Genito-Üriner Kanserler

Best of ASCO İstanbul

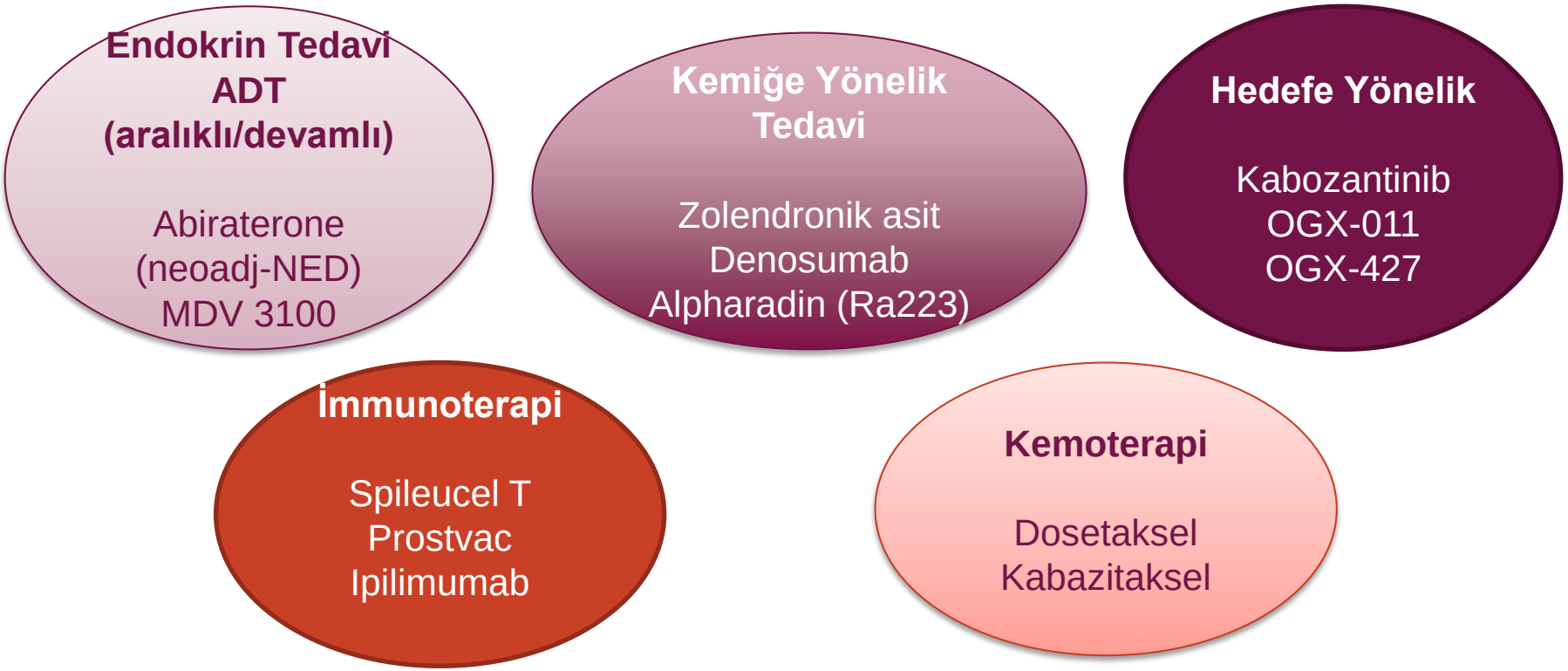
Dr. Mert Başaran

İ. Ü. Onkoloji Enstitüsü

Prostat Kanseri

PRESENTED BY:

Prostat Kanserinde Sistemik Tedavi 2012



- Neoadjuvan sistemik tedavi ?
- Kastrasyon dirençli NED hastalık döneminde tedavi ?
- Kemiğe yönelik koruyucu tedavi ?
- Radyoterapinin sağkalımdaki yeri ?

Intermittent versus Continuous Androgen Deprivation in Hormone Sensitive Metastatic Prostate Cancer Patients: Results of SWOG 9346 (INT-0162) an International Phase III Trial

Hussain M, Tangen CM, Higano CS, Crawford ED, Liu G, Wilding G, Prescott S, Akdas A, Small EJ, Dawson NA, Donnelly BJ, Venner P, Vaishampayan UN, Schellhammer PF, Quinn DI, Raghavan D, Vogelzang NJ, Thompson Jr, IM

Univ. of Michigan, Ann Arbor, MI; SWOG Statistical Center, Seattle, WA; Fred Hutchinson Cancer Research Center, Seattle, WA; University of Colorado Health Science Center, Aurora, CO; University of Wisconsin Carbone Cancer Center, Madison, WI; St. James University Hopsital, Leeds, UK; Marmara University, Istanbul, Turkey; University of California, San Francisco, San Francisco, CA; Georgetown University Hospital Lombardi Comprehensive Cancer Center, Washington, DC; Prostate Cancer Institute, Calgary, Alberta, Canada, Calgary, AB; Cross Cancer Institute, Edmonton, AB; Karmanos Cancer Institute, Wayne State University, Detroit, MI; Urology of Virginia, Norfolk, VA; University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA; Levine Cancer Institute, Carolinas HealthCare System, Charlotte NC; US Oncology Research, LLC, McKesson Specialty Health, The Woodlands, TX, and Comprehensive Cancer Centers of Nevada, Las Vegas, NV; University of Texas Health Science Center at San Antonio, San Antonio, TX

S9346 (INT-0162): Objectives

Primary

- Determine if survival with IAD is Not Inferior to survival with CAD.
- QOL*: To compare 3 treatment-specific symptoms (Impotence, Libido, Energy/Vitality) and physical and emotional functioning between arms

Secondary:

-More general QOL measures
-PSA dynamics between arms, and correlations with other endpoints

******Moinpour et-al, Abstract # 4571 describes results for QOL***

Step 1: Induction Registration
Key Eligibility Criteria

- PSA $\geq$ 5 ng/ml prior to initiation of AD.
- Prior neoadjuvant or adjuvant hormone therapy or prior finasteride was allowed with some restrictions.
- SWOG PS 0-2.

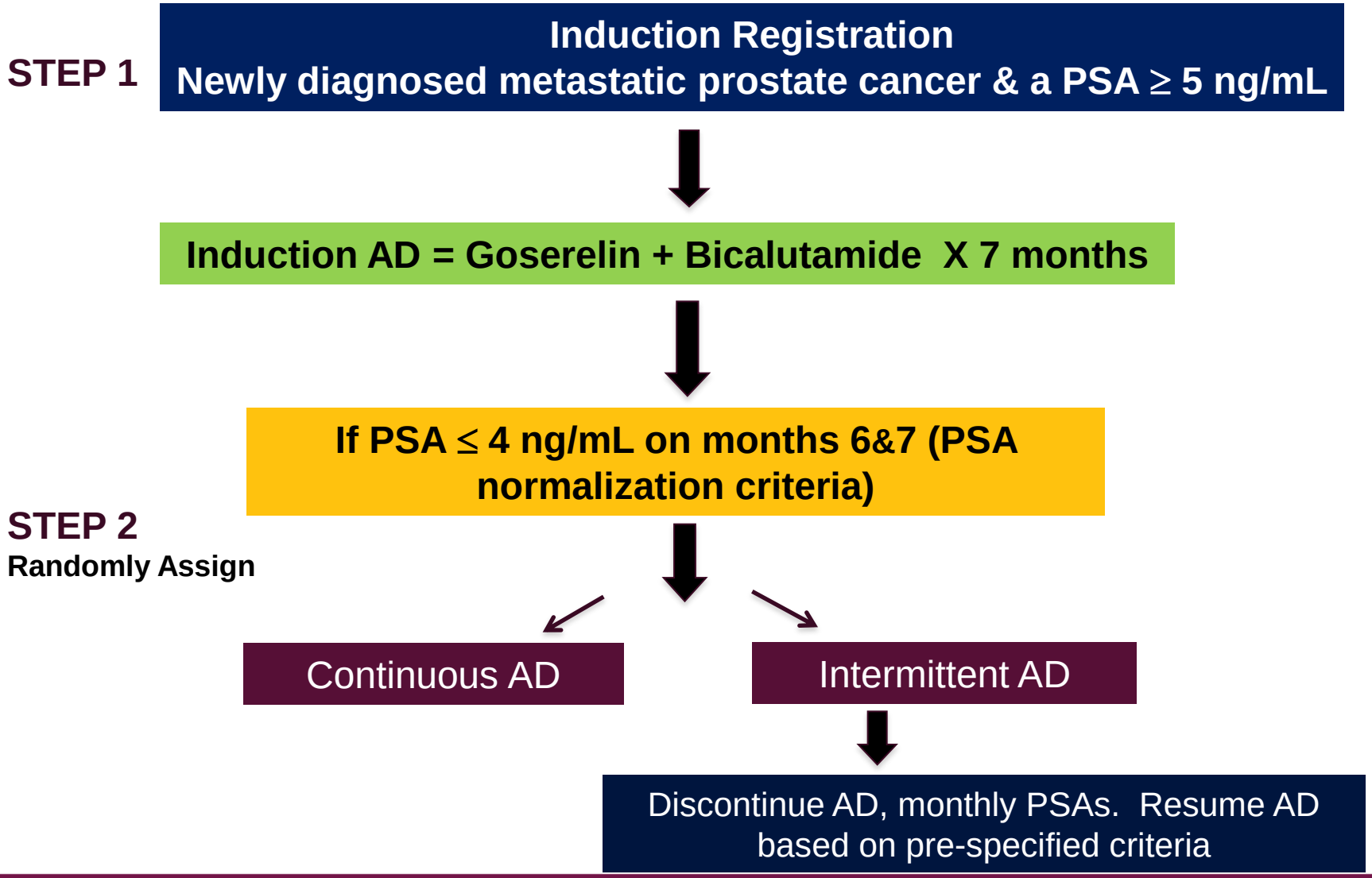
Stratification factors:

- Performance Status: 0 - 1 vs. 2
- Extent of Disease:
  - Minimal: Spine, pelvis &/or Lymph nodes

  vs.
  - Extensive: Ribs, long bones and / or visceral organs (Liver, lung)

- Prior hormone therapy:
  - Neoadjuvant therapy vs. finasteride vs. neither

Study Design



Aralıklı Kullanım

- PSA 20 ng/ml düzeyine gelince veya, 20'den küçük değerlerde başlanmışsa baseline değere gelince tedavi tekrar başlandı

- 7 ay tedavi ile PSA normale gelirse tekrar takip dönemine alındı

- 6-7 aylık tedavide PSA ≥ 4 olursa devamlı tedaviye alındı

S9346 Study Information

Activated: 5/15/1995 **Closed**: 9/1/2008

Step 1: Induction Registrations:
3040 pts *(90 ineligible)*

Step 2: Randomization to CAD vs. IAD:
1535 eligible pts
(projected 50% randomized)

IAD
770 eligible patients

CAD
765 eligible patients

Patients Characteristics at Randomization (Step 2)

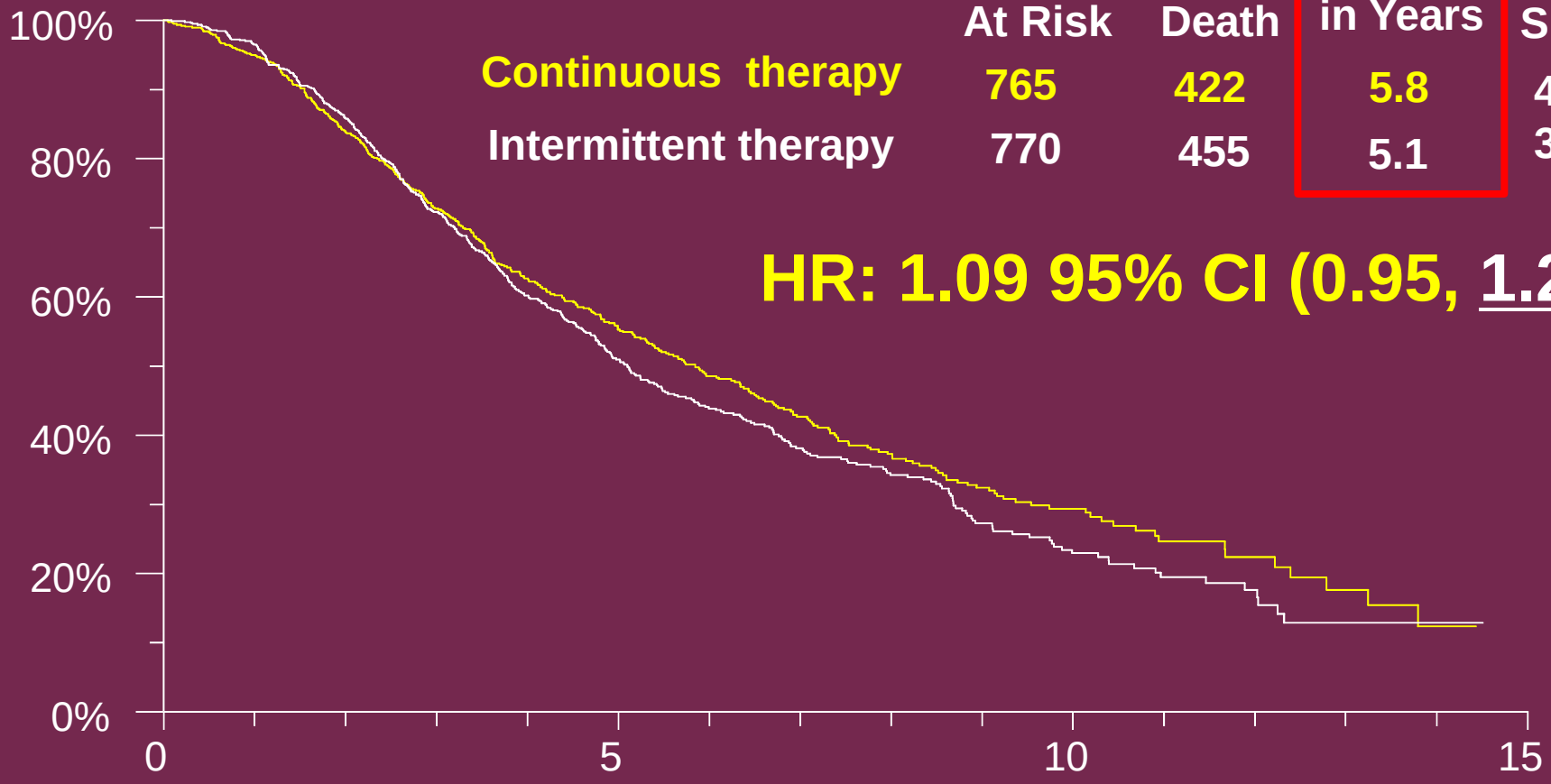
		IAD (N=770)	CAD (N=765)
Age (yrs)	median (range)	70 (39, 97)	70 (39, 92)
PSA (ng/ml) at Randomization			
	≤ 0.2	35.4%	34.9%
	0.3 – 4.0	64.6%	65.1%
Performance Status:	0-1 vs. 2	96%, 4%	96%, 4%
Disease Extent:	Extensive	49%	47%
	Minimal	51%	53%
Visceral Disease:	Any	7.1%	6.3%
Prior hormone therapy:	None	87%	88%
	Neoadjuvant, Finasteride	12%, 1%	11%, 1%
Bone Pain:	present	28%	26%
Gleason score:	≤ 6	23%	25%
	7	50%	48%
(31% missing)	8-10	27%	27%

Adverse Events with a Grade 4 Reported*

	IAD (N=703)		CAD (N=731)	
AE Category	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**
Cardiovascular	8	3	10	5
Flu-like Symptoms	18	2	26	2
Gastrointestinal	4	0	6	3
Hemorrhage	0	1	3	0
Liver	7	0	3	1
Lung	9	2	12	1
Musculoskeletal	1	1	2	1
Neurologic	15	1	15	2
Pain	26	1	30	2
Renal/Bladder	11	0	4	1
Max Grade Any AE	**203**	**11**	**224**	**15**

*** Treatment attribution: possible, probable, or definite, No Grade 5 reported**

Overall Survival: Intermittent Therapy is Inferior Compared to Continuous Therapy



	At Risk	Death	Median in Years	7 yr Survival
Continuous therapy	765	422	5.8	42%
Intermittent therapy	770	455	5.1	38%

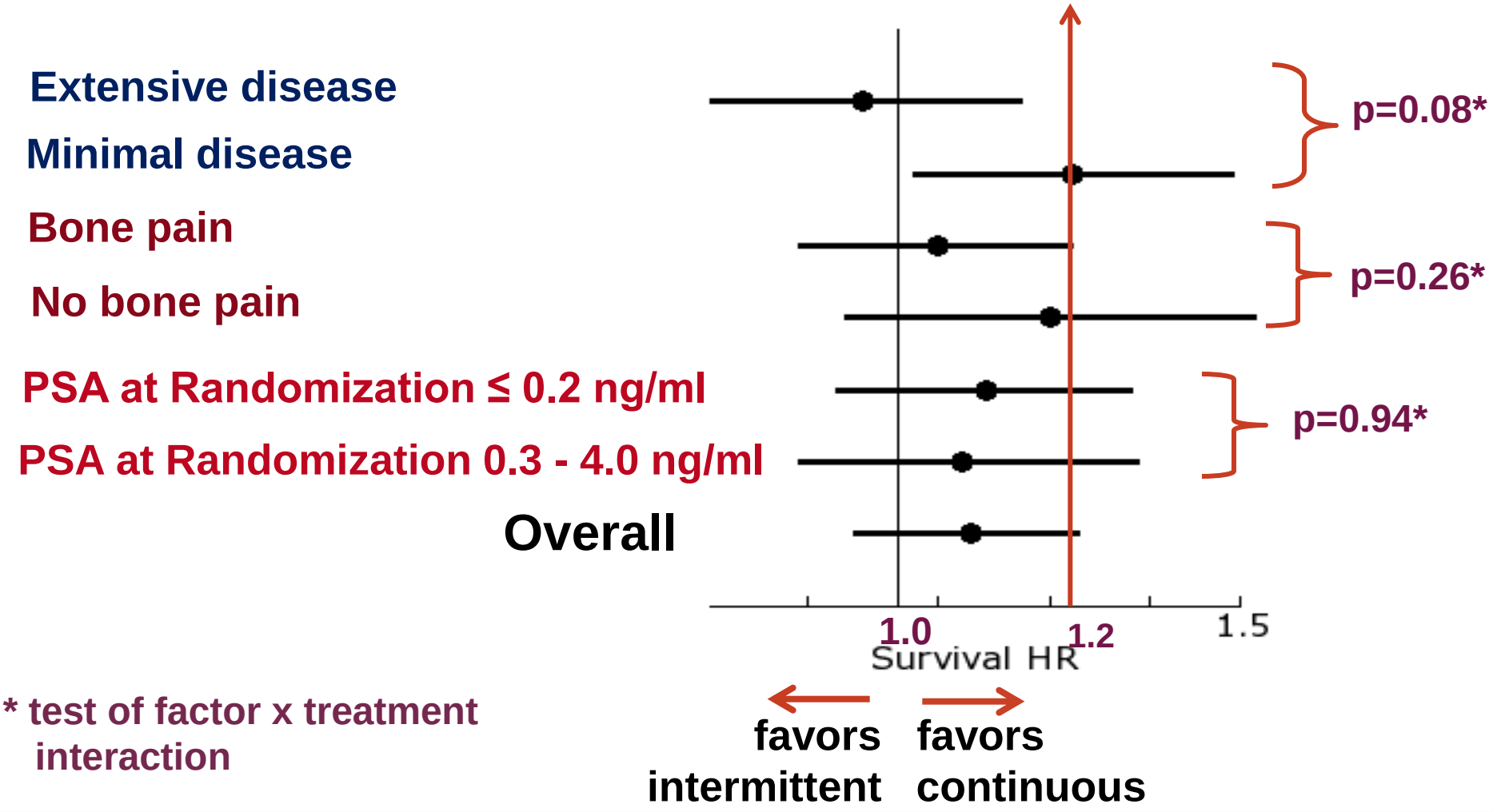
HR: 1.09 95% CI (0.95, 1.24)

At risk		
Intermittent	267	47
Continuous	301	53

PRESENTED BY: Maha Hussain, MD, FACP

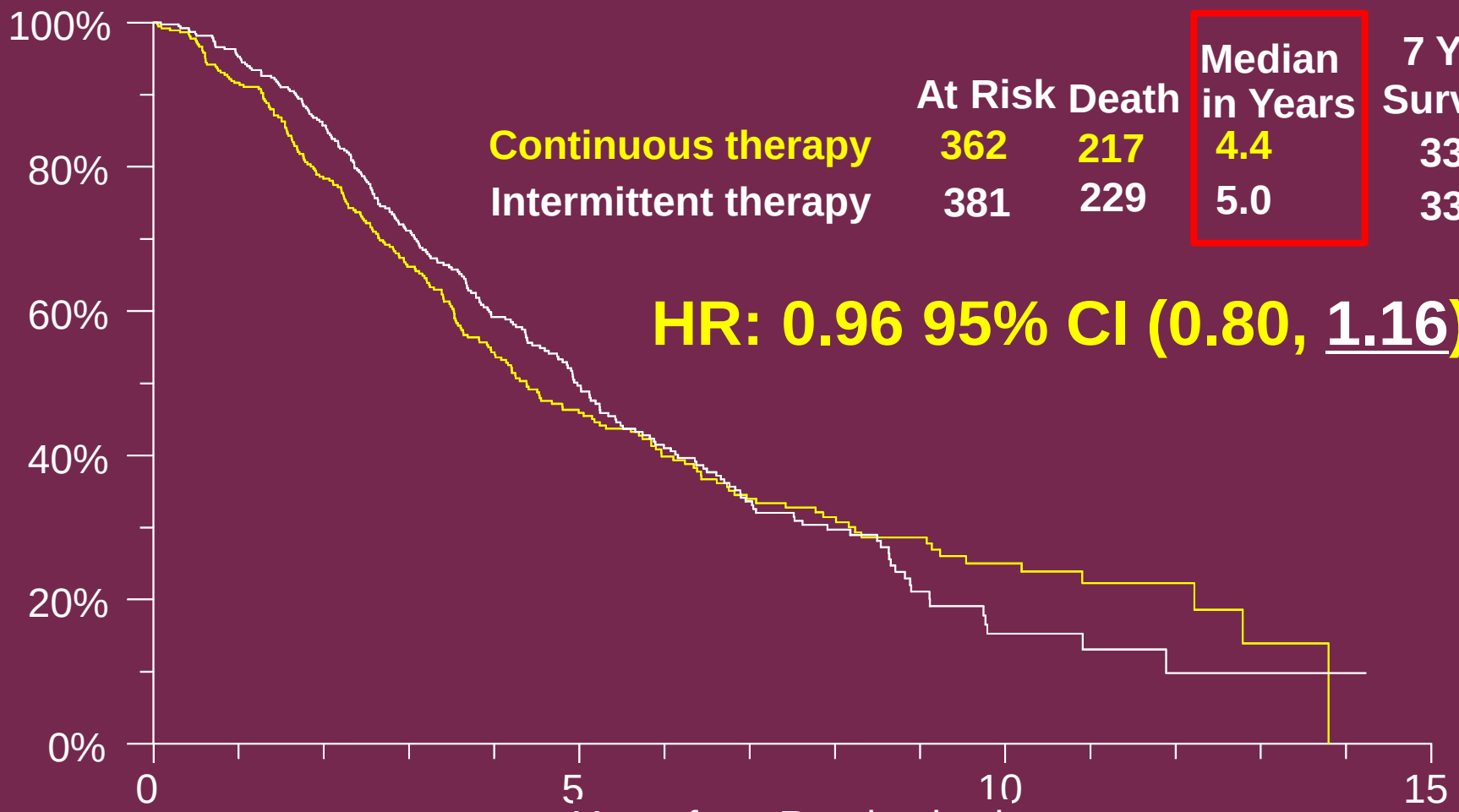
PRESENTED AT: ASCO Annual '12 Meeting

Evaluating Homogeneity of Treatment Effect Across Subsets of Patients



* test of factor x treatment interaction

Overall Survival for Patients with Extensive Disease by Treatment Arm



	At Risk	Death	Median in Years	7 Year Survival
Continuous therapy	362	217	4.4	33%
Intermittent therapy	381	229	5.0	33%

HR: 0.96 95% CI (0.80, 1.16)

At risk		
Intermittent	119	11
Continuous	106	22

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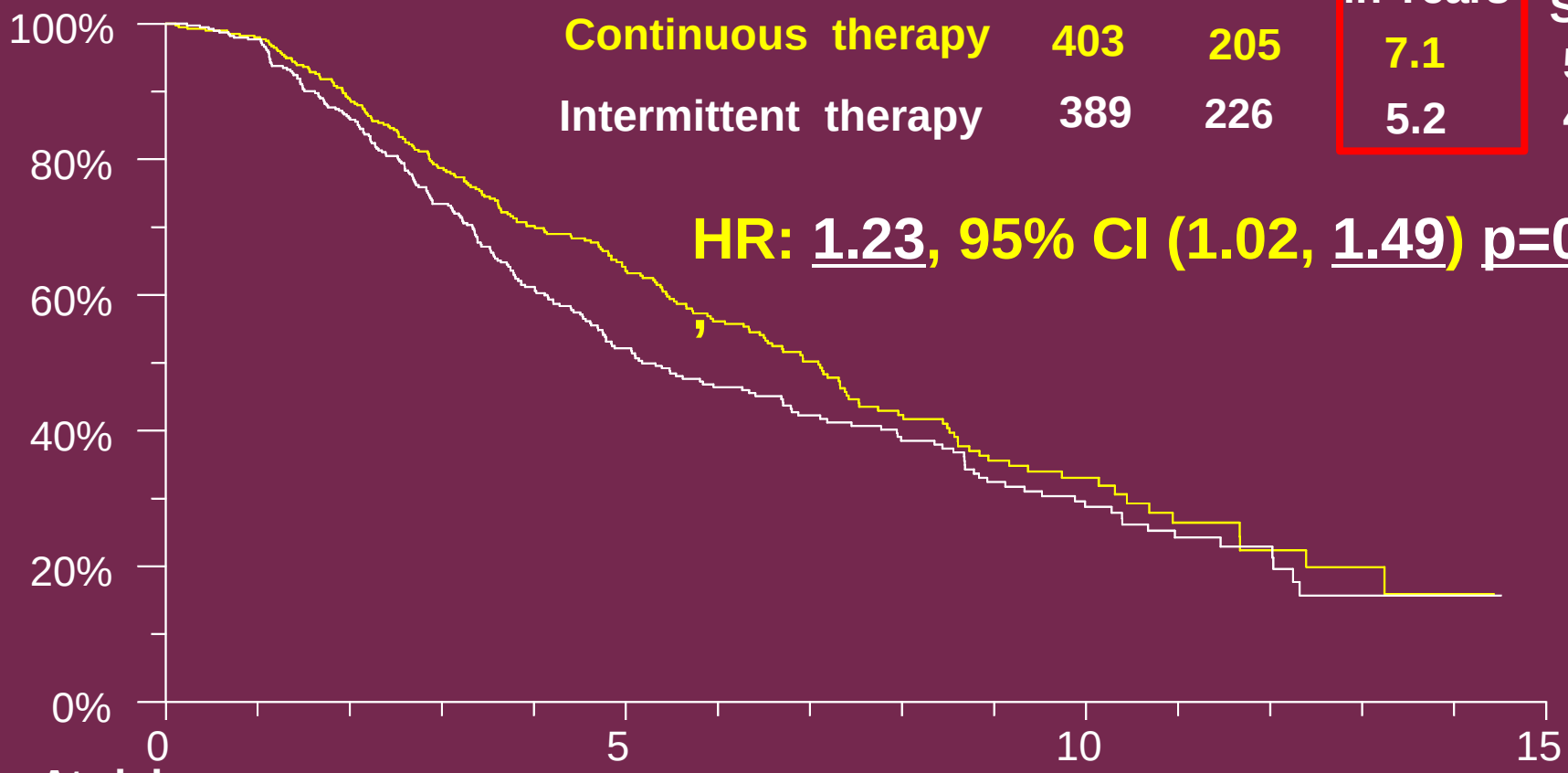
PRESENTED AT: ASCO Annual '12 Meeting

Overall Survival for Patients with Minimal Disease by Treatment Arm



	At Risk	Death	Median in Years	7 yr. Survival
Continuous therapy	403	205	7.1	50%
Intermittent therapy	389	226	5.2	42%

HR: 1.23, 95% CI (1.02, 1.49) p=0.034

At risk		
Intermittent	143	35
Continuous	194	30

PRESENTED BY: Maha Hussain, MD, FACP

PRESENTED AT: ASCO Annual '12 Meeting

Conclusions

In this international phase III trial in patients with metastatic hormone sensitive prostate cancer :

1. IAD was inferior to CAD based on our pre-specified definition of survival comparability [HR: 1.09, 95% CI (0.95, 1.24)]. Therefore, CAD continues to be the standard of care.

2. In a secondary analysis:
   - IAD was not-inferior to CAD in patients with extensive disease. [HR: 0.96 95% CI (0.80, 1.16)].
   - IAD was inferior in patients with minimal disease & CAD was statistically significantly superior [HR: 1.23, 95% CI (1.02, 1.49), p=0.034].

MRC Clinical Trials Unit

NCIC Clinical Trials Group
NCIC Groupe des essais cliniques

Southwest Oncology Group
A National Clinical Research Group

Final analysis of intergroup randomized phase III study of androgen deprivation therapy (ADT) + radiation therapy (RT) in locally advanced prostate cancer (CaP) (NCICCTG, SWOG, MRC-UK, INT: T94-0110).

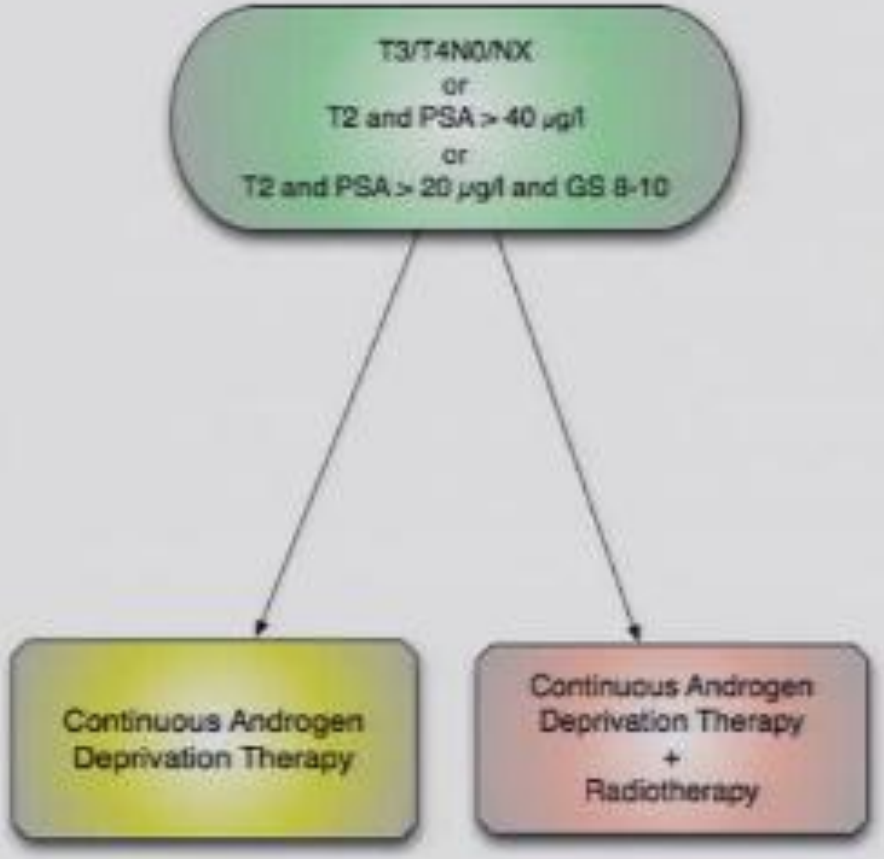
M.D. Mason, W. Parulekar, M.R. Sydes, M. Parmar, J. Anderson, J. Barber, M.D. Brundage, R. Cowan, M.K. Gospodarowicz, C. Hayter, J. Hetherington, A.C. Hiltz, P. Kirkbride, E. Kostashuk, K. Sanders, J. Sathya, G.P. Swanson, B.E. Chen, & P.R. Warde

On behalf of the NCICCTG PR3/MRC UK PR07 investigators

Presented at the 2012 ASCO Annual Meeting. Presented data is the property of the author.

ASCO Annual '12 Meeting

NCIC CTG PR3/MRC PR07/SWOG JPR3
Study scheme



- Initial PSA level:

< 20 vs 20-50 vs >50

- Hormonal therapy:

Orchiectomy vs LHRH analogue + antiandrogen

- Lymph node staging:

Radiological vs surgical vs none

- Gleason score:

<8 vs 8-10

- Prior hormonal therapy:

Yes vs no

- Centre

Planned Treatment

- Androgen deprivation therapy
  - Bilateral orchiectomy or LHRH agonist (with 2 weeks' anti-androgen, option to continue)

- Radiotherapy
  - 45 Gy /25 fr / 5 weeks to pelvis
  - Plus 20-24 Gy / 10-12 fr / 2-2.5 weeks to prostate
  - If treating physician felt that patient unsuitable for whole pelvic radiotherapy, RT to prostate alone, 65-69 Gy /35-37 fr / 7-7.5 weeks

Baseline Characteristics

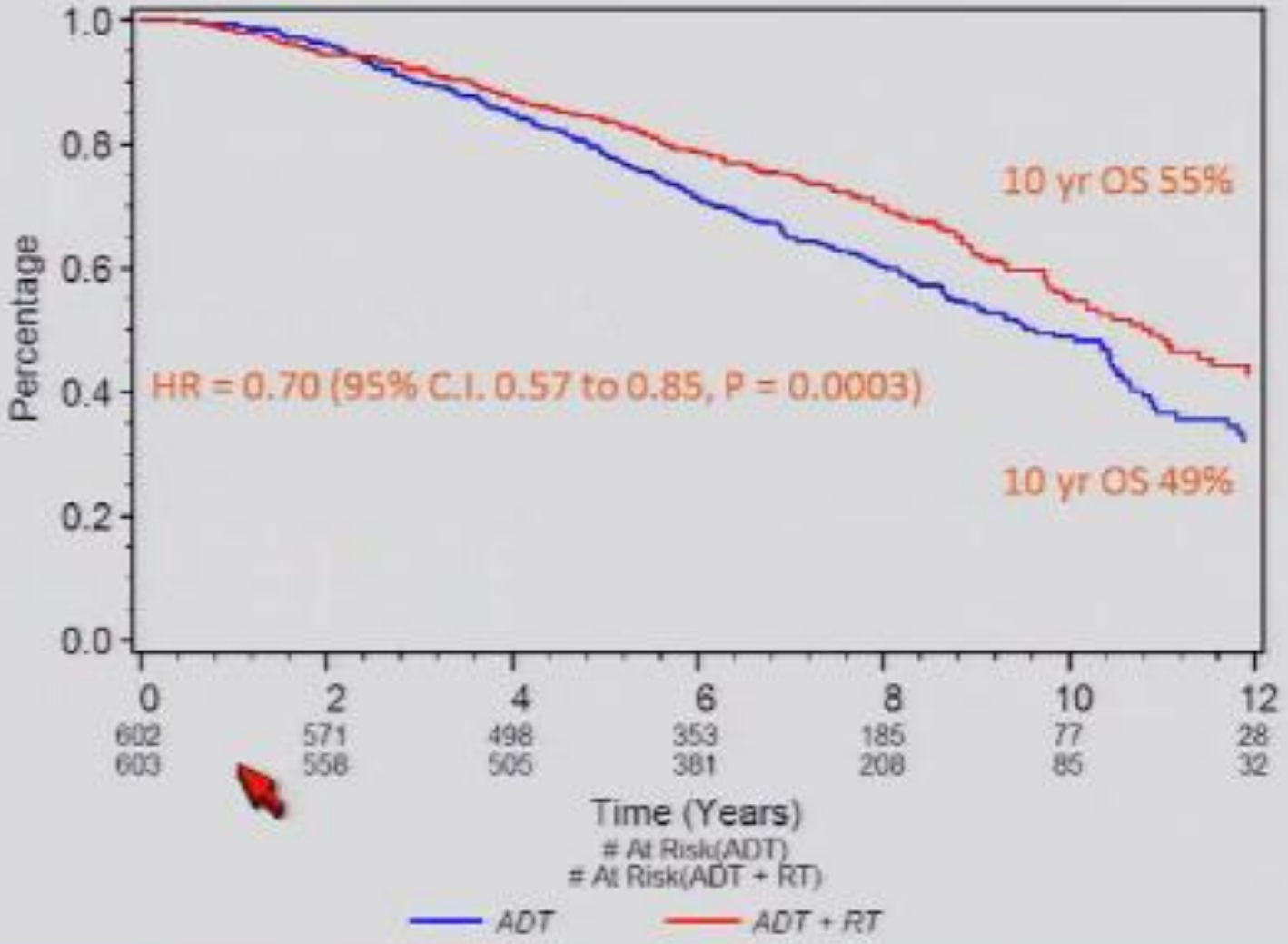
Characteristic	ADT Alone	ADT+RT
Median Age	70 years	70 years
T Category		
≤ T2c	11%	10%
T3/T4	89%	88%
Gleason Score		
≤ 7	81%	81%
8-10	18%	18%
PSA ng/ml		
<20	37%	36%
20-50	38%	38%
>50	25%	26%

Radiotherapy doses/volumes (Combined ADT + RT arm)

≤ 64 Gy	43
65-69 Gy	533
> 69 Gy	10

Prostate plus pelvic RT	420
Prostate Only	166

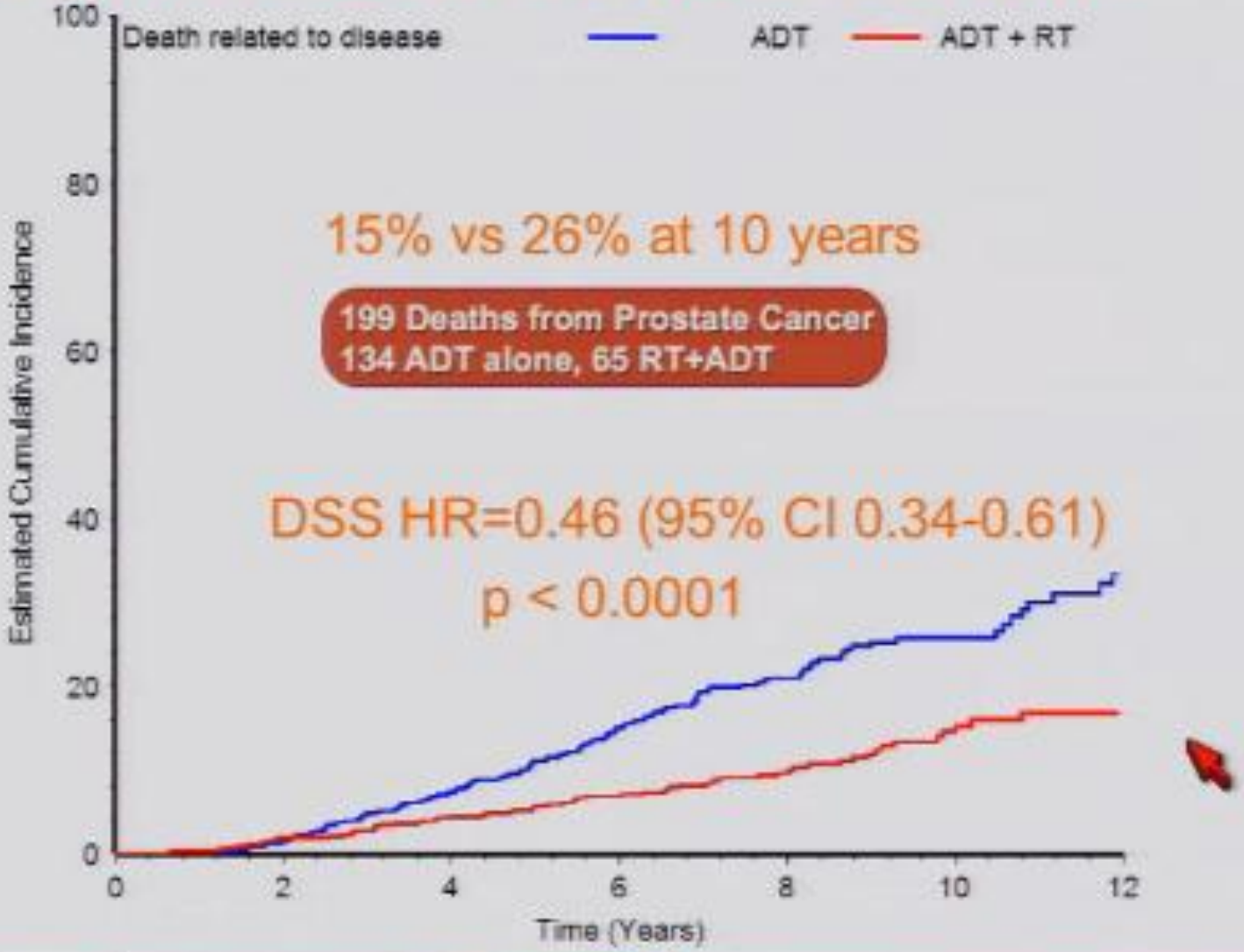
Final Analysis - overall survival



Investigator reported causes of death n (%)

	ADT Alone n=260	ADT+RT n=205	Total n=465
Prostate Cancer	134 (52)	65 (32)	199 (43)
Cardiac/Stroke	37 (14)	33 (16)	70 (15)
Other Cancer	31 (12)	44 (17)	75 (16)
Pneumonia	11 (4)	11 (9)	22 (5)
Other	31 (12)	34 (21)	65 (14)
Unknown	16 (6)	18 (5)	34 (7)

Final Analysis: Cumulative Incidence Probability for Disease-Specific Survival



Conclusions

- Combined ADT + RT should be offered to all men with locally advanced prostate cancer who are suitable for RT

- ADT + RT is the only guideline-recommended therapeutic approach backed by level 1 evidence

COU-AA-302'nin Ara Analiz Sonuçları, Abirateron Asetat ın (AA) Metastatik Kastrasyona Dirençli Prostat Kanserli (mCRPC) Kemoterapi Almamış (Kemoterapinaïv) Hastalarda Bir Randomize Faz 3 Çalışması

CJ Ryan,[1] MR Smith,[2] JS de Bono,[3] A Molina,[4] C Logothetis,[5] P De Souza,[6] K Fizazi,[7] P Mainwaring,[8] JR Piulats,[9] S Ng,[10] J Carles,[11] PFA Mulders,[12] T Kheoh[4], T Griffin[4], EJ Small,[1] HI Scher,[13] D Rathkopf,[13] on behalf of the COU-AA-302 Investigators

[1]Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, CA; [2]Massachusetts General Hospital Cancer Center, Boston, MA; [3]Royal Marsden Hospital, Sutton, UK; [4]Janssen Research & Development, Los Angeles, CA; [5]MD Anderson Cancer Center, Houston, TX; [6]St. George Private Hospital, Kogarah, Australia; [7]Institut Gustave Roussy, University of Paris Sud, Villejuif, France; [8]Haematology and Oncology Clinics of Australia, Brisbane, Australia; [9]Institut Català d'Oncologia de l'Hospitalet, Barcelona, Spain; [10]St. John of God Hospital, Subiaco, Australia; [11]Hospital Universitari Vall d´Hebron, Barcelona, Spain; [12]Radboud University Medical Centre, Nijmegen, Netherlands; [13]Memorial Sloan-Kettering Cancer Center, New York, NY

Ryan et al. ASCO 2012; Abstract LBA4518 (Sözel Sunum)

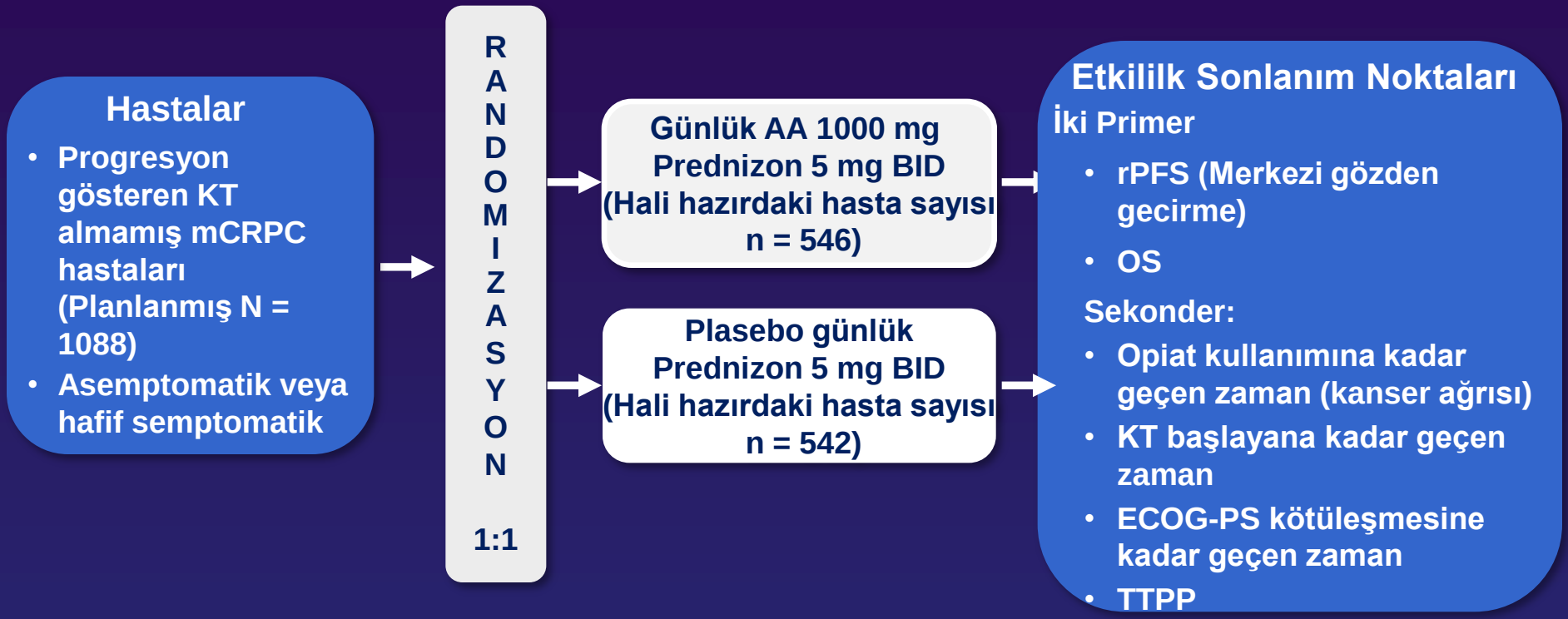
Abirateron Asetat:

mCRPC'li hastalarda Kemoterapi Sonrası Tedavi Düzeneğinde OS Faydası

Medyan Sağkalım 14.8 aydır ve Prednizon kontrol koluna göre 3.9 aylık düzelme

de Bono J, N Engl J Med. 2011; 364:1995-2005
Ryan et al. ASCO 2012; Abstract LBA4518 (Sözel Sunum)

COU-AA-302'ni Çalışma Dizaynı



- 12 ülkede 151 merkezde yürütülen Faz 3 çok merkezli, randomize, çift kör, plasebo kontrollü çalışma; ABD, Avrupa, Avustralya, Kanada
- Alt analiz ECOG performans statüsü 0'a karşı 1

Ryan et al. ASCO 2012; Abstract LBA4518 (Sözel Sunum)

COU-AA-302: rPFS'nin Tanımı

- Kemik Görüntülemesinde Progresif Hastalık (PD) : Prostat Kanseri Çalışma Grubu 2 Konsensus Kriterlerinden Uyarlanmıştır
  - Körleştirme yapılmış merkezi radyolog gözden geçirmesi
  - Randomizasyondan < 12 hafta sonra
    - ≥ 2 yeni kemik lezyonu + konfirmasyonda 2 ilave ("2+2")
  - Randomizasyondan ≥ 12 hafta sonra
    - Takip eden konfirmasyonda ≥ 2 yeni kemik lezyonu
- CT veya MR görüntüleme ile PD (yumuşak doku lezyonları) RECIST kriterlerine göre modifiye edilmiş
- Herhangi bir nedenden dolayı exitus

Ryan et al. ASCO 2012; Abstract LBA4518 (Sözel Sunum)

Treatment Arms Evenly Matched

	AA + P (n = 546)	Placebo + P (n = 542)
Median age, years (range)	71 (44-95)	70 (44-90)
Median time from initial diagnosis to first dose (years)	5.5	5.1
Median PSA (ng/mL)	42.0	37.7
Median testosterone (ng/dL)	4.0	4.0
Median alkaline phosphatase (IU/L)	93.0	90.0
Median hemoglobin (g/dL)	13.0	13.1
Median lactate dehydrogenase (IU/L)	187.0	184.0
Gleason score (≥8) at initial diagnosis	54%	50%
Extent of disease		
Bone metastases	83%	80%
>10 bone lesions	48%	47%
Soft tissue or node	49%	50%
Pain (BPI Short Form)		
0-1	66%	64%
2-3	32%	33%

Ryan et al. ASCO 2012; Abstract LBA4518 (Oral Presentation)

Tedavi Süresi ve Tedavinin Sonlandırılması

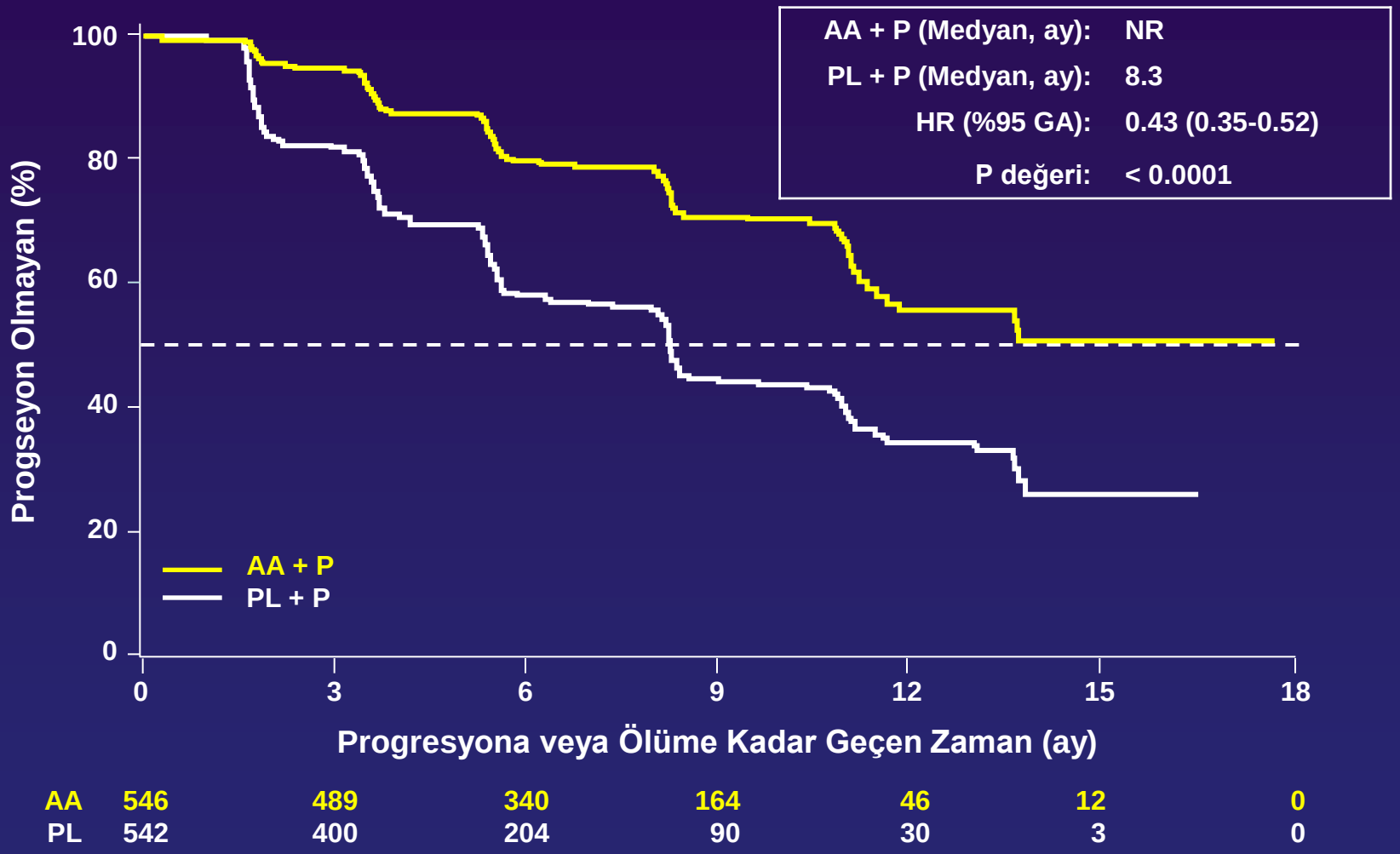
	AA+P (n=540)	Plasebo + P (n=542)
Medyan takip süresi	22.3 ay	
Medyan tedavi siklusu sayısı, aralık	15 (1-33)	9 (1-31)
Tedaviye devam edilmeyen	69%	84%
Tedaviye devam etmeme nedeni		
Tek başına radyolojik progresyon	21%	30%
Tek başına açık klinik progresyon*	21%	25%
Radyolojik + açık klinik progesyon	11%	10%
Advers olay	7%	5%
Kesme kararı	6%	9%
Diğer	4%	5%

*Eşdeğer olmayan klinik progresyon şunlardan bir veya daha fazlası: opist gerektiren ağrı, KT, palyatif RT, ECOG PS'unda düşme, cerrahi müdahale

Veriler güvenlilik popülasyonundan.

Ryan et al. ASCO 2012; Abstract LBA4518 (Sözel Sunum)

Sonlanım Noktası rPFS'de İstatistiksel Olarak Anlamlı Düzelme



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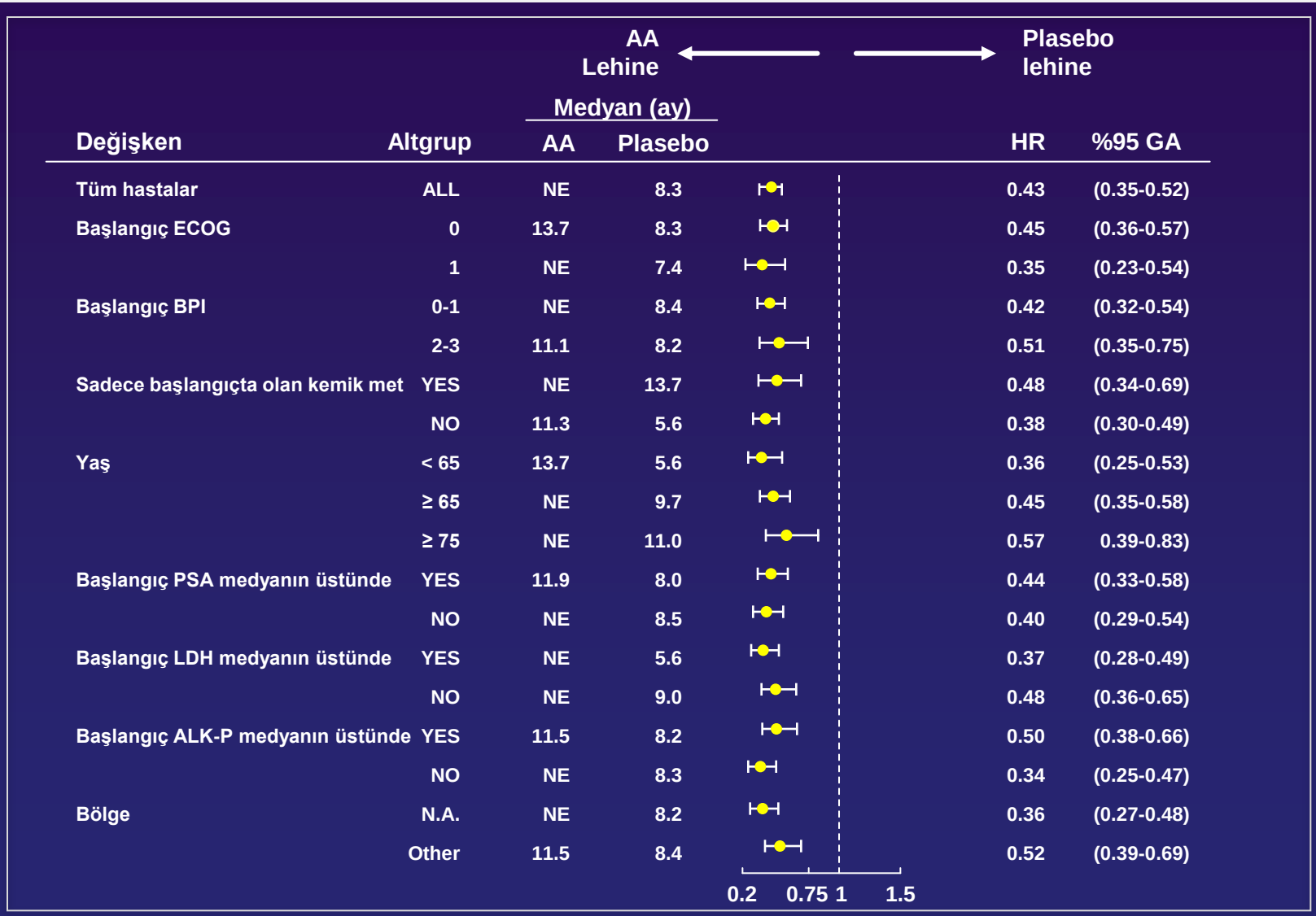
Ryan et al. ASCO 2012; Abstract LBA4518 (Sözel Sunum)

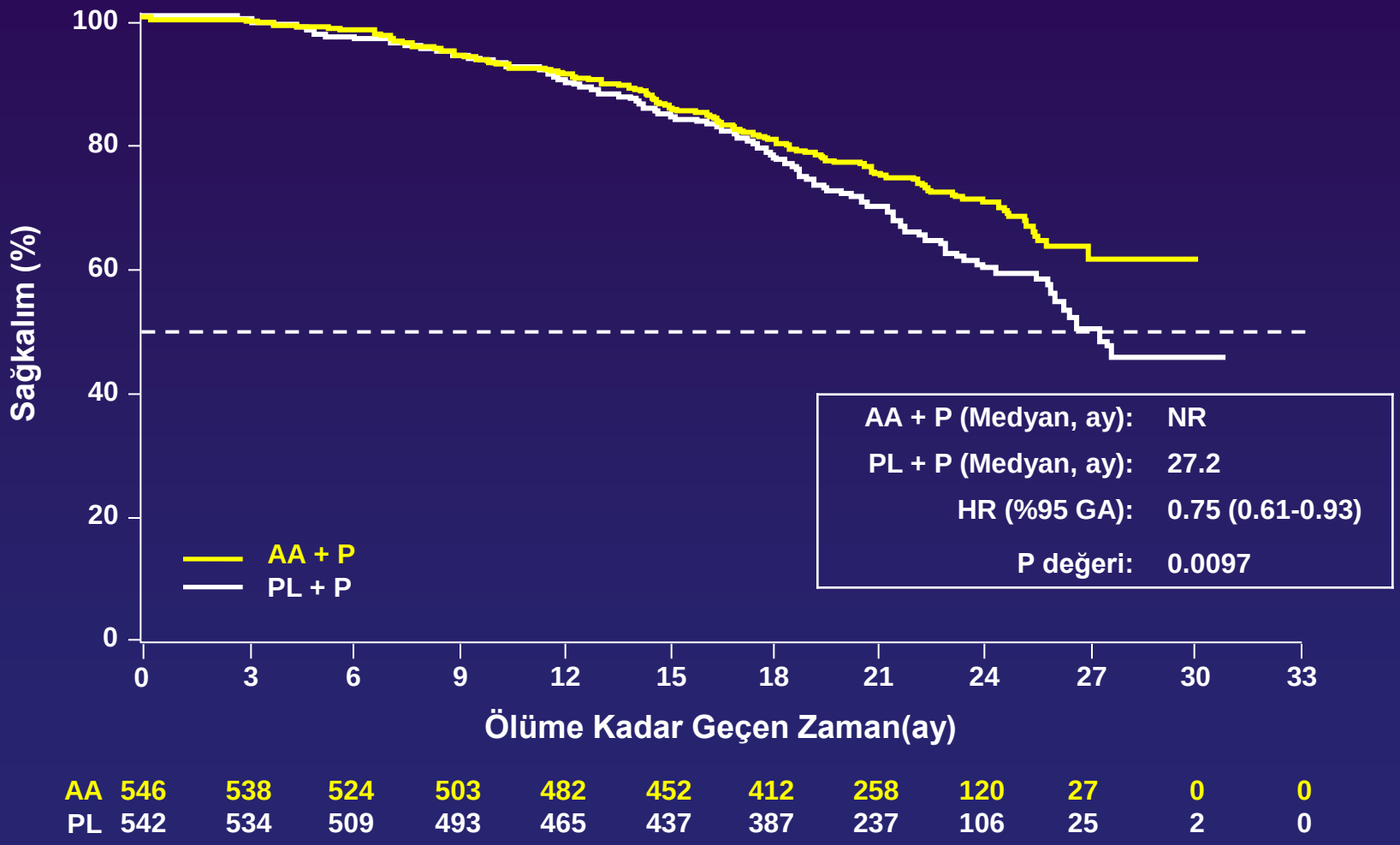
Tüm Hasta Altgruplarında Gösterilmiş rPFS Faydası



Değişken	Altgrup	AA	Plasebo	HR	%95 GA
Tüm hastalar	ALL	NE	8.3	0.43	(0.35-0.52)
Başlangıç ECOG	0	13.7	8.3	0.45	(0.36-0.57)
	1	NE	7.4	0.35	(0.23-0.54)
Başlangıç BPI	0-1	NE	8.4	0.42	(0.32-0.54)
	2-3	11.1	8.2	0.51	(0.35-0.75)
Sadece başlangıçta olan kemik met	YES	NE	13.7	0.48	(0.34-0.69)
	NO	11.3	5.6	0.38	(0.30-0.49)
Yaş	< 65	13.7	5.6	0.36	(0.25-0.53)
	≥ 65	NE	9.7	0.45	(0.35-0.58)
	≥ 75	NE	11.0	0.57	0.39-0.83)
Başlangıç PSA medyanın üstünde	YES	11.9	8.0	0.44	(0.33-0.58)
	NO	NE	8.5	0.40	(0.29-0.54)
Başlangıç LDH medyanın üstünde	YES	NE	5.6	0.37	(0.28-0.49)
	NO	NE	9.0	0.48	(0.36-0.65)
Başlangıç ALK-P medyanın üstünde	YES	11.5	8.2	0.50	(0.38-0.66)
	NO	NE	8.3	0.34	(0.25-0.47)
Bölge	N.A.	NE	8.2	0.36	(0.27-0.48)
	Other	11.5	8.4	0.52	(0.39-0.69)

Ryan et al. ASCO 2012; Abstract LBA4518 (Sözel Sunum)

OS Primer Sonlanım Noktasında Güçlü Trend

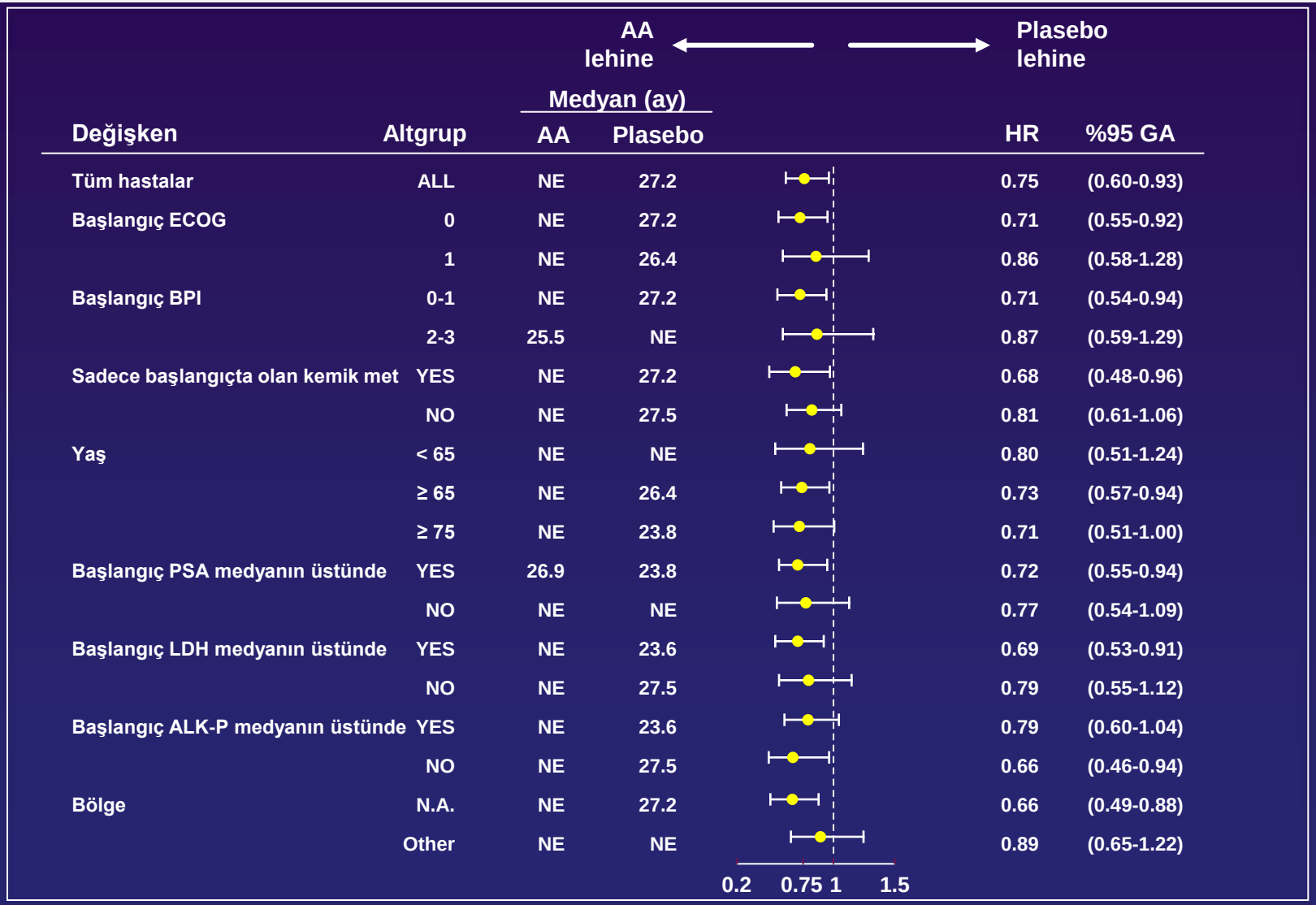


O'Brien-Fleming Sınırı ile öndeden belirlenmiş anlamlılık seviyesi = 0.0008

Son veri toplama tarihi 20/12/2011

Ryan et al. ASCO 2012; Abstract LBA4518 (Sözel Sunum)

Point Estimates for OS Favor AA in All Patient Subgroups



Değişken	Altgrup	Medyan (ay) AA	Medyan (ay) Plasebo	HR	%95 GA
Tüm hastalar	ALL	NE	27.2	0.75	(0.60-0.93)
Başlangıç ECOG	0	NE	27.2	0.71	(0.55-0.92)
	1	NE	26.4	0.86	(0.58-1.28)
Başlangıç BPI	0-1	NE	27.2	0.71	(0.54-0.94)
	2-3	25.5	NE	0.87	(0.59-1.29)
Sadece başlangıçta olan kemik met	YES	NE	27.2	0.68	(0.48-0.96)
	NO	NE	27.5	0.81	(0.61-1.06)
Yaş	< 65	NE	NE	0.80	(0.51-1.24)
	≥ 65	NE	26.4	0.73	(0.57-0.94)
	≥ 75	NE	23.8	0.71	(0.51-1.00)
Başlangıç PSA medyanın üstünde	YES	26.9	23.8	0.72	(0.55-0.94)
	NO	NE	NE	0.77	(0.54-1.09)
Başlangıç LDH medyanın üstünde	YES	NE	23.6	0.69	(0.53-0.91)
	NO	NE	27.5	0.79	(0.55-1.12)
Başlangıç ALK-P medyanın üstünde	YES	NE	23.6	0.79	(0.60-1.04)
	NO	NE	27.5	0.66	(0.46-0.94)
Bölge	N.A.	NE	27.2	0.66	(0.49-0.88)
	Other	NE	NE	0.89	(0.65-1.22)

Ryan et al. ASCO 2012; Abstract LBA4518 (Sözel Sunum)

Yaygın Biçimde Sonradan Tedavi Verildi

	AA + P (n = 546) n (%)	Plasebo + P (n = 542) n (%)
mCRPC için seçilmiş sonraki tedavilerin sayısı	242 (44.3)	327 (60.3)
Dosetaksel	207 (37.9)	287 (53.0)
Kabasitaksel	45 (8.2)	52 (9.6)
Ketockonazole	39 (7.1)	63 (11.6)
Sipuleucel-T	27 (4.9)	24 (4.4)
Abirateron Asetat*	26 (4.8)	54 (10.0)

*Körleme öncesi (yani çalışma protokolüne göre değil

Ryan et al. ASCO 2012; Abstract LBA4518 (Sözel Sunum)

Serologic and Clinical Responses

	AA + P (n = 546)	Placebo + P (n = 542)	RR (95% CI)	P Value
PSA decline ≥50%	62%	24%	NA	<0.0001
	N=220	**N=218**		
RECIST: Defined objective response	**36%**	**16%**	2.273 (1.591, 3.247)	<0.0001
Complete response	11%	4%		
Partial response	25%	12%		
Stable disease	61%	69%		
Progressive disease	2%	15%		

Ryan et al. ASCO 2012; Abstract LBA4518 (Oral Presentation)

Tüm Sekonder Sonlanım Noktalarında İstatiksel Olarak Anlamlı Düzelme

	AA + P	Plasebo + P		
	Medyan (ay)	Medyan (ay)	HR (%95 GA)	P değeri
Opiat Kullanımına Kadar geçen zaman (kanser ağrısı)	NR	23.7	0.69 (0.57, 0.83)	0.0001
KT başlangıcına kadar geçen zaman	25.2	16.8	0.58 (0.49, 0.69)	<0.0001
ECOG PS kötüleşmesine kadar geçen zaman	12.3	10.9	0.82 (0.71, 0.94)	0.0053
PSA Progresyonuna Kadar Geçen Zaman	11.1	5.6	0.49 (0.42, 0.57)	<0.0001

Not: Çokluluk testine göre ayarlığında da tüm sekonder sonlanım noktalarının anlamlı düzeyde kalmıştır

Hasta Tarafından Bildirilen Sonuç AA +P lehine idi (Plasebo +P'ye karşı)
Tüm veriler ayrıca bildirliecektir

Son veri toplama tarihi 20/12/2011

Ryan et al. ASCO 2012; Abstract LBA4518 (Sözel Sunum)

301 Çalışmasından Farklı Güvenlilikle İlgili Yeni Bir Farklı Durum Tespit Edilmedi

	AA + P (n = 542) %		Plasebo + P (n = 540) %	
	Tüm grede'ler	Grade 3/4	Tüm Grade'ler	Grade 3/4
Yorgunluk	39	2	34	2
Sıvı retansiyonu	28	0.7	24	1.7
Hipokalemi	17	2	13	2
Hipertansiyon	22	4	13	3
Kardiyak bozukluklar	19	6	16	3
Atriyal fibrilasyon	4	1.3	5	0.9
ALT artışı	12	5.4	5	0.8
AST artışı	11	3.0	5	0.9

Çoğu ALT ve AST iartışları tedavinin ilk 3 ayında olmuştur

Ryan et al. ASCO 2012; Abstract LBA4518 (Sözel Sunum)

Özet

- Asemptomatik veya hafif semptomalrı olan kemoterapi almamış mCRPC'li hastalarda, Abirateron Asetat + Prednizon Tedavisi:
  - Hastalık progresyonunu geciktirir
  - Sağkalımı uzatır
  - Geçen zamanda minimal veya sıfır semptom
  - Önemli yeni bir güvenlilik sinyali yok

Ryan et al. ASCO 2012; Abstract LBA4518 (Sözel Sunum)

ASCO
American Society of Clinical Oncology
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The ROYAL MARSDEN
NHS Foundation Trust

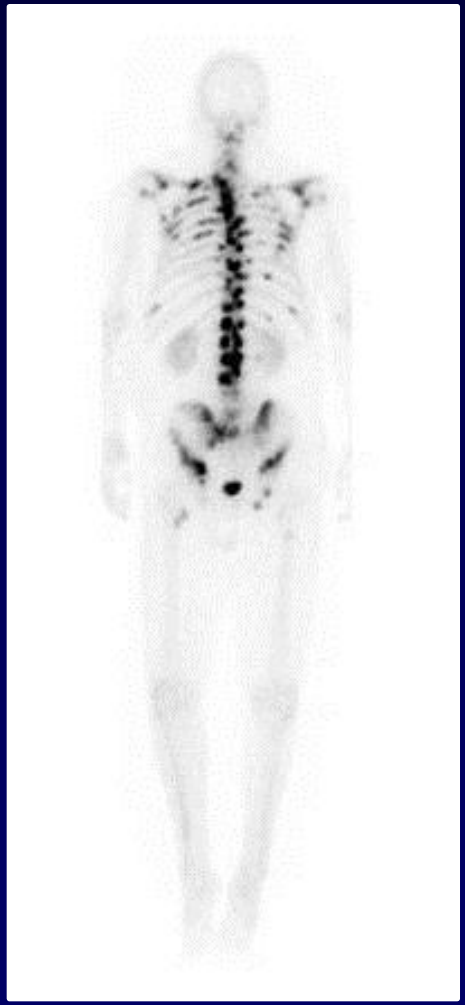
Updated analysis of the phase III, double-blind, randomized, multinational study of radium-223 chloride in castration-resistant prostate cancer (CRPC) patients with bone metastases (ALSYMPCA)

C. Parker,[1] S. Nilsson,[2] D. Heinrich,[3] J.M. O'Sullivan,[4] S. Fosså,[5] A. Chodacki,[6] P. Wiechno,[7] J. Logue,[8] M. Seke,[9] A. Widmark,[10] D.C. Johannessen,[11] P. Hoskin,[12] D. Bottomley,[13] R. Coleman,[14] N. Vogelzang,[15] C.G. O'Bryan-Tear,[16] J. Garcia-Vargas,[17] M. Shan,[17] and O. Sartor[18]

[1]The Royal Marsden NHS Foundation Trust, Sutton, UK; [2]Karolinska University Hospital, Stockholm, Sweden; [3]Akershus University Hospital, Lørenskog, Norway; [4]Centre for Cancer Research and Cell Biology, Queen's University, Belfast, Northern Ireland; [5]Radiumhospitalet, Oslo, Norway; [6]Hospital Kochova, Chomutov, Czech Republic; [7]Centrum Onkologii – Instytut im Sklodowskiej-Curie, Warsaw, Poland; [8]Christie Hospital, Manchester, UK; [9]Centrallasarettet Växjö, Växjö, Sweden; [10]Umeå University, Umeå, Sweden; [11]Ullevål University Hospital, Oslo, Norway; [12]Mount Vernon Hospital Cancer Centre, Middlesex, UK; [13]St. James Hospital, Leeds, UK; [14]Weston Park Hospital, Sheffield, UK; [15]Comprehensive Cancer Centers of Nevada, Las Vegas, NV, USA; [16]Algeta ASA, Oslo Norway; [17]Bayer Healthcare Pharmaceuticals, Montville, NJ, USA; [18]Tulane Cancer Center, New Orleans, LA, USA

Background and Rationale

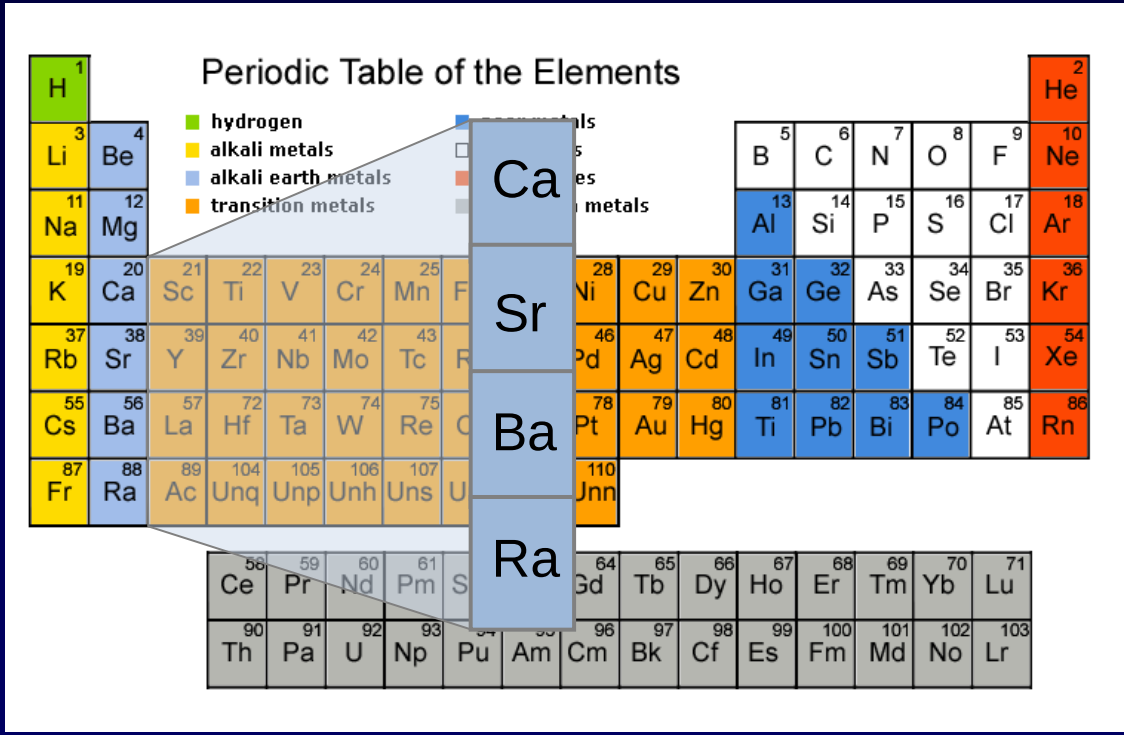
- **> 90% of patients with metastatic CRPC have radiologic evidence of bone metastases[1]**
- **Skeletal-related events (SREs) include spinal cord compression, pathological fracture, and need for surgery or external beam radiotherapy[2]**
- **Bone metastases are a major cause of death, disability, decreased quality of life, and increased treatment cost[3]**
- **Current bone-targeted therapies have not been shown to improve survival**



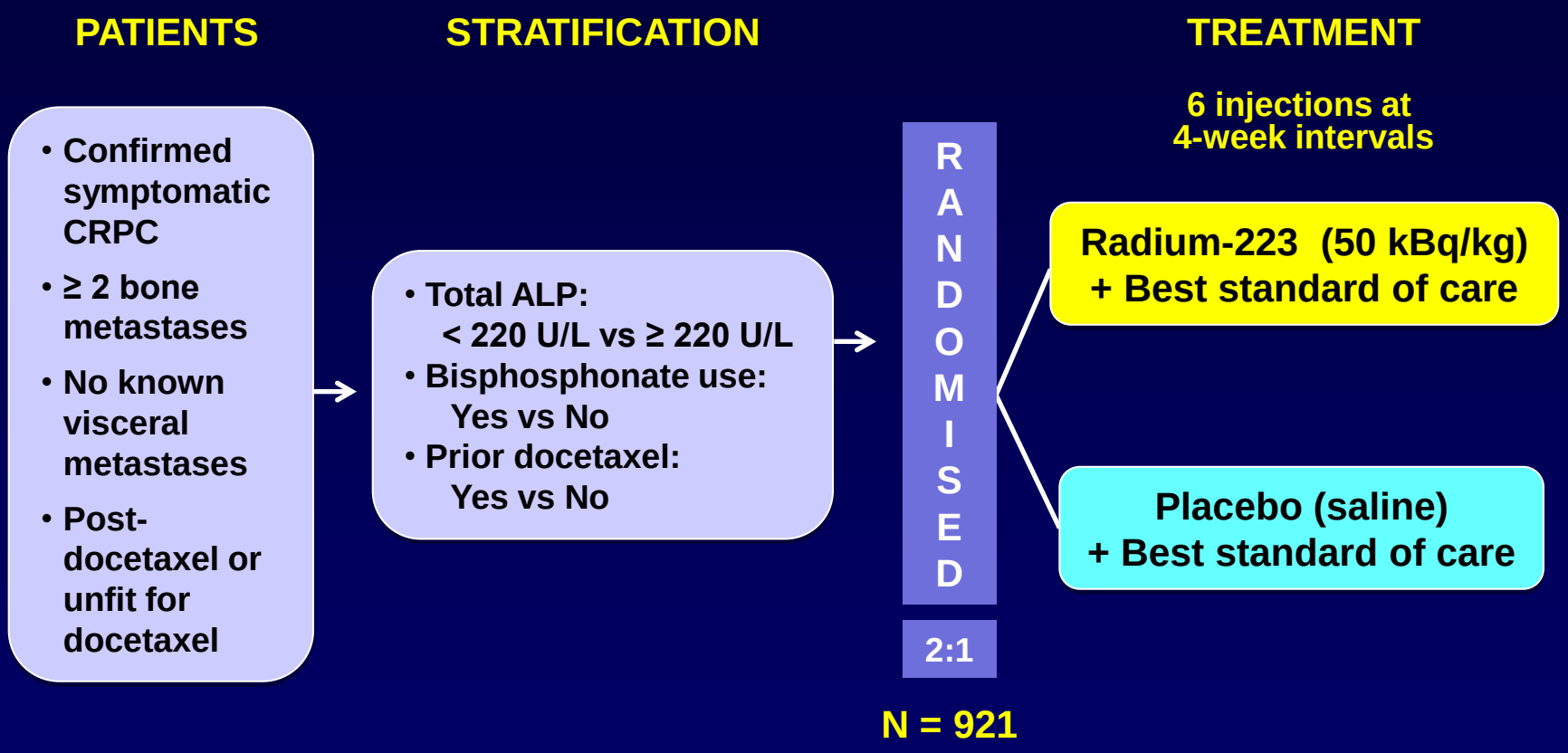
1. Tannock et al. *N Engl J Med.* 2004;351:1502-1512.
2. Lipton. *Semin Oncol.* 2010;37:S15-S29.
3. Lange and Vasella. *Cancer Metastasis Rev.* 1999;17:331-336.

Radium-223 Targets Bone Metastases

- Radium-223 acts as a calcium mimic
- Naturally targets new bone growth in and around bone metastases
- Radium-223 is excreted by the small intestine



ALSYMPCA (ALpharadin in SYMptomatic Prostate CAncer) Phase III Study Design



Planned follow-up is 3 years

Clinicaltrials.gov identifier: NCT00699751

ALSYMPCA Study Endpoints

- Primary Endpoint
  - Overall survival (OS)

- Secondary Endpoints
  - Time to first SRE
  - Time to total ALP progression
  - Total ALP response
  - Total ALP normalization
  - Time to PSA progression
  - Safety
  - Quality of life

ALSYMPCA Updated Analysis Patient Demographics and Baseline Characteristics (ITT N = 921)

Parameter	Radium-223 n = 614	Placebo n = 307
Age, y		
Mean	70.2	70.8
Race, n (%)		
Caucasian	575 (94)	290 (95)
Baseline ECOG score, n (%)		
≤ 1	536 (87)	265 (86)
2	76 (12)	40 (13)
Extent of disease, n (%)		
< 6 metastases	100 (16)	38 (12)
6–20 metastases	262 (43)	147 (48)
> 20 metastases/superscan	249 (41)	121 (40)
WHO ladder, cancer pain index ≥ 2, n (%)	345 (56)	168 (55)

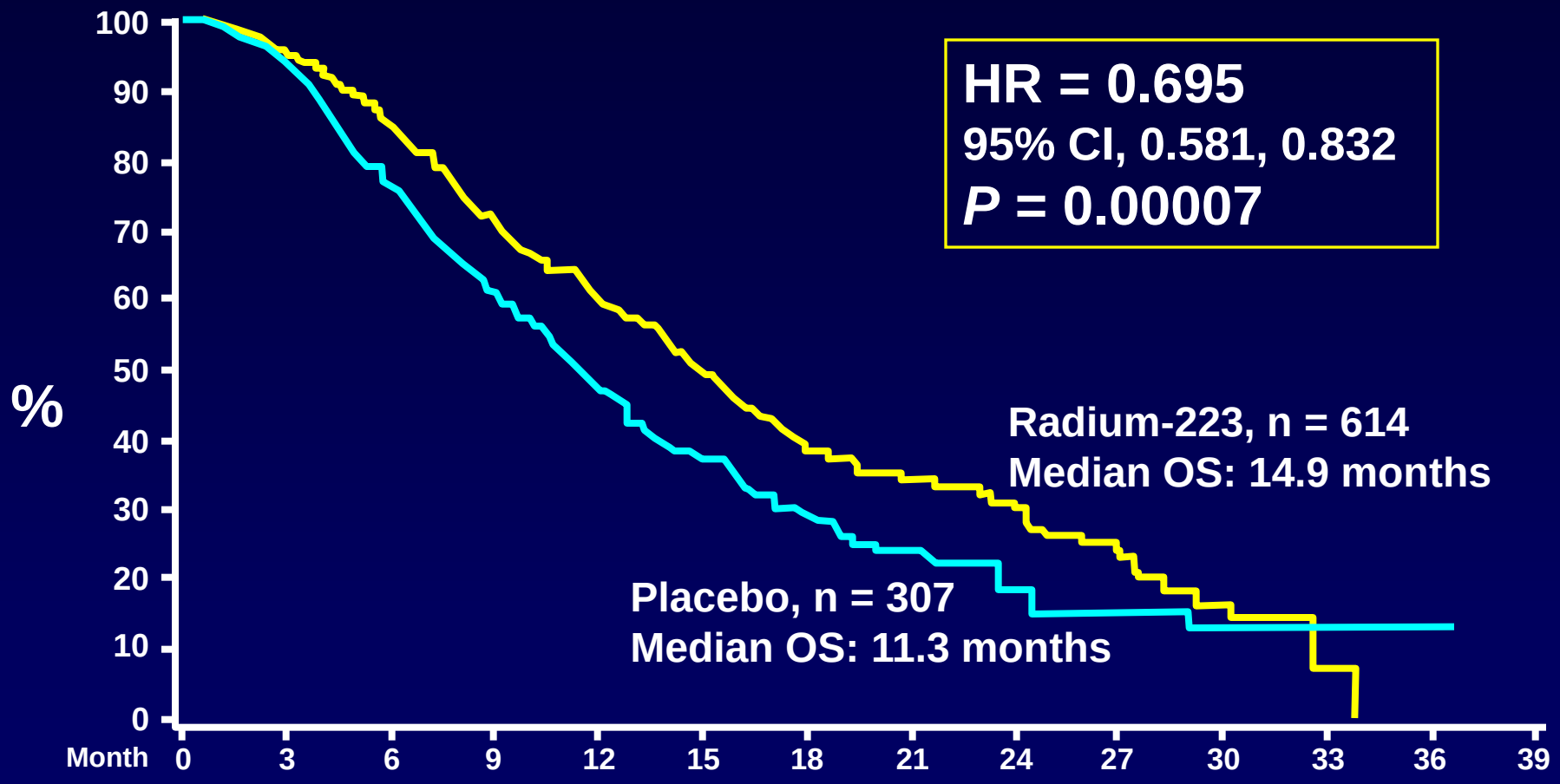
ALSYMPCA Updated Analysis
Patient Baseline Characteristics (ITT N = 921)

Parameter Median (min, max)	Radium-223 (n = 614)	Placebo (n = 307)
Haemoglobin, g/dL	12.2 (8.5-15.7)	12.1 (8.5-16.4)
Albumin, g/L	40 (24-53)	40 (23-50)
Total ALP, µg/L	211 (32-6431)	223 (29-4805)
LDH, U/L	315 (76-2171)	336 (132-3856)
PSA, µg/L	146 (3.8-6026)	173 (1.5-14500)
Current bisphosphonates Yes, n (%)	250 (40.7)	124 (40.4)
Prior docetaxel Yes, n (%)	352 (57.3)	174 (56.7)

ALSYMPCA Updated Analysis
Patient Disposition

	Radium-223 N = 614	Placebo N = 307
Patients treated, n	599	302
Median number of injections, range	6 (1-6)	5 (1-6)
Received all 6 injections, n (%)	387 (63)	145 (47)

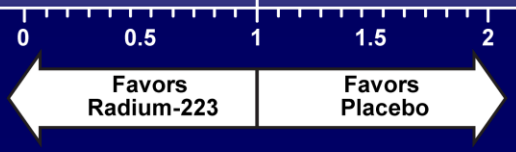
ALSYMPCA Updated Analysis
Overall Survival



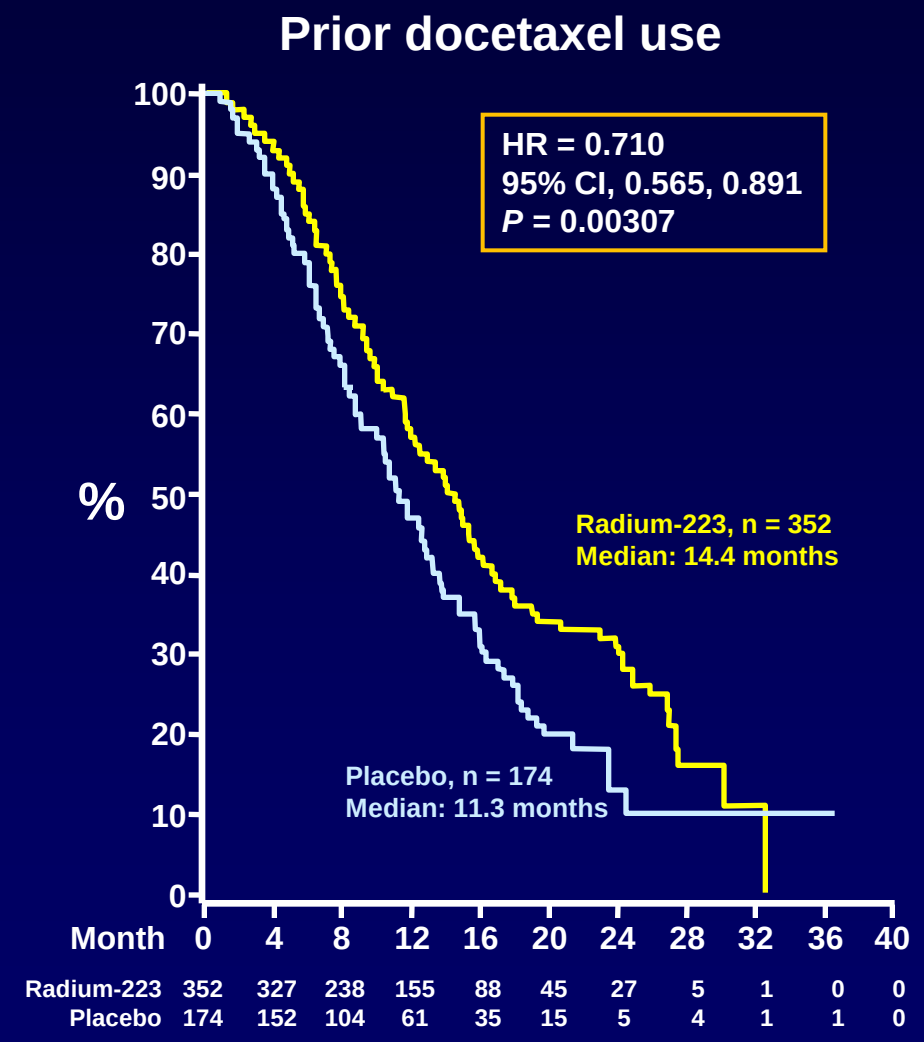
Radium-223	614	578	504	369	274	178	105	60	41	18	7	1	0	0
Placebo	307	288	228	157	103	67	39	24	14	7	4	2	1	0

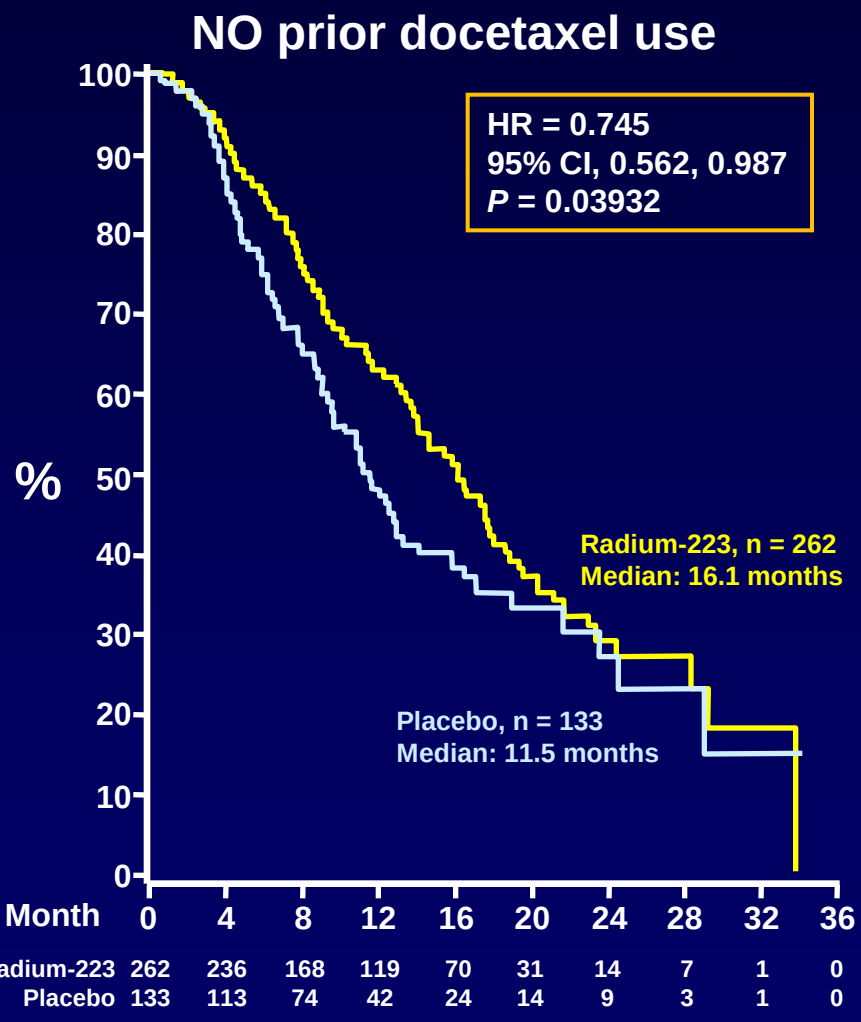
ALSYMPCA Updated Analysis
Survival Benefit Across Patient Subgroups

Variable	Subgroup	N	HR	95% CI
Overall Survival		921	0.695	0.581–0.832
Total ALP #	< 220 U/L	517	0.825	0.635–1.072
	>= 220 U/L	404	0.619	0.486–0.788
Current Use of Bisphosphonates #	Yes	374	0.699	0.525–0.931
	No	547	0.736	0.587–0.923
Prior Use of Docetaxel #	Yes	526	0.710	0.565–0.891
	No	395	0.745	0.562–0.987
Baseline ECOG Status	0 or 1	801	0.675	0.555–0.821
	2 or Higher	118	0.820	0.498–1.351

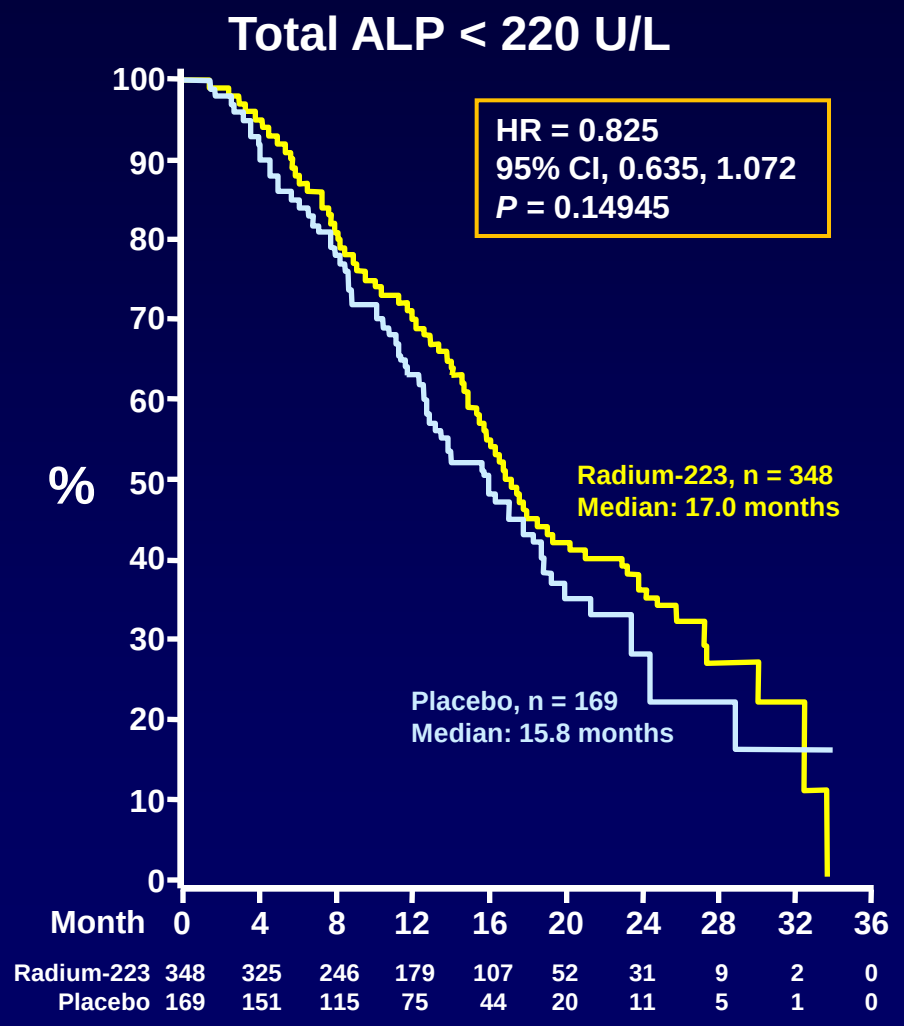


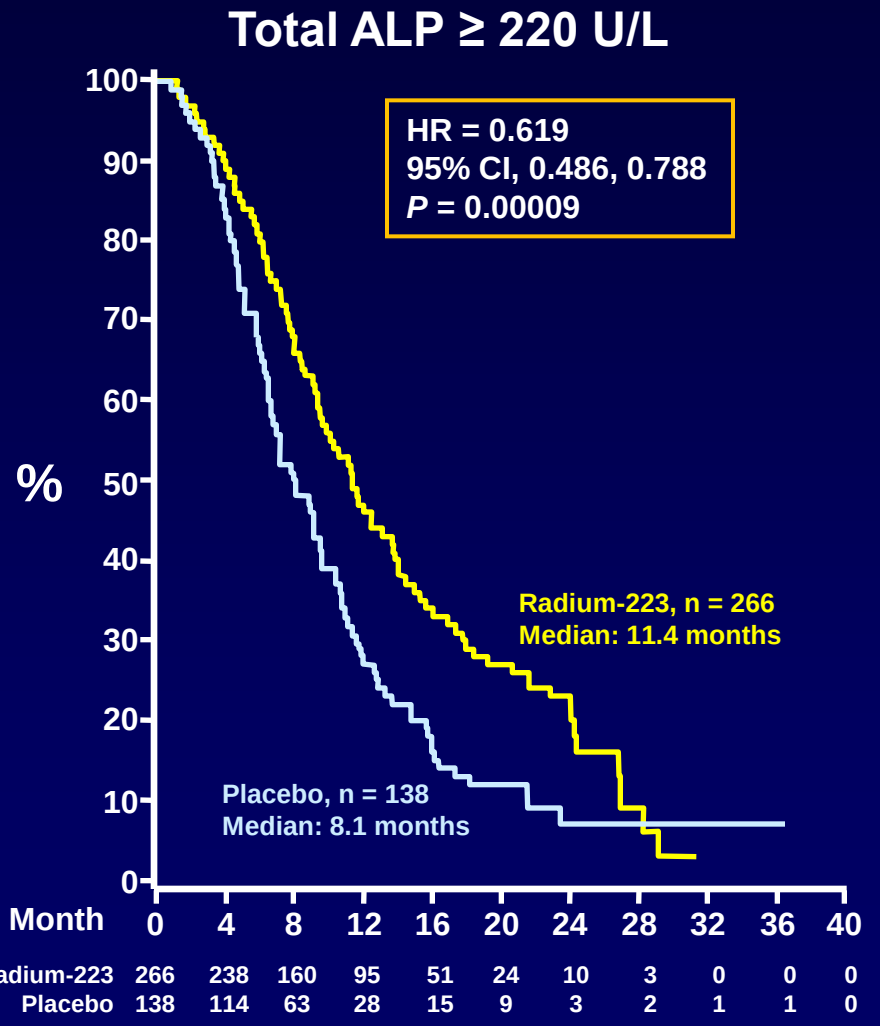
ALSYMPCA Updated Analysis OS by Stratification Variables: Prior Docetaxel Use



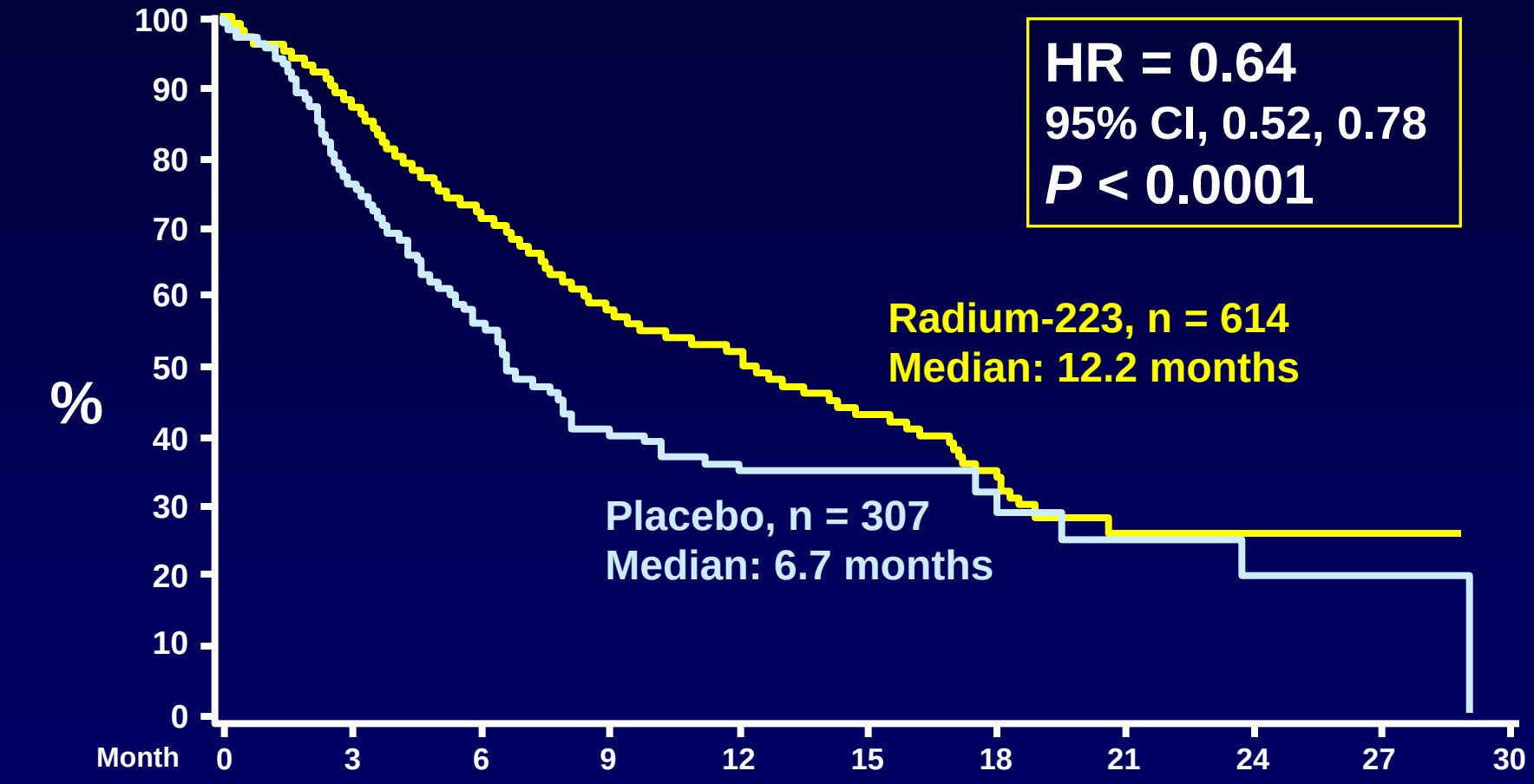


ALSYMPCA Updated Analysis OS by Stratification Variables: Baseline ALP





ALSYMPCA Updated Analysis
Time To First SRE*



Radium-223	614	487	332	193	125	62	31	8	8	1	0
Placebo	307	207	108	51	33	17	8	6	3	1	0

*Provisional data

ALSYMPCA Updated Analysis
Summary of Patients With Adverse Events: Safety Population*

Patients With Adverse Events (AEs), n (%)	Radium-223 n = 600	Placebo n = 301
All grade AEs	558 (93)	290 (96)
Grade 3 or 4 AEs	339 (57)	188 (63)
Serious AEs (SAEs)	281 (47)	181 (60)
Discontinuation due to AEs	99 (17)	62 (21)

*Safety population comprised patients who received at least 1 dose; 1 patient in the placebo group received one injection of Radium-223 (Week 0) and is included in the Radium-223 safety analysis.

ALSYMPCA Updated Analysis
AEs of Interest

	All Grades		Grades 3 or 4	
Patients with AEs n, (%)	**Radium-223 n = 600**	**Placebo n = 301**	**Radium-223 n = 600**	**Placebo n= 301**
Hematologic				
Anemia	187 (31)	92 (31)	77 (13)	39 (13)
Neutropenia	30 (5)	3 (1)	13 (2)	2 (1)
Thrombocytopenia	69 (12)	17 (6)	38 (6)	6 (2)
Non-Hematologic				
Bone pain	300 (50)	187 (62)	125 (21)	77 (26)
Diarrhea	151 (25)	45 (15)	9 (2)	5 (2)
Nausea	213 (36)	104 (35)	10 (2)	5 (2)
Vomiting	111 (19)	41 (14)	10 (2)	7 (2)
Constipation	108 (18)	64 (21)	6 (1)	4 (1)

ALYSMPCA Updated Analysis Conclusions

- **Radium-223 compared with placebo in CRPC patients with bone metastases:**
  - **Significantly prolonged median OS by 3.6 months (HR = 0.695; *P* = 0.00007)**
    - **30.5% reduction in risk of death**
  - **Significantly prolonged median time to first SRE by 5.5 months (HR = 0.64; *P* < 0.0001)**

- **Further follow-up in all randomized patients continues to show highly favorable safety profile**

Radium-223, a first-in-class alpha-emitter, may provide a new standard of care for the treatment of CRPC patients with bone metastases

Phase 3 Trial (AFFIRM) of Enzalutamide (MDV3100), an Androgen Receptor Signaling Inhibitor: Primary, Secondary, and Quality-of-Life Endpoint Results.

Johann de Bono MB ChB (Glasgow) FRCP MSc PhD
The Institute of Cancer Research and Royal Marsden, London, UK

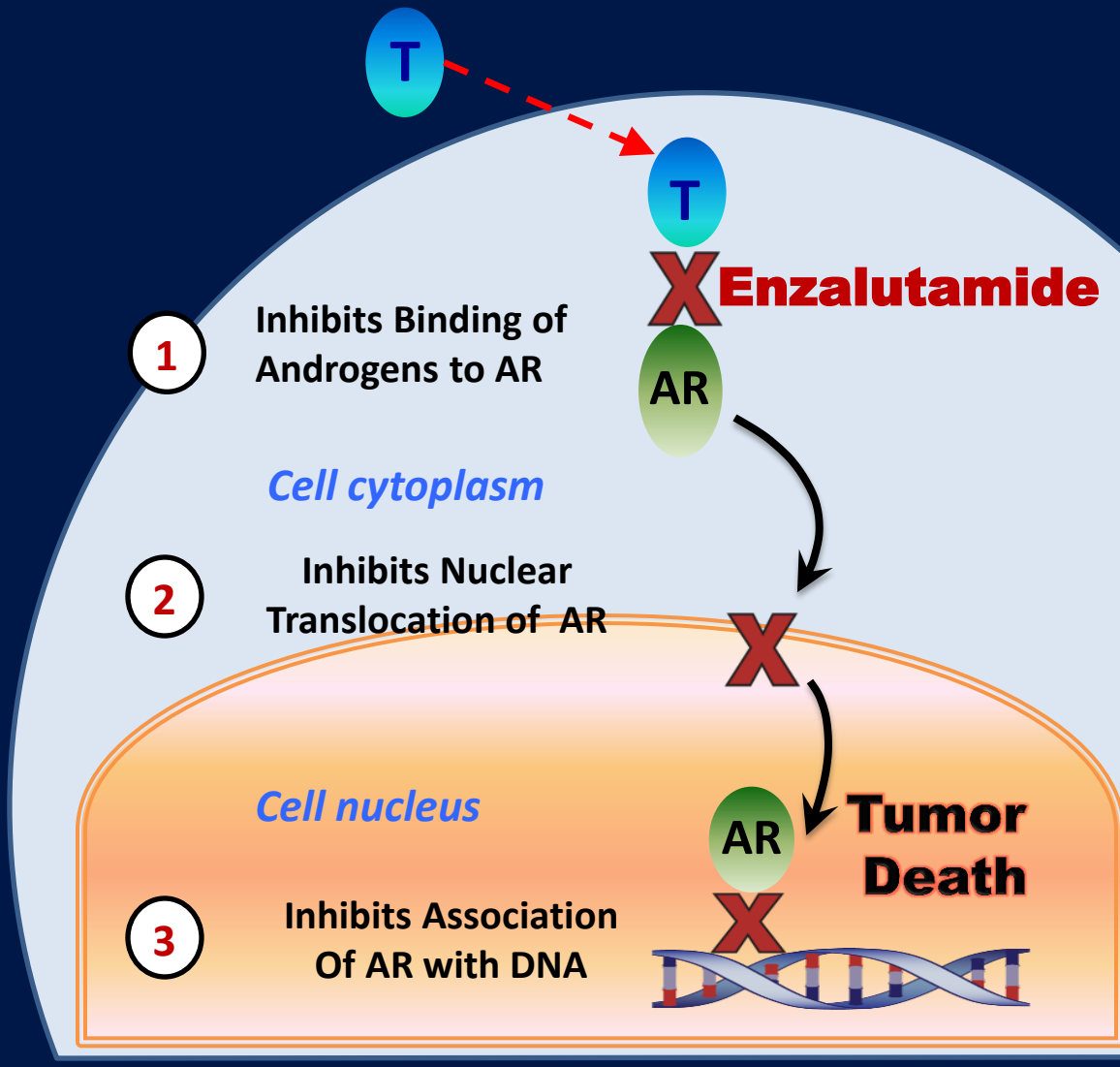
Karim Fizazi, Fred Saad, Mary-Ellen Taplin, Cora N. Sternberg, Kurt Miller, Peter Mulders, Kim N. Chi, Andrew J. Armstrong, Mohammad Hirmand, Brian Selby, Howard I. Scher, for the AFFIRM Investigators

ICR The Institute of Cancer Research 1909 2009

THE ROYAL MARSDEN

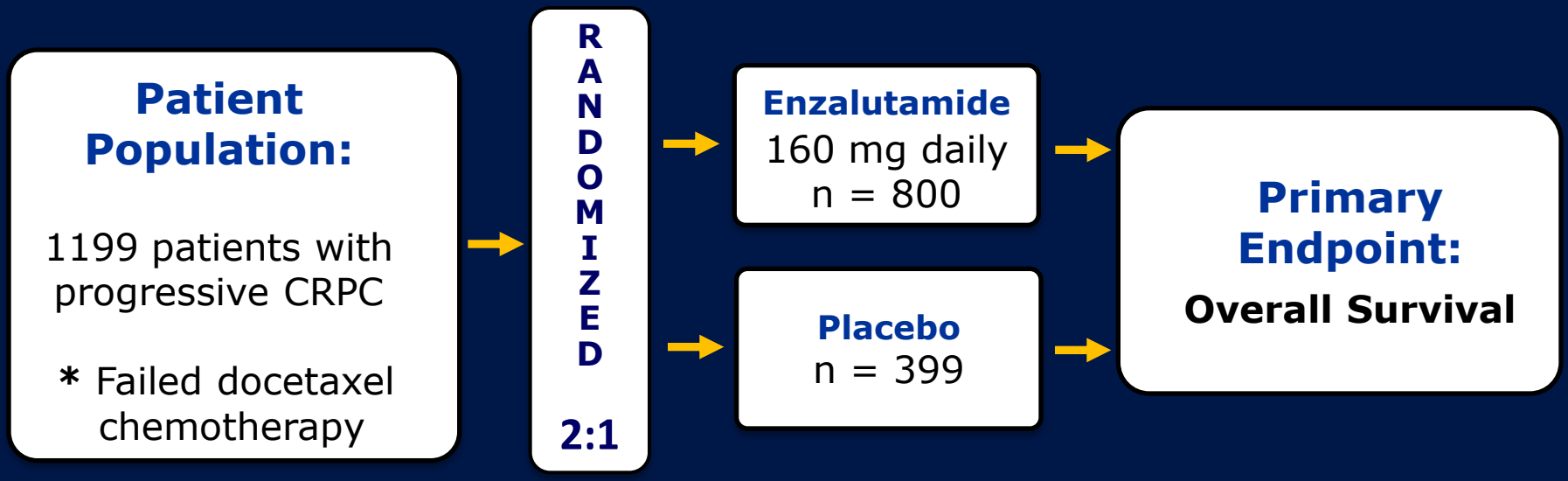
Enzalutamide (MDV3100)

- Oral investigational drug rationally designed to target AR signaling, impacting multiple steps in AR signaling pathway.
- No demonstrated agonist effects in pre-clinical models.



Tran et al. Science 2009;324:787–90.
Charles Sawyers & Michael Jung

AFFIRM Trial Design



Glucocorticoids were not required but allowed.

PCWG2 criteria used (continue therapy through minor PSA changes; confirm bone scan 'progression'; focus on benefit not response).*

Recruitment in 156 centers from 15 countries and 5 continents.
Enrollment between September 2009 and November 2010.

** Scher et al, 2008*

AFFIRM Study Design

- Primary endpoint: Overall survival
- Stratification variables:
  - ECOG Performance Status (0-1, 2)
  - Mean Brief Pain Inventory Q#3 Score (<4, ≥ 4)
- Statistical design:
  - Cumulative alpha: 0.05 (2-sided)
  - Power: 90% to detect a 24% reduction in mortality (target HR = 0.76)
  - One planned interim analysis at 520 events

Baseline Patient Demographics

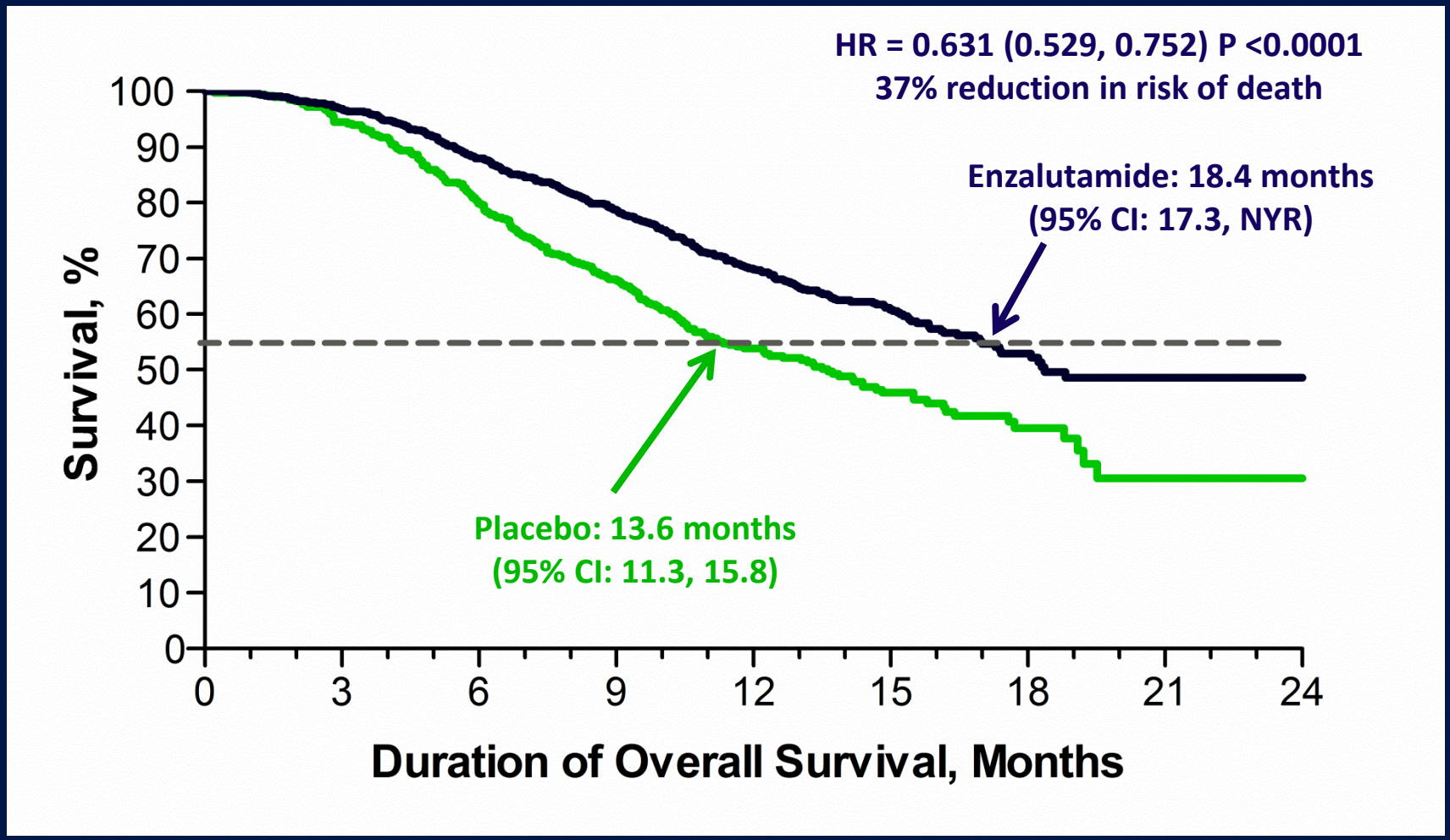
	Enzalutamide (n = 800)	**Placebo (n = 399)**
Age (median in yrs, range)	69 (41–92)	69 (49–89)
ECOG – Performance Status - 2	8.8%	8.0%
Mean Brief Pain Inventory Score ≥4 on Question 3	28.3%	28.8%
Bone Disease	91.3%	91.2%
Soft Tissue Disease	70.9%	68.9%
Visceral Liver	11.6%	8.5%
Visceral Lung	15.4%	14.8%

Prior Hormonal and Chemotherapy Treatments

	Enzalutamide (n = 800)	**Placebo (n = 399)**
Prior Lines of Hormonal Drug Therapy*		
1	8.2%	8.8%
2	42.3%	37.9%
≥ 3	**49.1%**	**53.1%**
Number of Prior Chemotherapy Regimens		
1	72.4%	74.2%
2	24.5%	23.8%
≥ 3	3.1%	2.0%
Median Number of Prior Docetaxel Cycles	8.5	8.0

**Abiraterone naïve*

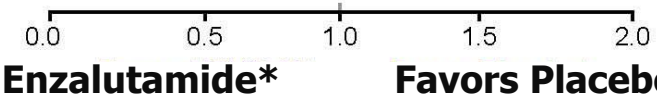
Enzalutamide Prolonged Survival, Reducing Risk of Death



Enzalutamide	800	775	701	627	400	211	72	7	0
Placebo	399	376	317	263	167	81	33	3	0

Survival Benefit Across All Subgroups

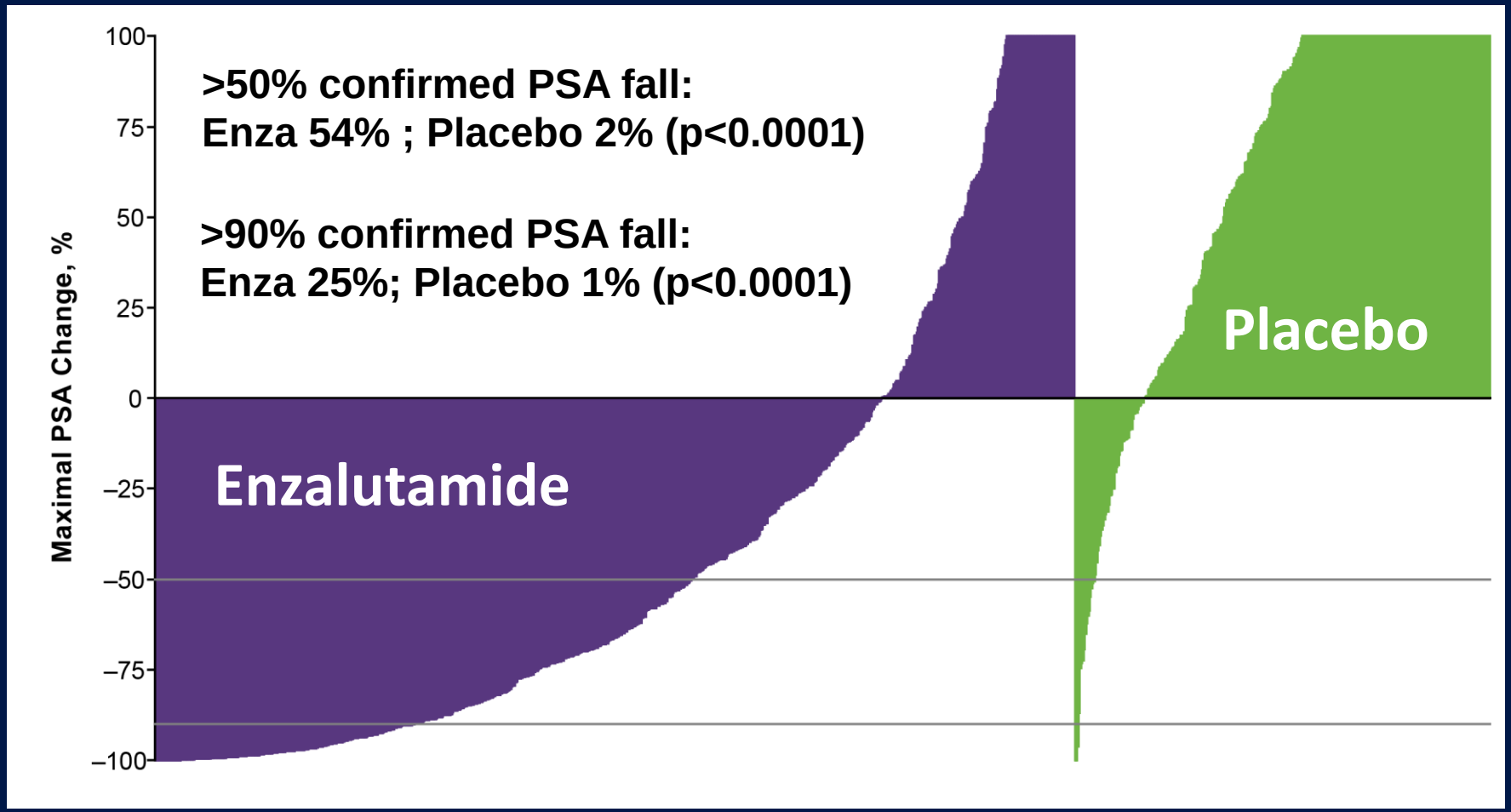
Subgroup	Hazard Ratio for Death (95% CI)	Overall Survival median (mo) Enzalutamide / Placebo
All Subjects	0.63 (0.53–0.75)	18.4 / 13.6
Age		
<65	0.63 (0.46–0.87)	— / 12.4
≥65	0.63 (0.51–0.78)	18.4 / 13.9
Baseline ECOG Performance Status Score		
0–1	0.62 (0.52–0.75)	— / 14.2
2	0.65 (0.39–1.07)	10.5 / 7.2
Baseline Mean Pain Score on BPI-SF (Question #3)		
<4	0.59 (0.47–0.74)	— / 16.2
≥4	0.71 (0.54–0.94)	12.4 / 9.1
Geographic Region		
North America	0.63 (0.47–0.83)	17.4 / 12.3
Other	0.64 (0.51–0.80)	— / 14.4
Number of Prior Chemotherapy Regimens		
1	0.59 (0.48–0.73)	— / 14.2
≥2	0.74 (0.54–1.03)	15.9 / 12.3
Type of Progression at Study Entry		
PSA Progression Only	0.62 (0.46–0.83)	— / 19.5
Radiographic Progression ± PSA Progression	0.64 (0.52–0.80)	17.3 / 13.0
Baseline value >Median		
PSA	0.62 (0.50–0.78)	15.3 / 10.3
LDH	0.61 (0.50–0.76)	12.4 / 8.5



*Dots are approximately proportional to MDV3100 population

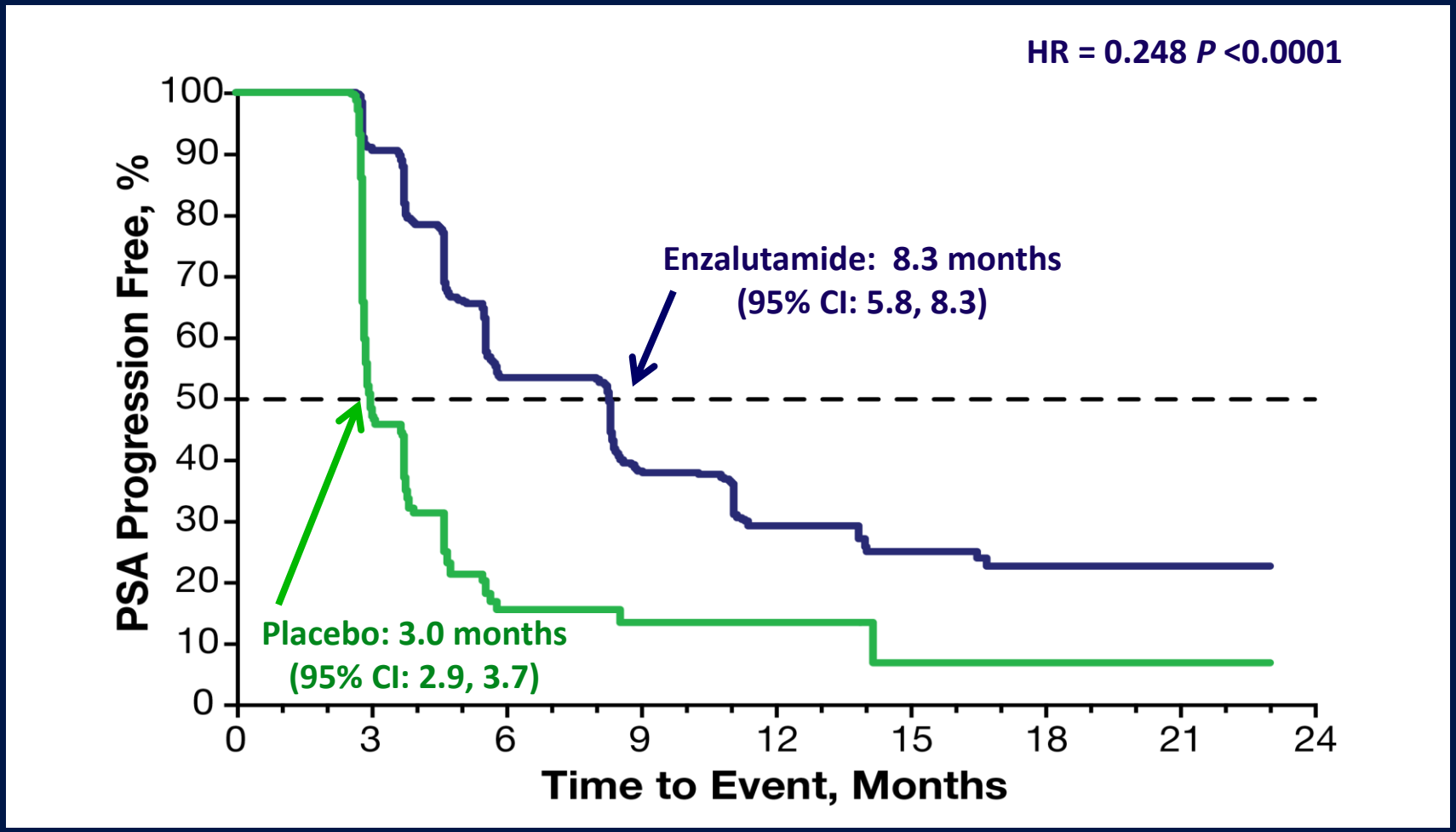
**Based on data analysis cutoff date for the planned interim analysis.*

Enzalutamide had a high PSA Response Rate



All the secondary endpoint measures favored the treatment arm

PSA Progression Free Survival



Enzalutamide	800	603	287	145	68	27	7	1	0
Placebo	399	107	12	5	2	1	0	0	0

PSA progression defined by PCWG2 criteria

Enzalutamide RECIST Response Rate

Response	Enzalutamide	Placebo	P-value
Objective Response (CR +PR)	28.9%	3.8%	< 0.0001
Best Overall Response for Study			
Complete response (CR)	3.8%	1.0%	
Partial response (PR)	25.1%	2.9%	
Stable disease	39.2%	29.3%	

Enzalutamide (n= 446); placebo (n= 208) with measurable disease
Response categories defined by RECIST 1.1

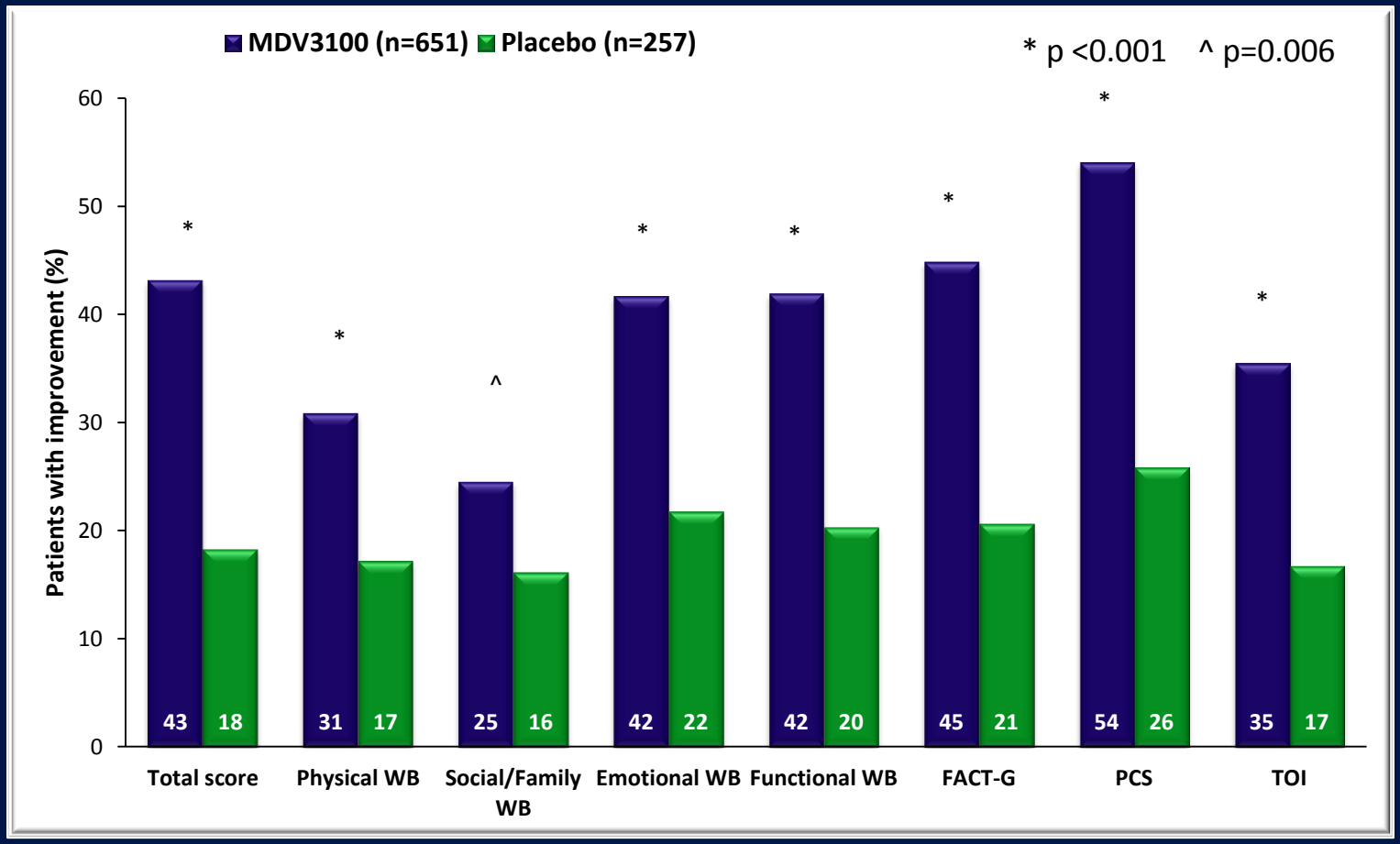
Quality-of-Life Responses by FACT-P

	Enzalutamide (n = 800)	Placebo (n = 399)
Number With Baseline and Post-baseline Assessment	651	257
Responders*	43.2%	18.3%
Difference in Response Rate with 95% Confidence Interval	24.9% (18.8%, 30.9%)	
	$p < 0.0001$	

*Response is defined as 10-point increase in the overall score (Cella, 2009).

Quality-of-Life Responses by FACT-P

Analysis includes all patients with baseline and post-baseline values.



Adverse Events

	All Grades		Grades ≥3*	
	Enzalutamide (n = 800)	**Placebo (n = 399)**	**Enzalutamide (n = 800)**	**Placebo (n = 399)**
AEs	98.1%	97.7%	45.3%	53.1%
Serious AEs	33.5%	38.6%	28.4%	33.6%
Discontinuations due to AEs	7.6%	9.8%	4.6%	7.0%
AEs leading to death	2.9%	3.5%	2.9%	3.5%

*AEs graded for severity; grades 1 and 2 milder and grades 3-5 more severe

Adverse Events of Special Interest

	All Grades		Grade ≥ 3 Events	
	Enzalutamide (n = 800)	Placebo (n = 399)	Enzalutamide (n = 800)	Placebo (n = 399)
Fatigue	33.6%	29.1%	6.3%	7.3%
Cardiac Disorders	6.1%	7.5%	0.9%	2.0%
Myocardial Infarction	0.3%	0.5%	0.3%	0.5%
LFT Abnormalities*	1.0%	1.5%	0.4%	0.8%
Seizure	0.6%	0.0%	0.6%	0.0%

*Includes terms hyperbilirubinaemia, AST increased, ALT increased, LFT abnormal, transaminases increased, and blood bilirubin increased.

Seizure Cases

CASE	1	2	3	4	5
Time on Study	**2 months**	**10 months**	**2 months**	**5 months**	**10 months**
On study drug?	Yes	Yes	Yes	Off trial drug for 26 days	Yes
Seizure type	Focal onset	Generalized	Complex partial status	Focal onset	Unknown, fall not witnessed
Recurrence	No	No	No	No	No
Potential confounding factors	Large 5 x 4 cm temporal lobe brain metastases	IV Lidocaine inadvertently given just before seizure*	Atrophy and leukoariosis on MRI brain; nil else	Multiple CNS metastases: Eye, meninges, cerebellar.	Alcohol excess; started on haloperidol 7 days prior

*40 mgs IV lidocaine (lignocaine); patient also on Na+ channel modulator: propafenone (flecainide like antidysrhythmic).

Post-Trial Anticancer Therapy

	Enzalutamide (n = 800)	Placebo (n = 399)
Patients with ≥1 post-treatment anticancer therapy	41.1%	58.4%
Most common post-protocol treatment		
Abiraterone	20.9%	24.3%
Cabazitaxel	9.8%	13.8%
Docetaxel	8.5%	14.3%
Mitoxantrone	2.6%	11.0%

* Patients living longer in second line setting

Conclusions

- Enzalutamide, a once a day oral Androgen Receptor Signaling Inhibitor, is well tolerated and prolongs survival in men with CRPC by almost 5 months.

- Enzalutamide improved secondary measures of antitumor activity including health-related quality of life, response, time to SRE and time to disease progression.

- The androgen receptor remains a valid therapeutic target for treating CRPC following chemotherapy.

Cabozantinib (XL184) in Chemotherapy-Pretreated Metastatic Castration Resistant Prostate Cancer (mCRPC): Results from a Phase 2 Non-Randomized Expansion Cohort

(Abstract #4513)

M.R. Smith, C. Sweeney, D.E. Rathkopf, H.I. Scher, C. Logothetis, D.J. George, C.S. Higano, E.Y. Yu, A.L. Harzstark, E.J. Small, A.O. Sartor, M.S. Gordon, N.J. Vogelzang, D.C. Smith, M. Hussain, J.S. de Bono, N.B. Haas, C. Scheffold, Y. Lee, P.G. Corn

Massachusetts General Hospital Cancer Center, Boston, MA; Dana-Farber Cancer Institute, Boston, MA; Sidney Kimmel Center for Prostate and Urologic Cancers, Memorial Sloan-Kettering Cancer Center, New York, NY; The University of Texas MD Anderson Cancer Center, Houston, TX; Duke University Medical Center, Durham, NC; Fred Hutchinson Cancer Research Center, Seattle, WA; University of California, San Francisco, San Francisco, CA; Tulane Cancer Center, New Orleans, LA; Pinnacle Oncology Hematology, Scottsdale, AZ; US Oncology Research/ Comprehensive Cancer Centers NV, Las Vegas, NV; University of Michigan, Ann Arbor, MI; Royal Marsden Hospital & Institute of Cancer Research, Sutton, United Kingdom; Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA; Exelixis, South San Francisco, CA

PRESENTED AT ASCO Annual '12 Meeting

Baseline Characteristics (100 mg, N=93)

Median age (range)	67 (46 – 85)
ECOG status, %	
0	34
1	65
2	1
Sites of disease, %	
Bone	100
Visceral	31
Measurable disease, %	46
Pain score ≥ 4, %	44
Pain ≥ 4 & narcotics, %	42
Fatigue any grade, %	52
≥ 2 prior regimens for CRPC, %	73

Prior therapies, %	
Docetaxel	100
Abiraterone/ MDV3100	35
Cabazitaxel	24
Alpharadin	1
Prior bone agents, %	
Bisphosphonate	57
Denosumab	14
PD from last taxane dose, %	
Less than 1 month	28
1-6 months	72
Median values	
PSA, ng/mL (range)	194 (0.2 – 2990)
CTC count (range)	49 (0 – 1659)

Bone Scan Response By Independent Radiology Review

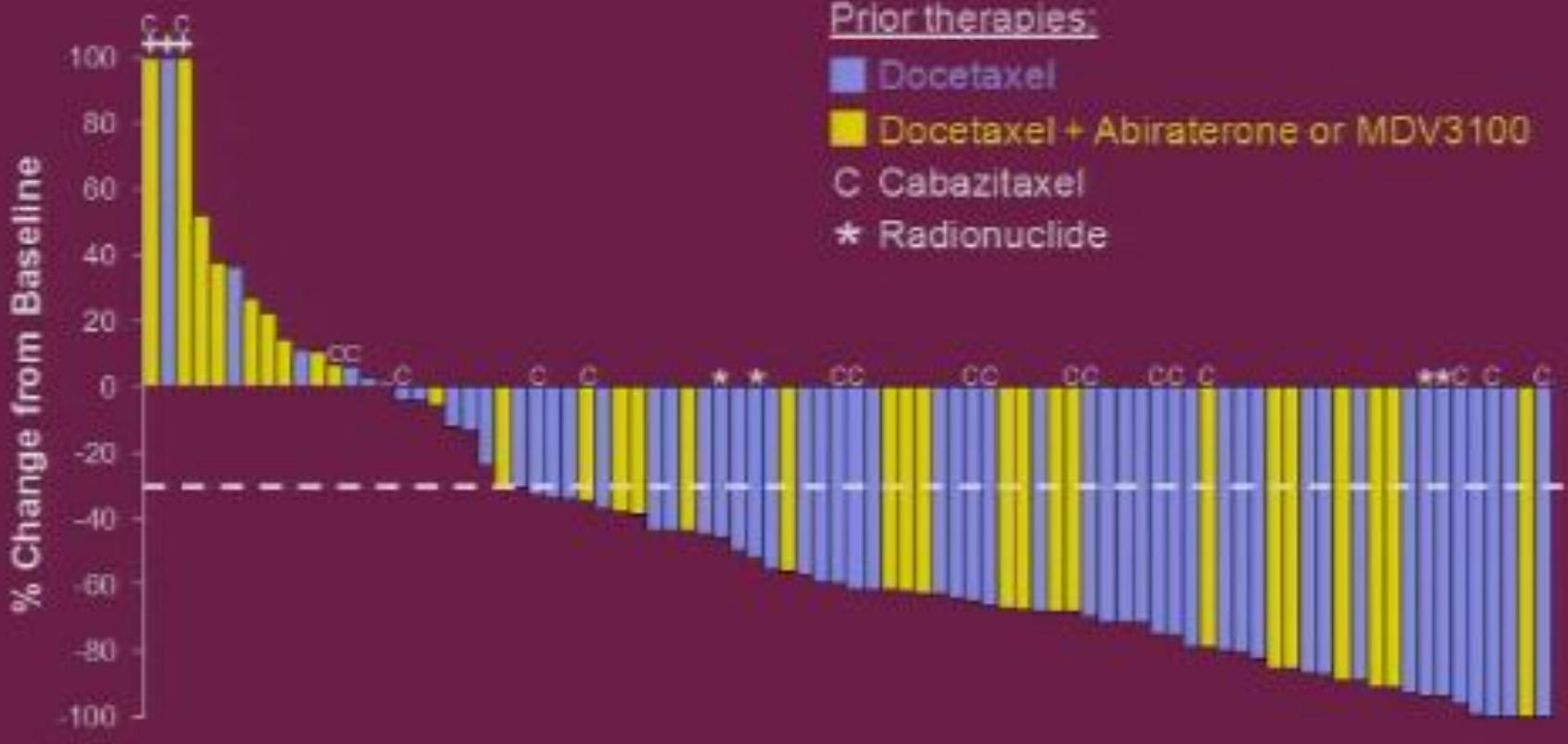
Computer-assisted evaluation of BSLA	
Bone scan evaluable (N=93)[a]	n (%)
Bone scan response	62 (67)
Complete (100% reduction of BSLA)	4 (4)
Partial (≥30% reduction of BSLA)	58 (62)
Stable	15 (16)
Progressive disease	7 (8)
Median duration of response, months (range)	5.4 (5.0 – 6.9)

BSLA, bone scan lesion area

[a] Bone metastases at baseline and ≥1 post-baseline scan available for 84 patients

Change in Bone Scan Lesion Area

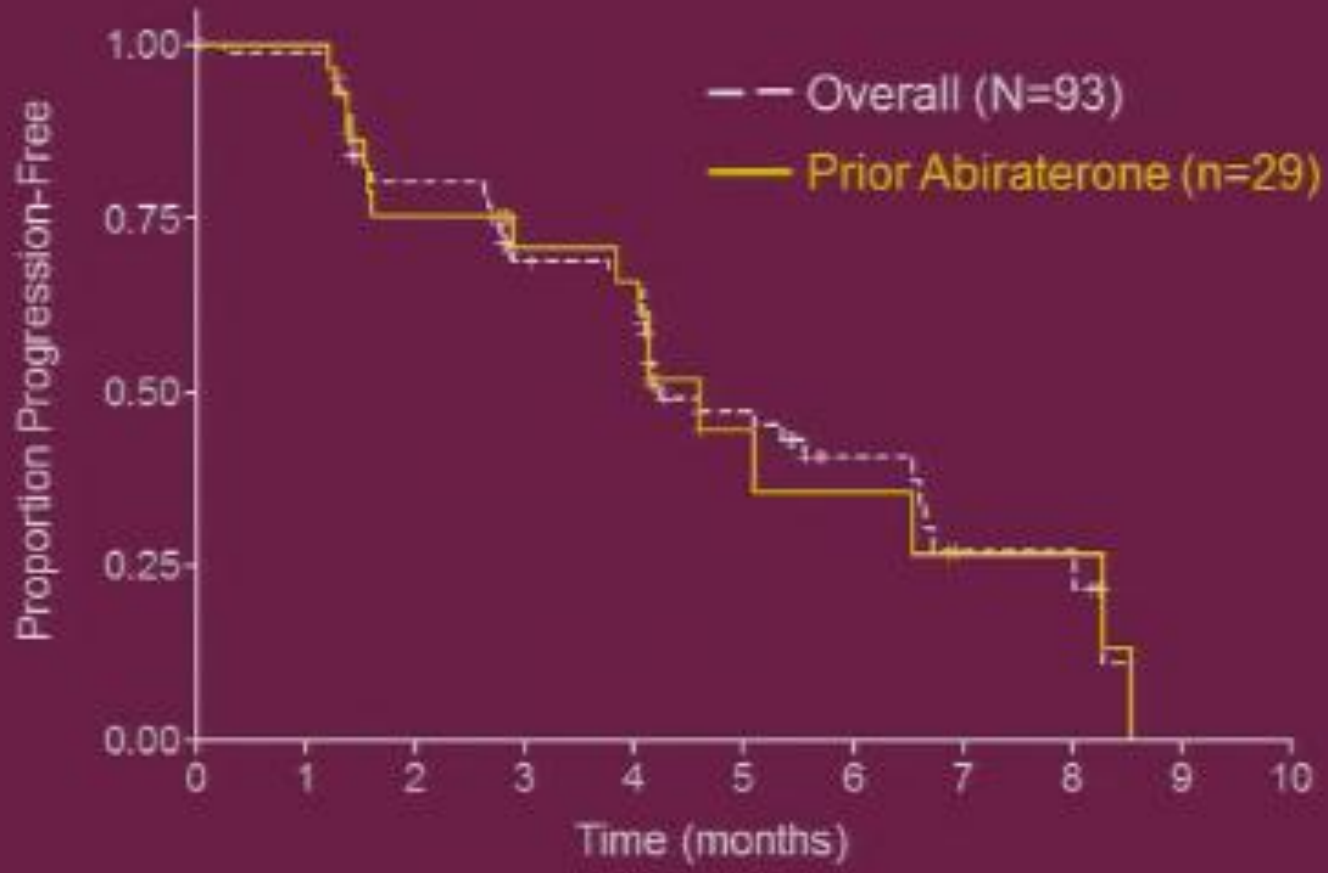
Patients with ≥1 post-baseline bone scan (n=84)



Median change in bone scan lesion area: 60% reduction

+: >100% increase

Radiographic Progression-Free Survival



	Median PFS (months)	95%CI	# Events
Overall	4.2	(4.1, 6.6)	50
Prior Abiraterone	4.6	(2.9, 8.3)	17

Effect of neoadjuvant abiraterone acetate (AA) plus leuprolide acetate (LHRHa) on PSA, pathological complete response (pCR), and near pCR in localized high-risk prostate cancer (LHRPC): Results of a randomized phase II study.

PASCO 4521 Taplin ME et al.

Baseline	12 wks AA/ 24 wks LHRHa n= 28	24 wks AA/ 24 wks LHRHa n=30
Gleason: 7/8/9/10	8/10/10/0	9/7/11/3
PSA (median)	10.6	6.8
PSA: < 10/10-20/≥ 20	12/9/7	20/6/4
Elevated PSA velocity	6	3
Stage T3	8	6
Results	n=27	n=29
PSA: wk 4/8/12/16/20/24	4.34/1.35/1.06/0.20/0.09/0.06	0.65/0.17/0.10/0.09/0.06/0.05
12 wk nadir PSA ≤ 0.2	1/27 (4%)	26/29 (90%) p<0.0001
24 wk nadir PSA ≤ 0.2	23/27 (85%)	25/29 (86%) p=0.9131
pCR	1/27 (4%)	3/29 (10%) p=0.3349
Near pCR (tumor ≤ 5mm)	3/27 (11%)	7/29 (24%) p=0.2034
Total pCR/near pCR	4/27 (15%)	10/29 (34%) p=0.0894
pT3	16/27	14/29
Positive nodes	3/27 (11%)	7/29 (24%)
Positive margins	5/27 (19%)	5/29 (17%)

Effect of denosumab on prolonging bone-metastasis free survival (BMFS) in men with nonmetastatic castrate-resistant prostate cancer (CRPC) presenting with aggressive PSA kinetics.

PASCO 4510, Saad F et al.

Population	Sample size	BMFS median (months)	BMFS treatment difference (months)	Hazard ratio	95% Confidence interval	p value
All patients	D: 716 P: 716	D: 29.5 P: 25.2	4.2	0.85	0.73 - 0.98	0.028
PSADT ≤6 months	D: 419 P: 427	D: 25.9 P: 18.7	7.2	0.77	0.64 - 0.93	0.0064

D=denosumab; P=placebo

Böbrek Kanseri

Abstract No. 4501

Tivozanib versus sorafenib as initial targeted therapy for patients with advanced renal cell carcinoma: Results from a Phase III randomized, open-label, multicenter trial

R. Motzer, D. Nosov, T. Eisen, I. Bondarenko, V. Lesovoy,
O. Lipatov, P. Tomczak, O. Lyulko, A. Alyasova, M. Harza,
M. Kogan, B.Y. Alexeev, C.N. Sternberg, C. Szczylik, J. Zhang,
A. Strahs, B. Esteves, W. Slichenmyer, A. Berkenblit,
T.E. Hutson, and the TIVO-1 Study Group

Background

- Tivozanib is a potent, selective inhibitor of VEGFRs 1, 2, and 3 with a long half-life that is designed to optimize blockade while minimizing off-target toxicities[1,2]
- Favorable pharmacokinetic profile:
  - $t_{1/2}$ of 3.7–4.7 days allows once-daily dosing (1.5 mg) with consistent serum concentration[2,3]
  - No interaction with CYP3A4 inhibitors[4]
- Phase II trial conducted in 272 advanced RCC patients[5]
  - Median PFS was 11.7 months
  - Hypertension was the predominant toxicity
  - Low incidence of 'off-target' AEs

AEs, adverse events; CYP3A4, cytochrome P450 3A4; PFS, progression-free survival; RCC, renal cell carcinoma; VEGFR, vascular endothelial growth factor receptor.

1. Nakamura K *et al*. *Cancer Res* 2006;66:9134–9142. 2. Eskens FA *et al*. *Clin Cancer Res* 2011;17:7156–7163. 3. Cotreau M *et al.* ASCO-NCI-EORTC; San Francisco, CA; November 12–16, 2011. 4. Data on file. 5. Nosov D *et al*. *J Clin Oncol* 2012;30:1678–1685.

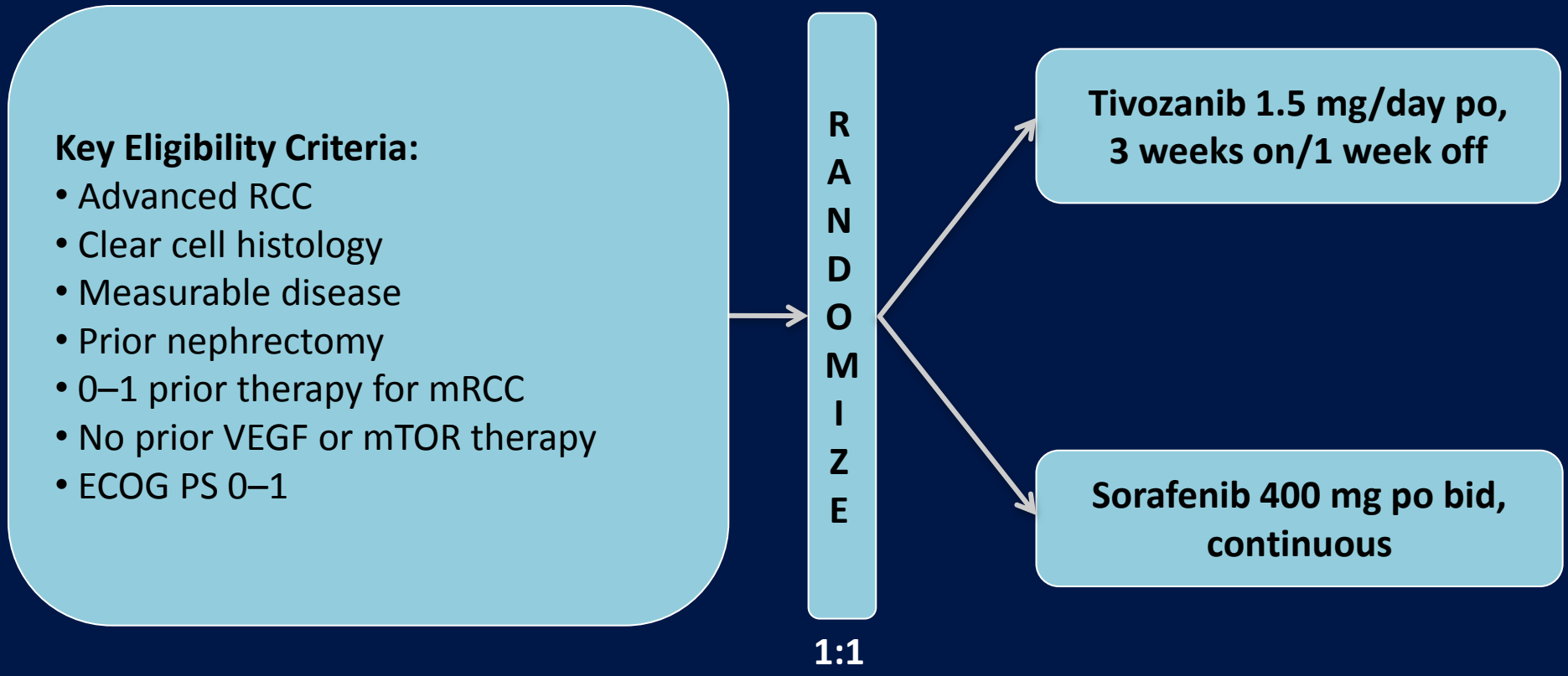
Study objectives

- Primary objective:
  - To demonstrate PFS superiority in patients with mRCC receiving tivozanib vs sorafenib as a first-line targeted therapy

- Secondary objectives:
  - Objective response rate
  - Safety
  - Overall survival[a]
  - Patient-reported outcomes[a]
  - Pharmacokinetics[a]

[a]Data not reported.

TIVO-1: Phase III superiority study of tivozanib vs sorafenib as first-line targeted therapy for mRCC



Stratification Factors:
- Geographic region
- Prior treatments for mRCC
- # of metastatic lesions

Baseline characteristics

Characteristic	Tivozanib	Sorafenib
No. of patients	260	257
Median age (range)	59 (23–83)	59 (23–85)
Gender, male, %	71	74
ECOG score,[a] %		
0	45	54
1	55	46
Number of organs involved, %		
1	29	34
≥2	71	66
Sites of metastases, %		
Lung	82	79
Liver	26	19
Bone	24	20

[a]Imbalance between arms. $P<0.05$ by Fisher exact test.

Baseline characteristics

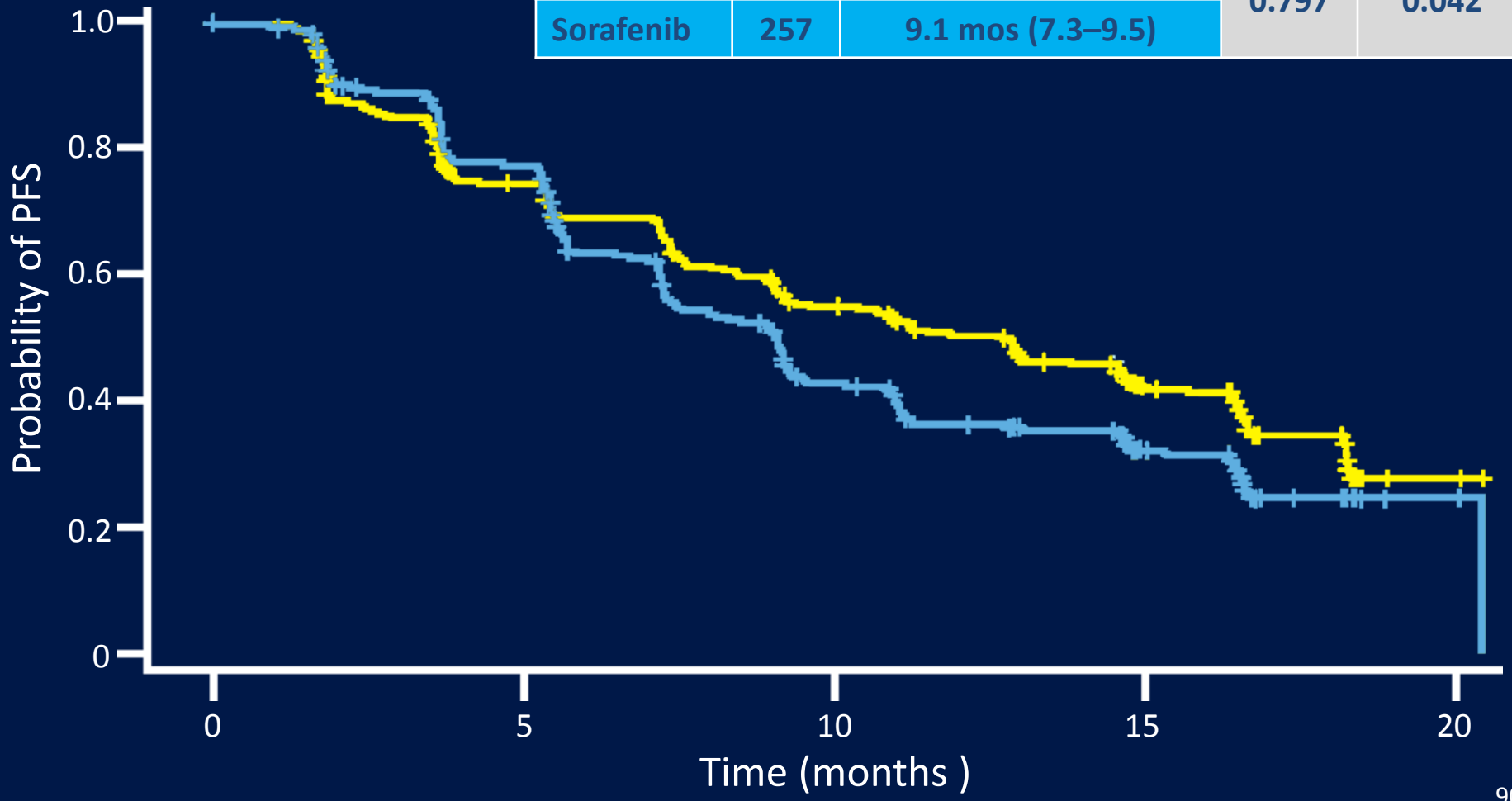
Characteristic	Tivozanib (N=260)	Sorafenib (N=257)
MSKCC prognostic group,[1] %		
Favorable	27	34
Intermediate	67	62
Poor	7	4
Prior systemic therapy for metastatic RCC, %		
0	70	70
1	30	30

MSKCC, Memorial Sloan-Kettering Cancer Center.

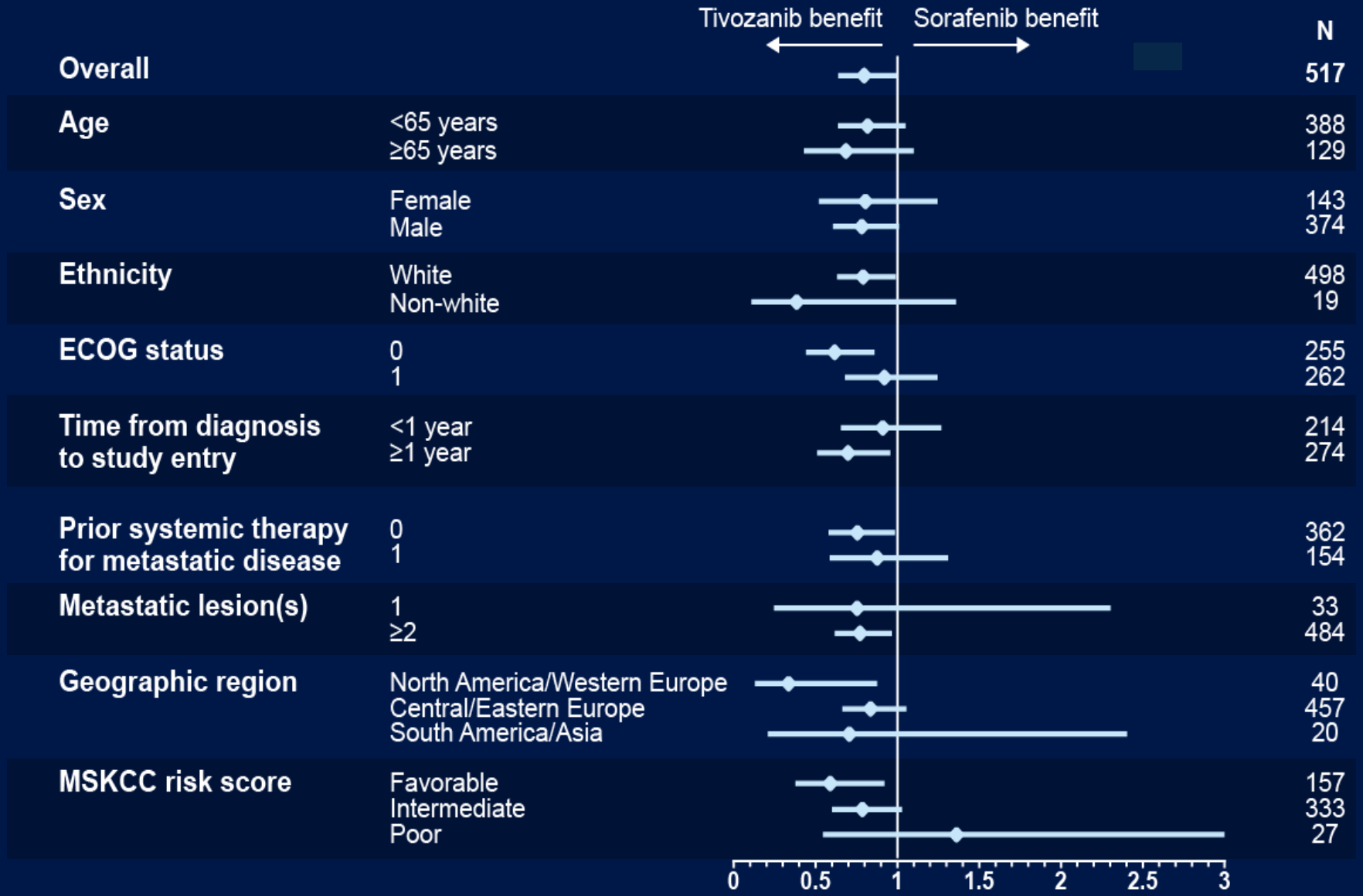
1. Motzer RJ *et al. J Clin Oncol* 1999;17:2530–2540.

Primary endpoint: Progression-free survival (independent review)

	N	Median PFS (95% CI)	HR	*P* value
Tivozanib	260	11.9 mos (9.3–14.7)	0.797	0.042
Sorafenib	257	9.1 mos (7.3–9.5)		

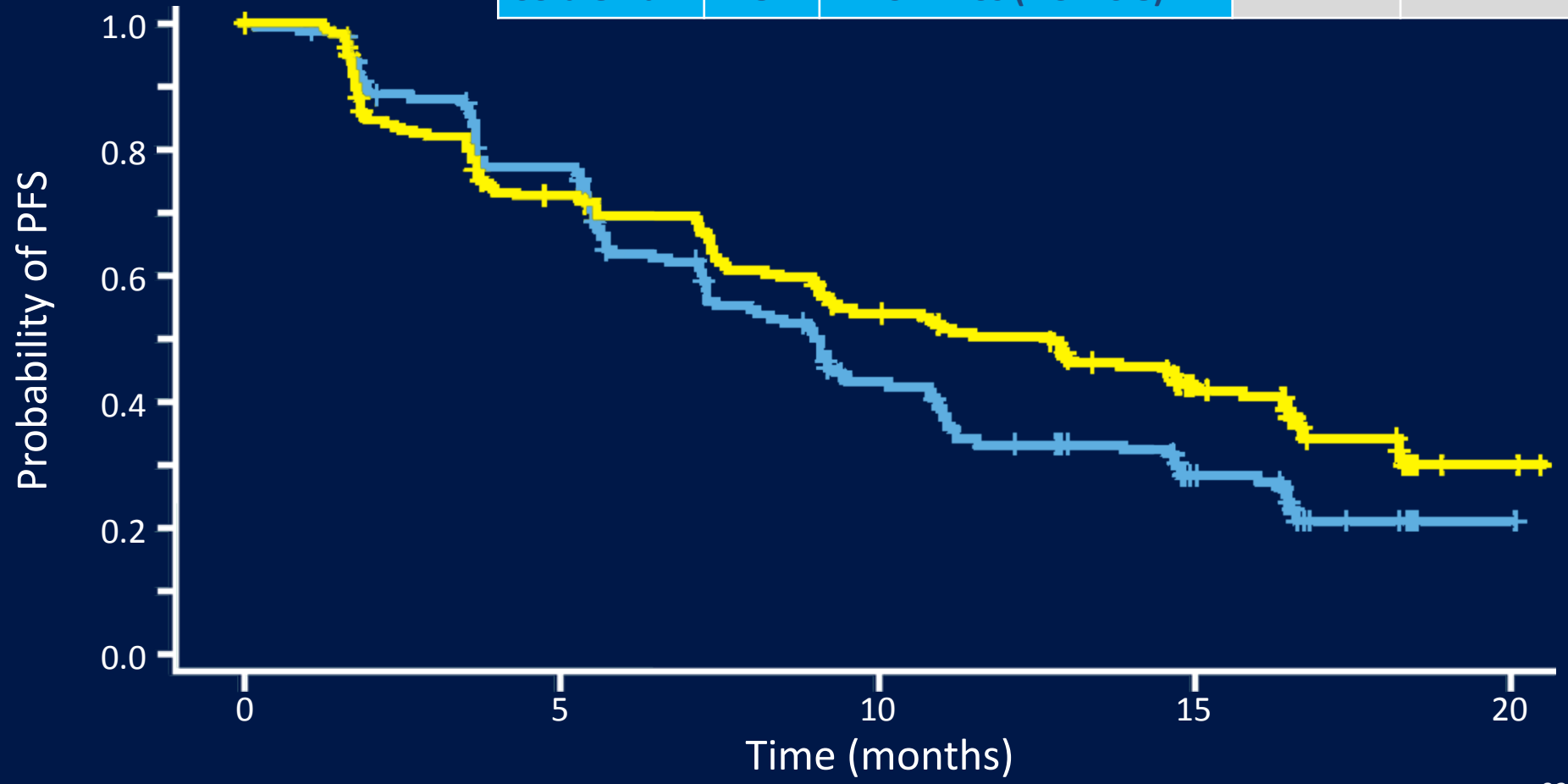


Hazard ratios for PFS by prognostic factors and baseline characteristics



Progression-free survival: Treatment-naïve for metastatic RCC (independent review)

	N	Median PFS (95% CI)	HR	*P* value
Tivozanib	181	12.7 mos (9.1–15.0)	0.756	0.037
Sorafenib	181	9.1 mos (7.3–10.8)		



Best response by RECIST 1.0 (independent review)

	Tivozanib (N=260)	Sorafenib (N=257)
Best overall response, %		
Complete response	1	1
Partial response	32	23
Stable disease	52	65
Progressive disease	13	7
Not evaluable	2	4
Objective response rate, %	**33**	**23**
95% CI	27–39	18–29
P value	0.014	

Dose adjustments due to AEs

	Tivozanib (n=259[a])	Sorafenib (n=257)
Dose interruptions,[b] %	18	35
Dose reductions,[b] %	12	43
Discontinuations,[c] %	4	5

[a]One patient was randomized but never received treatment.
[b]Difference between tivozanib and sorafenib, *P*<0.001 by Fisher exact test.
[c]Due to treatment-related adverse events.

Selected laboratory abnormalities

	Tivozanib (N=259, %)		Sorafenib (N=257, %)	
	All Grade	Grade 3 (4)	All Grade	Grade 3 (4)
Chemistries				
ALT increase	26	<1	34	3 (<1)
AST increase	34	2	49	3 (<1)
Amylase increase	40	4 (<1)	52	6 (<1)
Lipase increase	45	8 (2)	62	20 (4)
Hypophosphatemia	27	4	70	25
Proteinuria	68	3	72	2
Hematology				
Low hemoglobin	36	2 (2)	46	3 (<1)
Neutropenia	10	2 (<1)	9	1 (<1)
Thrombocytopenia	17	0 (<1)	11	0

- Patients with normal TSH levels that increased to >10 mIU/L after treatment: tivozanib, 24%; sorafenib, 6%
  - Few of these patients had low T3 (tivozanib 3%; sorafenib 2%) or low free T4 (tivozanib,2%; sorafenib, <1%) on or after date elevations in TSH were observed

Treatment-emergent AEs[a]

	Tivozanib (N=259, %)		Sorafenib (N=257, %)	
	All Grade	Grade 3 (4)	All Grade	Grade 3 (4)
Hypertension	44	24 (2)	34	17 (<1)
Diarrhea	22	2	32	6
Dysphonia	21	0	5	0
Fatigue	18	5	16	4
Weight decreased	17	<1	20	3
Asthenia	15	4 (<1)	16	3
Palmar-plantar erythrodysesthesia	13	2	54	17
Back pain	14	3	7	2
Nausea	11	<1	8	<1
Dyspnea	10	2[b]	8	2
Decreased appetite	10	<1	9	<1
Alopecia	2	0	21	0

[a]Occurring in ≥10% of patients. [b]One grade 5 dyspnea event was reported.

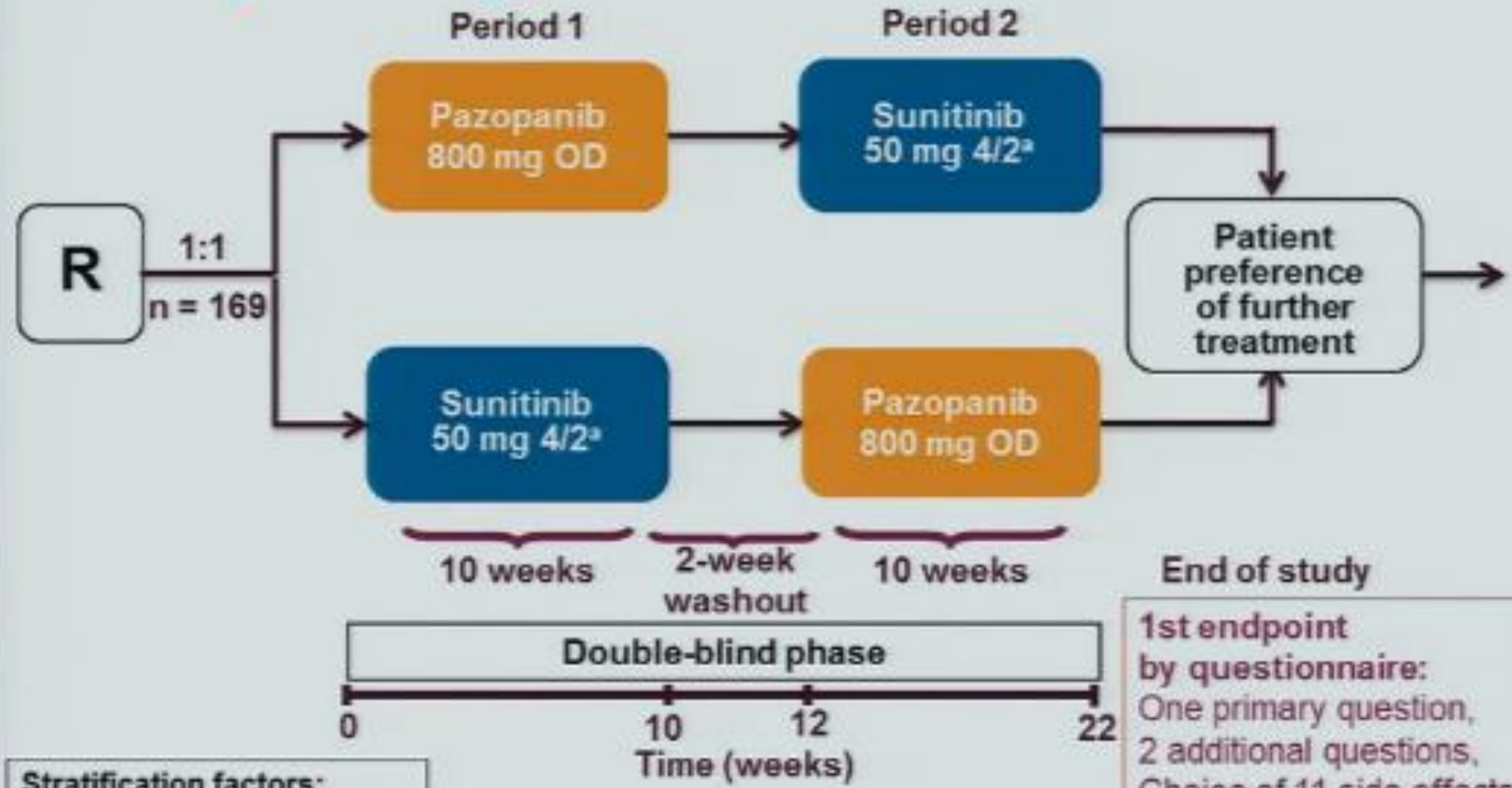
One death in the tivozanib group (hypertension, possible overdose) and one death in the sorafenib group (cerebrovascular accident) were considered drug-related by the investigator.

Conclusions

- Tivozanib sorafenibe kıyasla mRCC'de
  - daha az yan etki
  - yanıt anlamında daha etkin ve
  - daha uzun PFS sağladı
- Tivozanib mRCC'de ilk sıra tercih edilebilecek ilaçtır

PISCES Study, Escudier B., et al, ASCO 2012 abstr#4502

Study Design



End of study

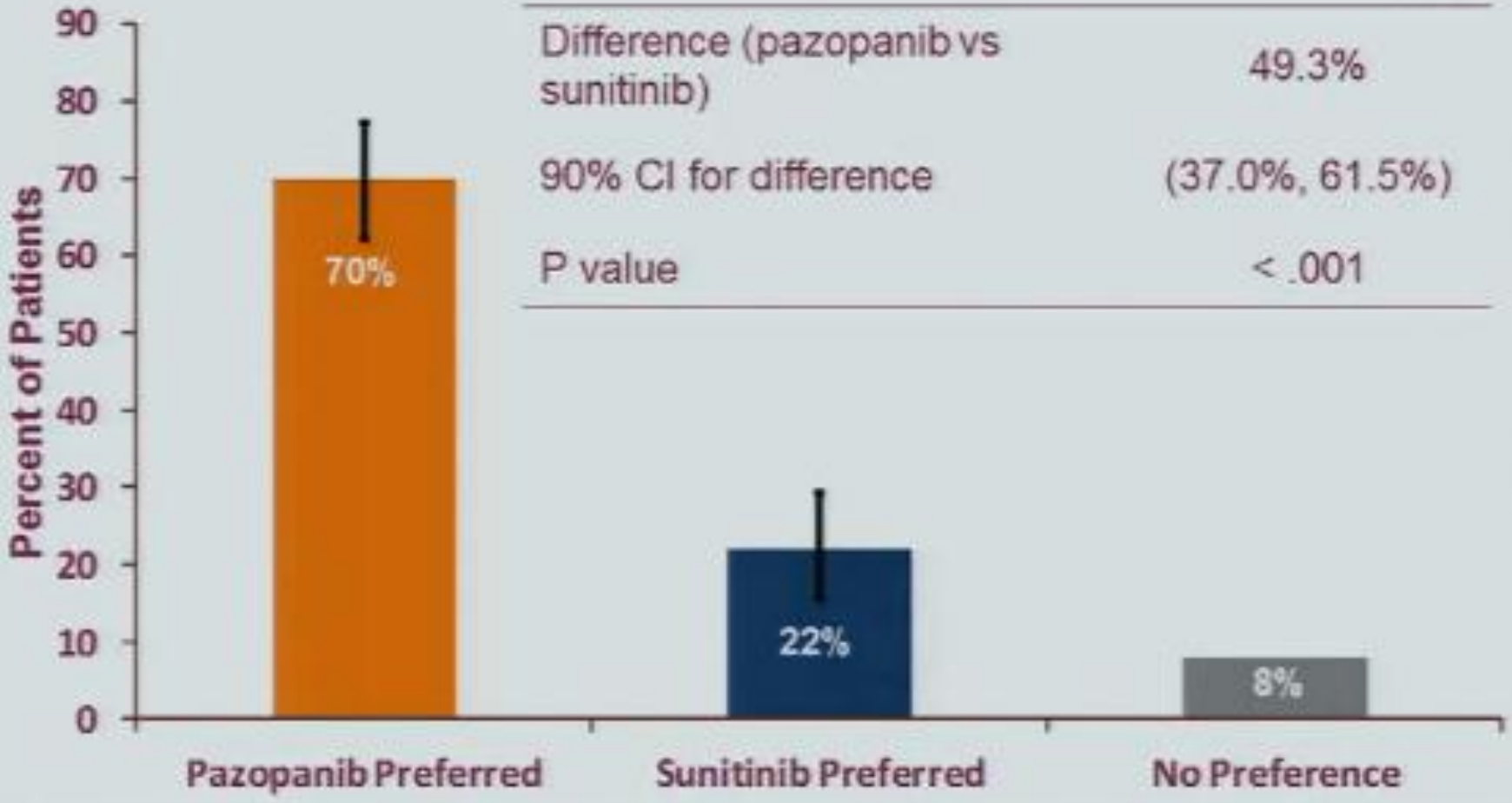
1st endpoint by questionnaire:
One primary question,
2 additional questions,
Choice of 11 side effects

Stratification factors:
- ECOG PS (0 vs 1)
- Metastatic sites (0/1 vs ≥ 2)

[a] 4 weeks on treatment → 2 weeks matching placebo → 4 weeks on treatment
ECOG PS, Eastern Cooperative Oncology Group performance status

Primary Endpoint: Patient Preference

Population: Primary Analysis Population



Difference (pazopanib vs sunitinib)	49.3%
90% CI for difference	(37.0%, 61.5%)
P value	< .001

Abbreviation: CI, confidence interval.

Novel targets, novel agents (early phase trials) overcoming resistance?

Agent	Main Targets	Med. Prior Tx	ORR	PFS (mo, 95% CI)	Comments
Cabozantinib (n=25)	VEGFR2 c-Met	2	28%	14.7 mo (7.3,--)	• VEGF TT refractory • Bone metastasis!
BMS-936558* (n=16 RCC)	PD-1*	2	31%	56% at 6mo	• Primary TT refractory

- Durable responses in heavily pre-treated patients

*PD-1 inhibitor: programmed death-1 is an inhibitory receptor expressed on T cells after activation

Mesane Kanseri

Gemsitabin/siplatin ± setuksimab ileri evre üretelyal karsinom: Faz II randomize

PASCO 4506 Grivas P et al

88 hasta

	CG	CG + S
RR %	57 (37-76)	62.5 (49-75)
PFS ay	8.5 (6-10)	7.6 (6-10)
OS ay	14	14

Thiazolidinediones and the risk of bladder cancer: A cohort study

R Mamtani, K Haynes, WB Bilker, DJ Vaughn,
BL Strom, K Glanz, JD Lewis

PRESENTED AT: ASCO Annual '12 Meeting

Thiazolidenoidler

- İnsülin duyarlaştırıcı (nükleer reseptör proteini PPAR'ye bağlanır

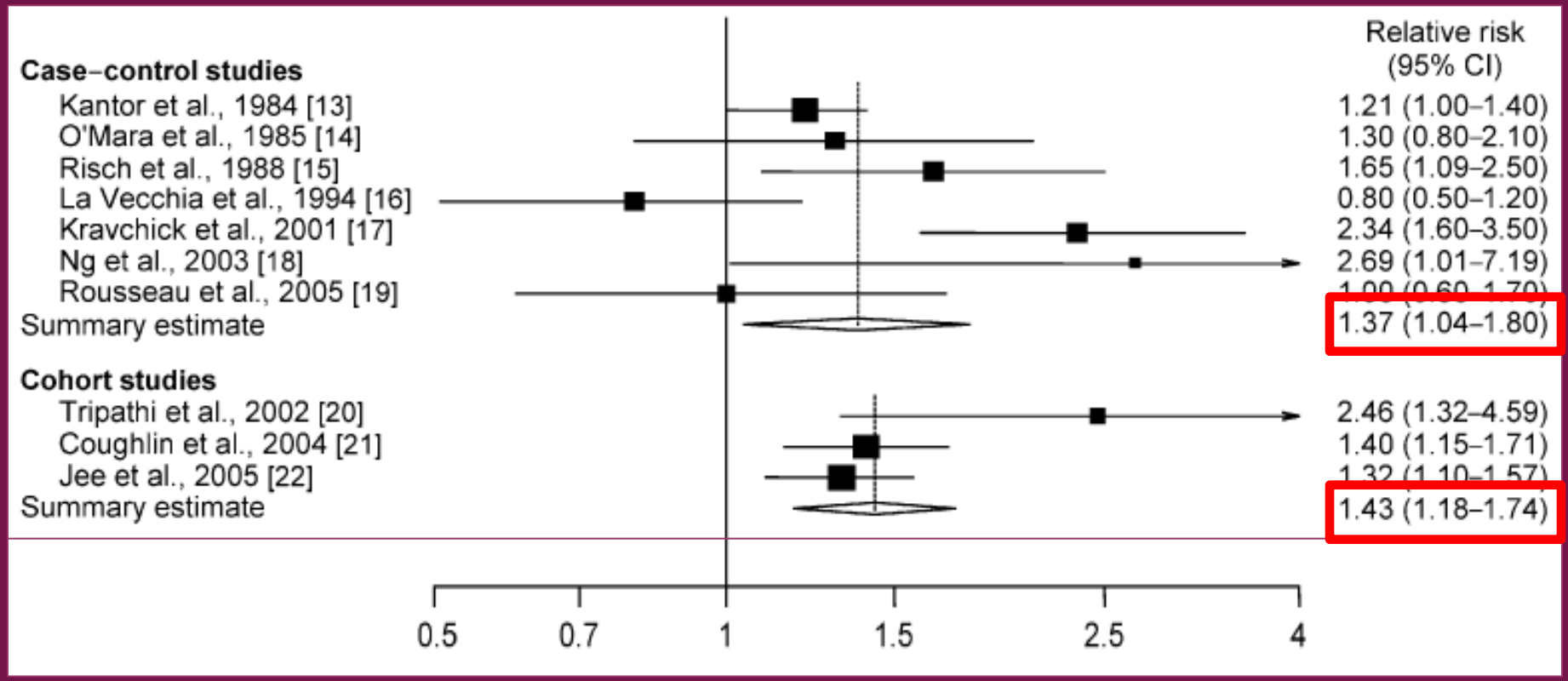
Bilinen Yan Etkiler

- İKH
- SVA
- Kemik kırıkları
- Makula ödemi
- Hepatotoksisite

Study objective

- To investigate the risk of bladder cancer associated with thiazolidinedione (TZD) therapy in patients with type II diabetes

Diabetes and risk of bladder cancer



Larsson SC Diabetologia 2006

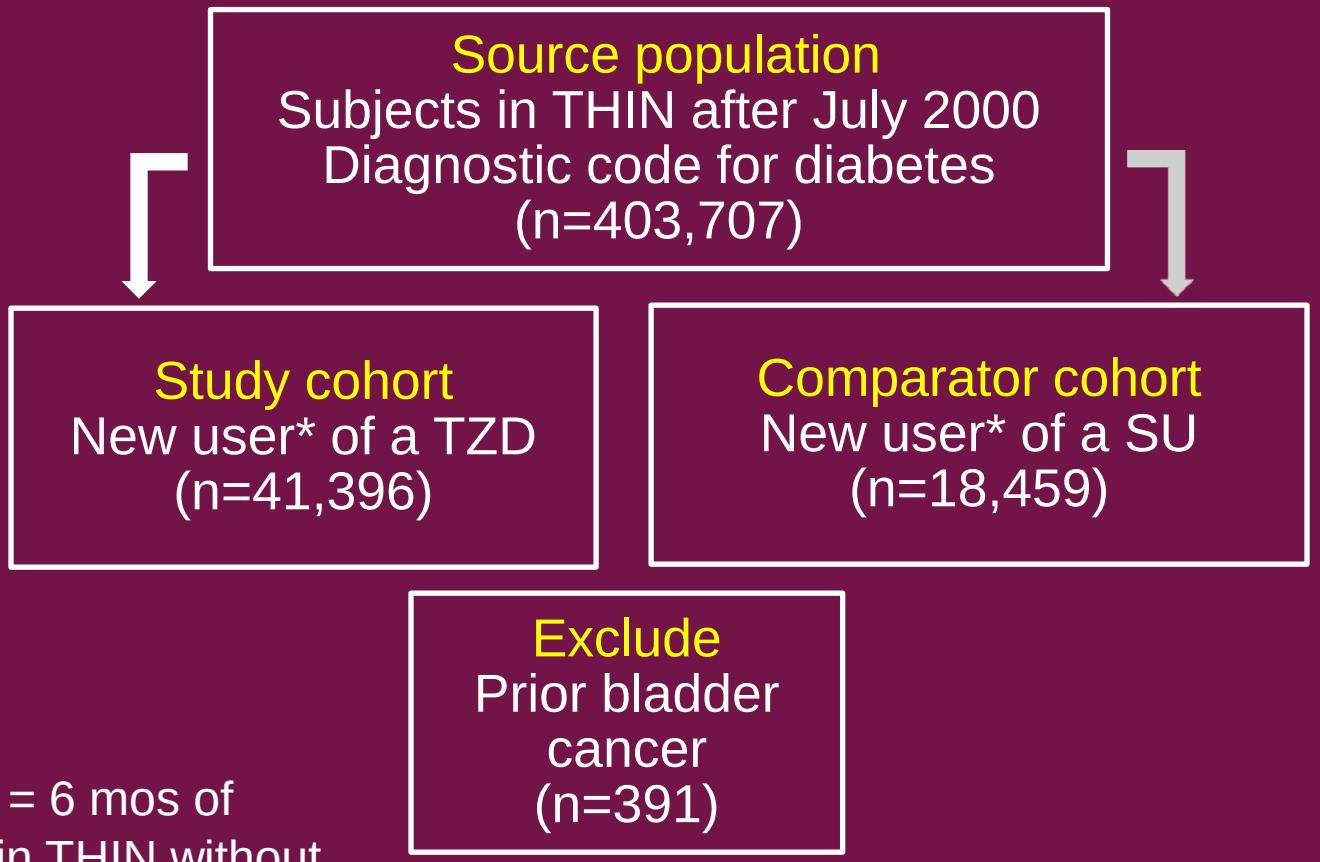
Unanswered questions

- Bladder cancer risk of TZDs relative to the common alternative therapy (sulfonylureas)?
- Unique to pioglitazone or TZD class effect?

Specific Aim

- To compare bladder cancer risk over time with use of TZDs relative to sulfonylureas (SUs), and between pioglitazone (PIO) and rosiglitazone (ROSI)

Population



* New user = 6 mos of enrollment in THIN without prior Rx for either drug

Outcome

- Incident diagnosis with bladder cancer occurring after the index date

Potential confounders

- Other diabetes medications
- Risk factors for bladder cancer
  - age, sex, smoking, recurrent urinary infection
- Variables associated with the likelihood of being prescribed a TZD
  - diabetes duration, hemoglobin A1C, congestive heart failure, renal impairment

Cohort demographics

	New TZD	New SU
N	18,459	41,396
Age, median (IQR), y	60 [51-69]	65 [55-74]
Sex (% M)	10,502 (56·9)	23,228 (56·1)
Smoking (% Ever)	12,220 (66·2)	27,163 (65·6)
A1C level, median, %	8·5 [7·7-9·7]	8·4 [7·6-10·1]
DM duration, median, y	3·8 [1·8-6·6]	2·3 [0·4-5·3]
Other diabetes drugs (%)		
Metformin	16,410 (88·9)	26,030 (62·9)
Insulin	708 (3·8)	1,060 (2·6)
Other	801 (4·3)	803 (1·9)

Cohort demographics

	New TZD	New SU
Congestive heart failure (%)	321 (1·7)	1,782 (4·3)
Renal impairment (%)	1,174 (6·4)	3,639 (8·8)
Recurrent urinary infection (%)	1,135 (6·1)	2,663 (6·4)
Myocardial infarction (%)	1,028 (5·6)	3,316 (8·0)
BMI, median, kg/m2	31·4 [27·9-35·6]	29·2 [25·9-33·4]
Time since initiation, median, y	3·7 [1·9-5·3]	2·4 [1·1-4·7]
Duration of therapy, median, y	2·1 [0·8-4·1]	2·1 [0·8-4·4]

HRs of bladder cancer
TZD vs SU

	IR*	HR, unadjusted	HR, adjusted†
New use of **SU**	107·2 [89·9-126·7]	1·00 (referent)	1·00 (referent)
New use of **TZD**	87·1 [66·5-112·1]	0·81 [0·60-1·10]	0·93 [0·68-1·29]

Incidence rate of bladder cancer in UK = 73/100,000 PYS
(http://www.ons.gov.uk/ons/)

* Incidence rate per 100,000 PYS
† Adjusted for age, sex, A1C level, and smoking

HRs of bladder cancer over time
TZD vs SU (referent)

Time since Initiation, y	HR, adjusted†	Duration of therapy, y	HR, adjusted†
<1 year	0·52 [0·25-1·07]	<1 year	0·95 [0·55-1·63]
1-<2	0·99 [0·52-1·89]	1-<2	0·87 [0·45-1·69]
2-<3	1·05 [0·51-2·16]	2-<3	0·72 [0·32-1·63]
3-<4	0·94 [0·39-2·36]	3-<4	1·50 [0·63-3·58]
4-<5	0·62 [0·20-1·93]	4-<5	0·51 [0·11-2·38]
≥5	2·53 [1·12-5·77]	≥5	3·25 [1·08-9·71]
P_{trend}	0·03	P_{trend}	0·20

† Adjusted for age, sex, A1C level, and smoking

Conclusion

- Long-term TZD use may increase the risk of bladder cancer in patients with type II diabetes

TEŞEKKÜR EDERİM

Dr. Mert Başaran