



# Radioterapia stereotassica e nuovi farmaci nel **tumore** e della **prostata metastatico**

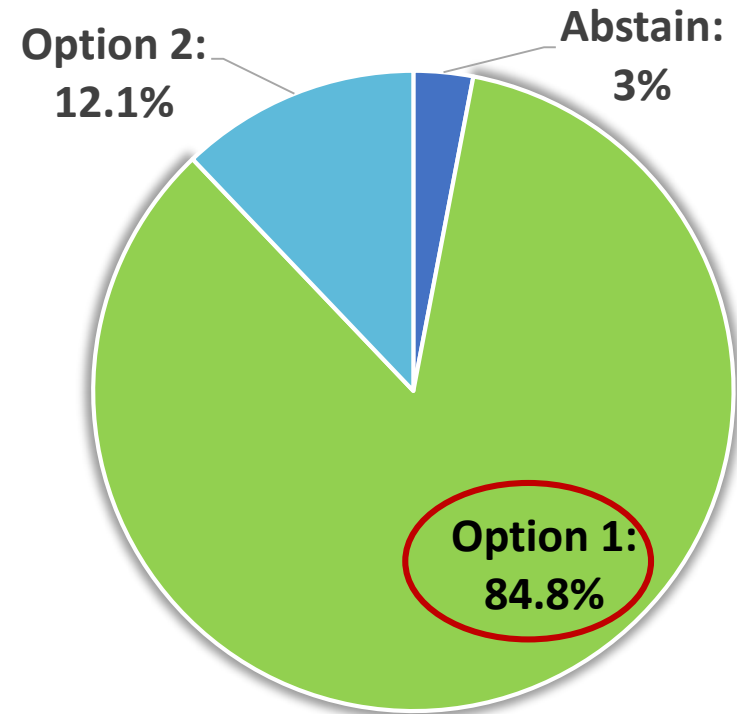
# Definition of Oligometastatic PCa

**1** -  $\leq 3$  synchronous metastases  
(bone and/or lymph nodes)

**2** -  $\leq 5$  synchronous metastases  
(bone and/or lymph nodes)

**3** - Other definition

**4** - Abstain



# Clinical scenarios

- ✓ Oligometastatic castration sensitive disease at diagnosis with untreated primary
- ✓ Oligometastatic castration sensitive disease after primary treatment (primary controlled)
- ✓ Oligometastatic castration resistant disease at its first occurrence
- ✓ Oligoprogressive castration resistant disease in treatment with Androgen Receptor Target Agent (ARTA)



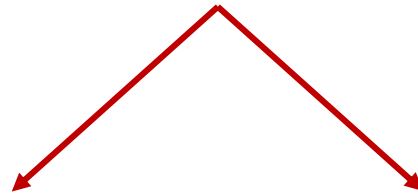
# Clinical scenarios

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# Scenario #1: Oligom+ PCa @ diagnosis

Oligom+ Pca @ diagnosis with untreated primary



Eligible for ADT only

Eligible for ADT+ABI



# Scenario #1.1: Oligom+ PCa @ diagnosis

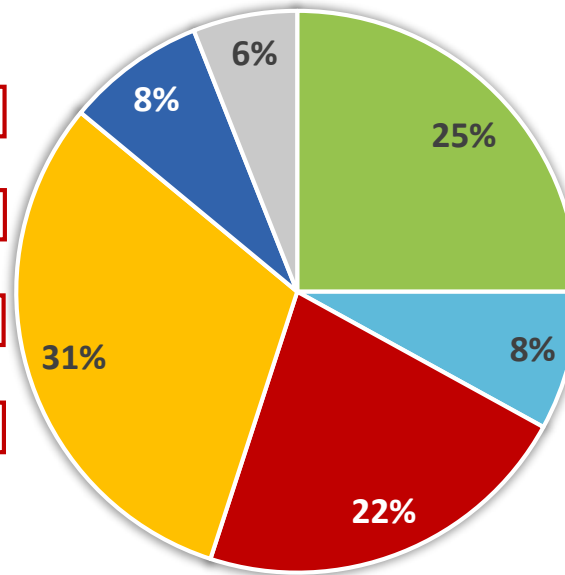
Oligom+ Pca @ diagnosis with **untreated primary eligible to receive ADT only**

De novo oligometastatic disease (no prior prostate treatment)

Which treatment do you recommend in men with newly-diagnosed oligometastatic prostate cancer with an untreated primary?

- 1) Lifelong ADT ± Docetaxel
- 2) Radical local treatment of all lesions including the primary (surgery or RT) without ADT or Docetaxel
- 3) Radical local treatment of all lesions including the primary (surgery or RT) + ADT 6-12m ± Docetaxel
- 4) Radical local treatment of all lesions including the primary (surgery or RT) + ADT 24-36m ± Docetaxel
- 5) Radical local treatment of all lesions including the primary (surgery or RT) + lifelong ADT ± Docetaxel
- 6) Abstain
- 7) Unqualified to answer

69%



■ Option 1   ■ Option 2   ■ Option 3  
■ Option 4   ■ Option 5   ■ Option 6

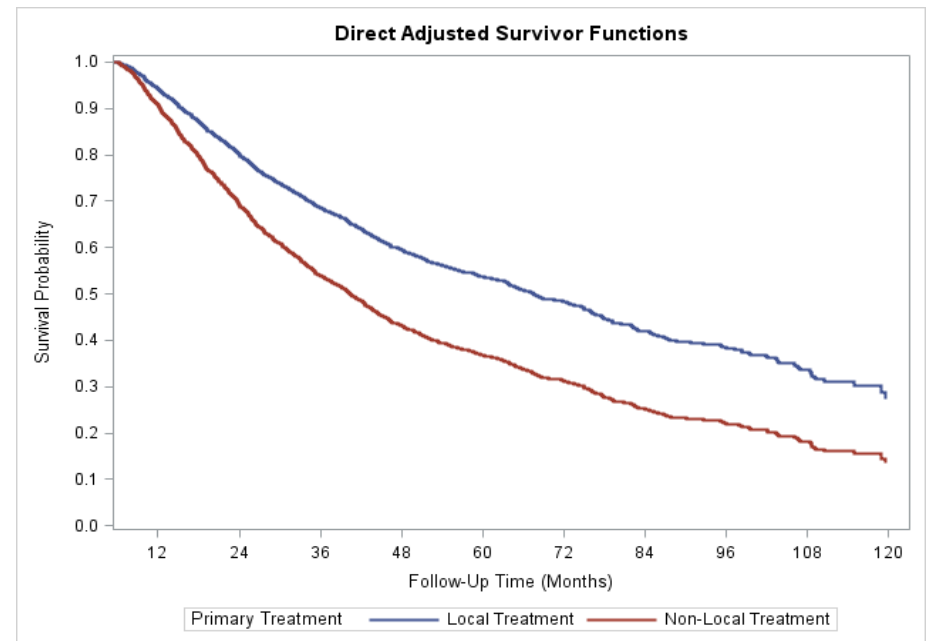
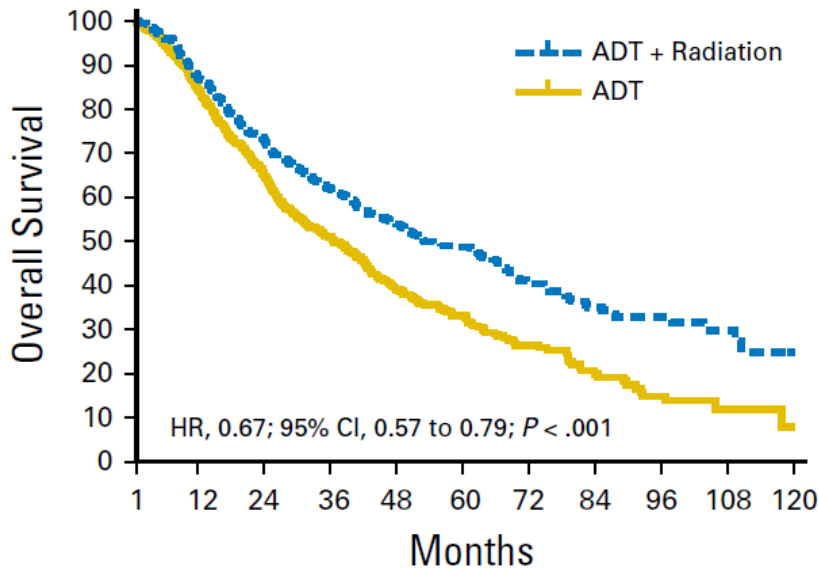
Details voting results

Opt	Votes
1	13
2	4
3	11
4	16
5	4
6	3
7	0
N	51

# Scenario #1.1: Oligom+ PCa @ diagnosis

Oligom+ Pca @ diagnosis with **untreated primary eligible to receive ADT only**

## Treatment of primary tumor



ADT + Radiation	537	357	201	86	33	2
ADT	537	315	152	55	15	2

**Propensity Score Matched (N = 1,074)**

*Rusthoven CG, J Clin Oncol 2016;34:2835-42.*

**Propensity Score Matched (N = 2,281)**

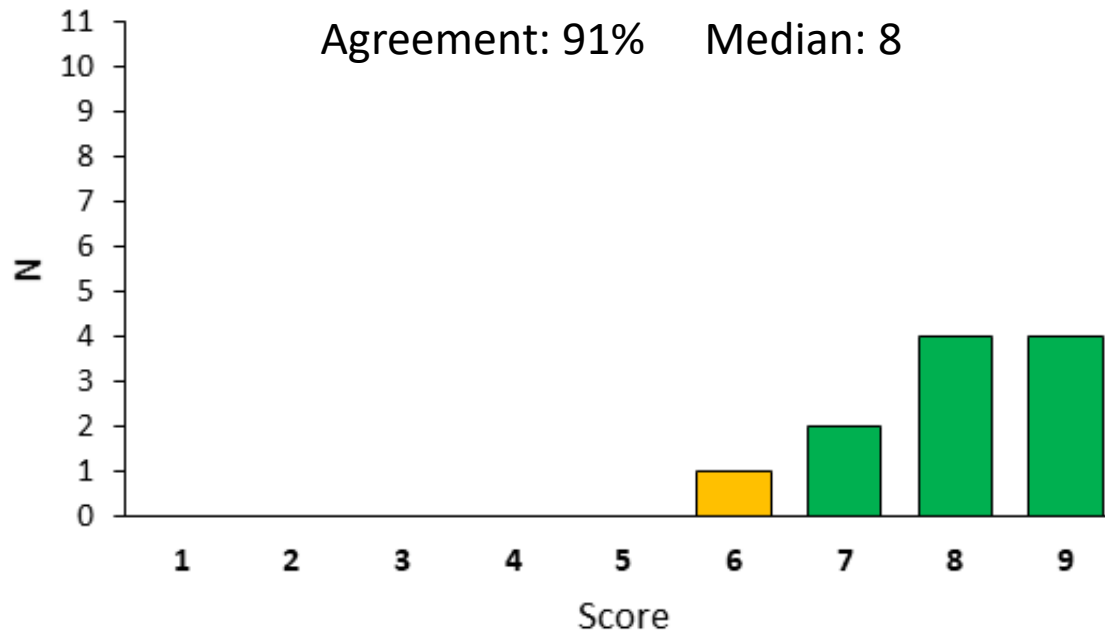
*Löppenber B, Eur Urol 2017;72:14-9.*



# Scenario #1.1: Oligom+ PCa @ diagnosis

## Statement 1.1

*In an oligometastatic patient, radiotherapy with radical intent to primary and metastatic sites along with androgen deprivation therapy, could be offered as alternative to androgen deprivation therapy alone.*





# Scenario #1: Oligom+ PCa @ diagnosis



Smarter Studies  
Global Impact  
Better Health



## Radiotherapy to the primary tumour for men with newly-diagnosed metastatic prostate cancer: Survival results from STAMPEDE

CC Parker, ND James, CD Brawley, NW Clarke, G Attard, S Chowdhury, W Cross, DP Dearnaley, S Gillessen, C Gilson, RJ Jones, MD Mason, R Millman, C Eswar, J Gale, JF Lester, DJ Sheehan, AT Tran, MKB Parmar, MR Sydes.



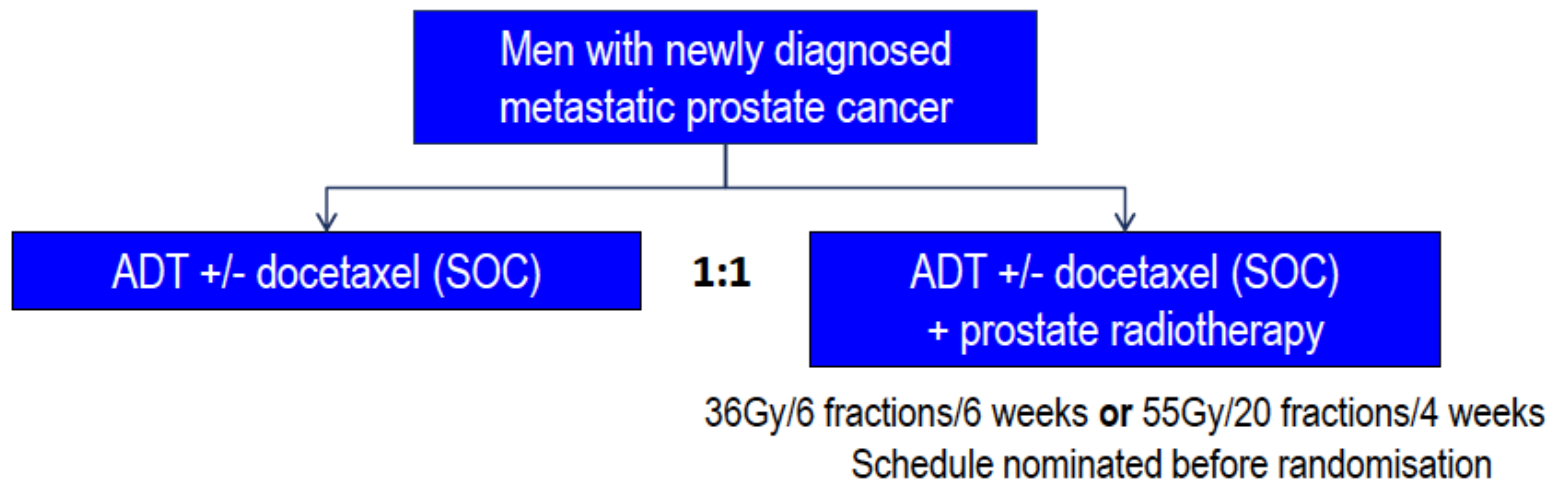
*The* ROYAL MARSDEN  
NHS Foundation Trust



# Scenario #1: Oligom+ PCa @ diagnosis

## Study design

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## Stratification variables

Age (<70 vs ≥70 years), nodal involvement (N0 vs N1 vs Nx), randomising site, WHO performance status (0 vs 1 or 2), type of ADT, aspirin or NSAID use, docetaxel use

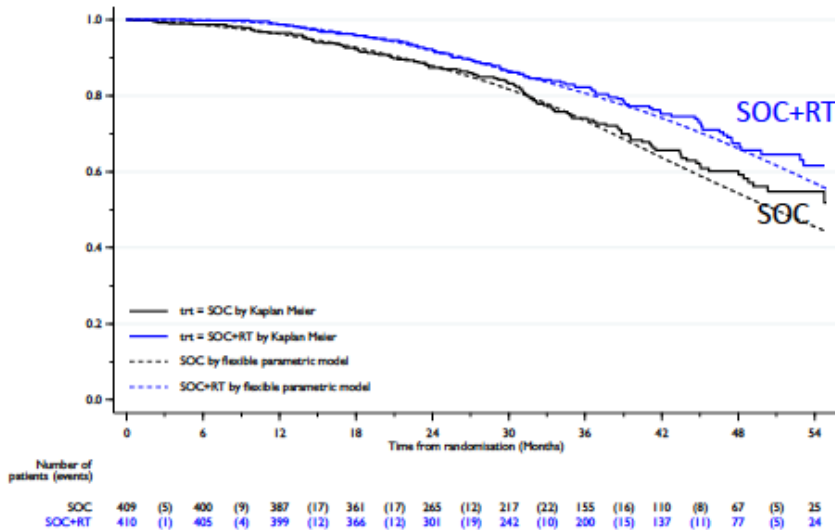
- Main outcome measure: **Overall survival**



# Scenario #1: Oligom+ PCa @ diagnosis

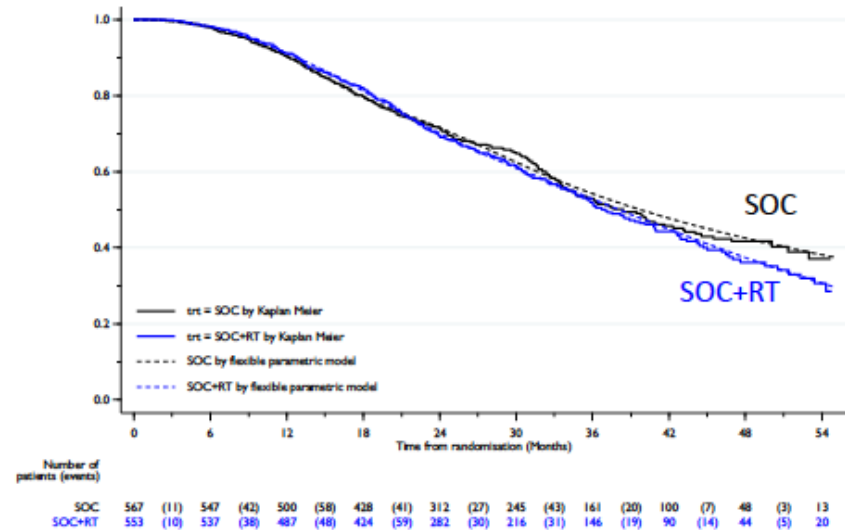
## Overall survival: metastatic burden subgroup analysis

Low burden



**HR: 0.68 (95% CI 0.52-0.90); p=0.007**  
**3 year OS (%): SOC = 73%**  
**SOC+RT = 81%**

High burden

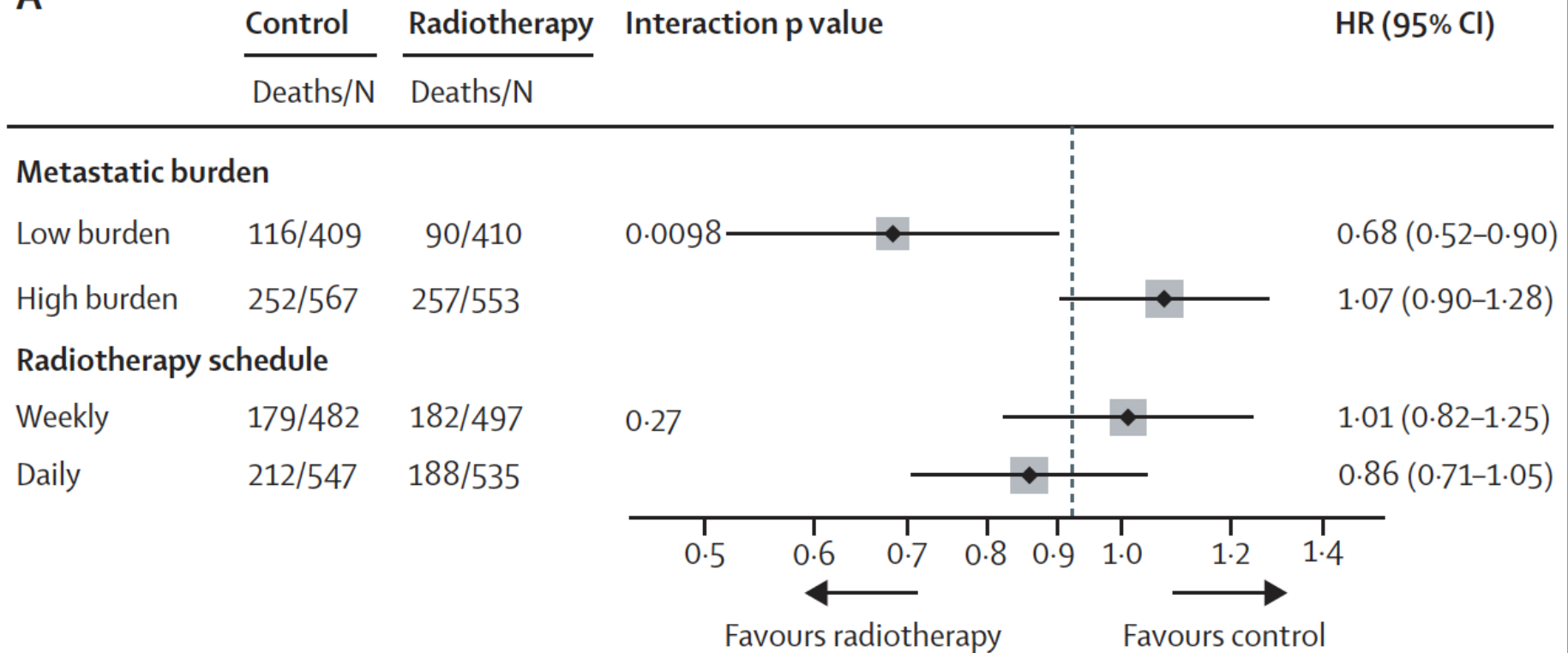


**HR: 1.07 (95% CI 0.90-1.28); p=0.420**  
**3 year OS (%): SOC = 54%**  
**SOC+RT = 53%**



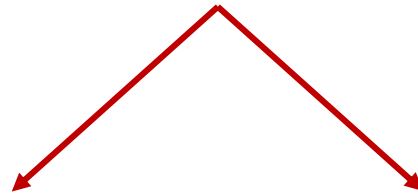
# Scenario #1: Oligom+ PCa @ diagnosis

A



# Scenario #1: Oligom+ PCa @ diagnosis

Oligom+ Pca @ diagnosis with untreated primary



Eligible for ADT only

Eligible for ADT+ABI

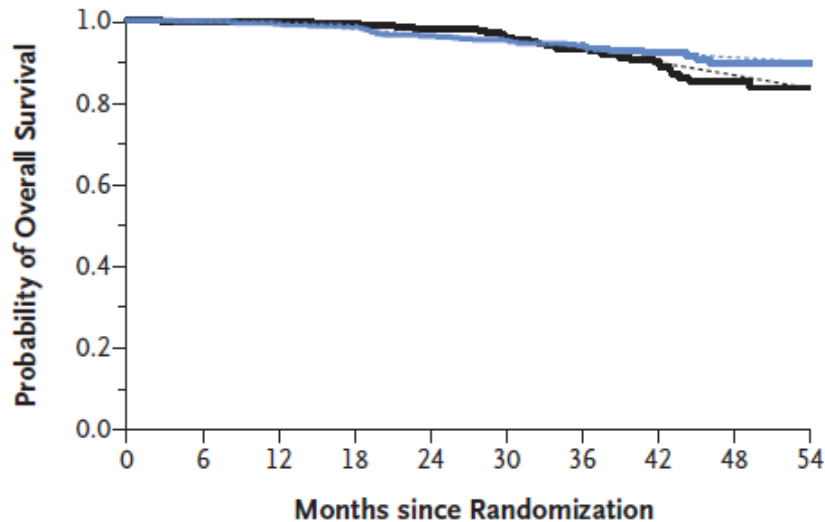


# Scenario #1.2: Oligom+ PCa @ diagnosis

Oligom+ Pca @ diagnosis with **untreated primary** eligible to receive ADT+Abi

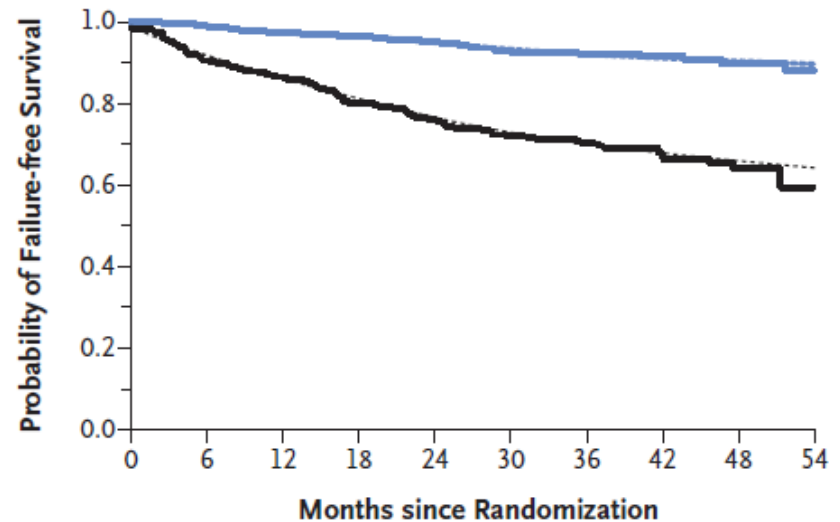
## Treatment of primary tumor

**E Overall Survival in Patients with Nonmetastatic Disease**



No. of Patients (no. of deaths)	0-6		6-12		12-18		18-24		24-30		30-36		36-42		42-48		48-54	
Combination therapy	460	(4)	448	(13)	425	(10)	285	(7)	80									
ADT alone	455	(2)	449	(8)	435	(19)	276	(13)	63									

**F Failure-free Survival in Patients with Nonmetastatic Disease**



No. of Patients (no. of treatment-failure events)	0-6		6-12		12-18		18-24		24-30		30-36		36-42		42-48		48-54	
Combination therapy	460	(12)	438	(10)	411	(12)	275	(3)	78									
ADT alone	455	(61)	389	(47)	337	(23)	201	(9)	39									

***No major concerns or unexpected local toxicity  
in combination arm (RT+ADT+AA)***

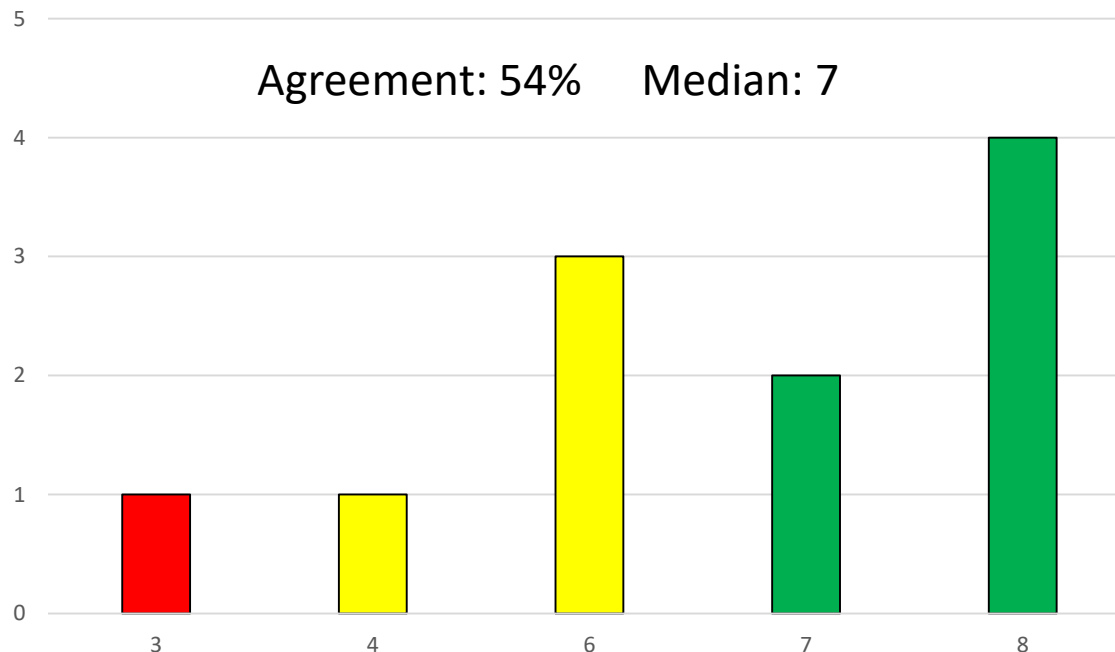
Stampede trial, *N Engl J Med* 2017;377:338-51.



# Scenario #1.2: Oligom+ PCa @ diagnosis

## Statement 1.2

*In an oligometastatic patient with three bone metastases candidate to androgen deprivation therapy plus Abiraterone Acetate and Prednisone, radiotherapy with radical intent to primary and metastatic sites could be offered together with androgen deprivation therapy plus Abiraterone Acetate and Prednisone*



# Clinical scenarios

- ✓ Oligometastatic castration sensitive disease at diagnosis with untreated primary
- ✓ **Oligometastatic castration sensitive disease after primary treatment (primary controlled)**
- ✓ Oligometastatic castration resistant disease at its first occurrence
- ✓ Oligoprogressive castration resistant disease in treatment with Androgen Receptor Target Agent (ARTA)





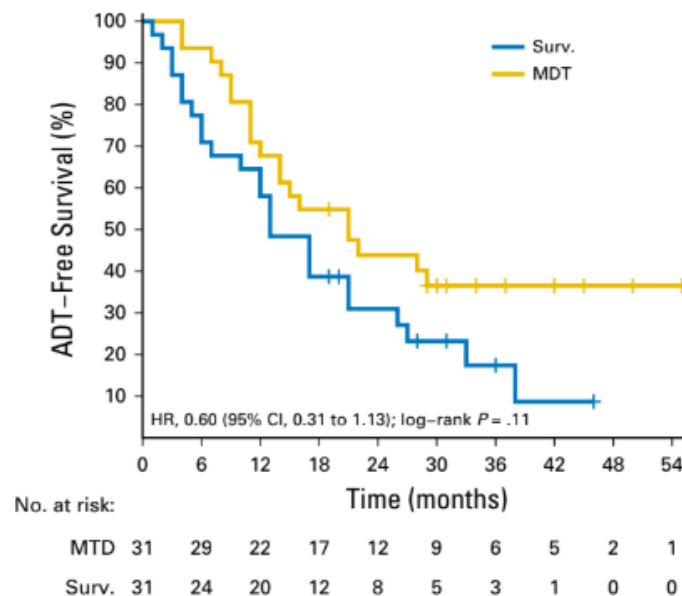
# Scenario #2: metachronous oligometastatic CSPC, primary controlled

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

## Surveillance or Metastasis-Directed Therapy for Oligometastatic Prostate Cancer Recurrence: A Prospective, Randomized, Multicenter Phase II Trial

- Biochemical recurrence after primary PCa treatment with curative intent
- < 3 extracranial metastatic lesions on choline positron emission tomography-computed tomography
- Patients were randomly assigned (1:1) to either surveillance or MDT of all detected lesions (surgery or stereotactic body radiotherapy).



Ost, Eur JCO, 2018



# Scenario #2: metachronous oligometastatic CSPC, primary controlled

European Journal of Cancer (2015) 51, 817–824



Available at [www.sciencedirect.com](http://www.sciencedirect.com)

ScienceDirect

journal homepage: [www.ejcancer.com](http://www.ejcancer.com)



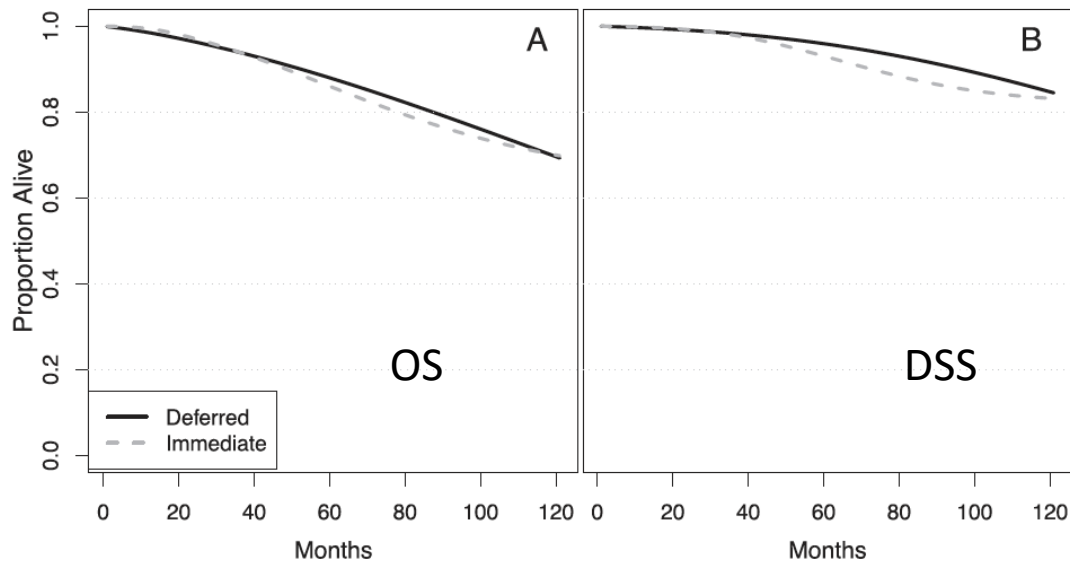
Immediate versus deferred initiation of androgen deprivation therapy in prostate cancer patients with PSA-only relapse. An observational follow-up study



X. Garcia-Albeniz<sup>a,\*</sup>, J.M. Chan<sup>b,c</sup>, A. Paciorek<sup>b</sup>, R.W. Logan<sup>a</sup>, S.A. Kenfield<sup>c</sup>,  
M.R. Cooperberg<sup>b,c</sup>, P.R. Carroll<sup>c</sup>, M.A. Hernán<sup>a,d,e</sup>



# Scenario #2: metachronous oligometastatic CSPC, primary controlled

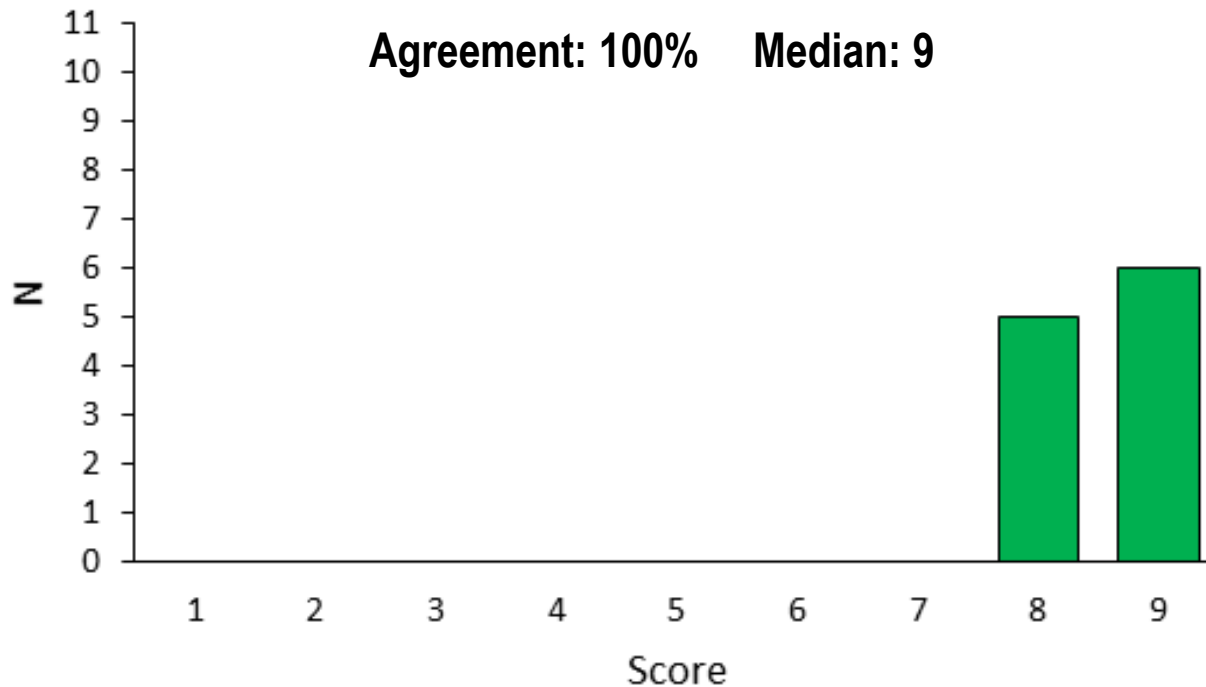


	Deferred ADT	Immediate ADT
Person-months	85,727	14,881
Deaths	140	33
Prostate cancer deaths	22	18
<b>All-cause mortality hazard ratio (95% confidence interval)</b>		
Unadjusted	1 (ref)	2.12 (1.42–3.17)
Adjusted for baseline variables <sup>a</sup>	1 (ref)	1.51 (0.99–2.33)
Adjusted for baseline- and time-varying <sup>b</sup> variables	1 (ref)	0.91 (0.52–1.60)
<b>Prostate cancer mortality hazard ratio (95% confidence interval)</b>		
Unadjusted	1 (ref)	7.57 (3.89–14.72)
Adjusted for baseline variables <sup>a</sup>	1 (ref)	4.65 (1.98–10.92)
Adjusted for baseline- and time-varying <sup>b</sup> variables	1 (ref)	1.09 (0.31–3.78)

## Scenario #2: metachronous oligometastatic CSPC, primary controlled

### Statement 2

*in an oligometastatic patient with primary tumor controlled, radiotherapy with radical intent to metastatic sites could be offered as alternative to androgen deprivation therapy to differ systemic treatment.*



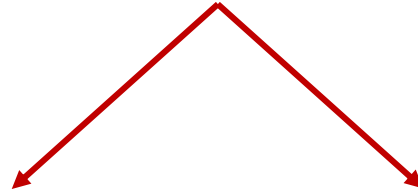
# Clinical scenarios

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# Scenario #3: Oligom+ CRPC (first occurrence)

Oligom+ CRPC @ first occurrence



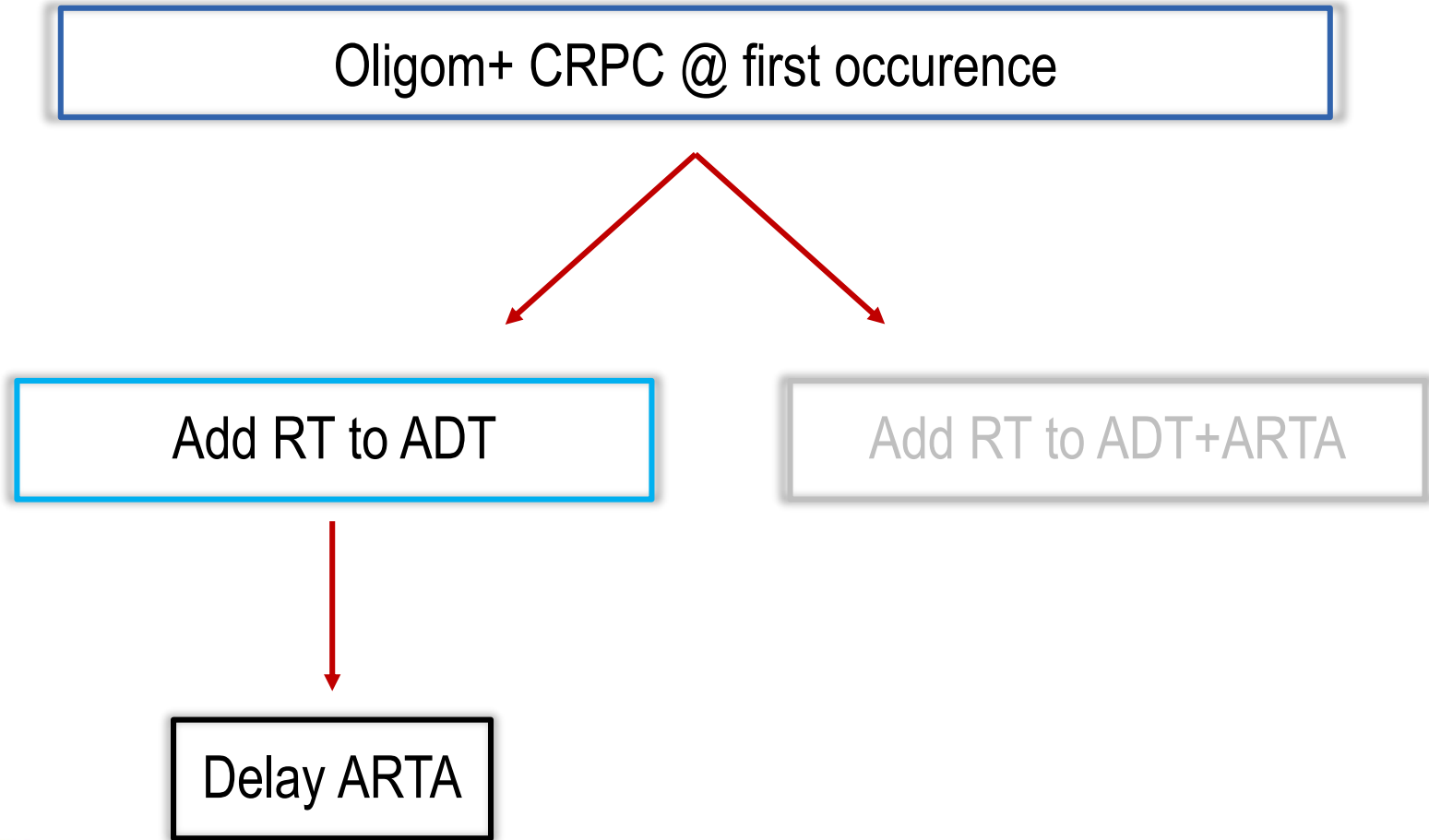
Add RT to ADT

Add RT to ADT+ARTA



Androgen Receptor Target Agent (ARTA)

# Scenario #3: Oligom+ CRPC (first occurrence)



# Scenario #3.1: Oligom+ CRPC (first occurrence)

## ADT+ additional tx vs. ADT + Ablative RT

### Results

#### ADT + AA/ENZA

# pts: 2805

**Efficacy** over placebo with:

OS: 35 mo

rPFS: 16-20 mo

#### ADT+Ablative RT

#pts: 107

**Activity** with:

Local control: 95%

dPFS: 11 mo

Ryan CJ et al, *Lancet Oncol* 2015 Feb;16(2):152-60  
Beer TM et al, *Eur Urol* 2017 Feb;71(2):151-54.

Muldermans et al. *Int J Radiat Oncol Biol Phys* 2016 Jun 1;95(2):696-702; Triggiani L et al *BJC* 2017,1-6 doi:10.1038





# Scenario #3.1: Oligom+ CRPC (first occurrence)

Oligom+ CRPC @ first occurrence

Add RT to ADT

Add RT to ADT+ARTA

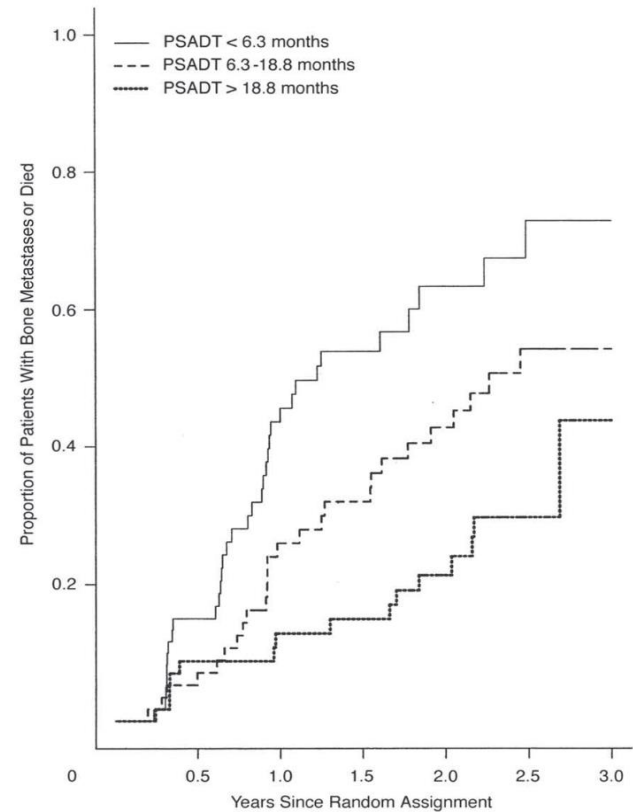
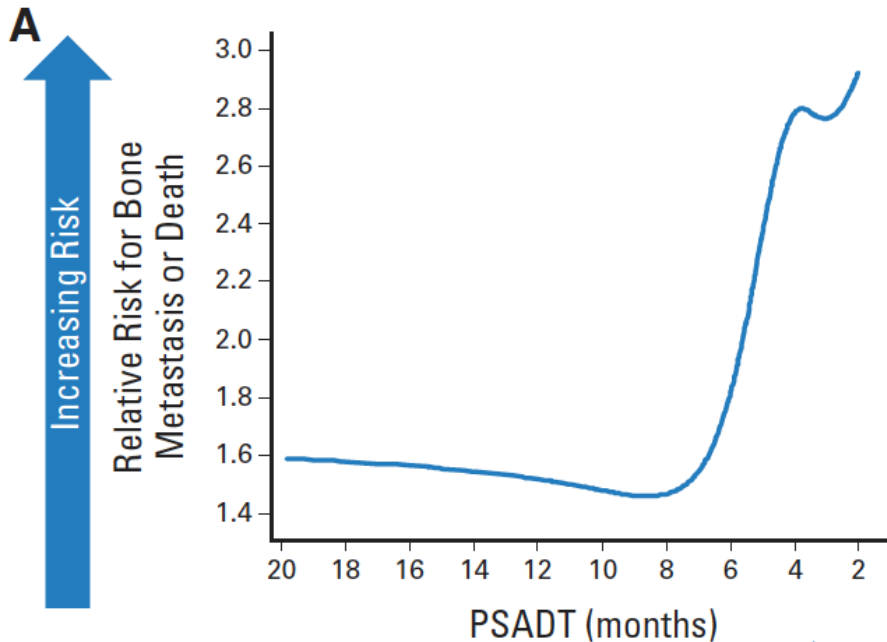
Delay ARTA → Which pt could benefit?



# Scenario #3.1: Oligom+ CRPC (first occurrence)

## Which patient could benefit adding RT to ADT only?

PSA-DT <6 mos & new bone mets



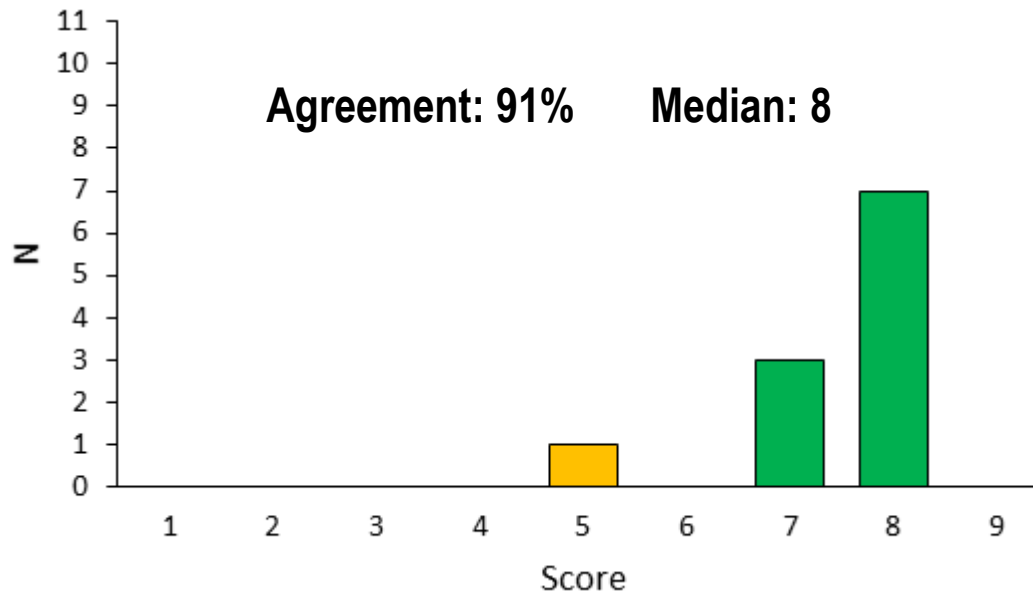
Smith MR et al. *J Clin Oncol* 2013;31:3800-06.  
Smith MR et al. *J Clin Oncol* 2005;23:2918-25.



# Scenario #3.1: Oligom+ CRPC (first occurrence)

## Statement 3.1

*In an asymptomatic or minimally symptomatic oligometastatic mCRPC patient, with a PSA doubling time > 6 months, time to castration resistant phenotype > 12 months, oligometastasis detected by metabolic imaging, radiotherapy with radical intent to metastatic sites could be offered as alternative to androgen receptor target agent to differ systemic treatment*



# Scenario #3: Oligom+ CRPC (first occurrence)

Oligom+ CRPC @ first occurrence

```
graph TD; A["Oligom+ CRPC @ first occurrence"] --> B["Add RT to ADT"]; A --> C["Add RT to ADT+ARTA"]; B --> D["Delay ARTA"];
```

Add RT to ADT

Add RT to ADT+ARTA

Delay ARTA

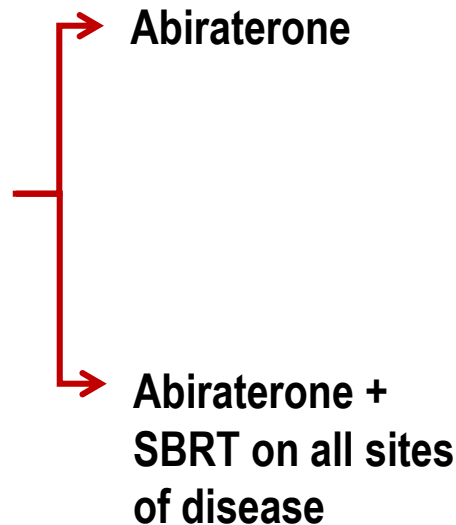


# Scenario #3.2: Oligom+ CRPC (first occurrence)

## Adding RT to ADT + AA, **activity**

ARTO trial (EUDRACT: 2016-005284-13)

- mCRPC
- < 3 lesions
- No visceral lesions
- No previous therapies for mCRPC (excluding OT)



### Primary endpoint

- PSA response rate

### Secondary endpoints

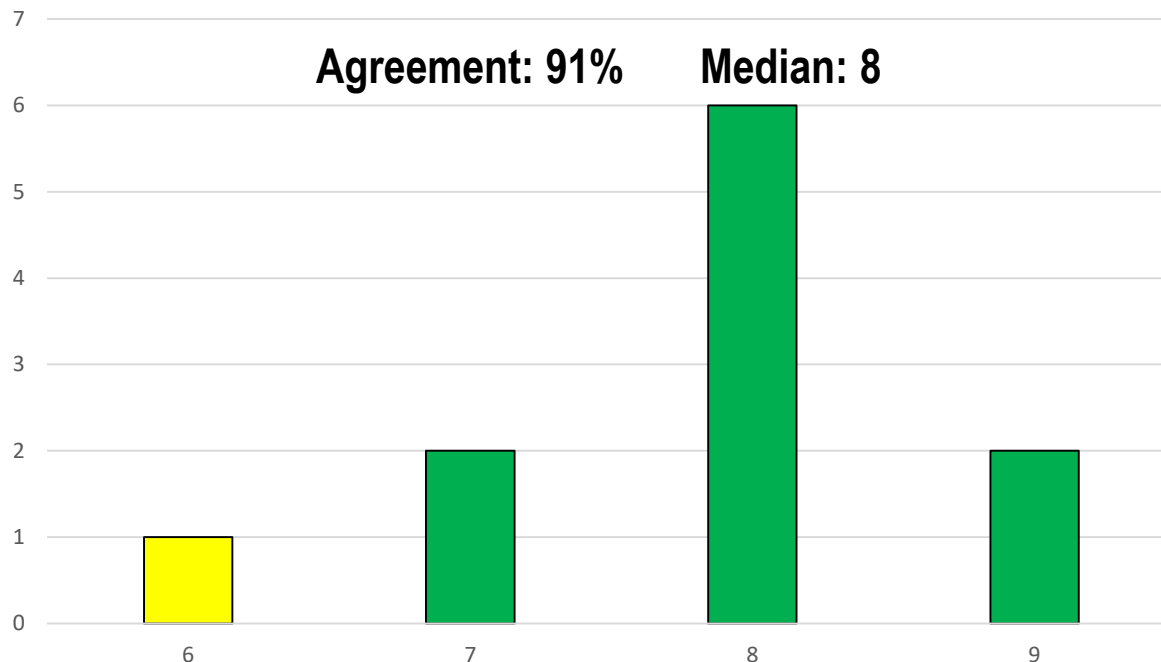
- The radiographic progression free survival (rPFS)
- Biochemical PFS
- SBRT+AA safety.
- OS
- Quality of life (QoL) (EORTC QLQ-C30)
- Presence/absence of symptoms (BPISF)



# Scenario #3.2: Oligom+ CRPC (first occurrence)

## Statement 3.2

*In an asymptomatic or minimally symptomatic oligometastatic mCRPC patient, candidate to androgen deprivation therapy plus ARTA, radiotherapy with radical intent to metastatic sites could be offered together with androgen deprivation therapy plus Abiraterone Acetate and Prednisone*



# Clinical scenarios

- ✓ Oligometastatic castration sensitive disease at diagnosis with untreated primary
- ✓ Oligometastatic castration sensitive disease after primary treatment (primary controlled)
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- ✓ **Oligoprogressive castration resistant disease in treatment with Androgen Receptor Target Agent (ARTA)**



# Scenario #4: Oligom+ CRPC in treatment with ARTA

VOLUME 34 • NUMBER 12 • APRIL 20, 2016

JOURNAL OF CLINICAL ONCOLOGY

SPECIAL ARTICLE

Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations From the Prostate Cancer Clinical Trials Working Group 3

## RECOMMENDATION FROM THE PROSTATE CANCER CLINICAL WORKING GROUP 3 (2016):

**In cases in which multiple sites of disease continue to respond but one to two sites grow, focal therapy such as radiation or surgery could be administered to the resistant site(s) and systemic therapy continued.**

*Scher, JCO, 2016*





# Scenario #4: Oligom+ CRPC in treatment with ARTA

## Statement 4

*In an asymptomatic or minimally symptomatic oligoprogressive mCRPC patient, up to two nodal or bone lesions, in treatment with ARTA from at least from 6 months, radiotherapy with radical intent to sites of progressive disease could be offered as alternative to change of systemic treatment.*

