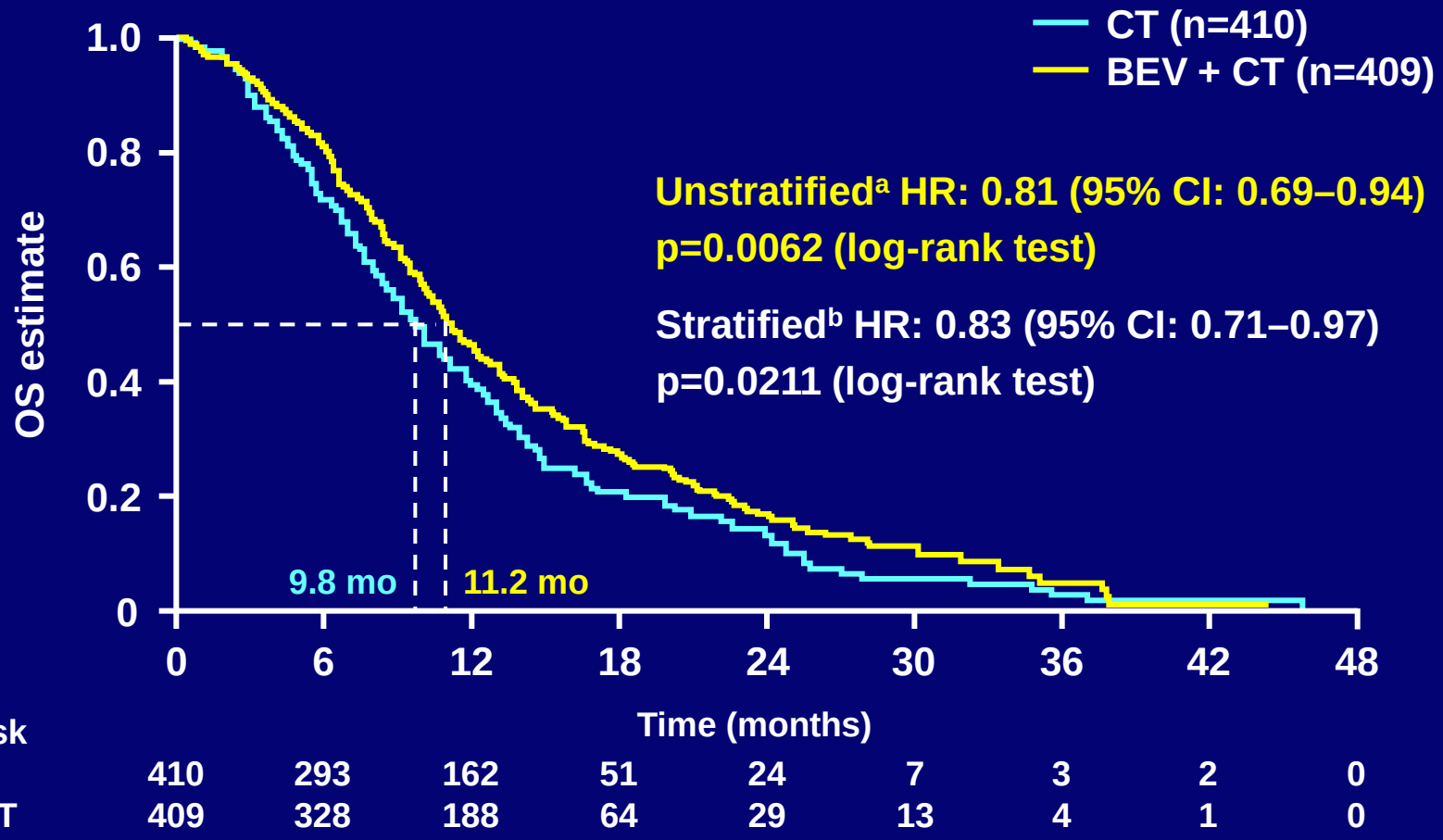
ASCO2012#3504

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

ASCO2012#3504

OS: ITT population



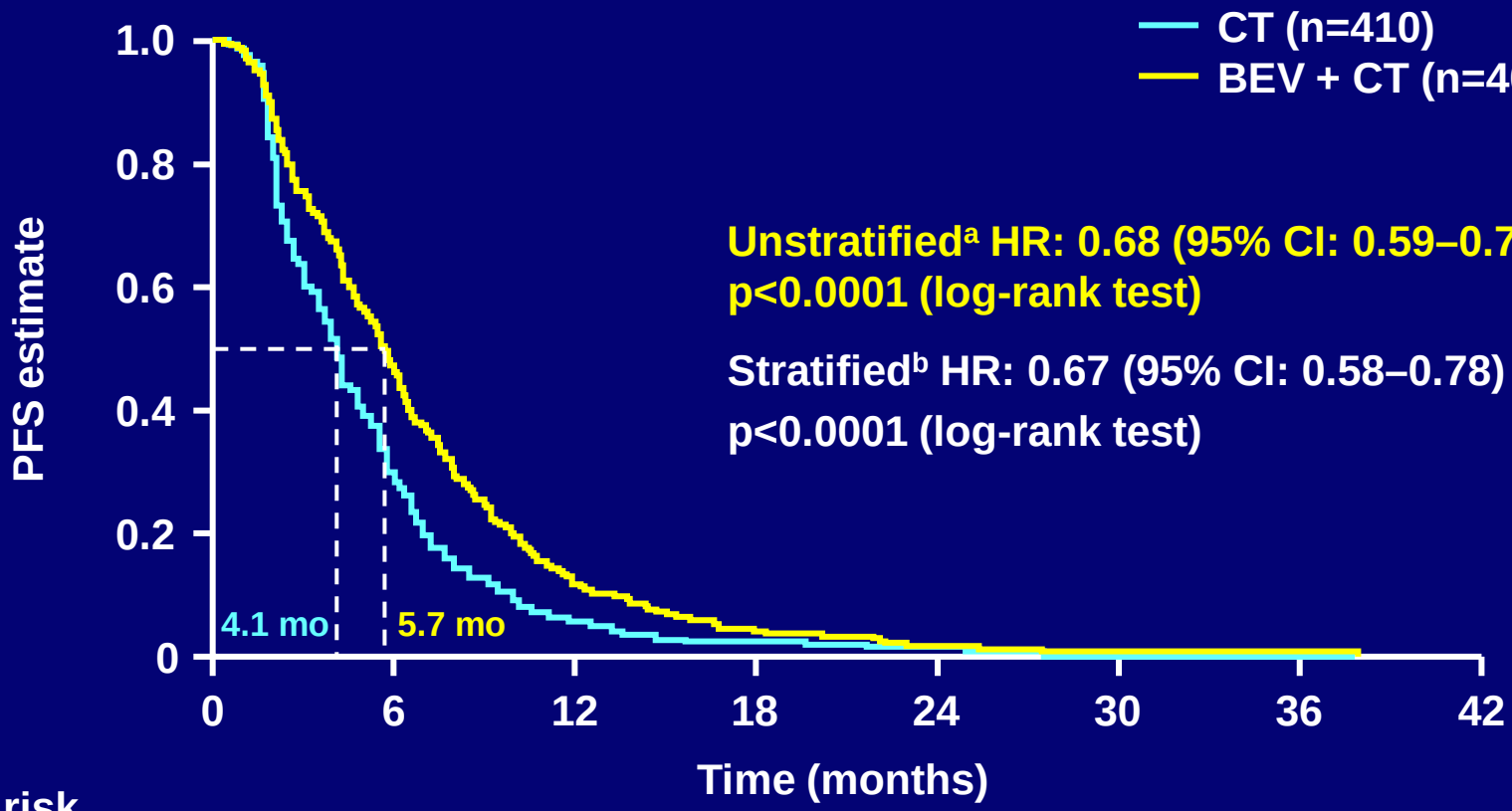
No. at risk									
CT	410	293	162	51	24	7	3	2	0
BEV + CT	409	328	188	64	29	13	4	1	0

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

[a]Primary analysis method; [b]Stratified 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)

ASCO2012#3504

PFS: ITT population



Unstratified[a] HR: 0.68 (95% CI: 0.59–0.78)
p<0.0001 (log-rank test)

Stratified[b] HR: 0.67 (95% CI: 0.58–0.78)
p<0.0001 (log-rank test)

No. at risk								
CT	410	119	20	6	4	0	0	0
BEV + CT	409	189	45	12	5	2	2	0

[a]Primary analysis method; [b]Stratified 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)

ASCO2012#3504

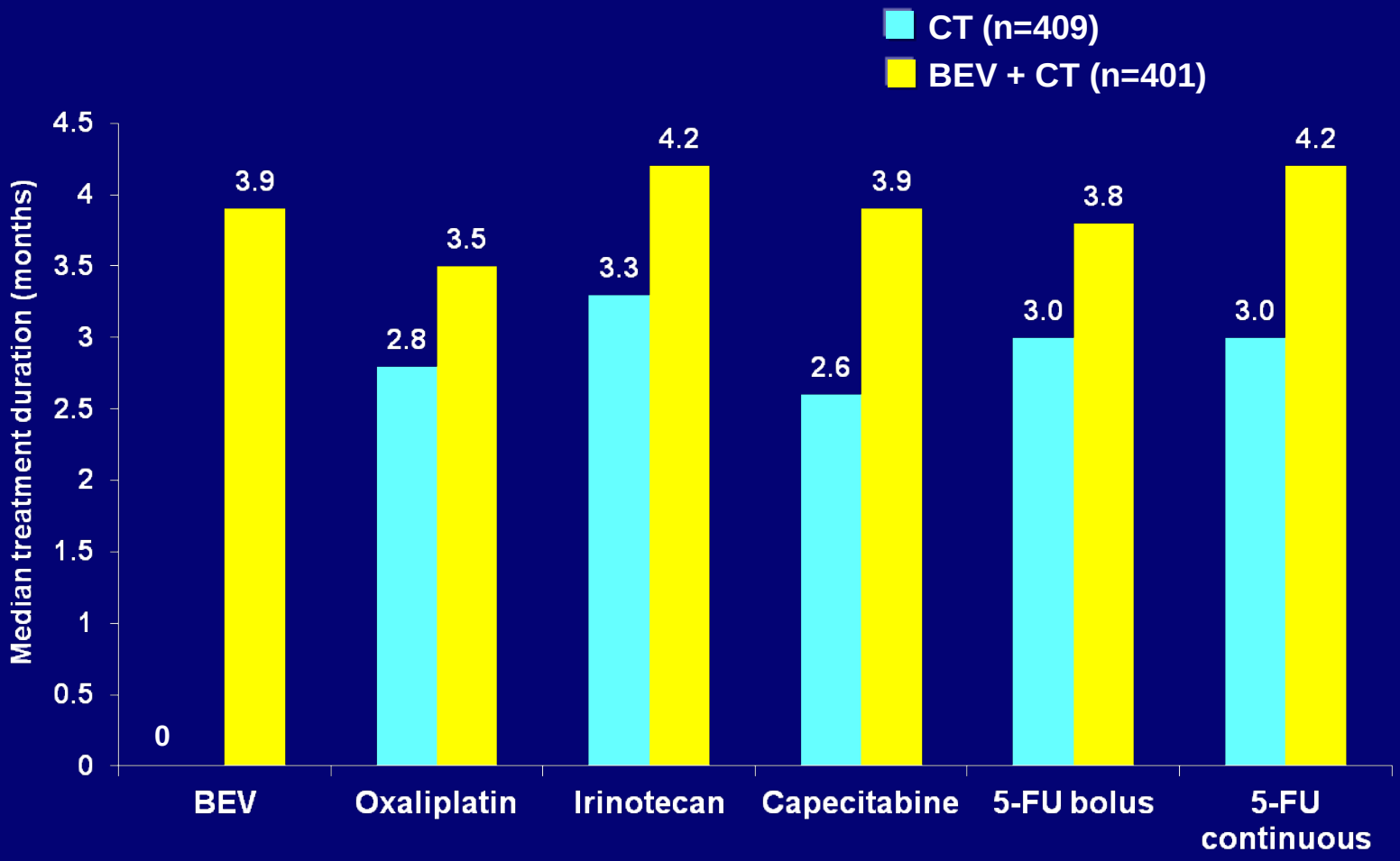
Best overall response: Measurable disease population

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)

[a]Patients with a best overall response of confirmed complete or partial response
[b]This analysis was not prespecified
[c]Includes 'not-evaluable' or 'no tumour assessment' following baseline visit

ASCO2012#3504

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

ASCO2012#3504

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

[a]PD leading to death captured for some patients as grade 5 AE; these events were excluded from this summary
AE: adverse event

ASCO2012#3504

Grade 3–5 adverse events (incidence ≥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

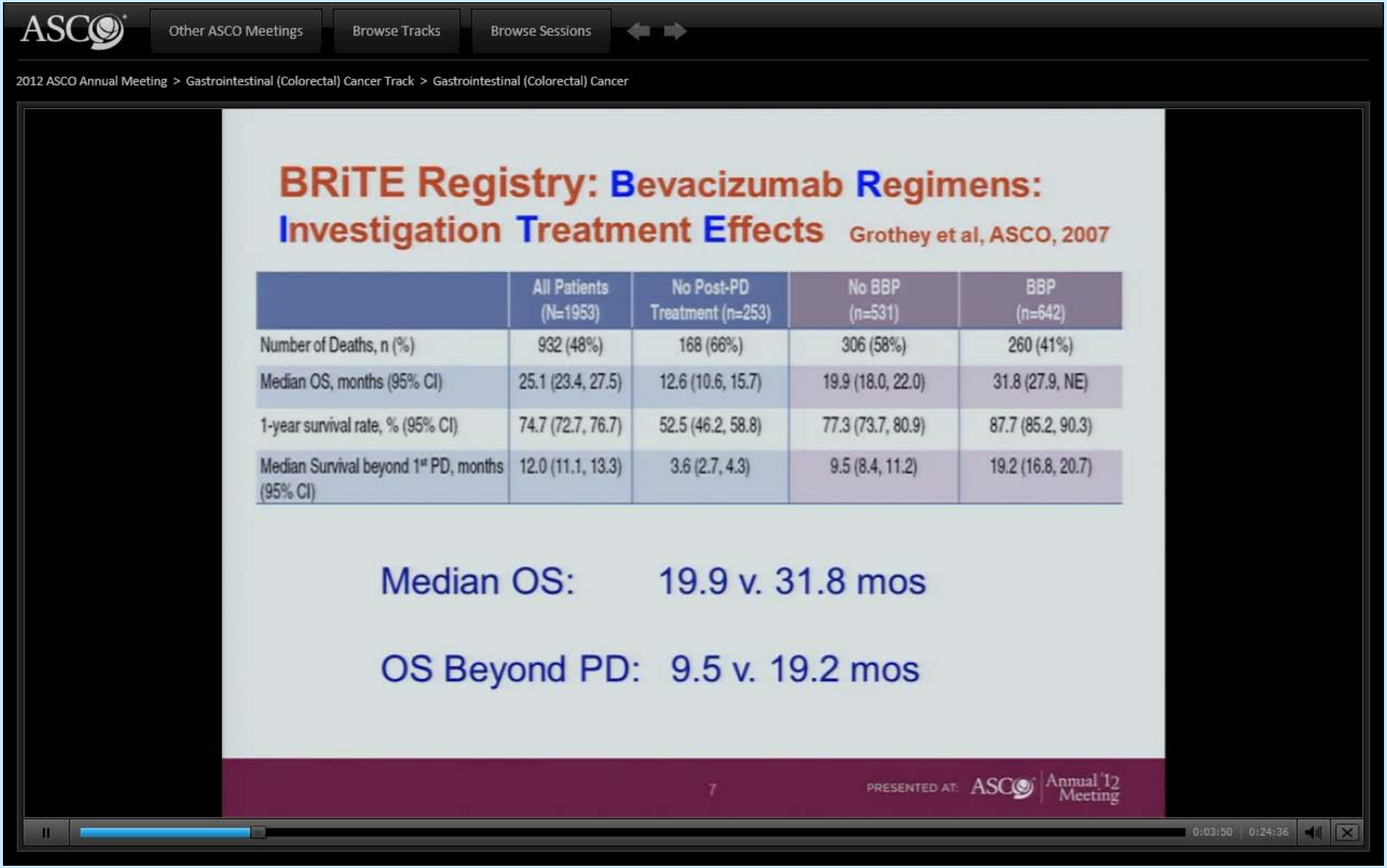
- BEV + standard second-line CT, crossed over from BEV + standard first-line CT, significantly prolongs OS and PFS
  - OS
    - Median: BEV + CT 11.2 months, CT 9.8 months
    - HR: 0.81 (95% CI: 0.69–0.94), p=0.0062[a]
  - PFS
    - Median: BEV + CT 5.7 months, CT 4.1 months
    - HR: 0.68 (95% CI: 0.59–0.78), p≤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

[a]Unstratified log-rank test

Conclusions

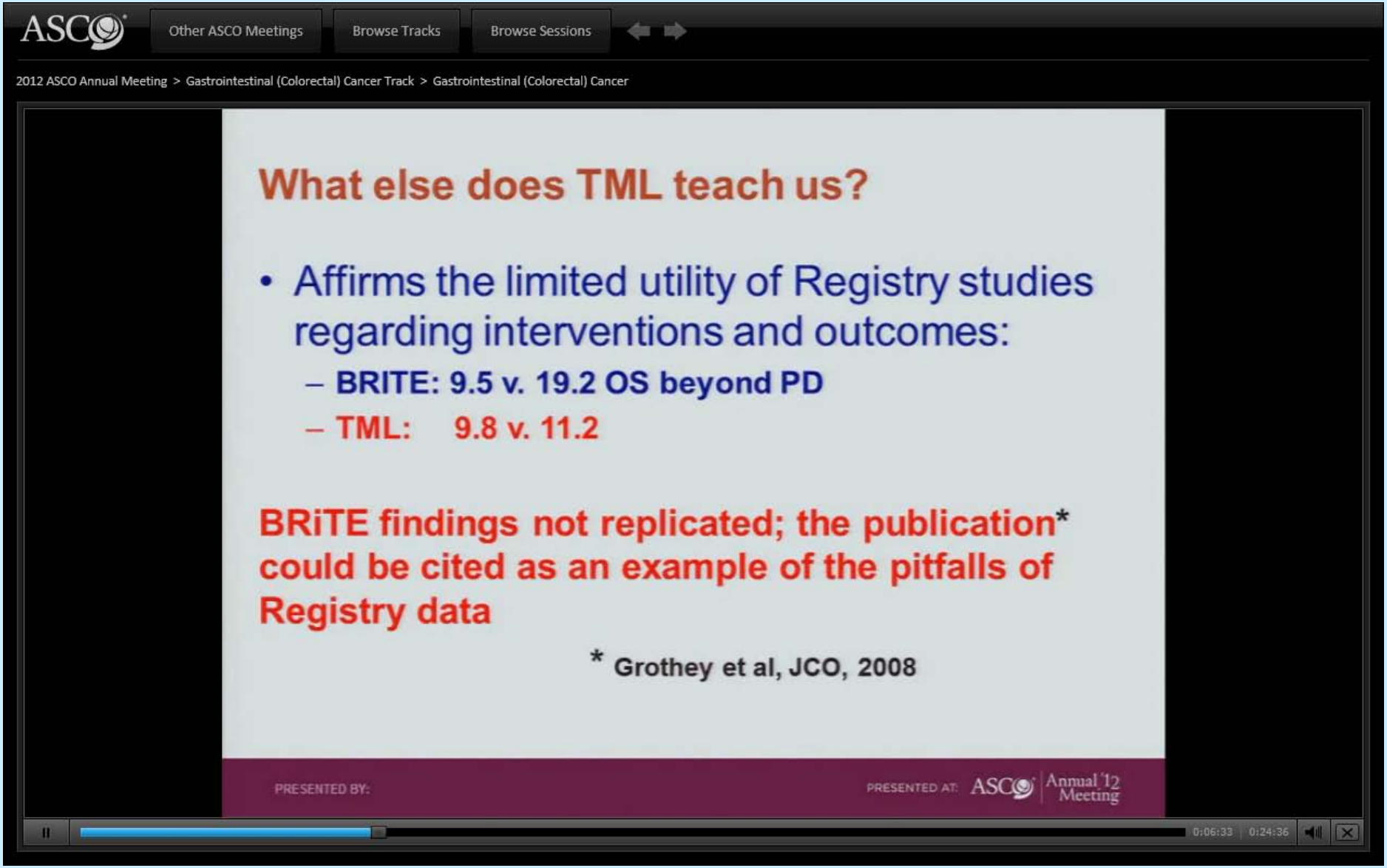
- First randomised clinical trial that prospectively investigated the impact of continued VEGF inhibition with BEV beyond first progression
- Study confirms that continuing BEV beyond first progression while modifying CT is beneficial for patients with mCRC and leads to a significant improvement in OS 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)



	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 1st 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)

Discussion to #3504 (P. Vencok)



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

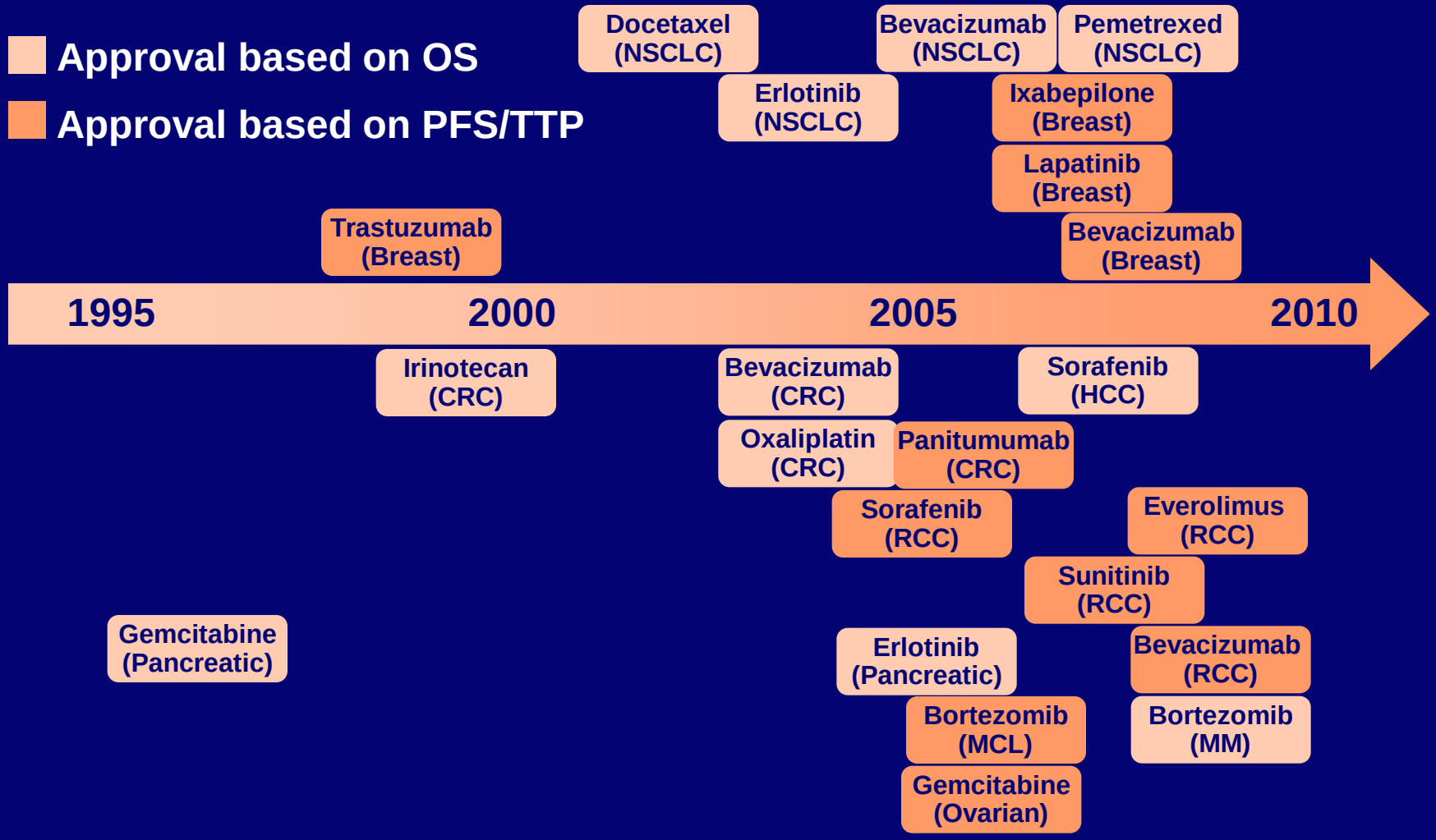
  bevacizumab in metastatic breast cancer

  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



www.cancer.gov/cancertopics/druginfo

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）

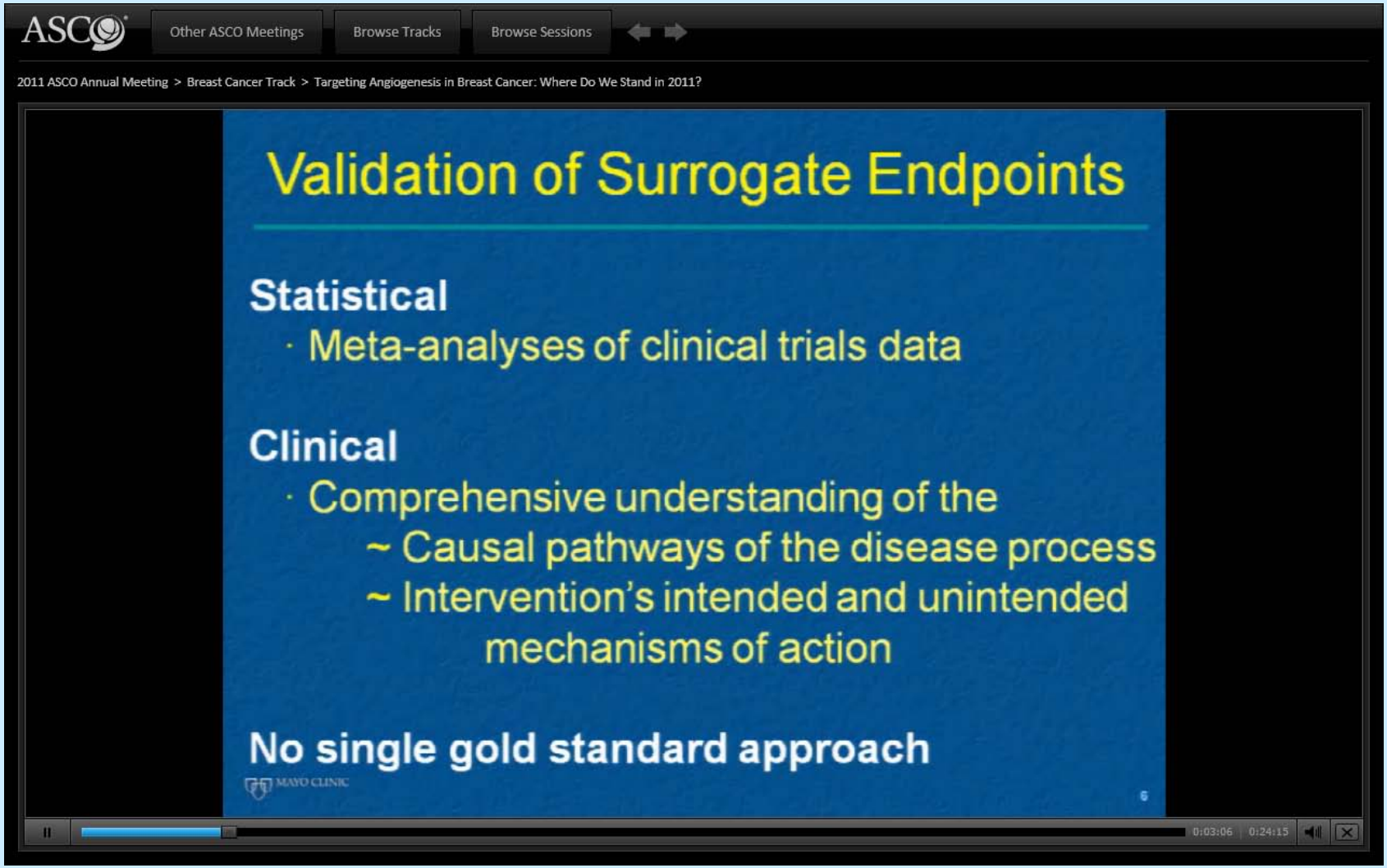
- PFSの曖昧さとそれに対する対処の必要性
- 大きなPFSの改善と優れたrisk/benefit profileなら（さらに経済的に許容できるなら）PFSによる承認は当然ありうる

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

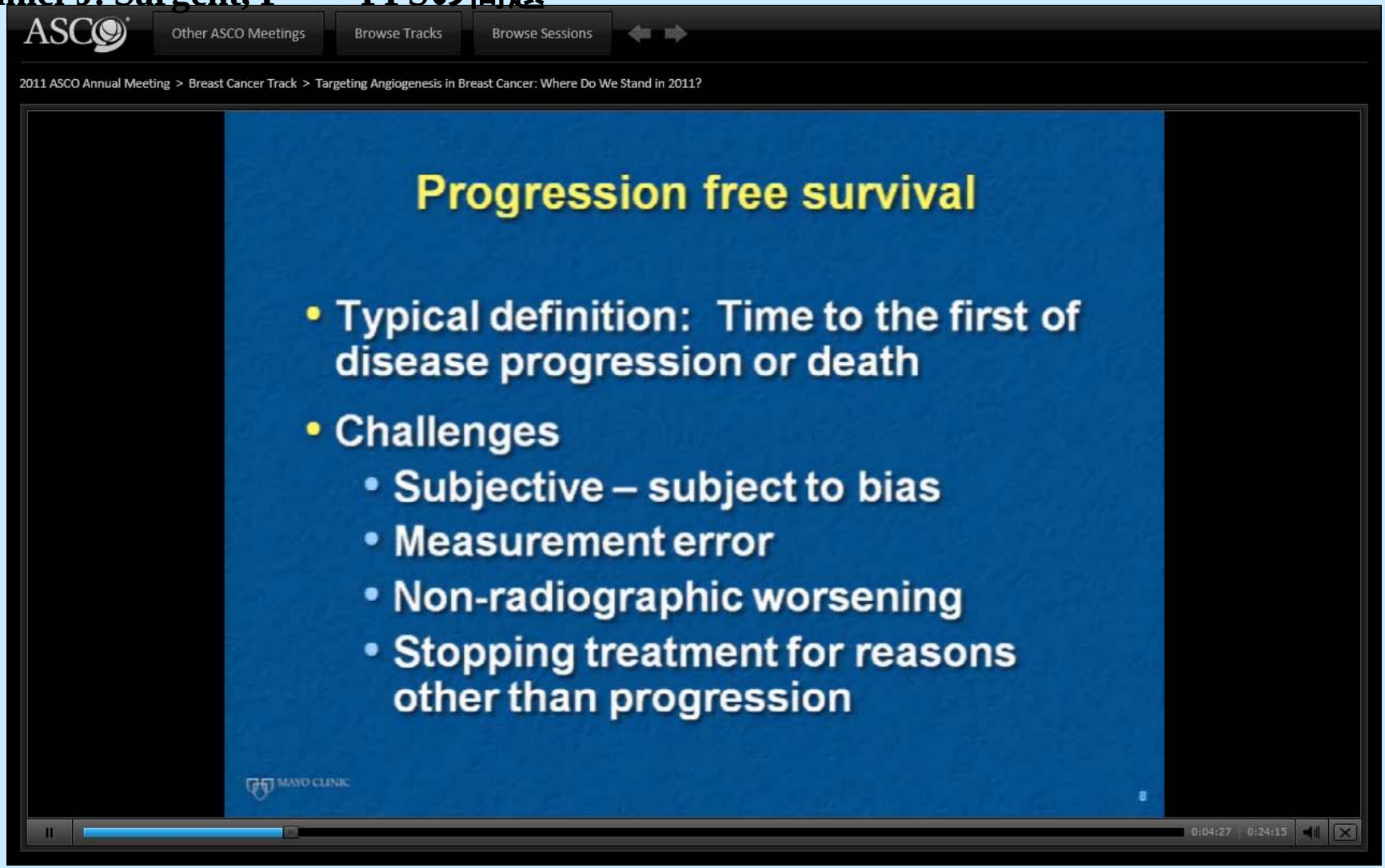
ASCO2011: Targeting Angiogenesis in Breast Cancer: Where Do We Stand in 2011? Appropriate Endpoints for Clinical Trials and Source of U.S. Food and Drug Administration/Oncologic Drugs Advisory Committee Controversy

Daniel J. Sargent, P　　代替性の評価：唯一の標準はない



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

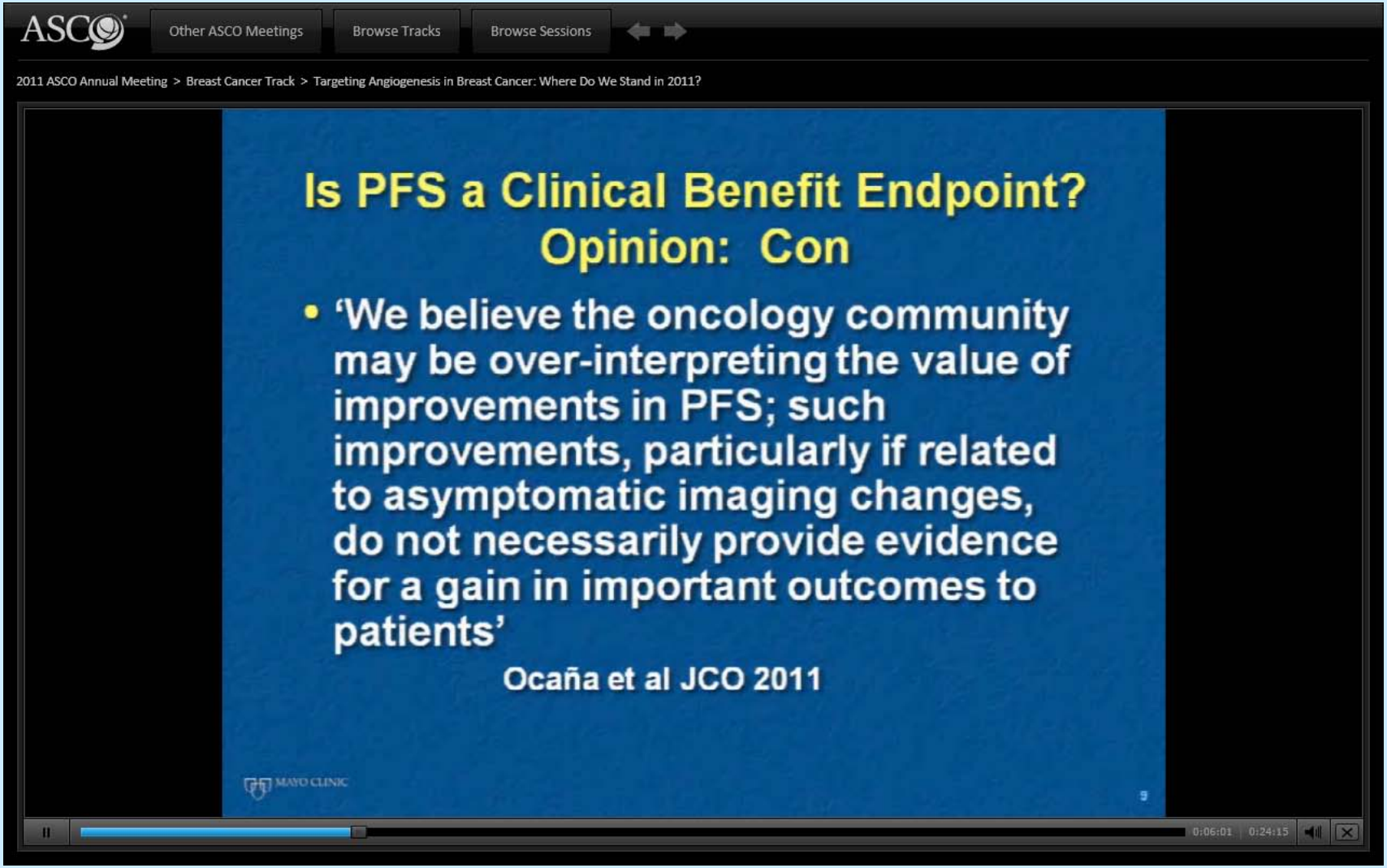
Daniel J. Sargent, P　　PFSの問題



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

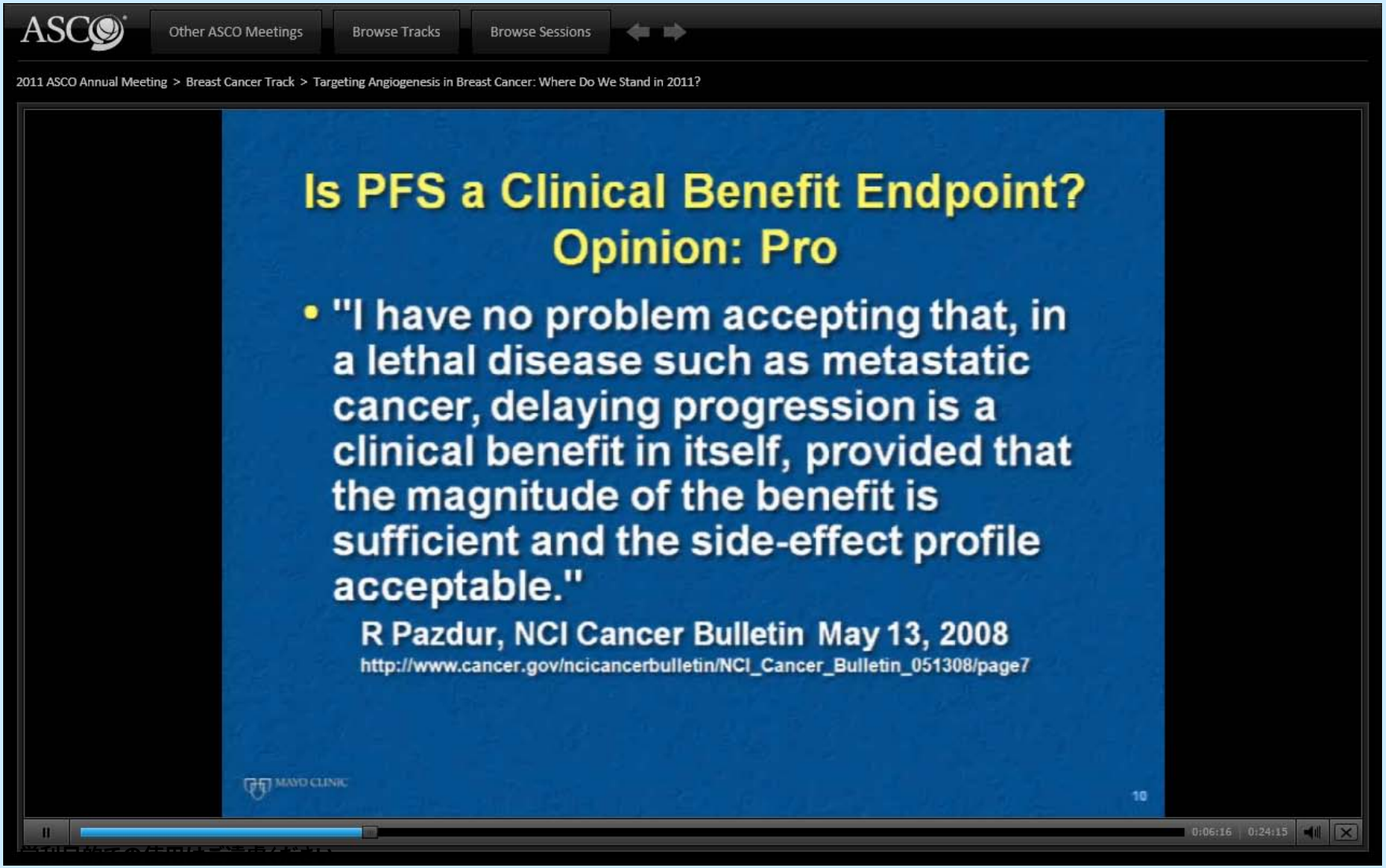
オンコロジストはPFS向上の意義を過大評価しがち



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

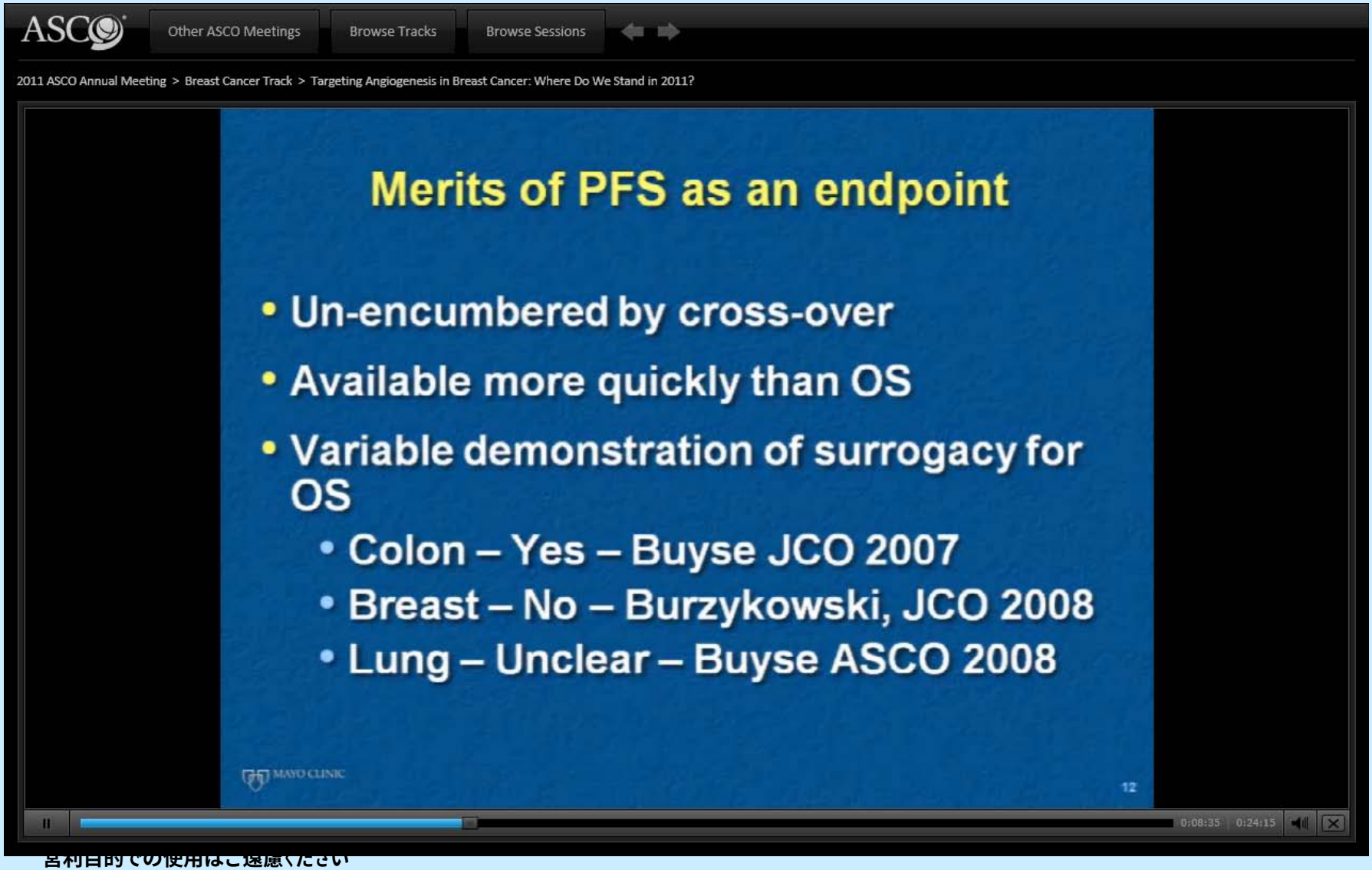
Daniel J. Sargent, PhD

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



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



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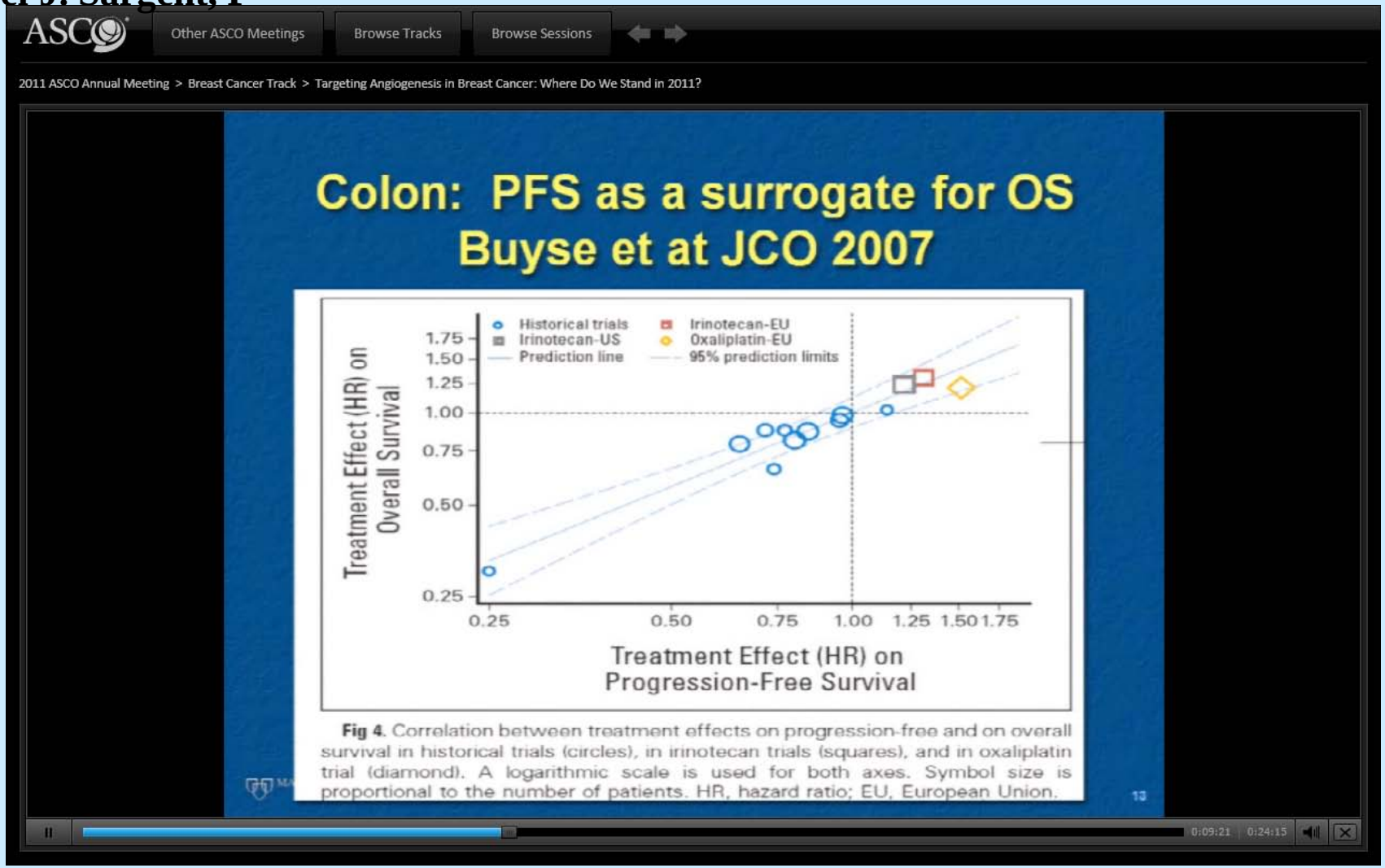
Daniel J. Sargent, P



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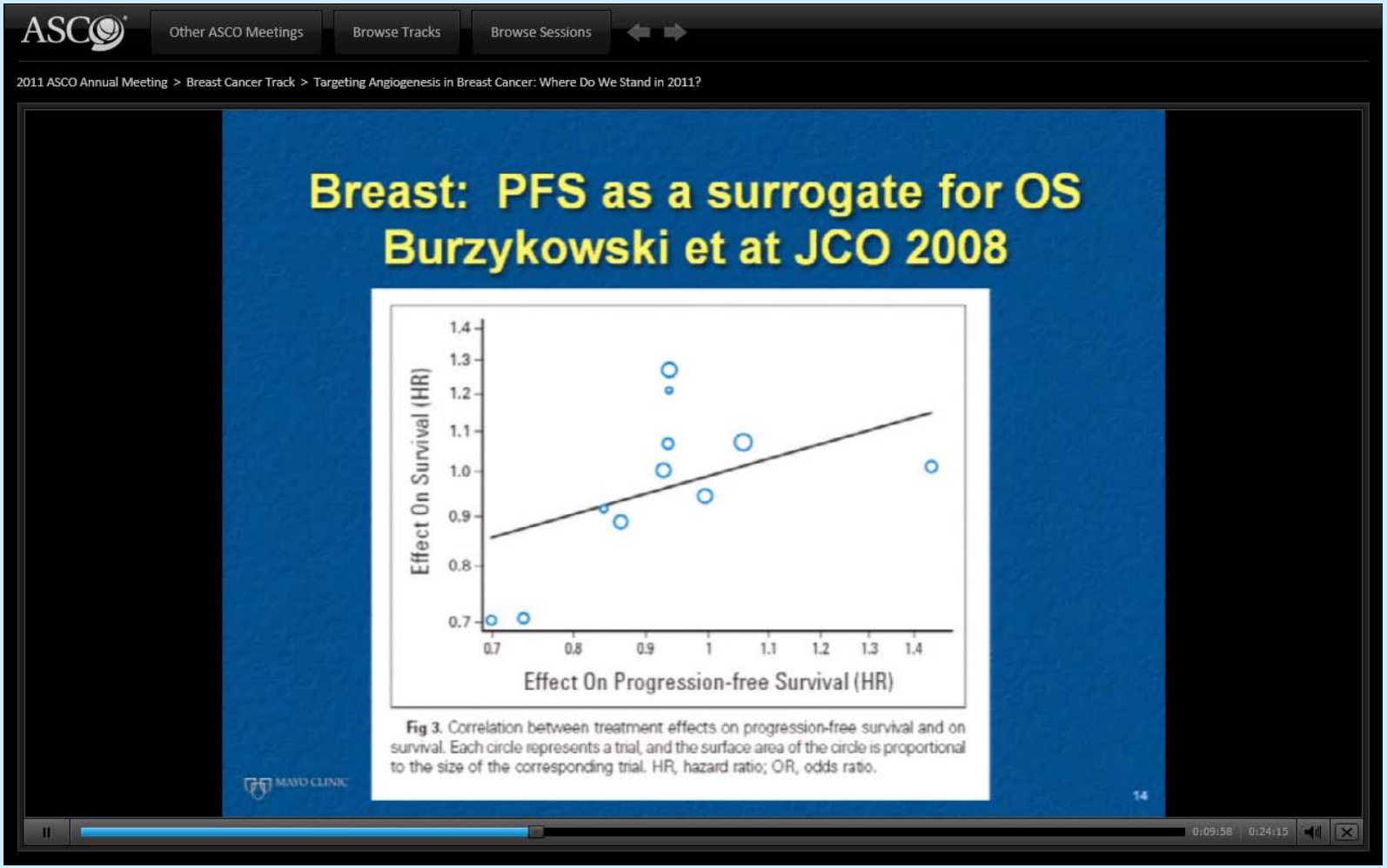

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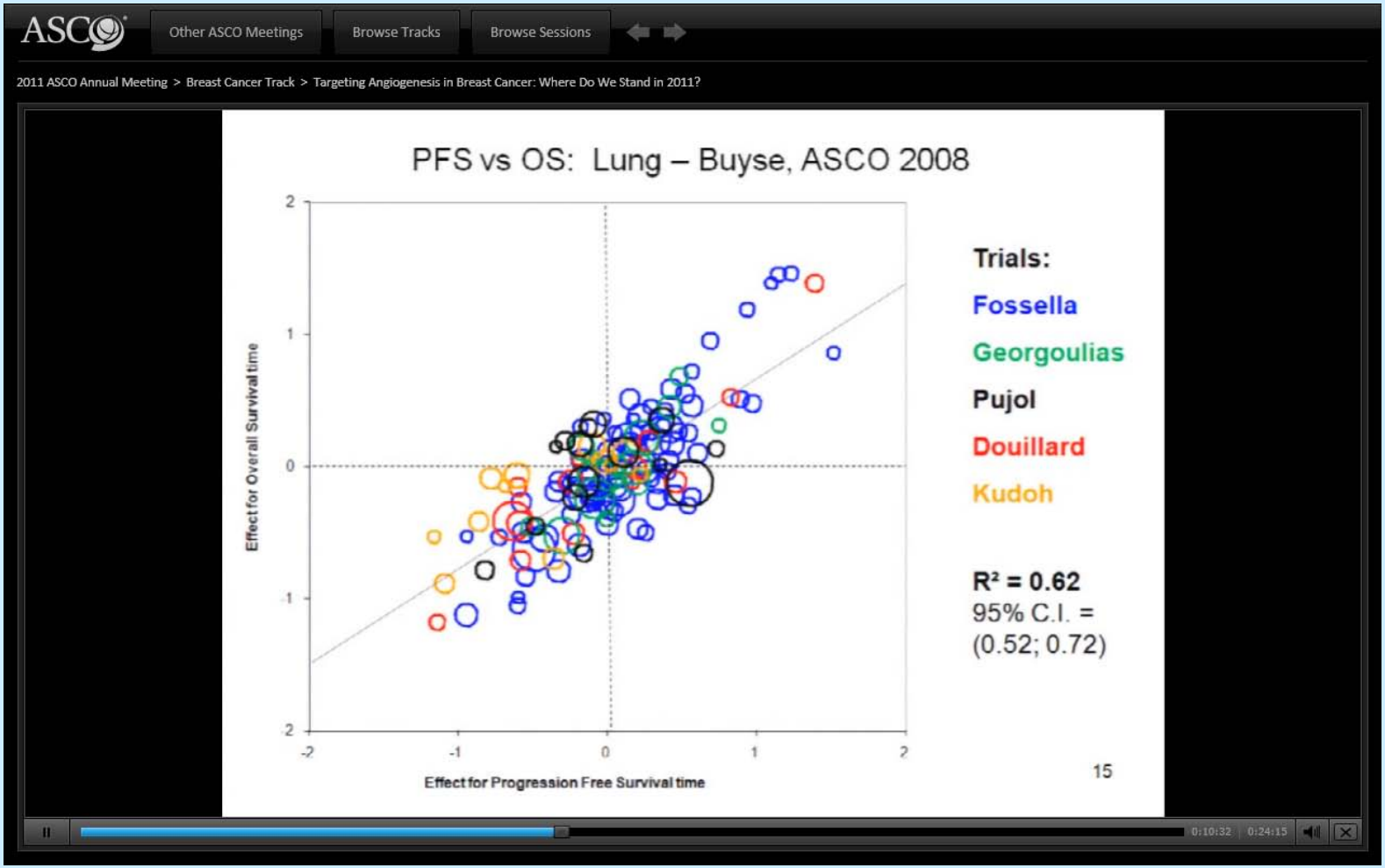

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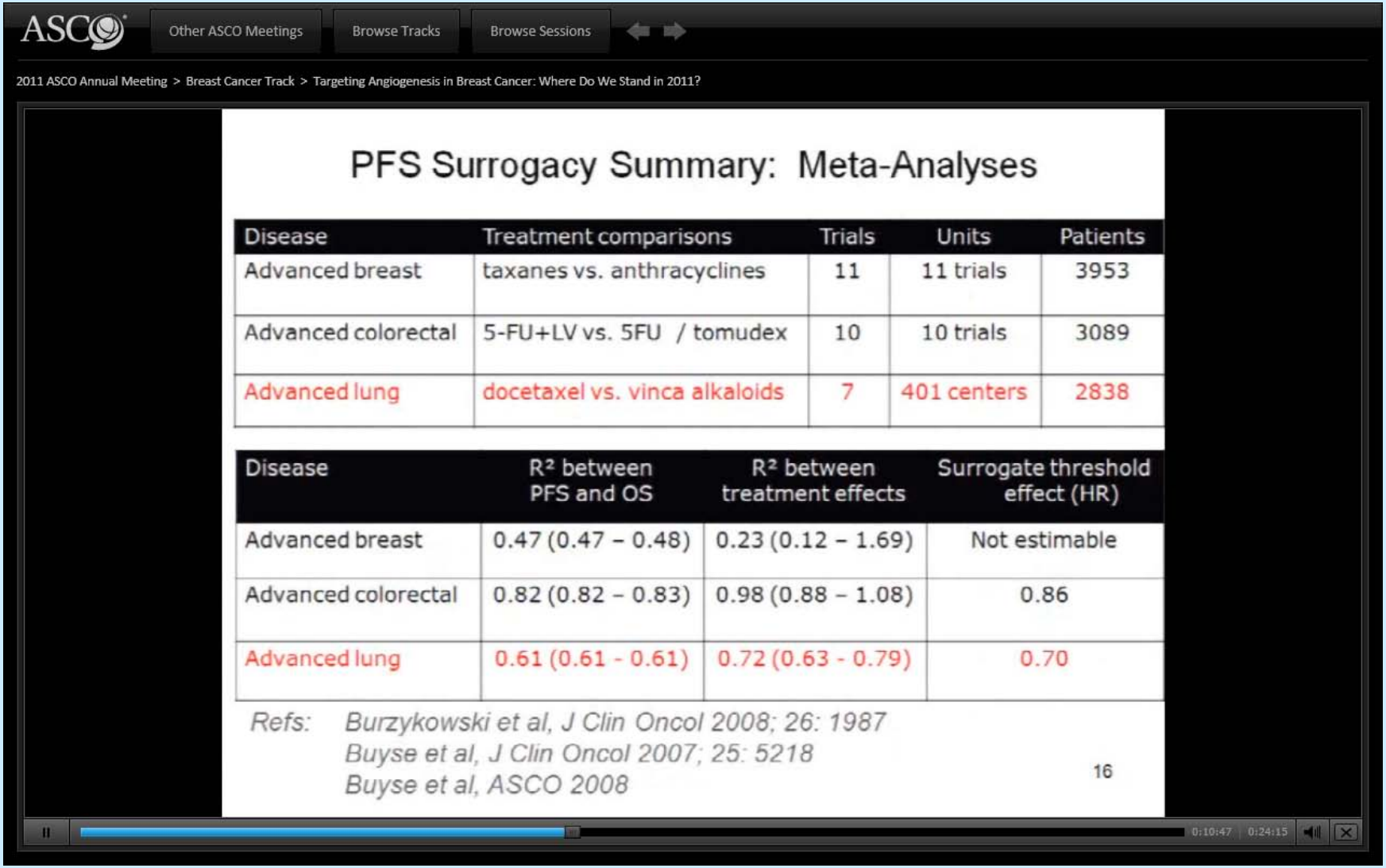

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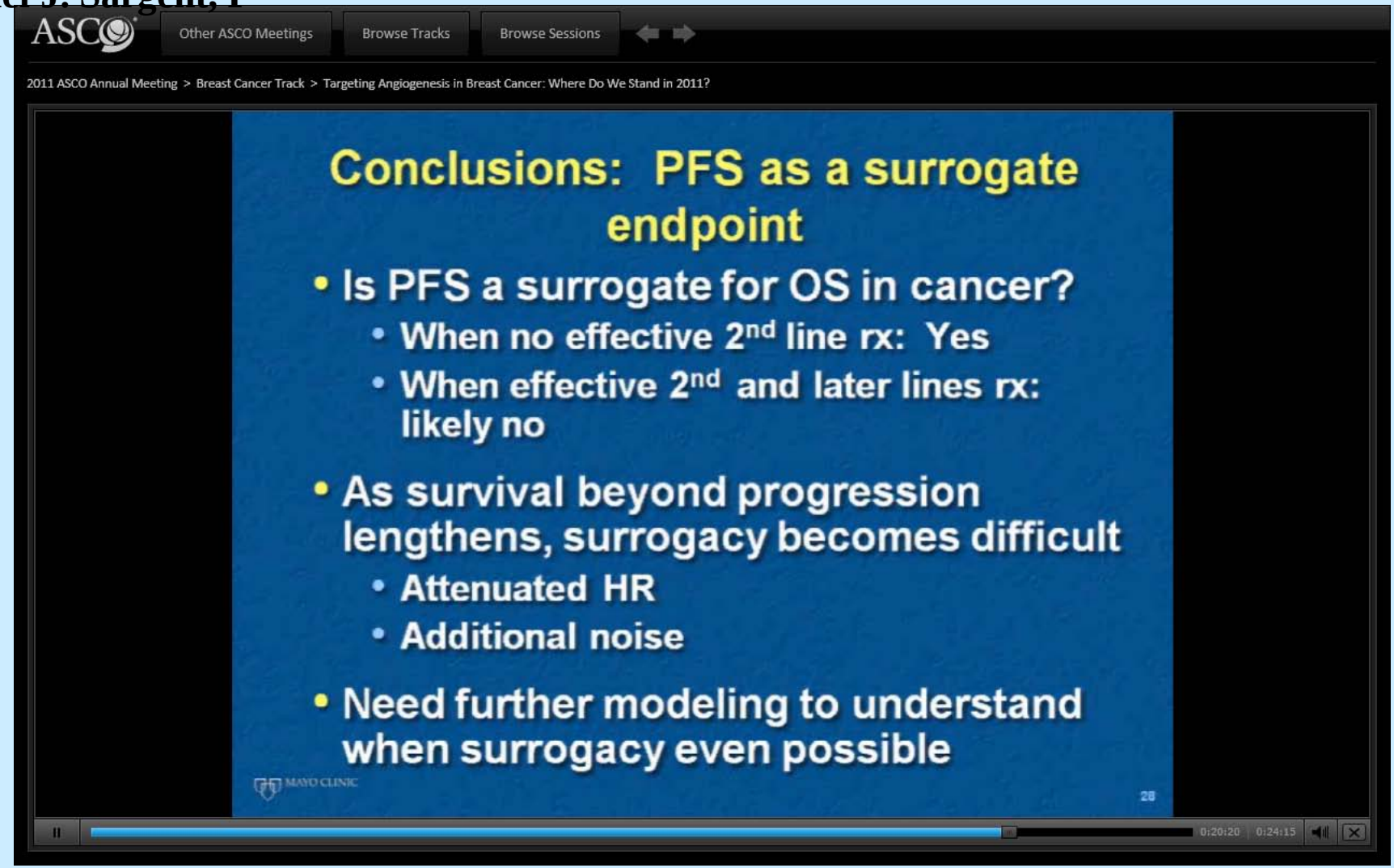

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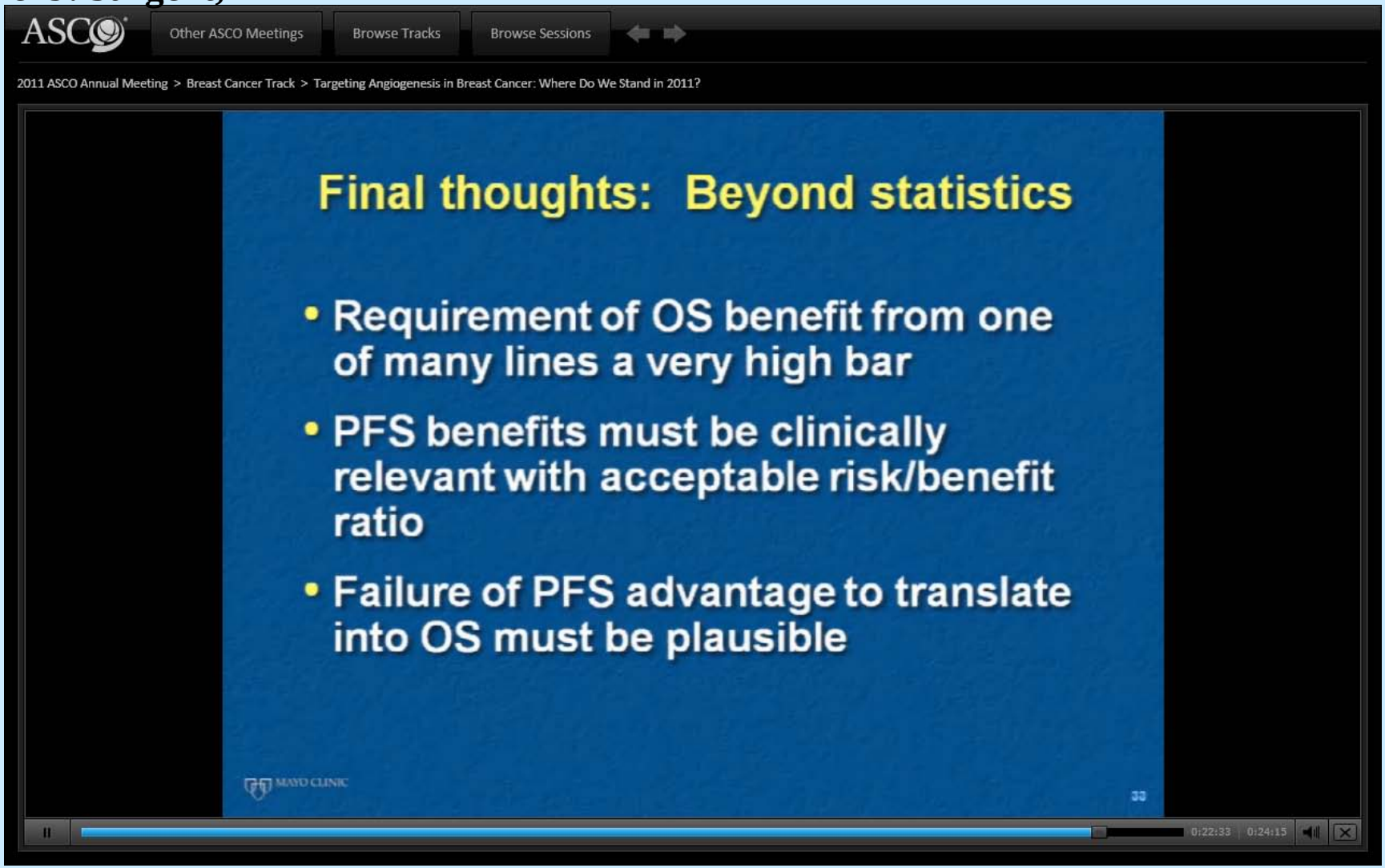
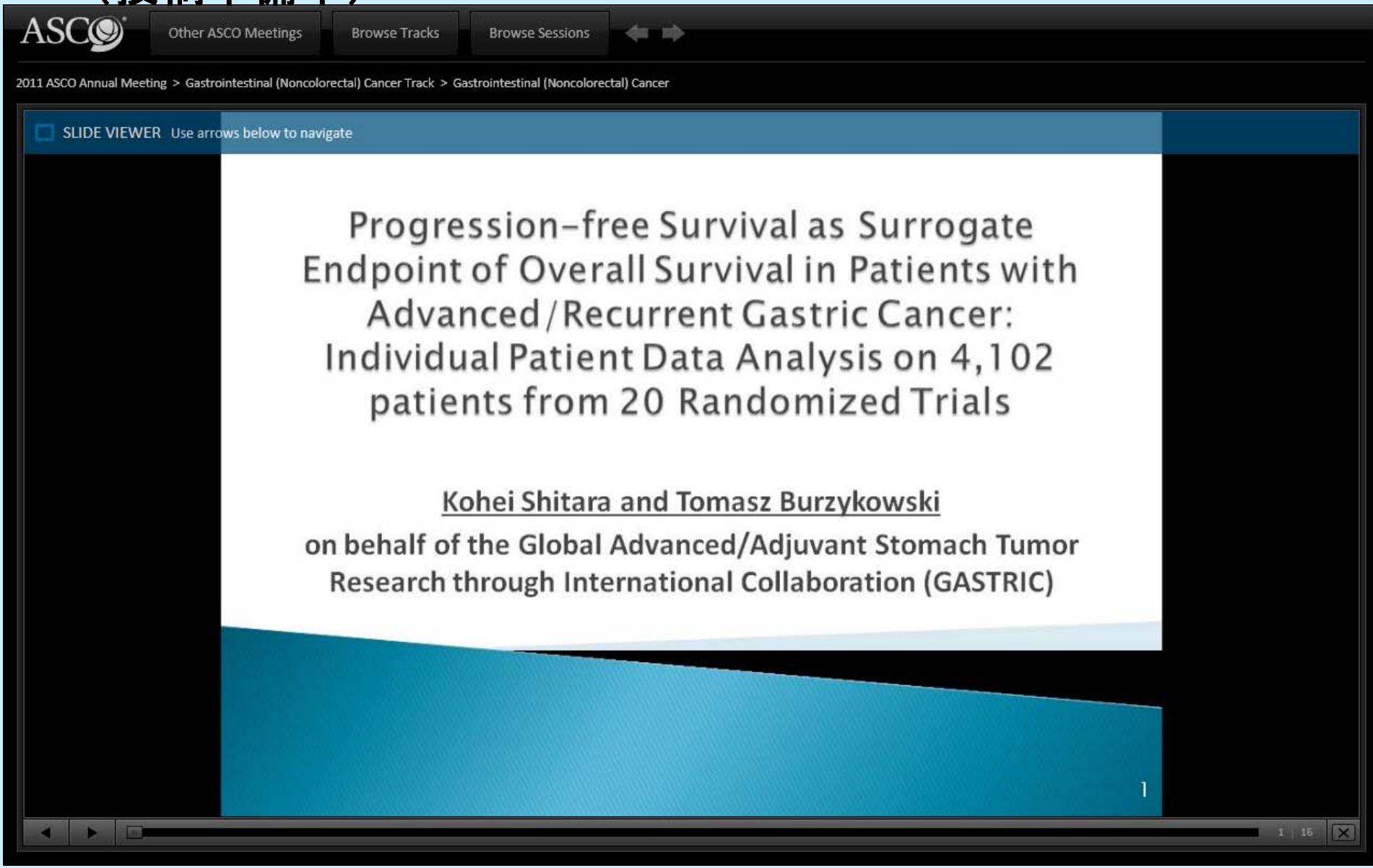
Daniel J. Sargent, P



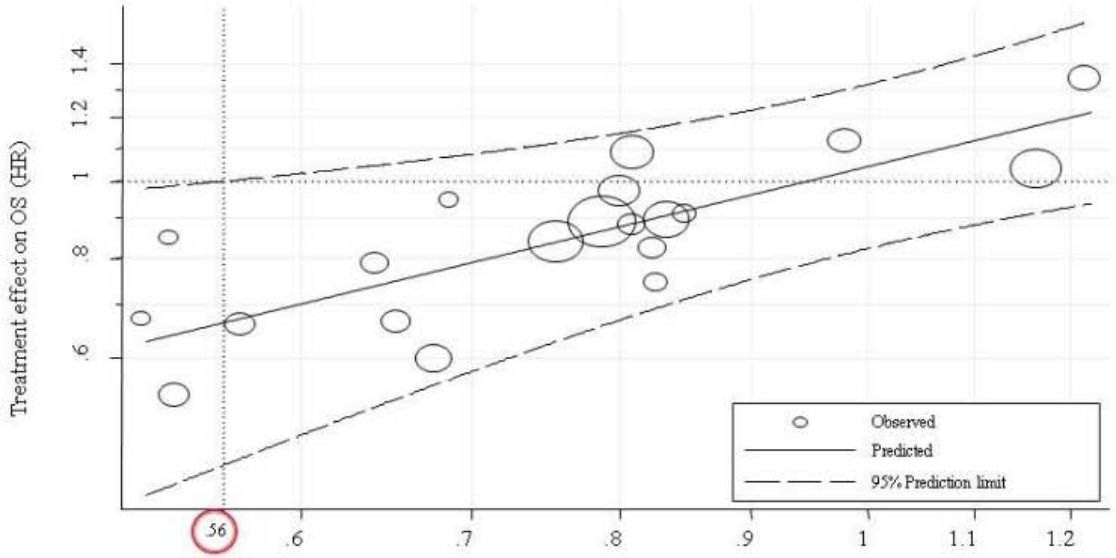
ASCO2011- 4095　GASTRICの胃癌メタアナリシスグループ（投稿準備中）



4095　試験内のOSとPFSの相関は高いものの、試験間は中間

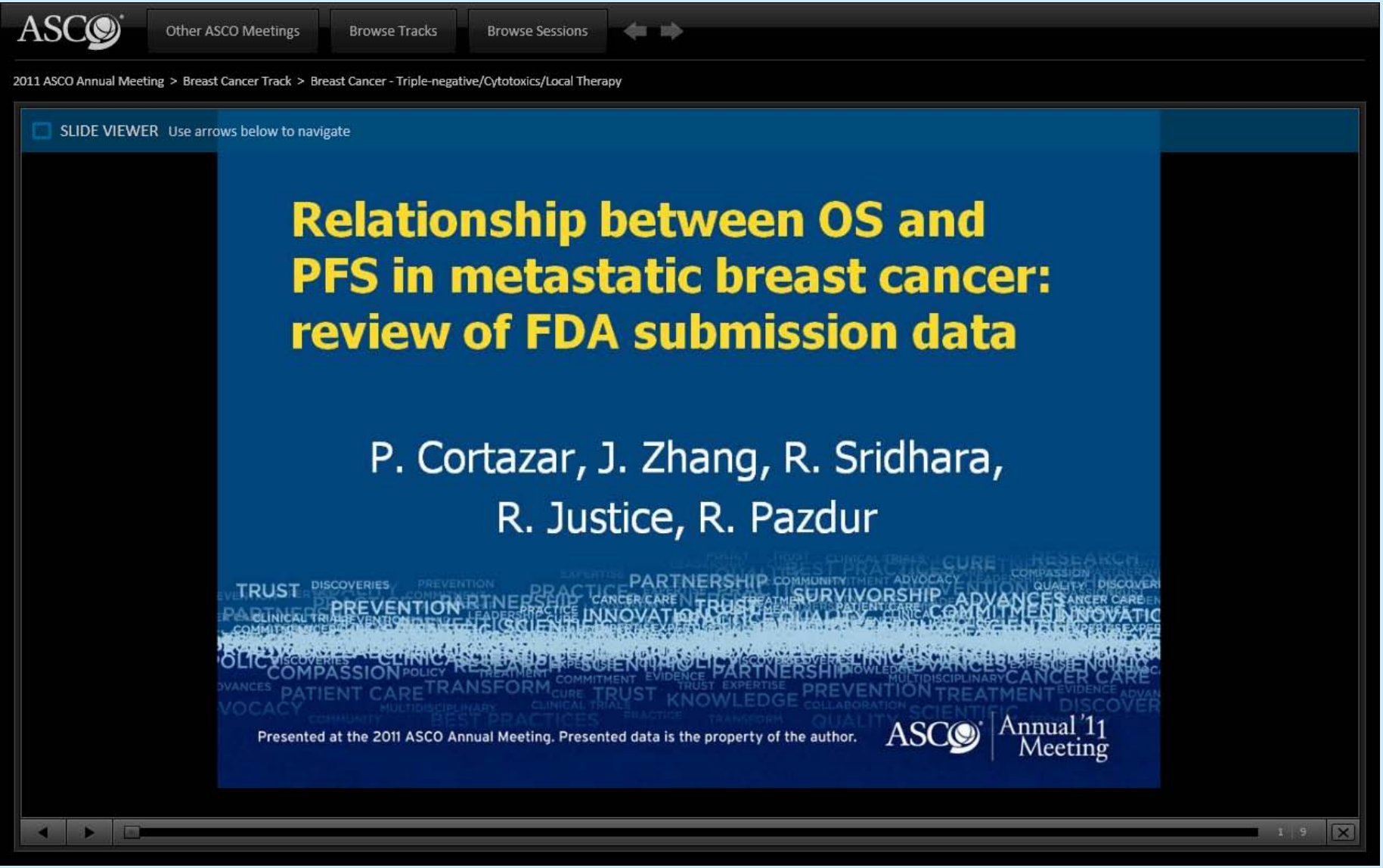
Treatment effects on OS and PFS

- 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(HROS) = 0.042 (0.079) + log(HRPFS) x 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



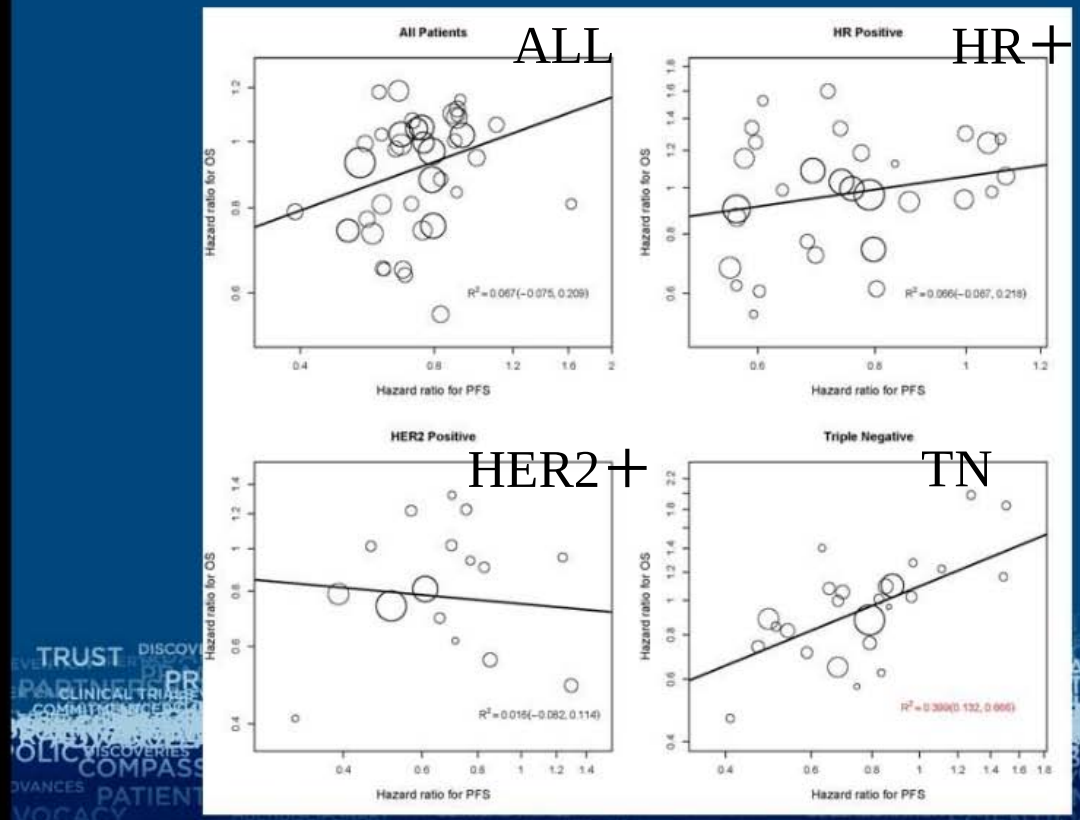
1035

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

1035　TNでは相関高い

ASCO | 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.

ASCO Annual '11 Meeting

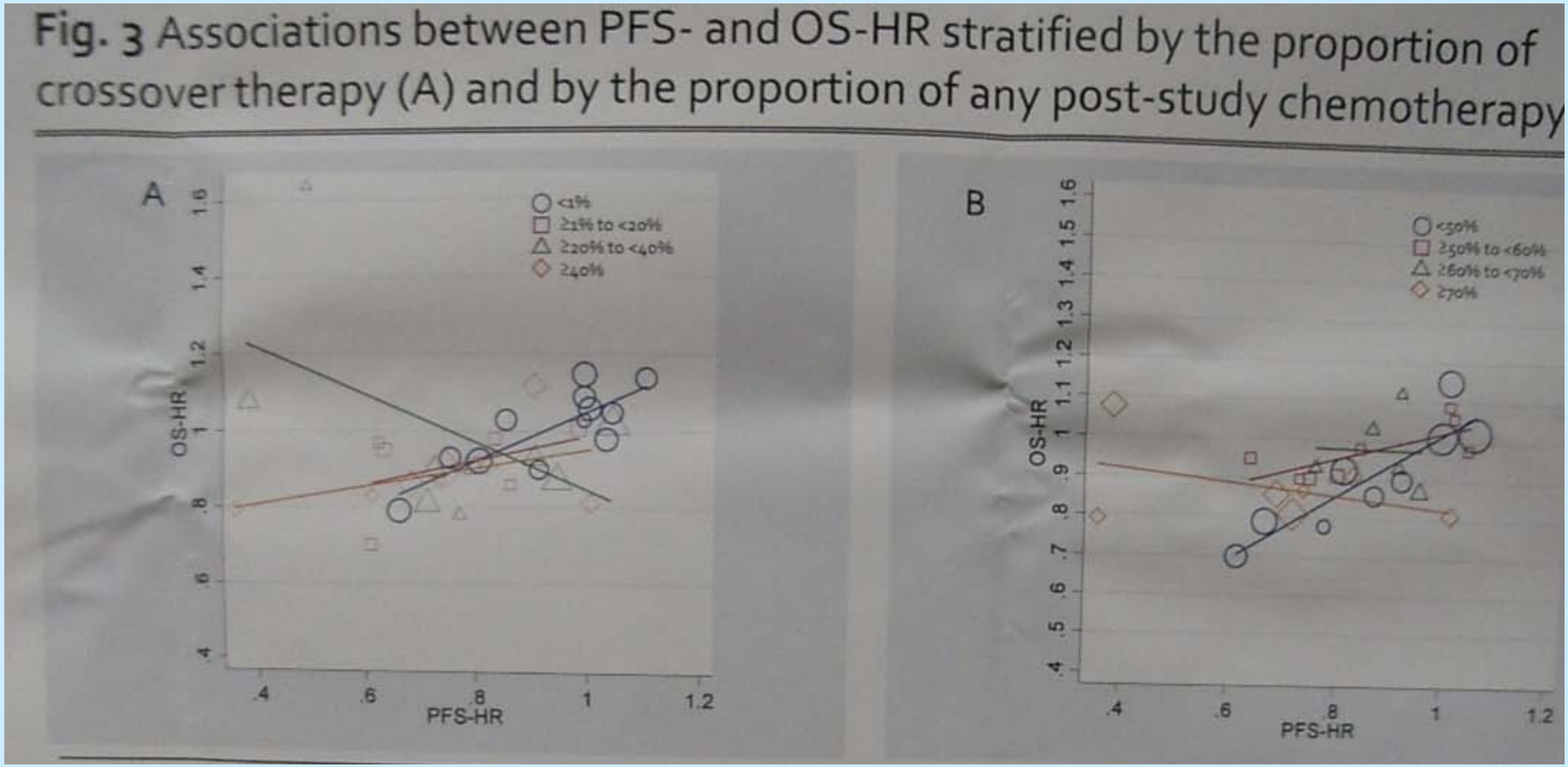
1035　TNは有効な2次治療が存在しない

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)**
1st line	5276 (56.7%)	0.162 (-0.087, 0.410)
2nd/3rd 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.

ASCO 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次治療へのクロスーオーバーによりPFS代替性失われる



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 *P* 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 *P* 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

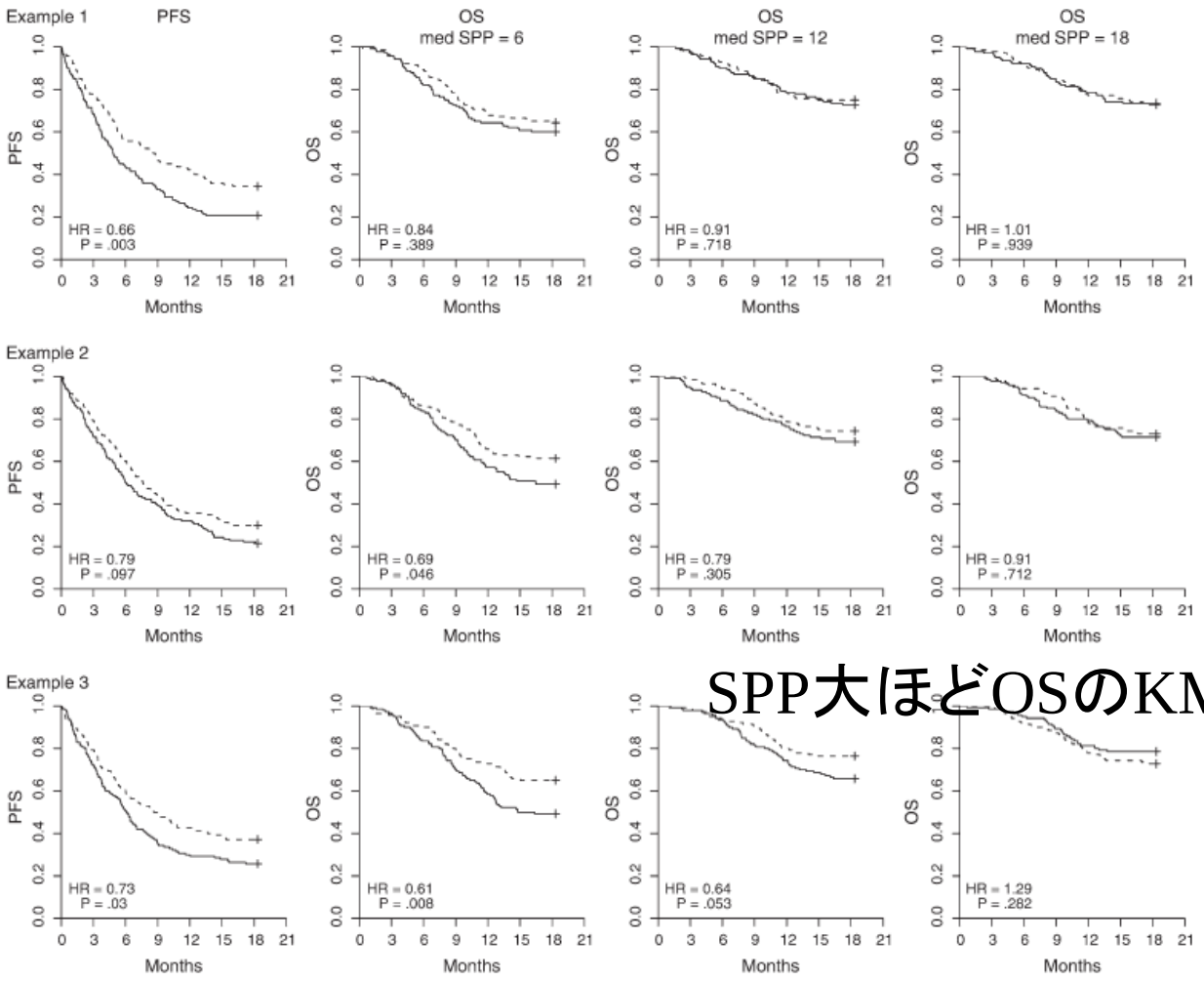
SPP(survival postprogression)=0 median PFS= 2:3 OS=PFS+SPP

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.

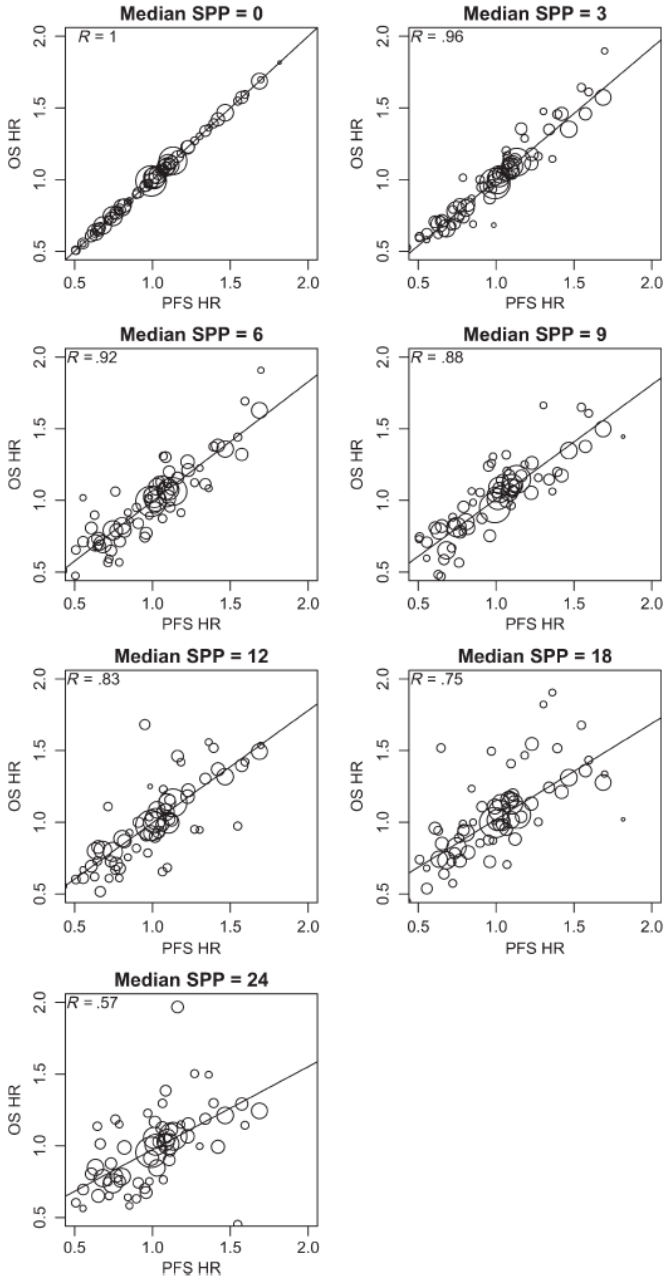


Figure 4. Association between progression-free survival (PFS) and overall survival (OS) for a single simulation of 67 trials. Each study had a randomly selected sample size and PFS hazard ratio, which remains fixed across scenarios, while median survival postprogression (SPP) [illegible] ratios (HRs) 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

median PFS= 2:3 OS=PFS+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

median PFS= 2:3 OS=PFS+SPP

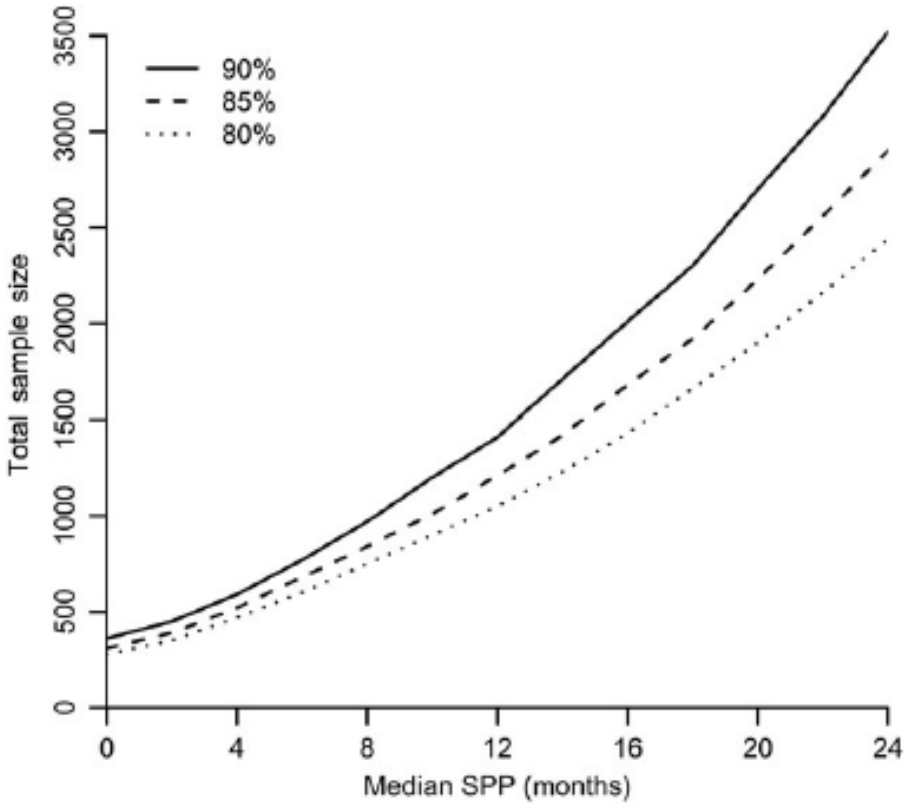


Figure 3. Sample sizes required for detecting a statistically significant difference in overall survival by median survival postprogression (SPP). The **three curves** were indexed by the power for overall survival (ie, powers of 90%, 85%, and 80%).

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

  Broglio 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

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.

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

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

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

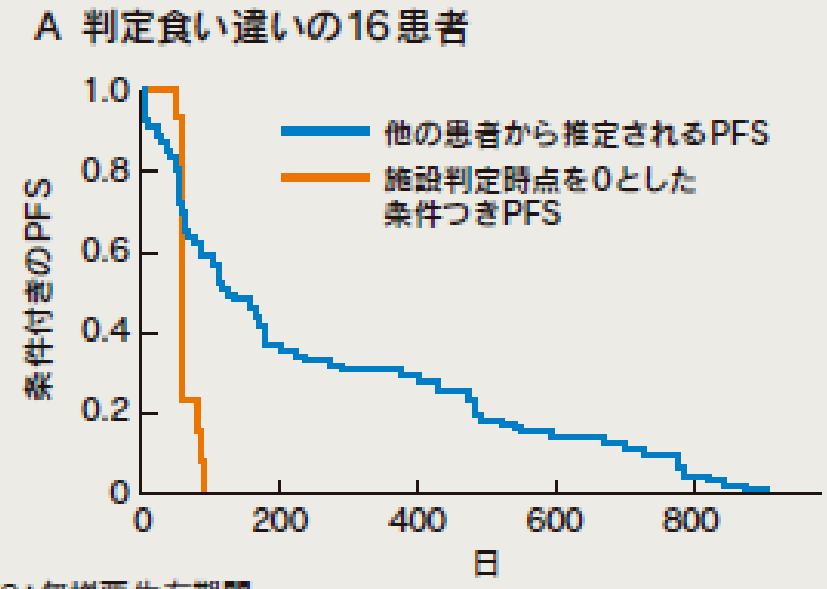
Informative censoring

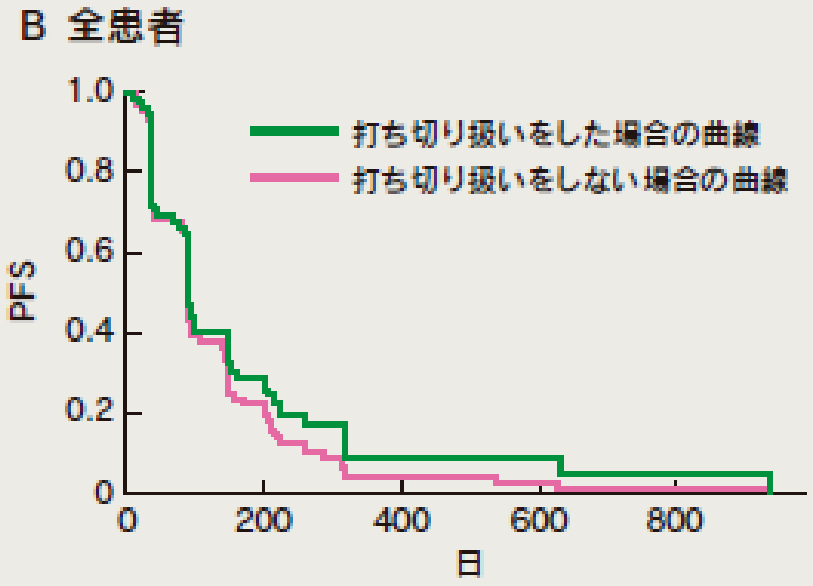
- 中央判定で進行とする前に施設で進行を判定
- 施設で進行が判定されれば治療法も変更され、それ以降の画像評価も行われないことが多い。つまり中央判定が不能となる。（わが国においても同様の状況）
- このような場合にFDAのガイドラインは打ち切り判定を推奨
- しかし、この種の打ち切りはinformativeであり評価にバイアス、みかけの成績を上げる効果
- もし対照治療群にこの打ち切りが多く発生すれば、治療効果が薄まる方向のバイアスが生ずる

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





PFS：無増悪生存期間

Dodd LE, *et al. J Clin Oncol.* 2008;26:3795.

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)[9]				
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が信じ、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蜃気楼とも呼ばれる
（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）

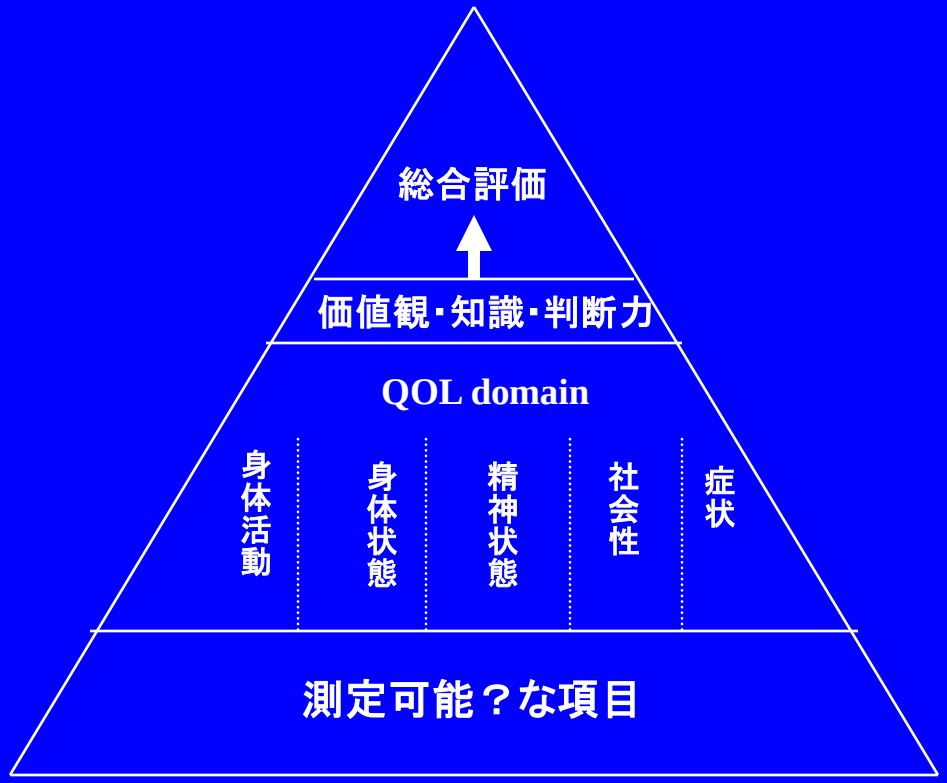
- 患者の立場にたった評価という点では一致

- 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

  ↕

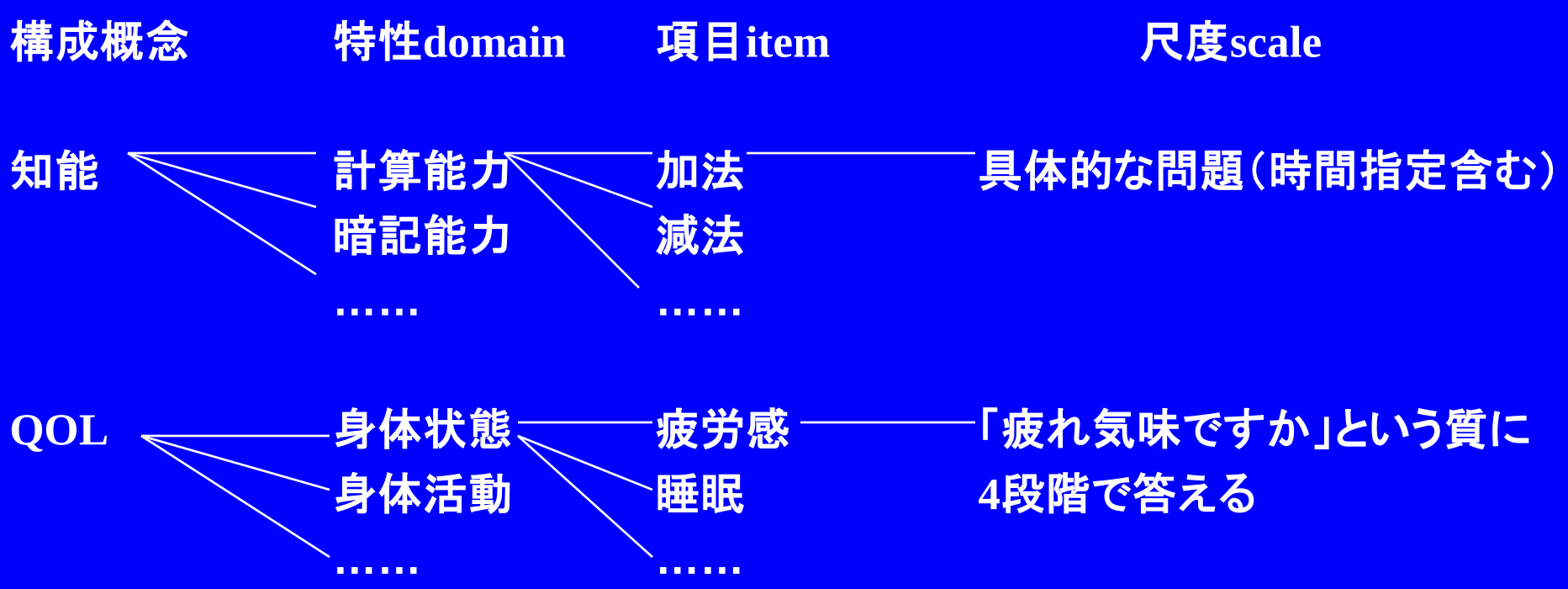
  - 患者自身による計量心理的特性の主観的評価
    （Patient Reported Outcome)
    - 構成概念constructとしてのQOL
    - 患者自身のフィルターを通した認識
    - 多次元
    - 尺度（調査票）開発

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？

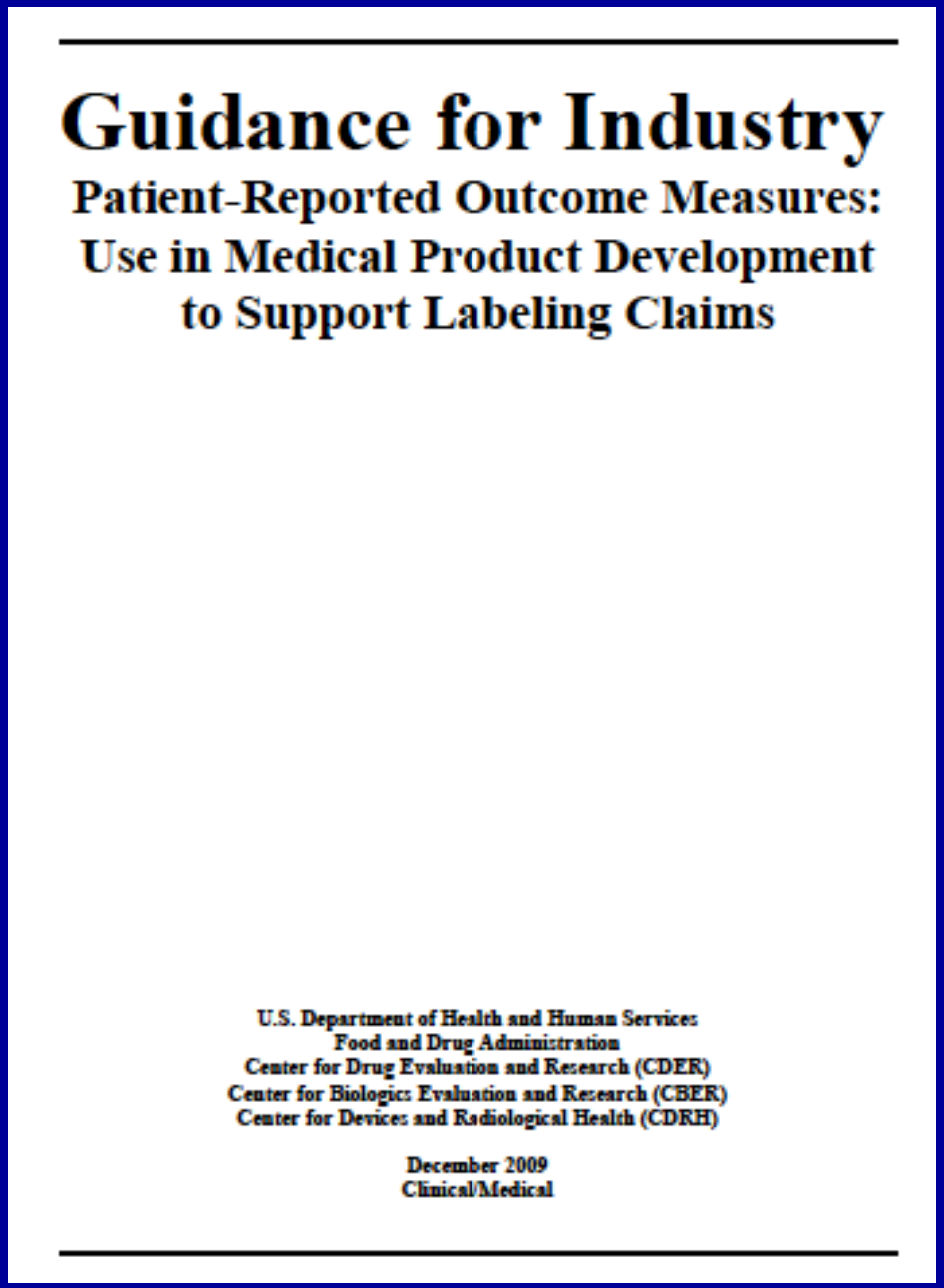
“Does subjective and vague measurement of QOL have any significance?”

“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（EMEA)
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

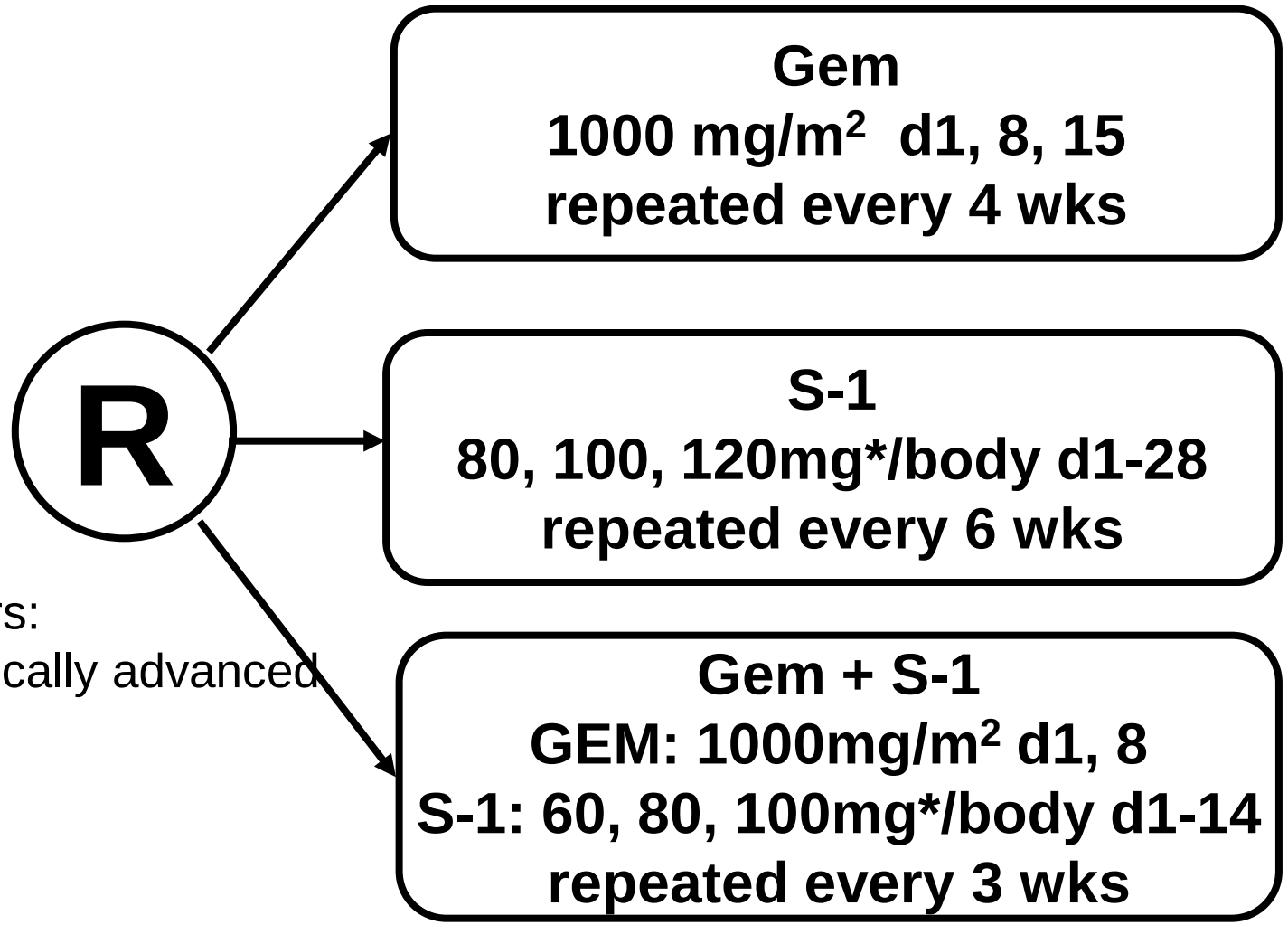
- 適切に定義され（well-defined）、信頼性の高い尺度で測定された結果は、医薬品の効能表示の裏付け根拠として使用可能である
- 患者自身が最も良く認識しているか、患者の視点からの測定が最も適切な概念については、PROの使用を推奨する

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

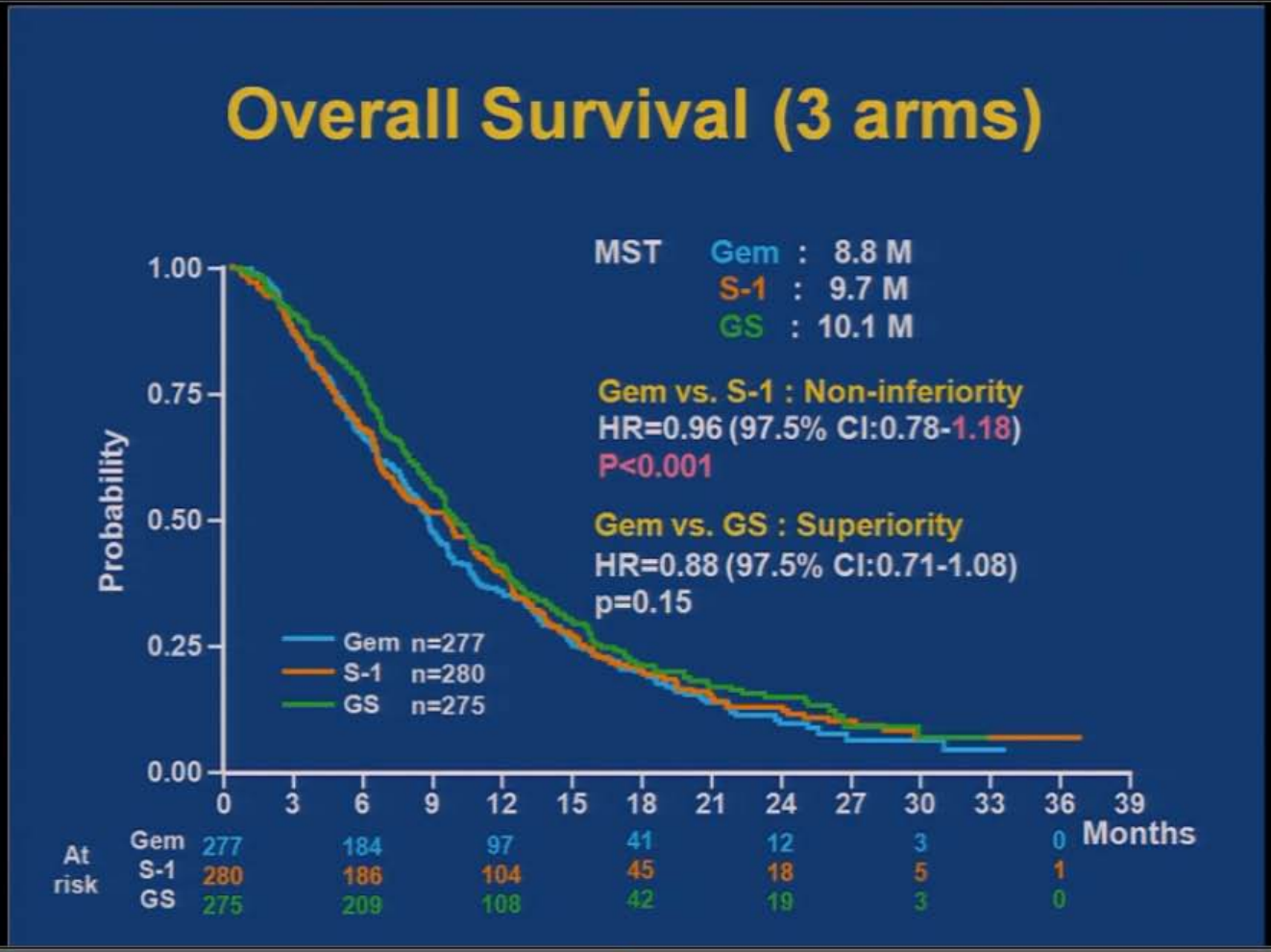


Stratification factors:
- Metastatic vs. Locally advanced
- Institution

*According to body surface area,
BSA < 1.25 m2, 1.25=<BSA <1.5, BSA >=1.5

ASCO | Other ASCO Meetings | Browse Tracks | Browse Sessions

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



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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 Usual activities Pain / Discomfort Anxiety / Depression	1: no problems 2: some problems 3: severe problems

- 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らかの問題がある
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らか問題がある
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

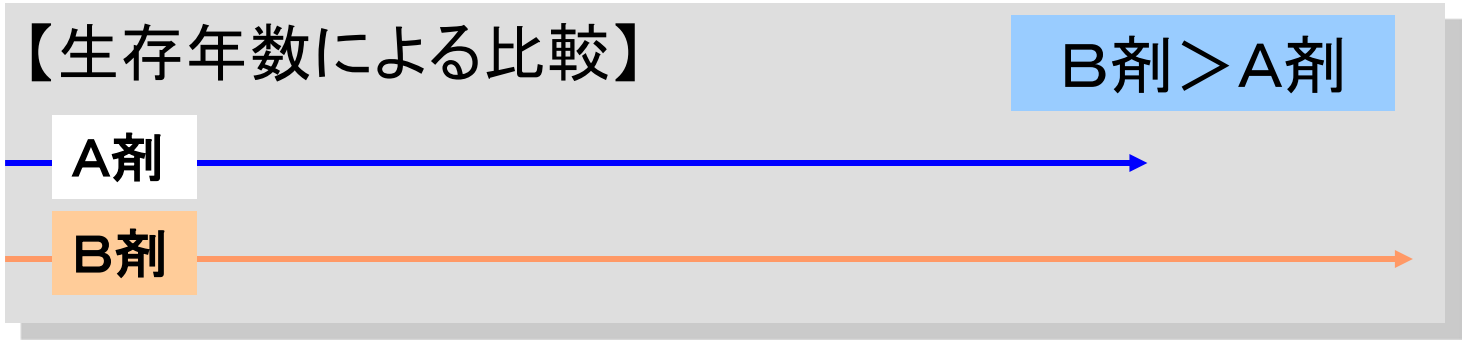
不安/ふさぎ込み

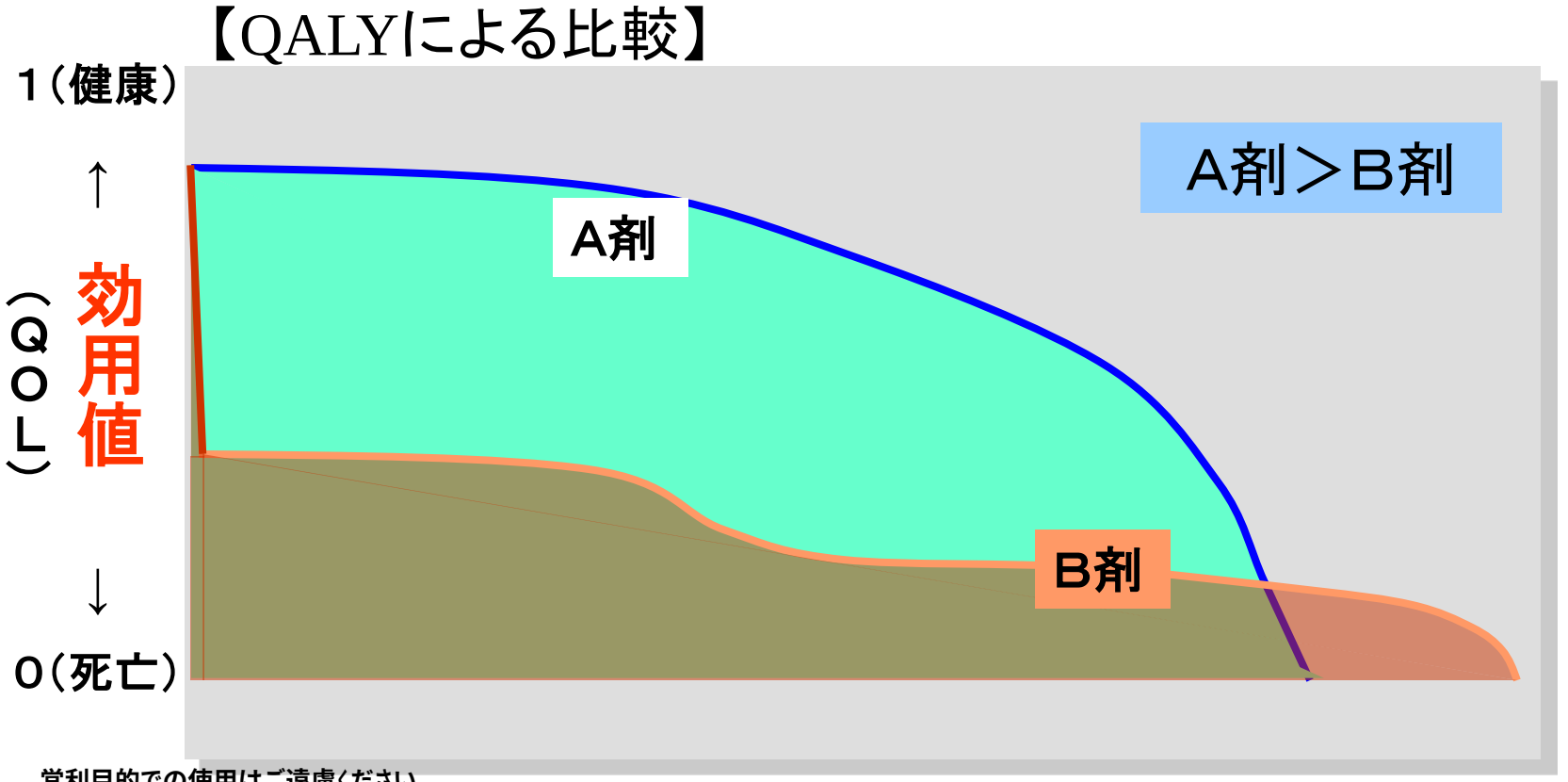
1. 私は不安でもふさぎ込んでもいない
2. 私は中程度に不安あるいはふさぎ込んでいる
3. 私はひどく不安あるいはふさぎ込んでいる

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

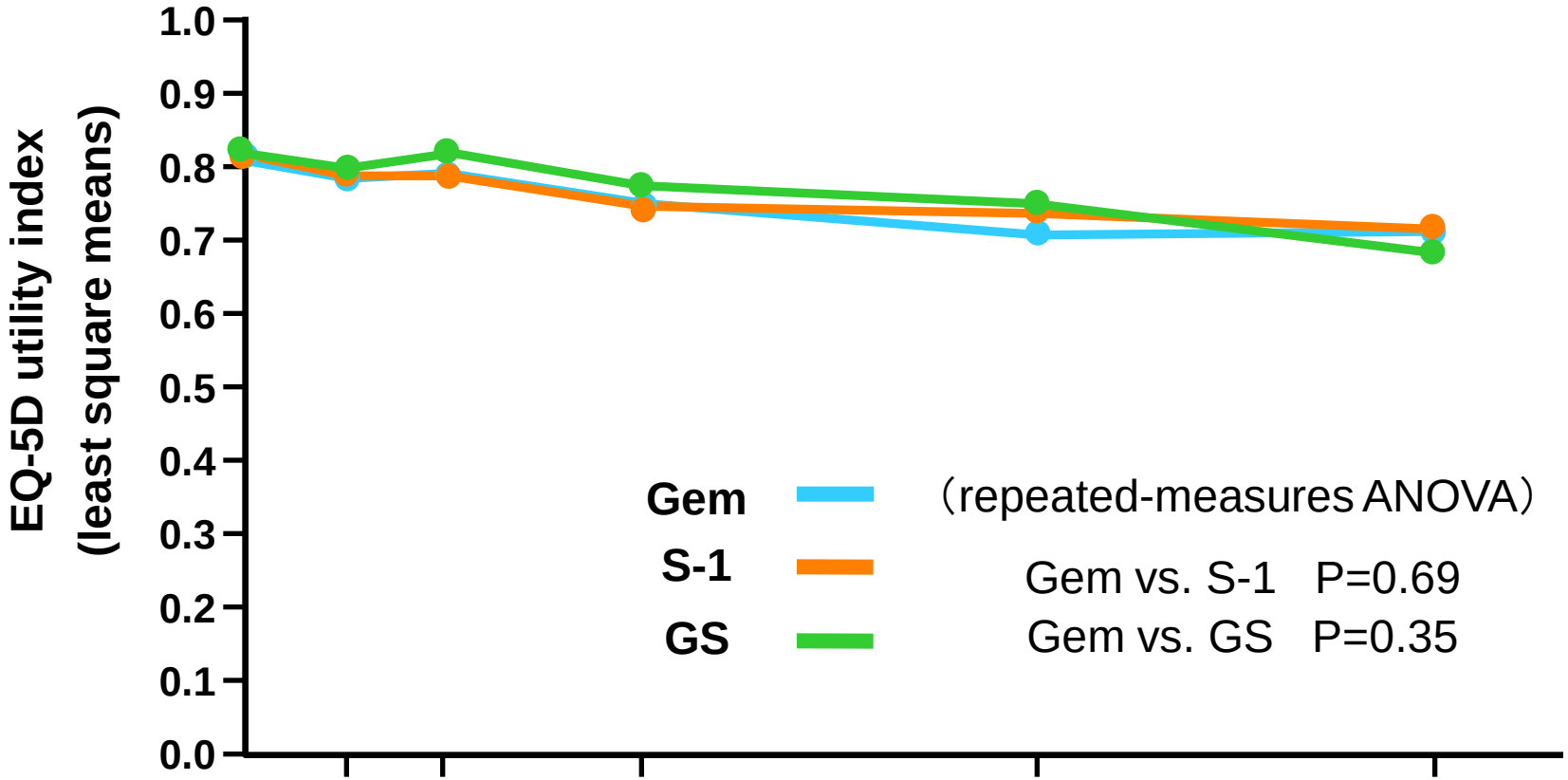
生存年数とQALY (Quality Adjusted Life Years)





EQ-5D utility index

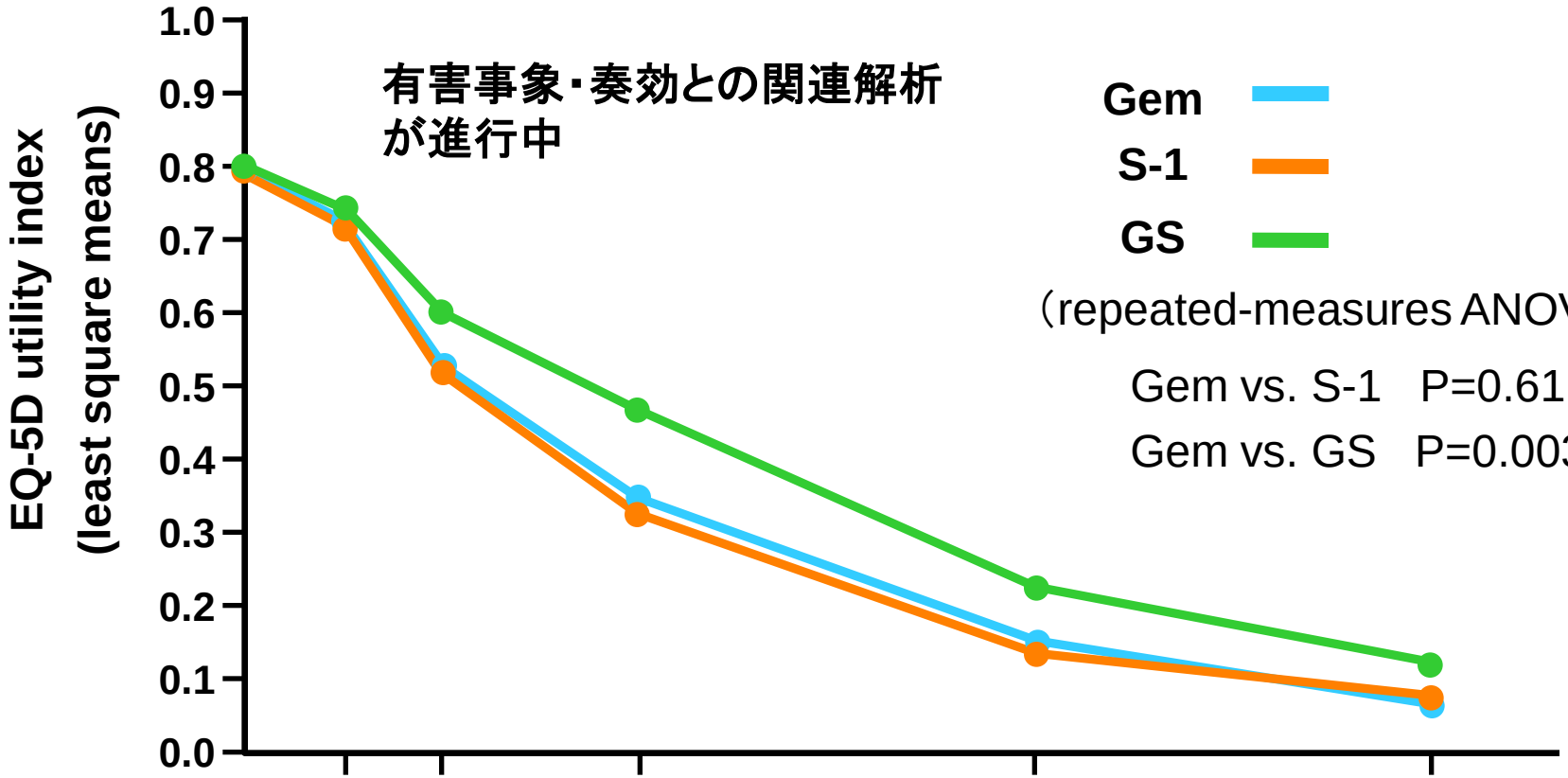
* Death : Not included



No. of patients	6W	12W	24W	48W	72W
Gem	244	218	149	105	40	15
S-1	245	210	145	88	28	13
GS	247	220	166	135	58	31

EQ-5D utility index

* Death : Treated as index 0



No. of patients	6W	12W	24W	48W	72W
Gem	244	237	235	239	232	226
S-1	245	234	232	226	220	217
GS	247	236	232	233	236	223

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

* 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（Patinet Reported Outcome)と経済評価の必要性

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

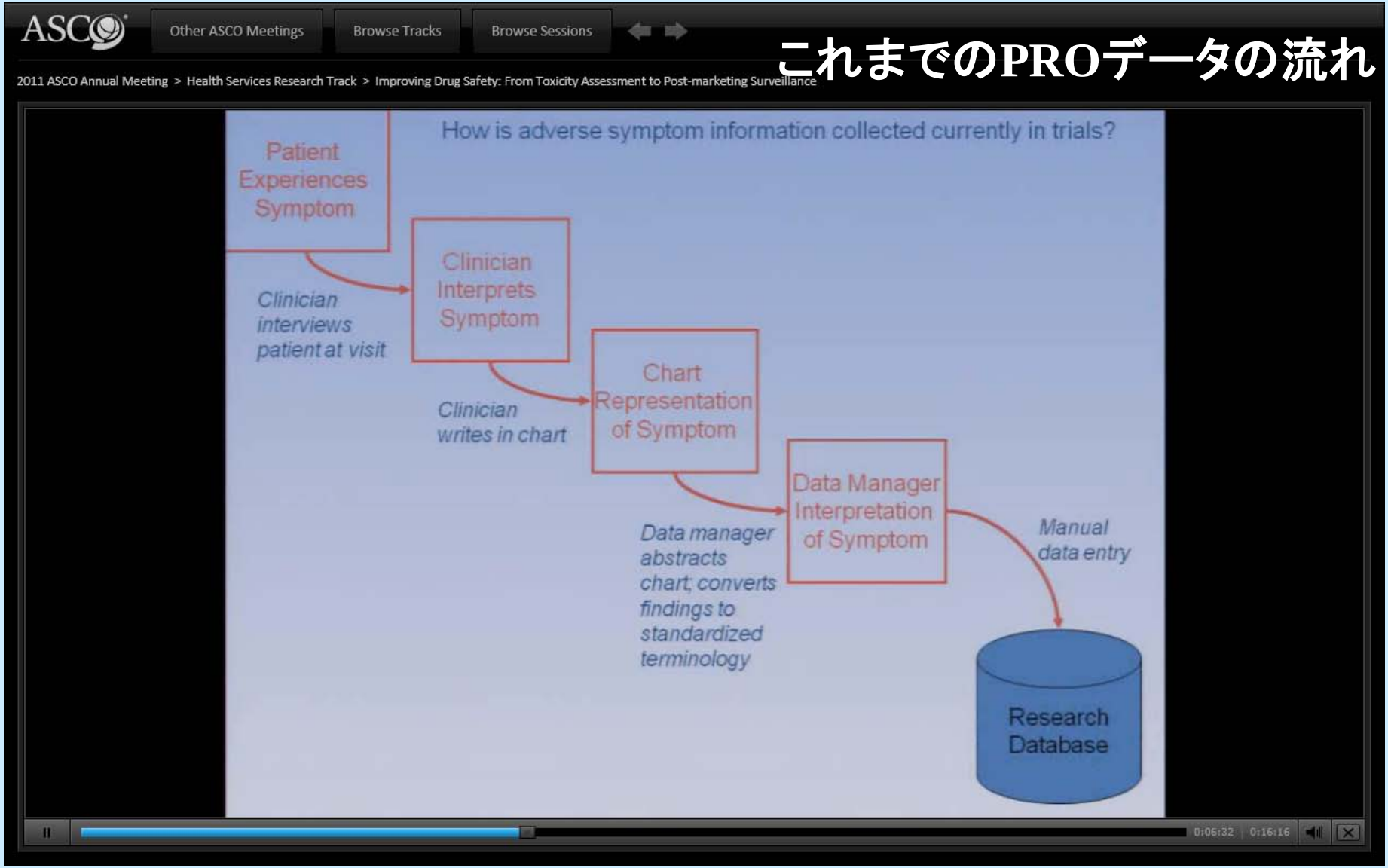
PRO

Education Session　Chair(s): David Cella, PhD

CellaはFACTの開発者

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

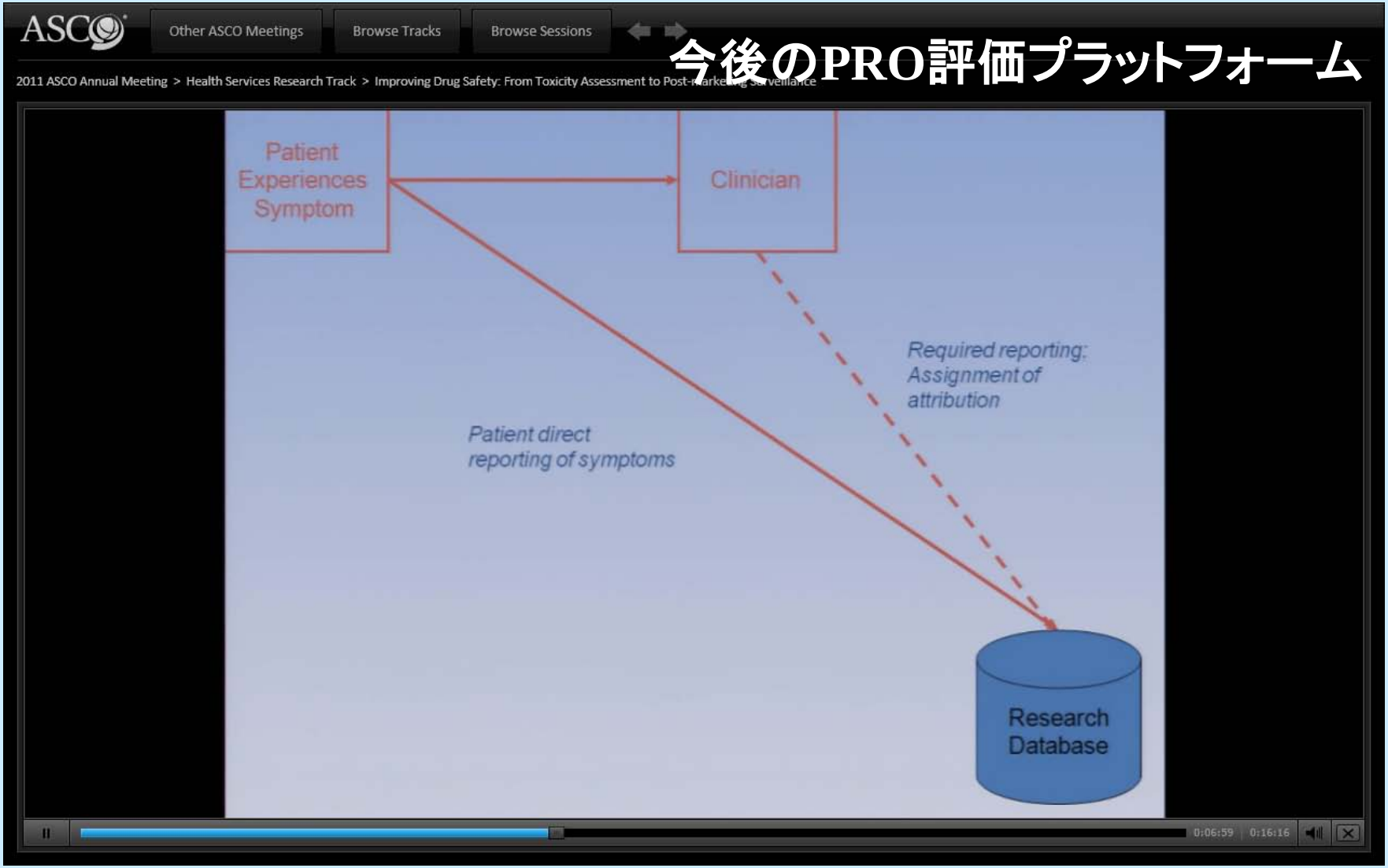
Education Session Chair(s): David Cella, PhD



これまでのPROデータの流れ

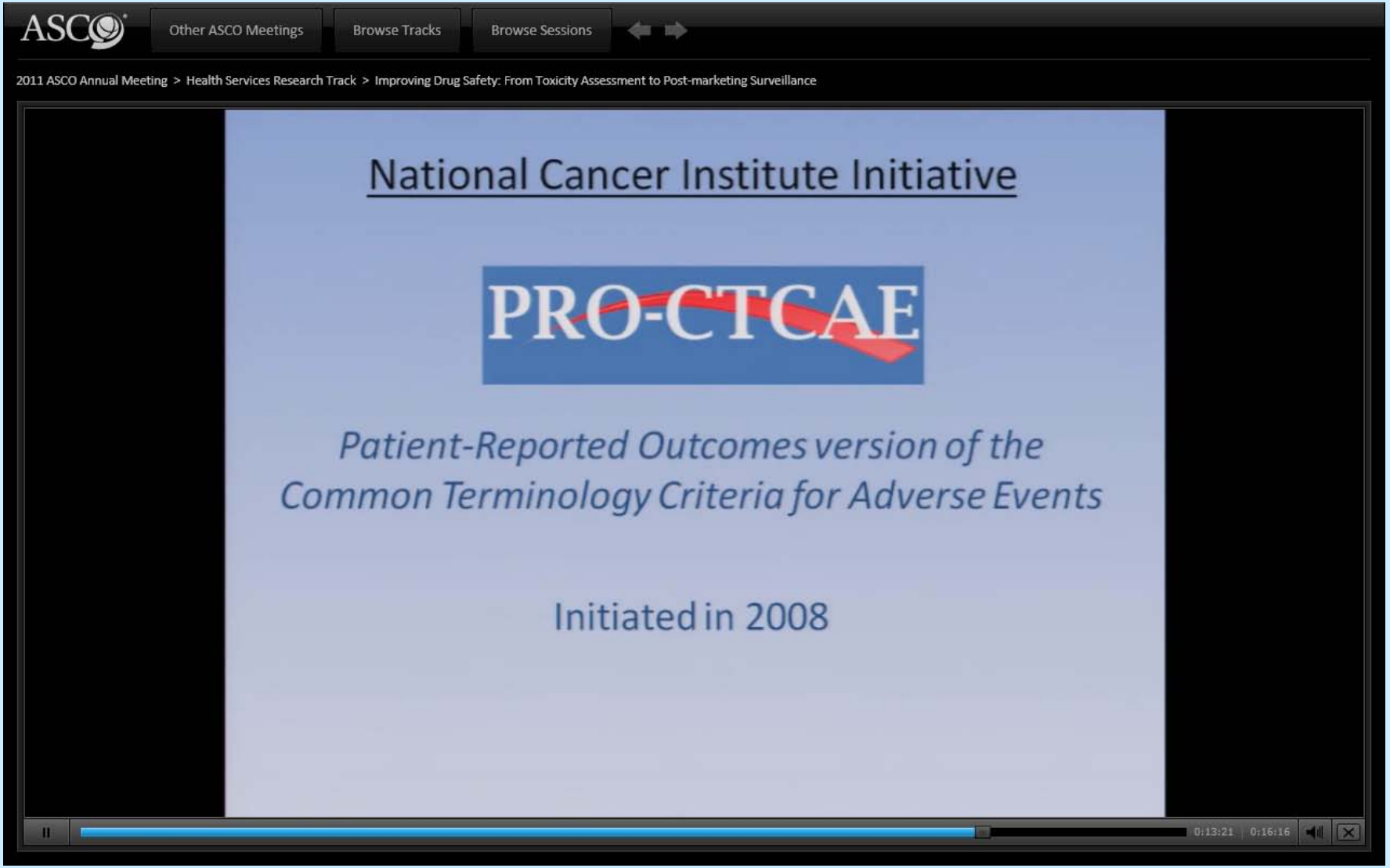
Improving Drug Safety: From Toxicity Assessment to Post-marketing Surveillance PRO

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



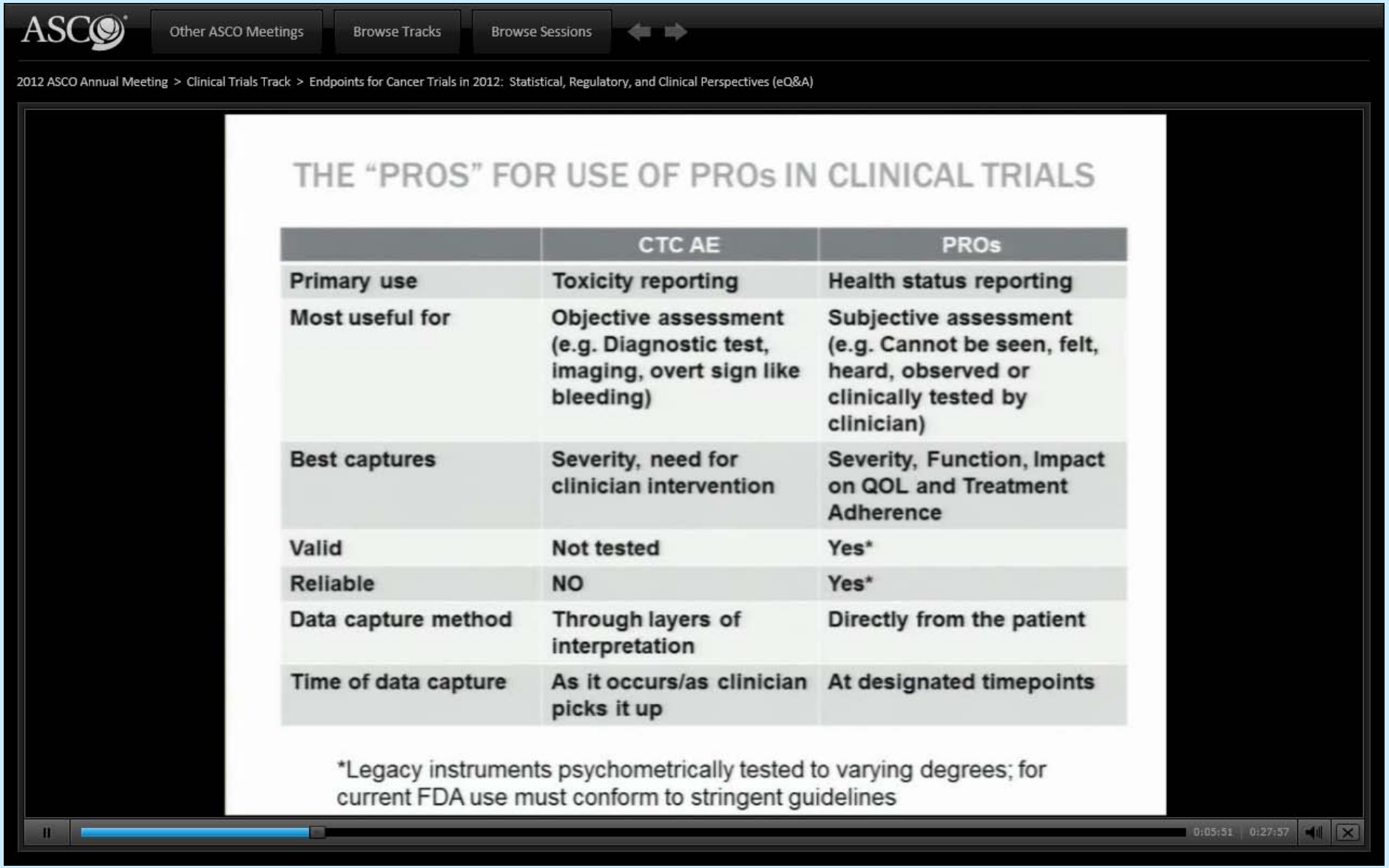
PROに関するASCO2011の発表から

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

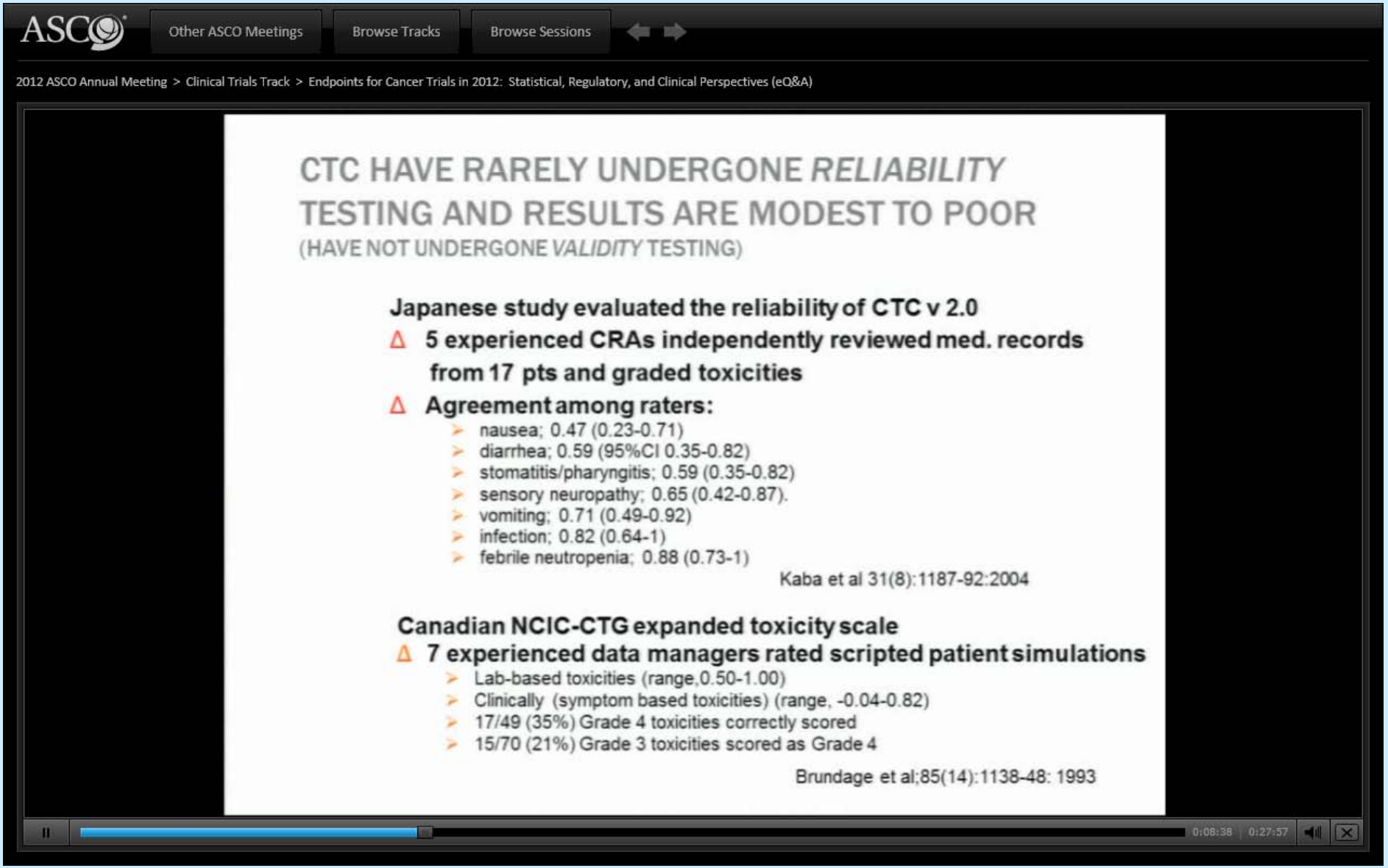
Comparative Effectiveness Researchにおける Patient Reported Outcomeの測定 ASCO2011　#6000のガイドライン案

- PROを測定せよ
- 重要な13症状と、対象・治療介入にと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

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



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



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

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

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

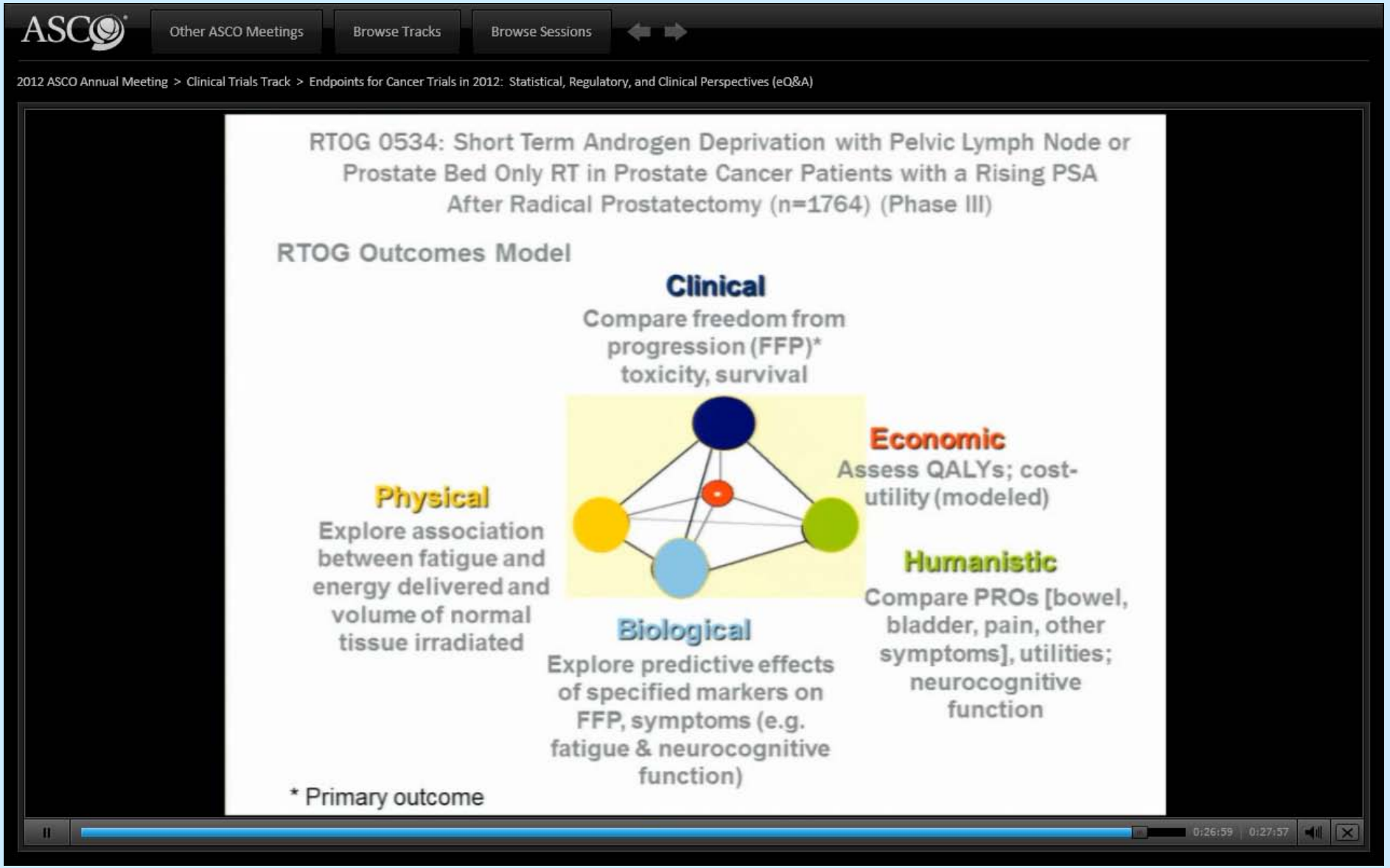
[Article in Japanese]

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

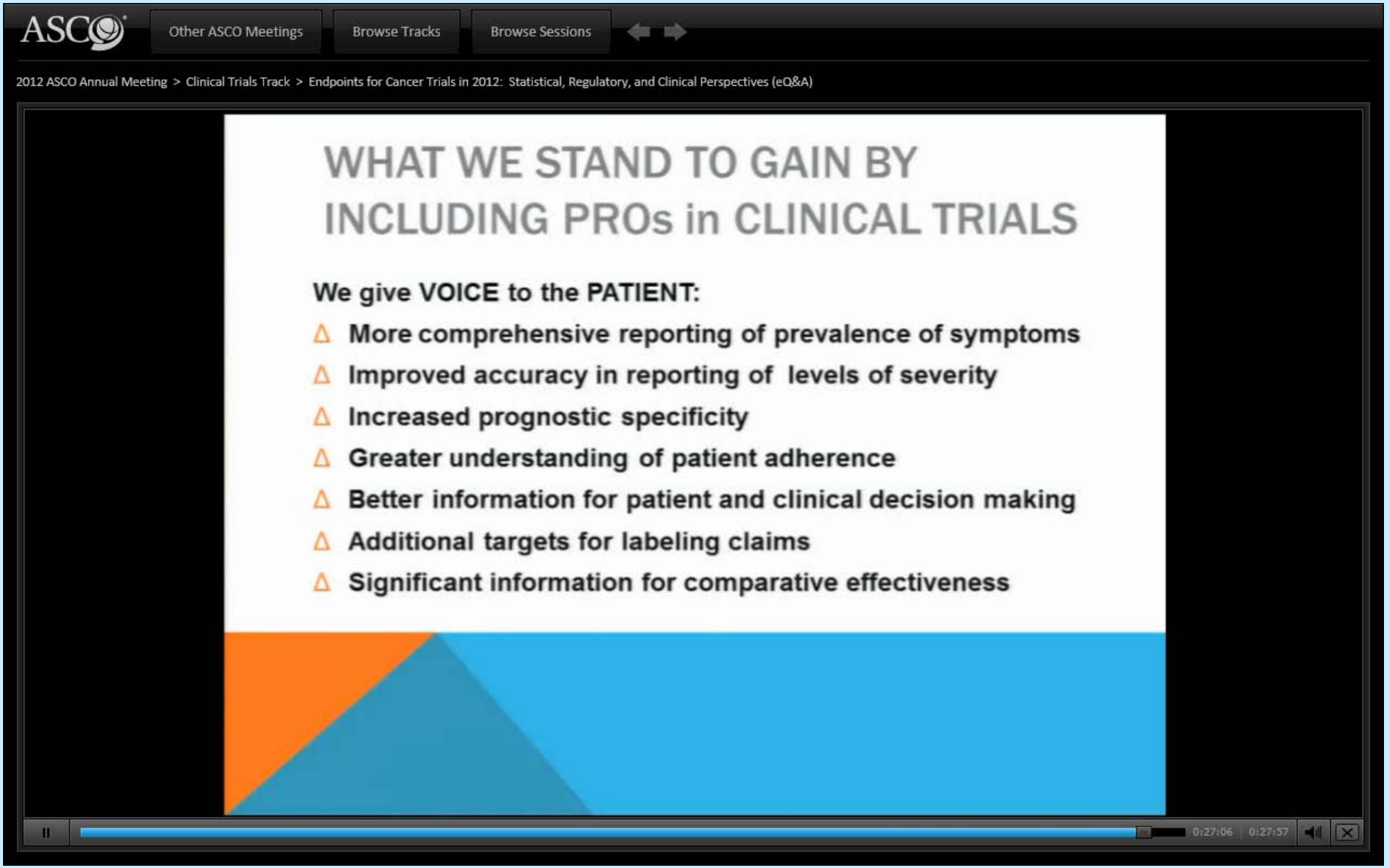
Statistics and Cancer Control Division, Research Center for Cancer Prevention and Screening, National Cancer Center Research Institute.

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.

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



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



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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

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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、これまで常識と思わ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