Con il Patrocinio di

AIOM Associazione Italiana Radioterapia e Oncologia clinica

IRCCS Sacro Cuore Don Calabria

2° Convegno Nazionale

IL TEAM INTERDISCIPLINARE NEL CARCINOMA DELLA PROSTATA

NEGRAR DI VALPOLICELLA 6-7 DICEMBRE 2019

Sala Perez - IRCCS Ospedale Sacro Cuore Don Calabria

Coordinatori: STEFANIA GORI - FILIPPO ALONGI - STEFANO CAVALLERI

Quinta Sessione CARCINOMA PROSTATICO LOCALMENTE AVANZATO E METASTATICO ORMONO-SENSIBILE

Moderatori ***Filippo Alongi, Michele Milella***

09,45 Carcinoma prostatico localmente avanzato: quale strategia terapeutica? **Carlo Messina**

10,15 Carcinoma metastatico "de novo" **Rocco De Vivo**

10,30 Carcinoma metastatico "in evoluzione" **Francesco Massari**

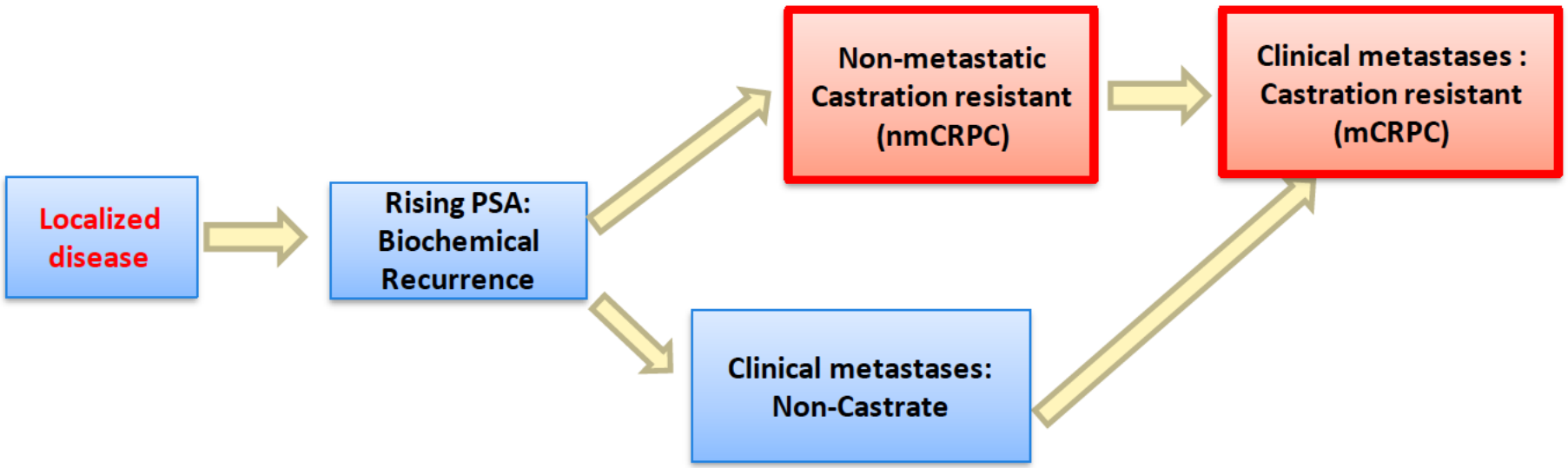
10,45 Ruolo Radioterapista **Stefano Arcangeli**

11,00 Discussione

G.L. Pappagallo: relazioni con l'Industria farmaceutica e potenziali conflitti di interesse (11.2019)

Azienda	Relazione	Patologia
Astellas	training, partecipazione advisory board	ca. prostata
AstraZeneca	partecipazione advisory board, valutazioni clinico-epidemiologiche	ca. polmone, ca. ovaio, ca. mammario, B-LLC
Clovis	partecipazione advisory board	ca. ovaio, ca. prostata
IPSEN	training, valutazioni clinico-epidemiologiche, partecipazione advisory board	ca. rene, epatocarcinoma
Janssen	partecipazione advisory board, valutazioni clinico-epidemiologiche	ca. prostata, depressione maggiore
MSD	valutazioni clinico-epidemiologiche	melanoma, ca. polmone, ca. vescica, VAP
Pierre Fabre	training, valutazioni clinico-epidemiologiche, partecipazione ad advisory board	ca. vescica, melanoma, ca. mammario
Pfizer	training, valutazioni clinico-epidemiologiche	ca. mammario, ca. rene, artrite reumatoide, m. cardiovascolari, amiloidosi
Roche	training, valutazioni clinico-epidemiologiche, partecipazione ad advisory board	ca. polmone, ca. mammella, ca. ovaio, sclerosi multipla, emofilia, linfomi, ACG
Servier	partecipazione advisory board, valutazioni clinico-epidemiologiche	ca. pancreas, ca. gastrico
Teva	training	emicrania

Non-Metastatic Castration Resistant Disease: Those Who NEVER Had Detectable Metastases On "Conventional/Standard" Imaging



- Rising PSA with castrate levels of testosterone (<50 ng/dl)
- No detectable disease on conventional imaging:
  - Radionuclide bone scan
  - CT abdomen and pelvis, +/- MRI

Memorial Sloan Kettering Cancer Center

Challenges and Recommendations for Early Identification of Metastatic Disease in Prostate Cancer

E. David Crawford, Nelson N. Stone, Evan Y. Yu, Phillip J. Koo, Stephen J. Freedland, Susan F. Slovin, Leonard G. Gomella, E. Roy Berger, Thomas E. Keane, Paul Sieber, Neal D. Shore, Daniel P. Petrylak, and the Prostate Cancer Radiographic Assessments for Detection of Advanced Recurrence (RADAR) Group

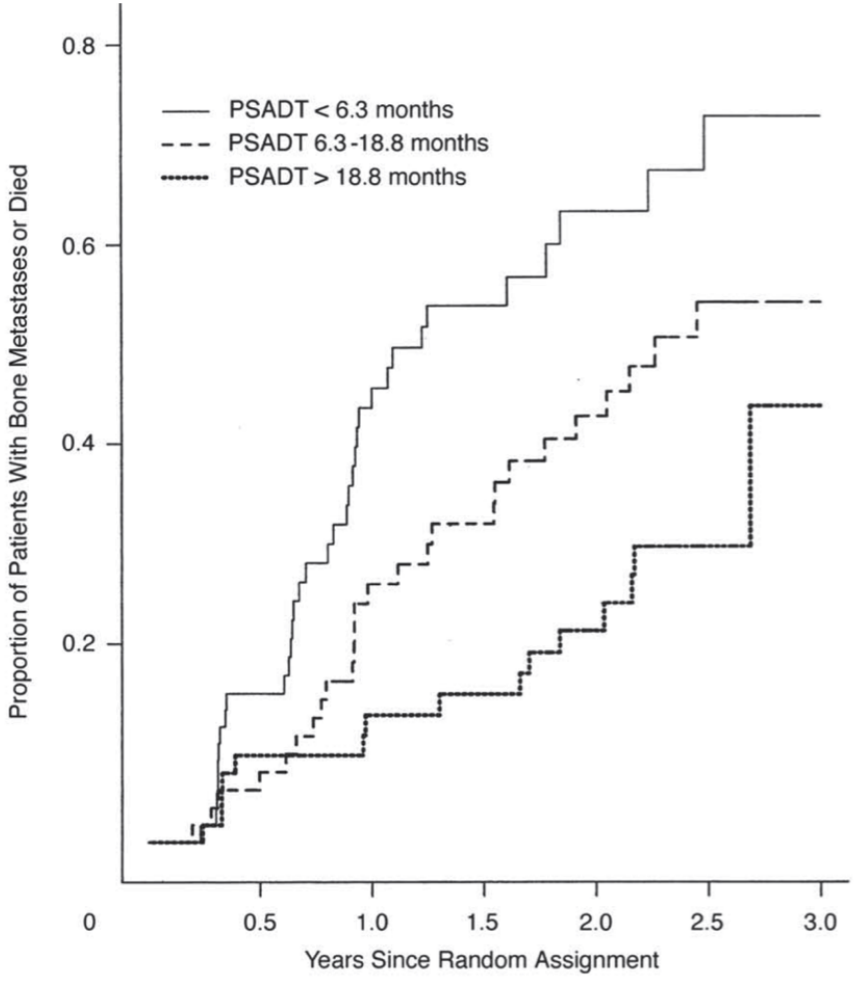
UROLOGY 83: 664–669, 2014.

The RADAR Group considered [redacted] and the most consistent predictor and useful in different patient groups. Limited data showed that acceleration or slow down of PSADT correlated with outcomes (eg, time to metastasis).

Natural History of Rising Serum Prostate-Specific Antigen in Men With Castrate Nonmetastatic Prostate Cancer

Matthew R. Smith, Fairooz Kabbinavar, Fred Saad, Arif Hussain, Marc C. Gittelman, David L. Bilhartz, Chris Wynne, Robin Murray, Norman R. Zinner, Claude Schulman, Ronald Linnartz, Ming Zheng, Carsten Goessl, Yong-Jiang Hei, Eric J. Small, Richard Cook, and Celestia S. Higano

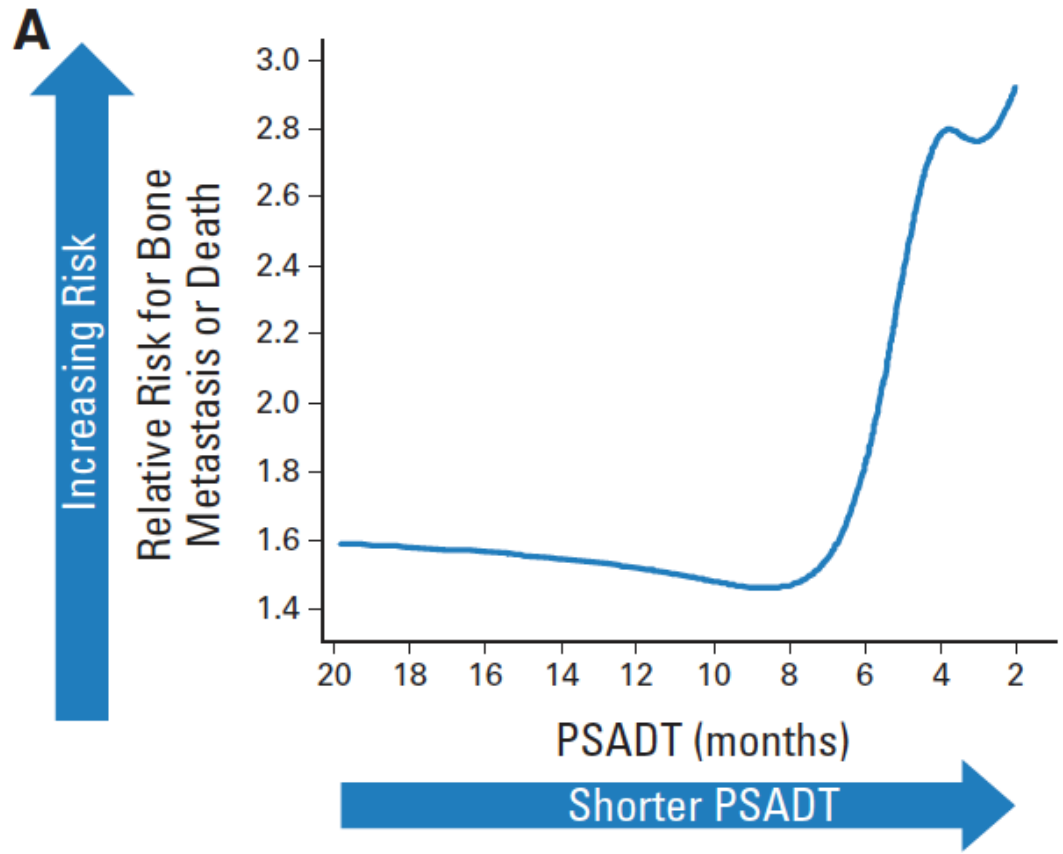
J Clin Oncol 23:2918-2925. © 2005 by American Society of Clinical Oncology



Denosumab and Bone Metastasis–Free Survival in Men With Nonmetastatic Castration-Resistant Prostate Cancer: Exploratory Analyses by Baseline Prostate-Specific Antigen Doubling Time

Matthew R. Smith, Fred Saad, Stephane Oudard, Neal Shore, Karim Fizazi, Paul Sieber, Bertrand Tombal, Ronaldo Damiao, Gavin Marx, Kurt Miller, Peter Van Veldhuizen, Juan Morote, Zhishen Ye, Roger Dansey, and Carsten Goessl

J Clin Oncol 31:3800-3806. © 2013 by American Society of Clinical Oncology



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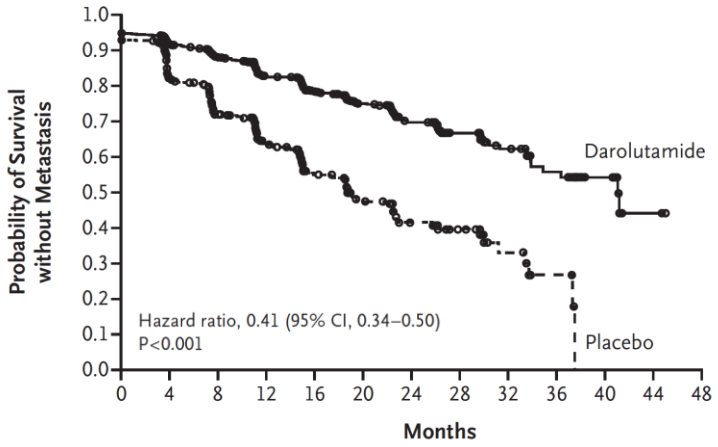
UROLOGY 83: 664–669, 2014.

The RADAR Group considered PSADT to be the best and the most consistent predictor and useful in different patient groups. Limited data showed that acceleration or slow down of PSADT correlated with outcomes (eg, time to metastasis).

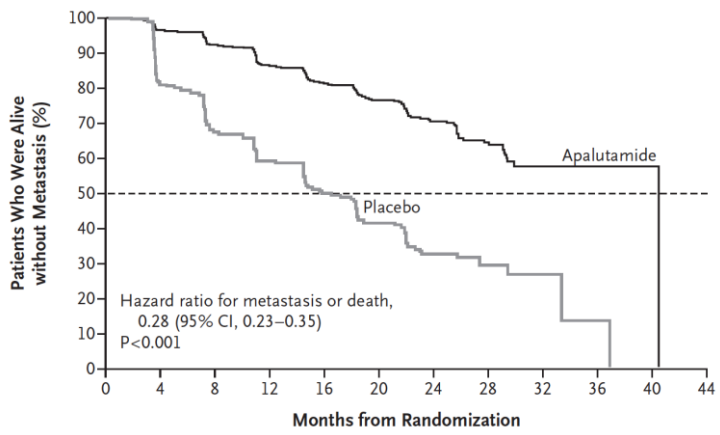
Considering the cost-effectiveness when implementing new techniques/strategies as the imaging modalities for initial testing.

Metastasis-Free Survival (MFS)

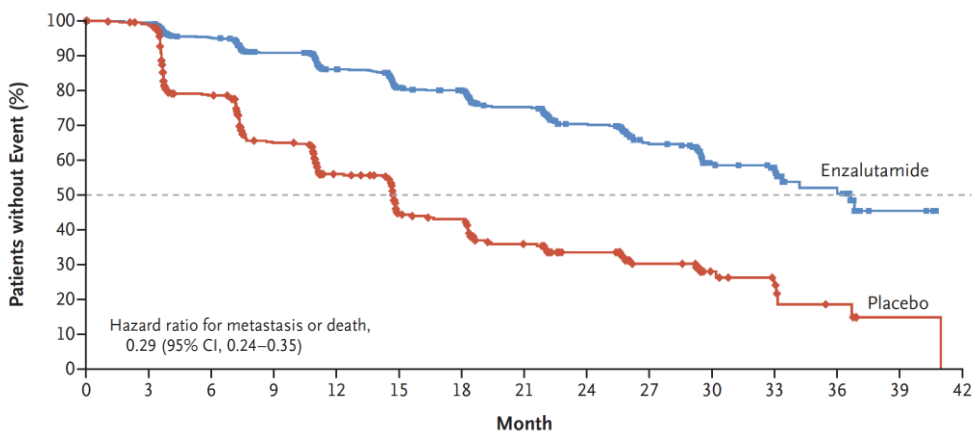
ARAMIS



SPARTAN



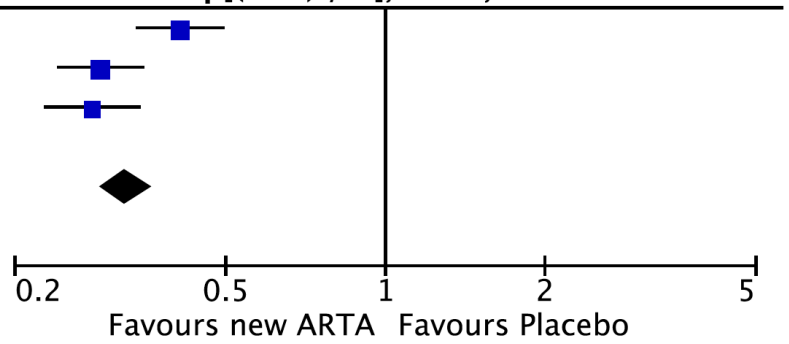
PROSPER



Study or Subgroup	new ARTA Events	new ARTA Total	Placebo Events	Placebo Total	O−E	Variance	Weight	Hazard Ratio Exp[(O−E) / V], Fixed, 95% CI
Aramis	221	995	216	554	−92.11	103.31	34.6%	0.41 [0.34, 0.50]
Prosper	219	993	228	468	−133.62	107.94	36.2%	0.29 [0.24, 0.35]
Spartan	184	806	194	401	−110.96	87.17	29.2%	0.28 [0.23, 0.35]
Total (95% CI)		**2794**		**1423**			**100.0%**	**0.32 [0.29, 0.36]**
Total events	624		638					

Heterogeneity: $Chi^2 = 8.91$, df = 2 (P = 0.01); $I^2 = 78\%$

Test for overall effect: Z = 19.49 (P < 0.00001)

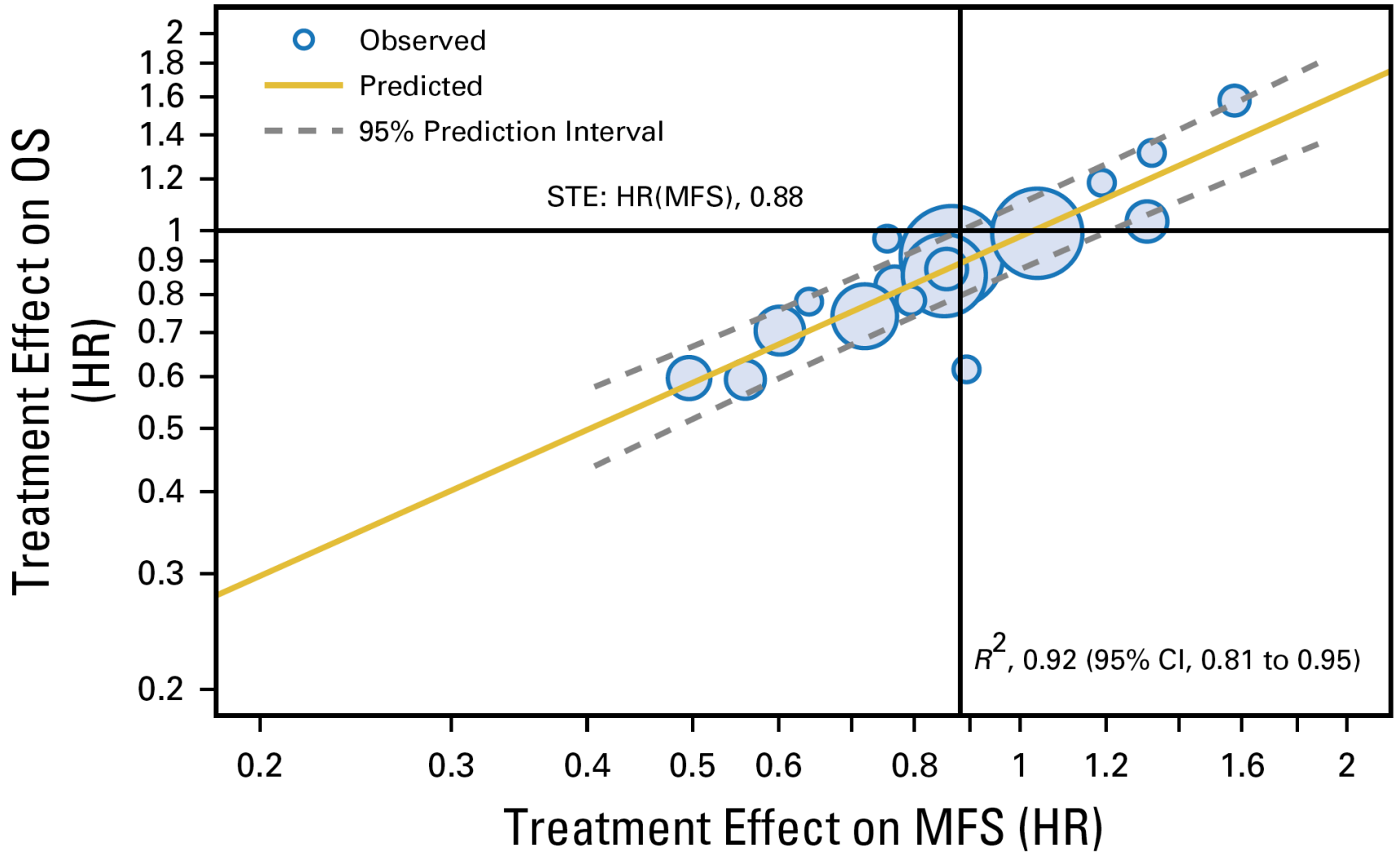


G.L. Pappagallo, 2019

Metastasis-Free Survival Is a Strong Surrogate of Overall Survival in Localized Prostate Cancer

Wanling Xie, Meredith M. Regan, Marc Buyse, Susan Halabi, Philip W. Kantoff, Oliver Sartor, Howard Soule, Noel W. Clarke, Laurence Collette, James J. Dignam, Karim Fizazi, Wendy R. Paruleker, Howard M. Sandler, Matthew R. Sydes, Bertrand Tombal, Scott G. Williams, and Christopher J. Sweeney, on behalf of the ICECaP Working Group

J Clin Oncol 35:3097-3104.



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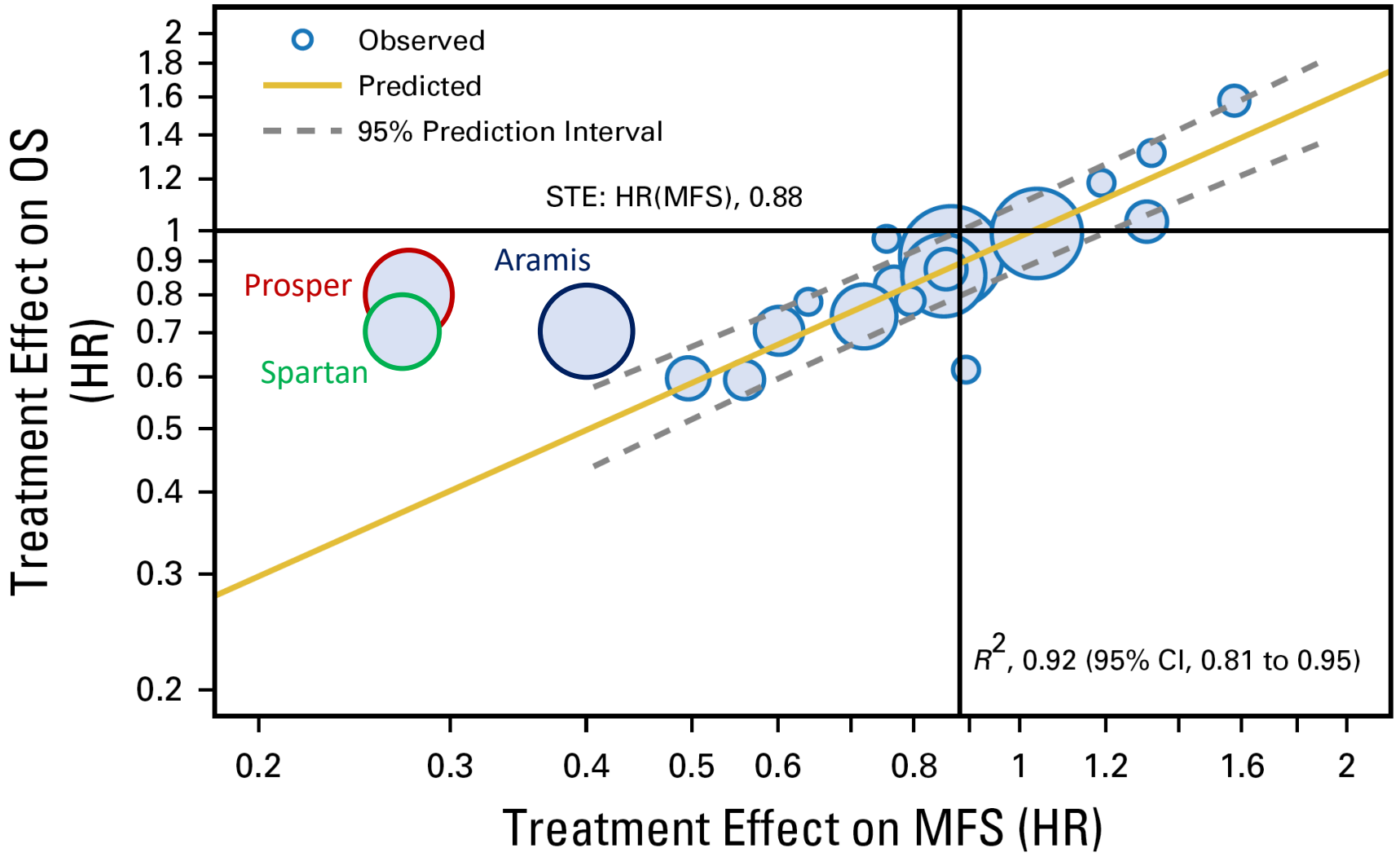
J Clin Oncol 35:3097-3104. © 2017 by American Society of Clinical Oncology



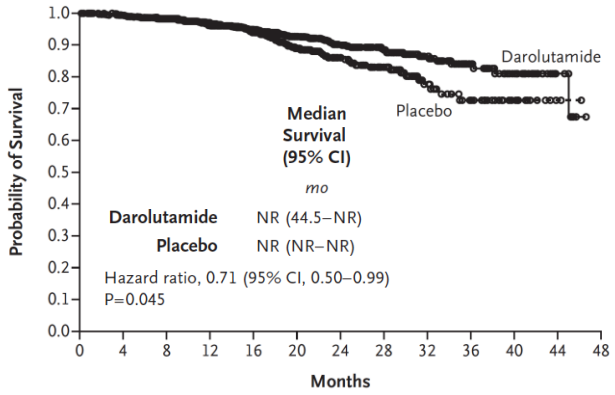
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

November 2018
Clinical/Medical

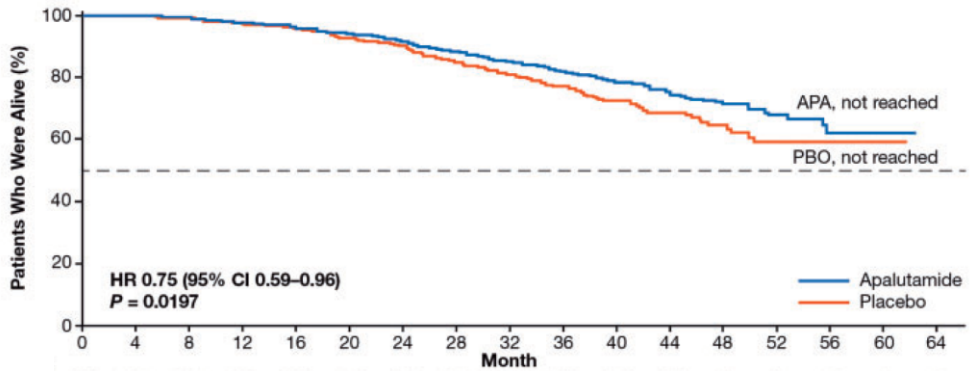
The Oncologic Drugs Advisory Committee (ODAC) noted that the transition from nmCRPC to radiographically detectable metastatic disease (e.g., bone disease) is a clinically relevant event that can be associated with morbidity and the need for additional medical interventions. Thus, a large magnitude of treatment effect on MFS with an acceptable safety profile could be used to demonstrate clinical benefit and support product approval.

Overall Survival (OS)

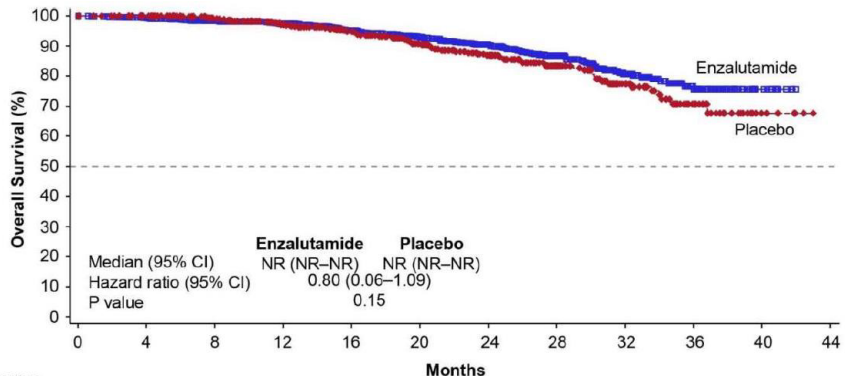
ARAMIS



SPARTAN



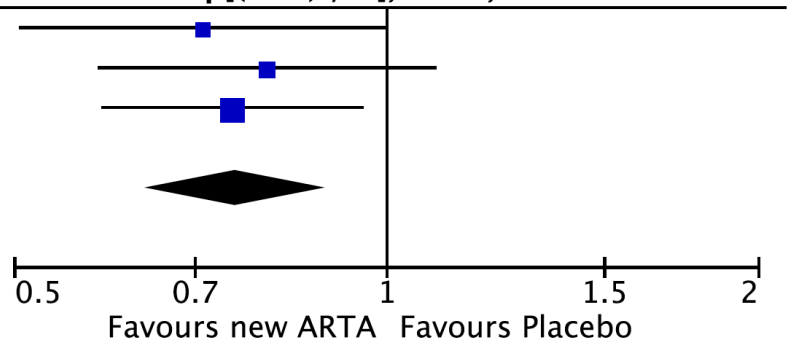
PROSPER



Study or Subgroup	new ARTA Events	Total	Placebo Events	Total	O–E	Variance	Weight	Hazard Ratio Exp[(O–E) / V], Fixed, 95% CI
Aramis	78	995	58	554	−11.28	32.93	24.1%	0.71 [0.50, 1.00]
Prosper	103	993	62	468	−8.61	38.6	28.3%	0.80 [0.58, 1.10]
Spartan	178	806	107	401	−18.65	64.84	47.5%	0.75 [0.59, 0.96]
Total (95% CI)		**2794**		**1423**			**100.0%**	**0.75 [0.64, 0.89]**
Total events	359		227					

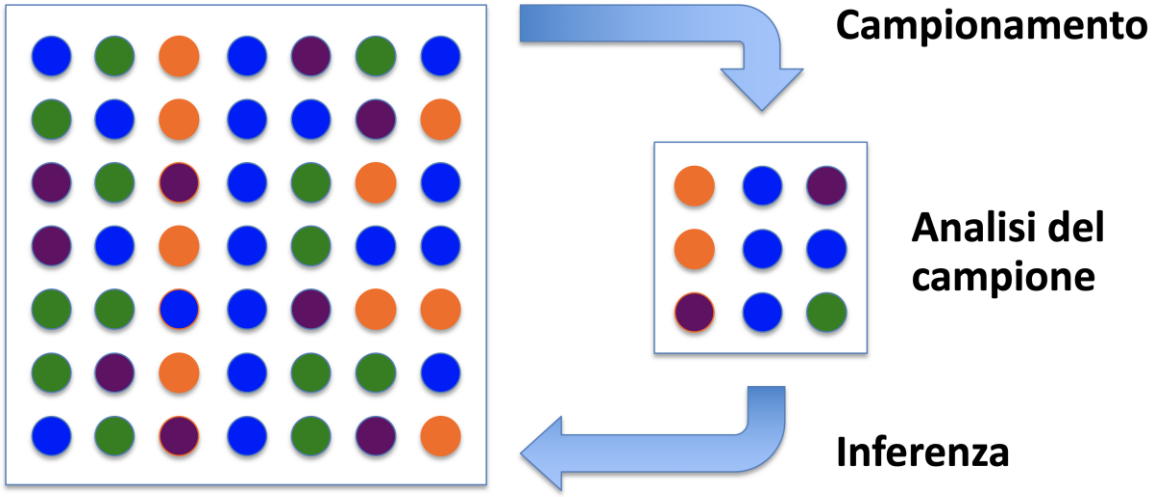
Heterogeneity: $Chi^2 = 0.26$, $df = 2$ ($P = 0.88$); $I^2 = 0\%$

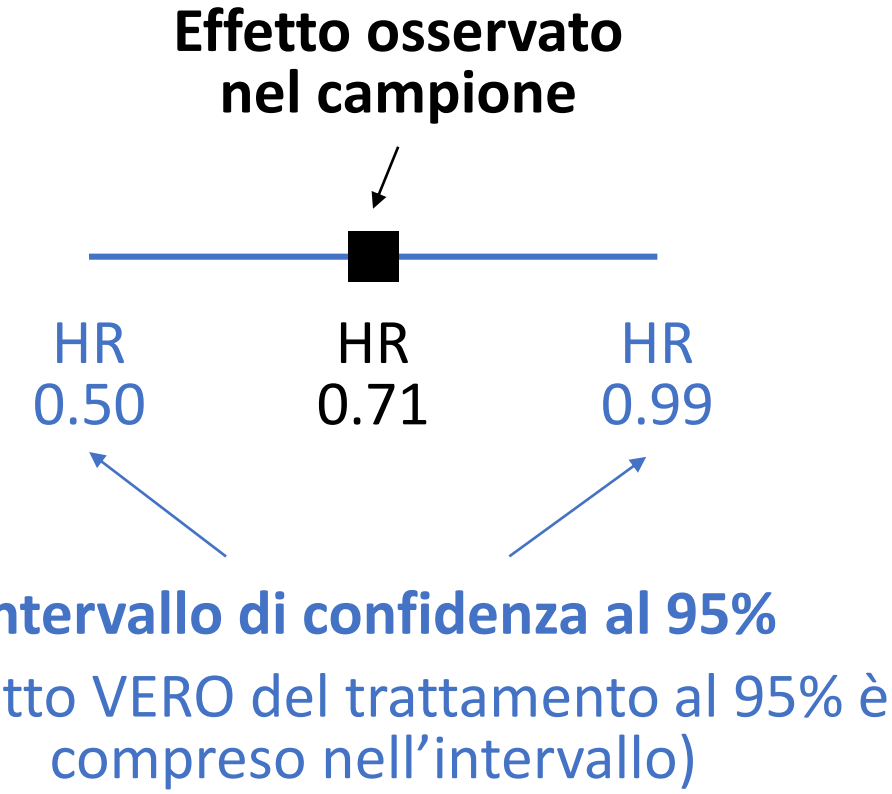
Test for overall effect: $Z = 3.30$ ($P = 0.0010$)



G.L. Pappagallo, 2019

Imprecisione



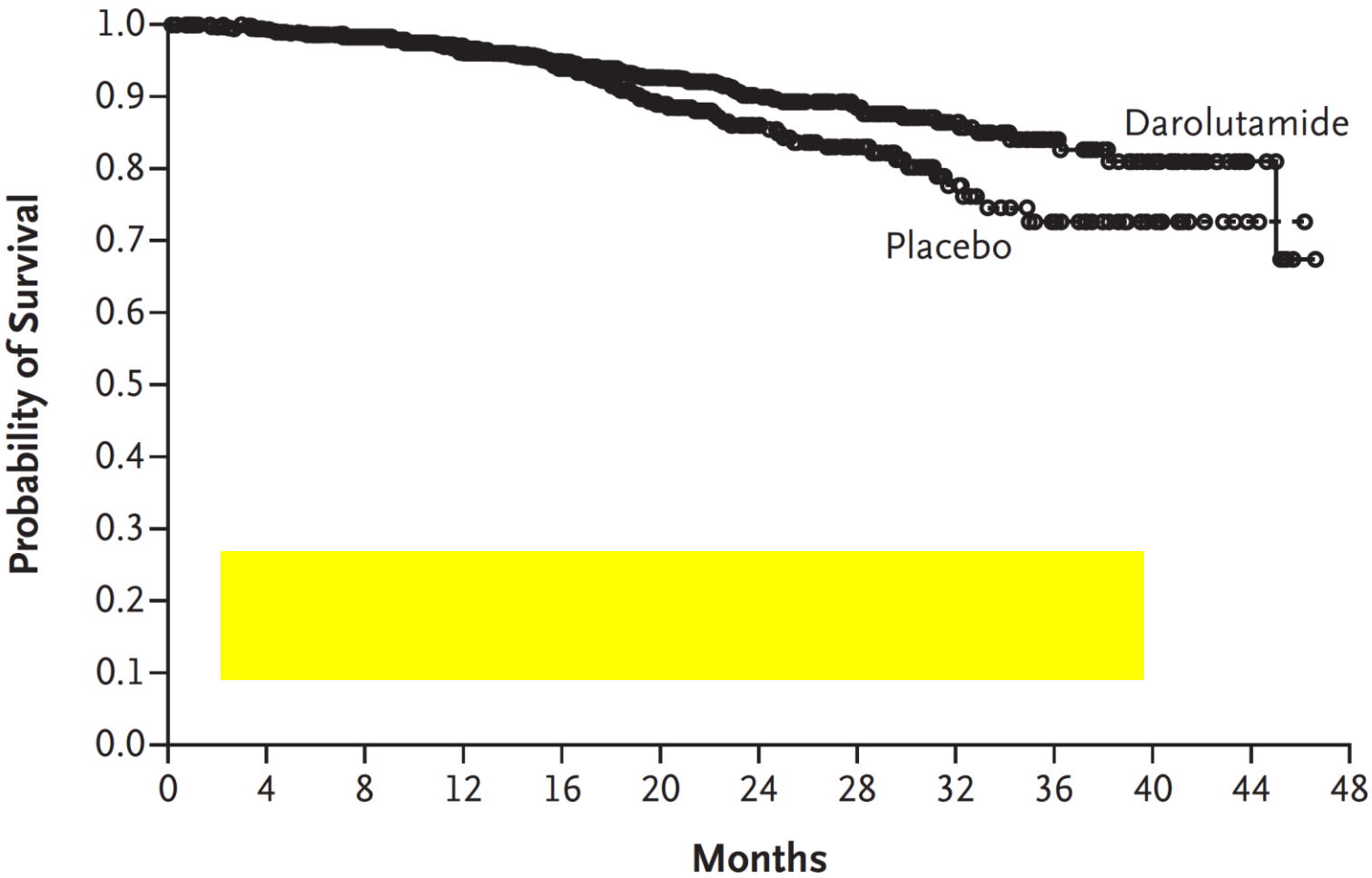


HR 0.50 e HR 0.99 conducono entrambi alla stessa interpretazione clinica?

Darolutamide in Nonmetastatic, Castration-Resistant Prostate Cancer

Karim Fizazi, M.D., Neal Shore, M.D., Teuvo L. Tammela, M.D., Ph.D., Albertas Ulys, M.D., Egils Vjaters, M.D., Sergey Polyakov, M.D., Mindaugas Jievaltas, M.D., Murilo Luz, M.D., Boris Alekseev, M.D., Iris Kuss, M.D., Christian Kappeler, Ph.D., Amir Snapir, M.D., Ph.D., Toni Sarapohja, M.Sc., and Matthew R. Smith, M.D., Ph.D., for the ARAMIS Investigators*

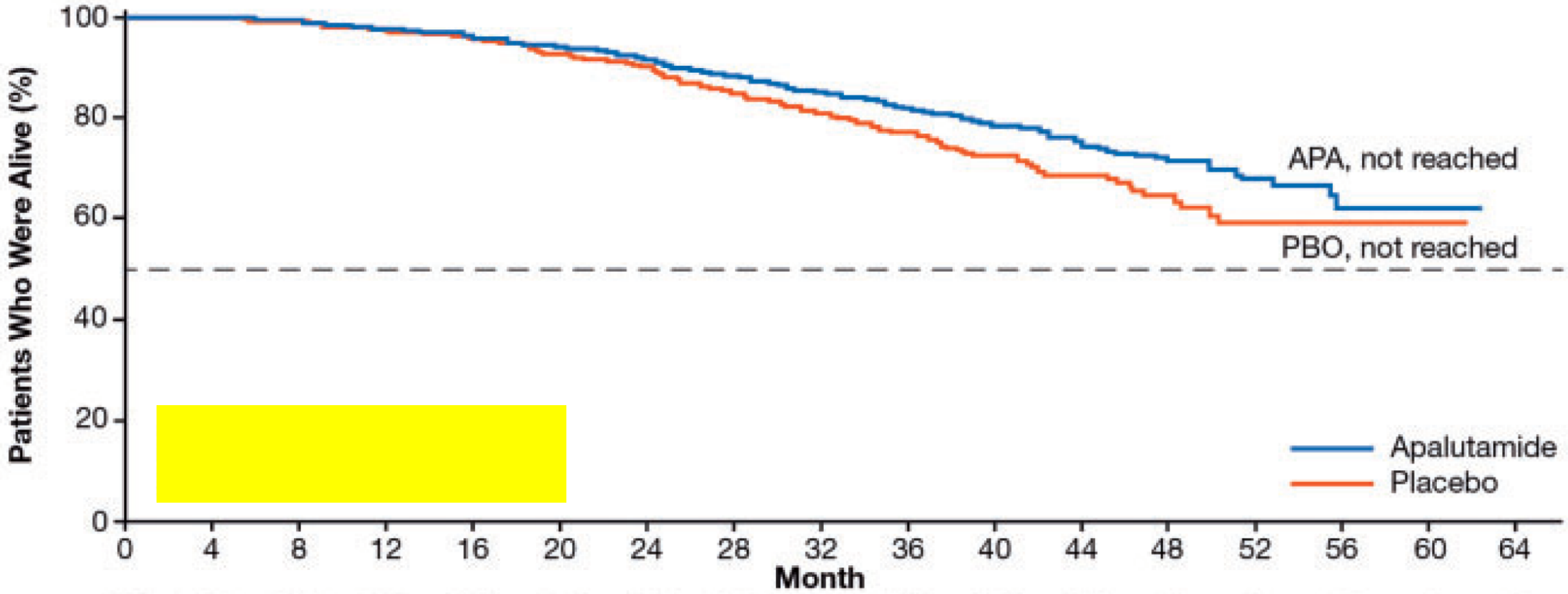
N Engl J Med 2019;380:1235-46.



Apalutamide and overall survival in non-metastatic castration-resistant prostate cancer

E. J. Small[1*], F. Saad[2], S. Chowdhury[3,4], S. Oudard[5], B. A. Hadaschik[6,7], J. N. Graff[8,9], D. Olmos[10,11], P. N. Mainwaring[12], J. Y. Lee[13], H. Uemura[14], P. De Porre[15], A. A. Smith[16], K. Zhang[17], A. Lopez-Gitlitz[18] & M. R. Smith[19,20]

Annals of Oncology 0: 1–8, 2019



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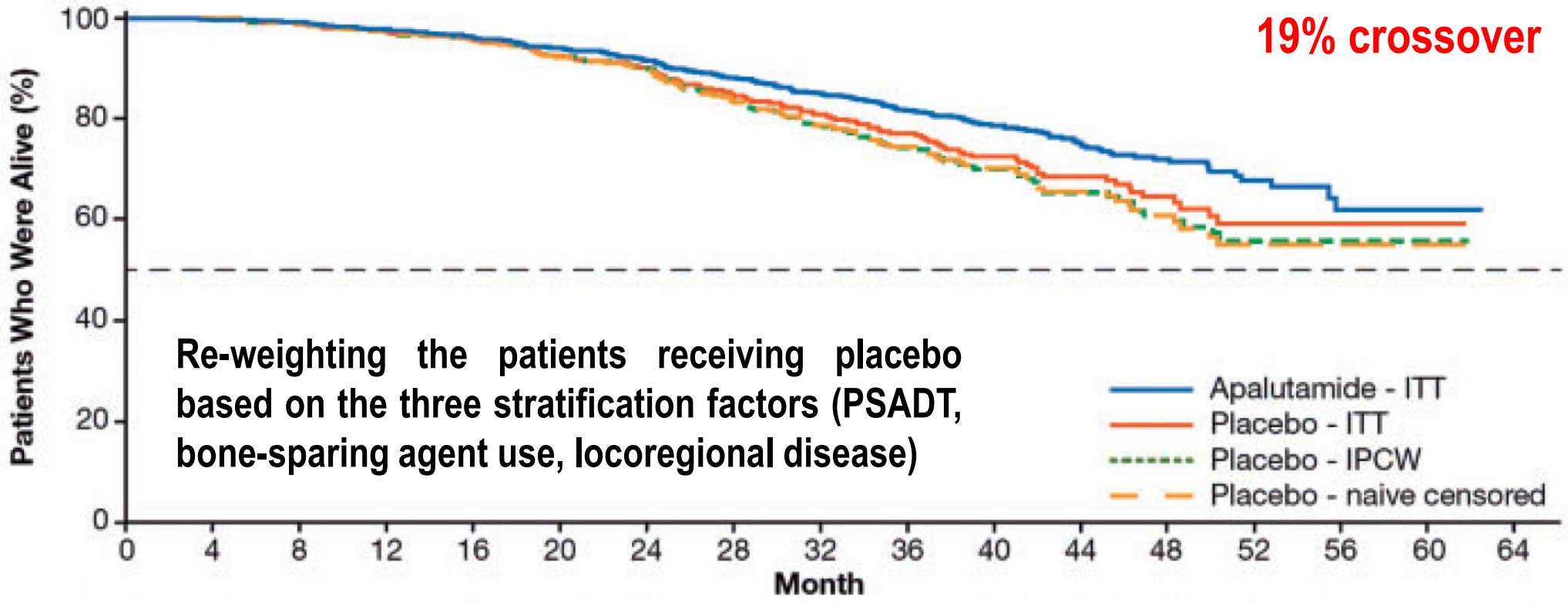
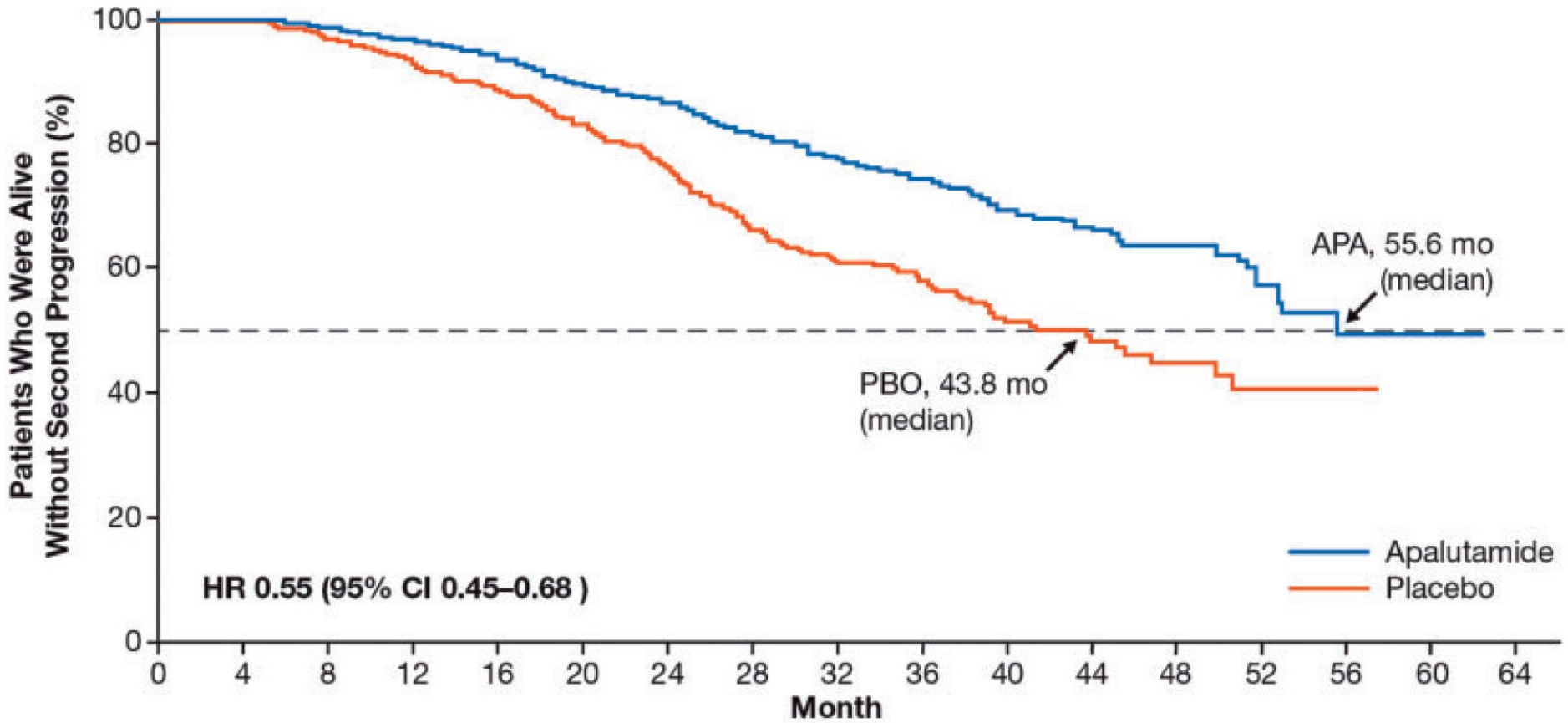


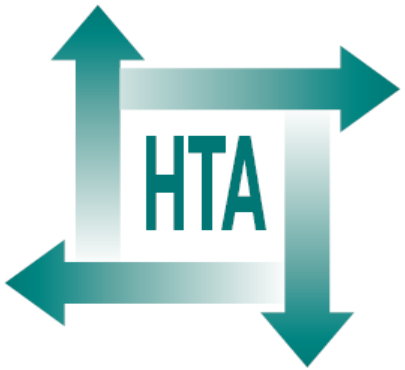
	Apalutamide with ongoing ADT (*n* = 806)	Placebo with ongoing ADT (*n* = 401)
First subsequent therapy		
Abiraterone acetate plus prednisone	235 (73.0)	199 (72.1)
Enzalutamide	31 (9.6)	38 (13.8)



Indirect comparisons of competing interventions

AM Glenny,[1*] DG Altman,[2] F Song,[3] C Sakarovitch,[2] JJ Deeks,[2] R D'Amico,[2] M Bradburn[2] and AJ Eastwood[4]

Health Technology Assessment 2005; Vol. 9: No. 26

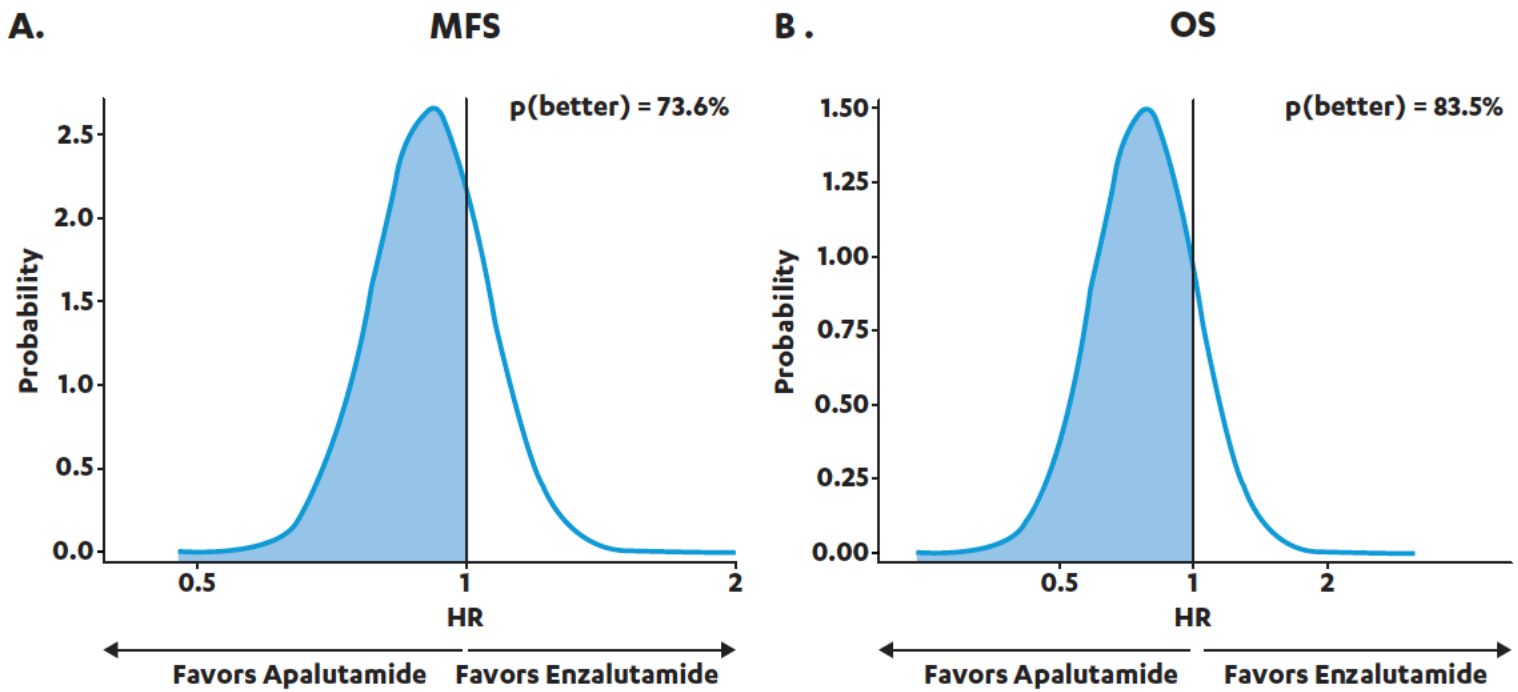


When conducting systematic reviews to evaluate the effectiveness of interventions, direct evidence from good-quality RCTs should be used wherever possible. If little or no such evidence exists, it may be necessary to look for indirect comparisons from RCTs. The reviewer needs, however, to be aware that the results may be susceptible to bias.

Matching-Adjusted Indirect Comparison of the Efficacy of Apalutamide and Enzalutamide in the Treatment of Non-Metastatic Castration-Resistant Prostate Cancer

S. Chowdhury,[1] S. Oudard,[2] B.A. Hadaschik,[3] H. Uemura,[4] S. Joniau,[5] D. Pilon,[6] M. Ladouceur,[6] A.S. Behl,[7] J. Liu,[7] L. Dearden,[8] J. Sermon,[9] S. Van Sanden,[9] J. Diels[9]

Apalutamide vs. Enzalutamide	MAIC-weighted	
	HR [95% CrI]	p(HR<1)
MFS	0.91 [0.68; 1.22]	73.6%
OS	0.77 [0.46; 1.30]	83.5%



868P. Safety of new androgen receptor inhibitors (ARi) in patients with nonmetastatic castration-resistant prostate cancer (nmCRPC): a network meta-analysis of randomized controlled trials (RCT)

Amelia Altavilla[1], Massimo Di Maio[2,3], Marcello Tucci [4], Cristian Lolli[1],Giuseppe Schepisi[1], Consuelo Buttigliero [2,5], Francesca Vignani[3], Ugo De Giorgi[1]
[1]Medical Oncology, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, 47014 - Meldola/IT; [2]Department of Oncology, University of Turin; [3]Ordine Mauriziano Hospital, Turin; [4]Medical Oncology, Cardinal Massaia Hospital, Asti; [5]Division Of Medical Oncology, “San Luigi Gonzaga" Hospital, Orbassano, Torino/IT

We performed literature-based meta-analysis to describe pooled odds ratio (OR) of new ARi vs placebo, and presence of heterogeneity in the effect among RCT. Network meta-analysis was performed to describe OR of indirect comparisons.

	A vs E	D vs E	D vs A
SAE	0.76 [0.51; 1.14]	0.92 [0.63; 1.34]	0.83 [0.57; 1.22]
AE discontinuation	0.97 [0.52; 1.82]	0.64 [0.36; 1.14]	0.66 [0.37; 1.18]

Nonmetastatic Castration-resistant Prostate Cancer: A Modern Perspective

Madeline Cancian and Joseph F. Renzulli II

UROLOGY ■■: ■■–■■, 2018.

Nonmetastatic castration-resistant prostate cancer (nmCRPC) presents a challenge to urologists as currently there are no Food and Drug Administration-approved therapies. However, there are [redacted] including fluciclovine positron emission tomography-computed tomography and Ga-PSMA (prostate specific membrane antigent) positron emission tomography computed tomography, [redacted] of diagnosis. With improved imaging, we are better able to target therapy.

A Clinician's Guide to Next Generation Imaging in Patients With Advanced Prostate Cancer (RADAR III)

THE JOURNAL OF UROLOGY® Vol. 201, 682-692, April 2019

M0 Castrate-Resistant Patients

RADAR I
Conventional Scan
Recommendations

1st conventional scan when PSA level ≥2 ng/ml

Imaging frequency if negative for previous conventional scan:

2nd conventional scan when PSA=5 ng/ml and every doubling of PSA level thereafter (based on PSA testing every 3 months)

RADAR III
NGI Recommendations

Only consider NGI in the setting of PSADT <6 months, when M1 therapies would be appropriate

American College of Radiology Diagnostic Efficacy Studies

JOHN W. LOOP[1] AND LEE B. LUSTED[2]

Am J Roentgenol 131:173–179, July 1978

"The fullest and most long-range expression of efficacy ought to include some measure of the influence of the examination on the final outcome of the episode of ill health."

The Efficacy of Diagnostic Imaging

DENNIS G. FRYBACK, PhD, JOHN R. THORNBURY, MD

Med Decis Making 1991;11:88–94

Clinical Efficacy of Diagnostic Imaging: Love It or Leave It

John R. Thornbury

AJR **1994;162:1–8**

Level 1, Technical Efficacy
Level 2, Diagnostic-Accuracy Efficacy
Level 3, Diagnostic-Thinking Efficacy
Level 4, Therapeutic Efficacy
Level 5, Patient-Outcome Efficacy
Level 6, Societal Efficacy

A framework for clinical evaluation of diagnostic technologies

Gordon H. Guyatt,* MD
Peter X. Tugwell, MD
David H. Feeny, PhD
R. Brian Haynes, MD, PhD
Michael Drummond, DPhil

CAN MED ASSOC J, VOL. 134, MARCH 15, 1986

Depending on the point of view, there are a number of criteria for concluding that a diagnostic technology is ready for dissemination.[5,6] These criteria can be considered to form a hierarchy of progressively more rigorous evaluation, as follows:

- The ability of the technology to perform to specifications in a laboratory setting has been demonstrated.
- The technology promises to provide important diagnostic information in a number of clinical situations.
- The technology provides information that allows health care workers to make a more accurate assessment regarding the presence and severity of disease.
- The technology allows health care workers to be more confident of their diagnoses and thereby decreases their anxiety and increases their comfort.
- The therapeutic decisions made by health care providers are altered as a result of application of the technology.
- Application of the technology results in benefit to the patient.

Impact of ^{68}Ga-PSMA-11 PET on Management in Patients with Biochemically Recurrent Prostate Cancer

Thomas A. Hope[1–3], Rahul Aggarwal[3,4], Bryant Chee[4], Dora Tao[1], Kirsten L. Greene[5], Matthew R. Cooperberg[3,5], Felix Feng[3,6], Albert Chang[6], Charles J. Ryan[3,4], Eric J. Small[3,4], and Peter R. Carroll[3,5]

J Nucl Med 2017; 58:1956–1961

The purpose of this prospective study was to estimate the effect of ^{68}Ga-labeled prostate-specific membrane antigen (PSMA)–11 PET on the intended management of patients with biochemically recurrent prostate cancer.

…

Conclusion: 68Ga-PSMA-11 PET resulted in a major change in management in 53% of patients with biochemical recurrence. Further studies are warranted to investigate whether PSMA-based management strategies result in improved outcomes for patients.

Peter X. Tugwell, MD
David H. Feeny, PhD
R. Brian Haynes, MD, PhD
Michael Drummond, DPhil

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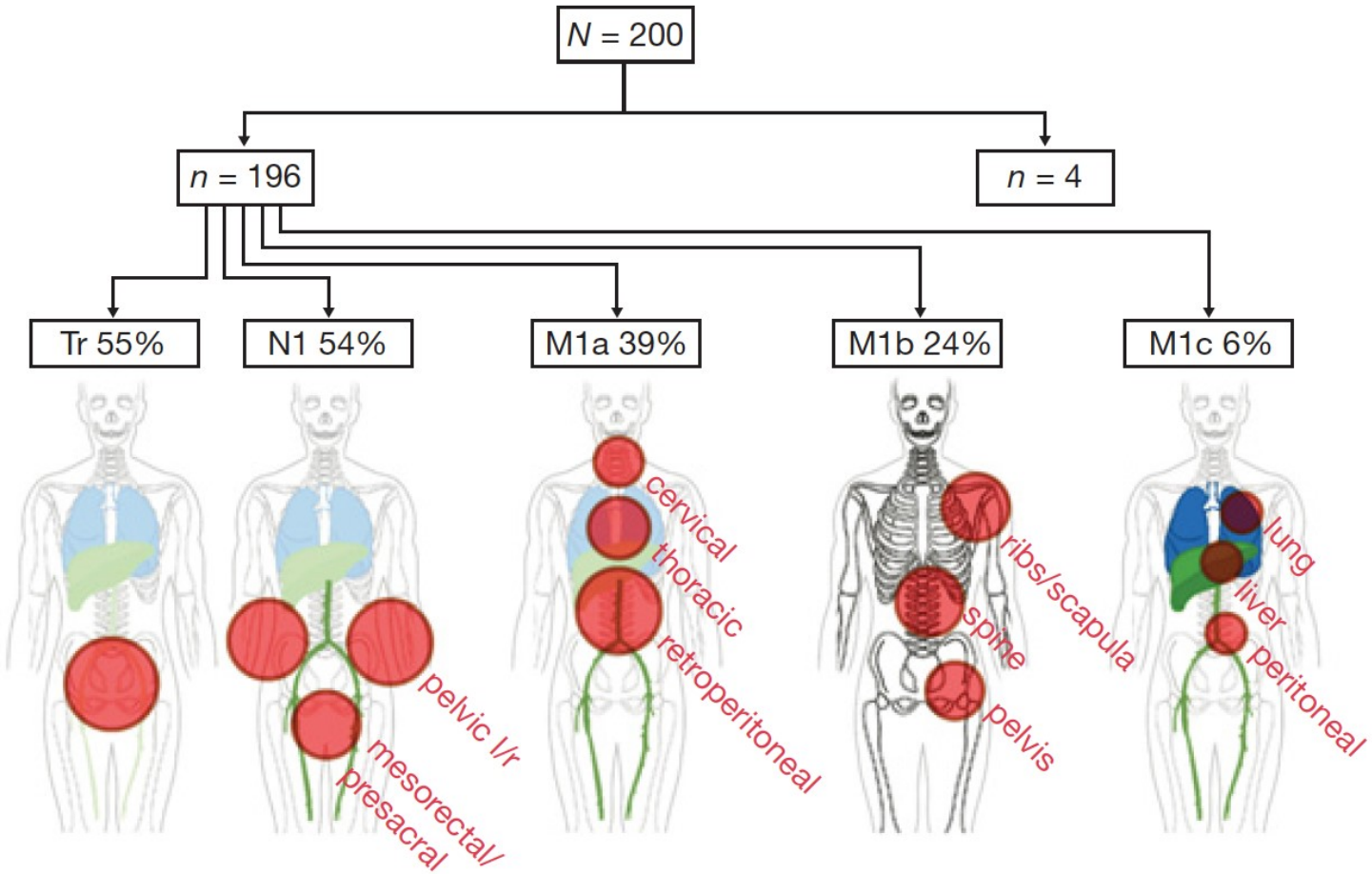
- Application of the technology results in benefit to the patient.

Prostate-Specific Membrane Antigen Ligand Positron Emission Tomography in Men with Nonmetastatic Castration-Resistant Prostate Cancer

Clin Cancer Res 2019;XX:XX–XX

PSMA-PET detected any disease in nearly all patients and M1 disease in 55% of patients previously diagnosed with nmCRPC, including subgroups with PSADT of ≤10 months and Gleason score of ≥8. The value of PSMA-PET imaging for treatment guidance should be tested in future studies.



Challenges and Recommendations for Early Identification of Metastatic Disease in Prostate Cancer

E. David Crawford, Nelson N. Stone, Evan Y. Yu, Phillip J. Koo, Stephen J. Freedland, Susan F. Slovin, Leonard G. Gomella, E. Roy Berger, Thomas E. Keane, Paul Sieber, Neal D. Shore, Daniel P. Petrylak, and the Prostate Cancer Radiographic Assessments for Detection of Advanced Recurrence (RADAR) Group

UROLOGY 83: 664–669, 2014.

The RADAR Group considered PSADT to be the best and the most consistent predictor and useful in different patient groups. Limited data showed that acceleration or slow down of PSADT correlated with outcomes (eg, time to metastasis).

Considering the cost-effectiveness when implementing new techniques/strategies for bone and soft tissue imaging, the RADAR Group recommended 99m Tc bone scintigraphy and abdomen/pelvis/chest CT as the imaging modalities for initial testing.

To definitively conclude that refinements in imaging could improve survival for patients with prostate cancer,