Optimal Integration of Chemotherapy into the Management of Metastatic Prostate Cancer

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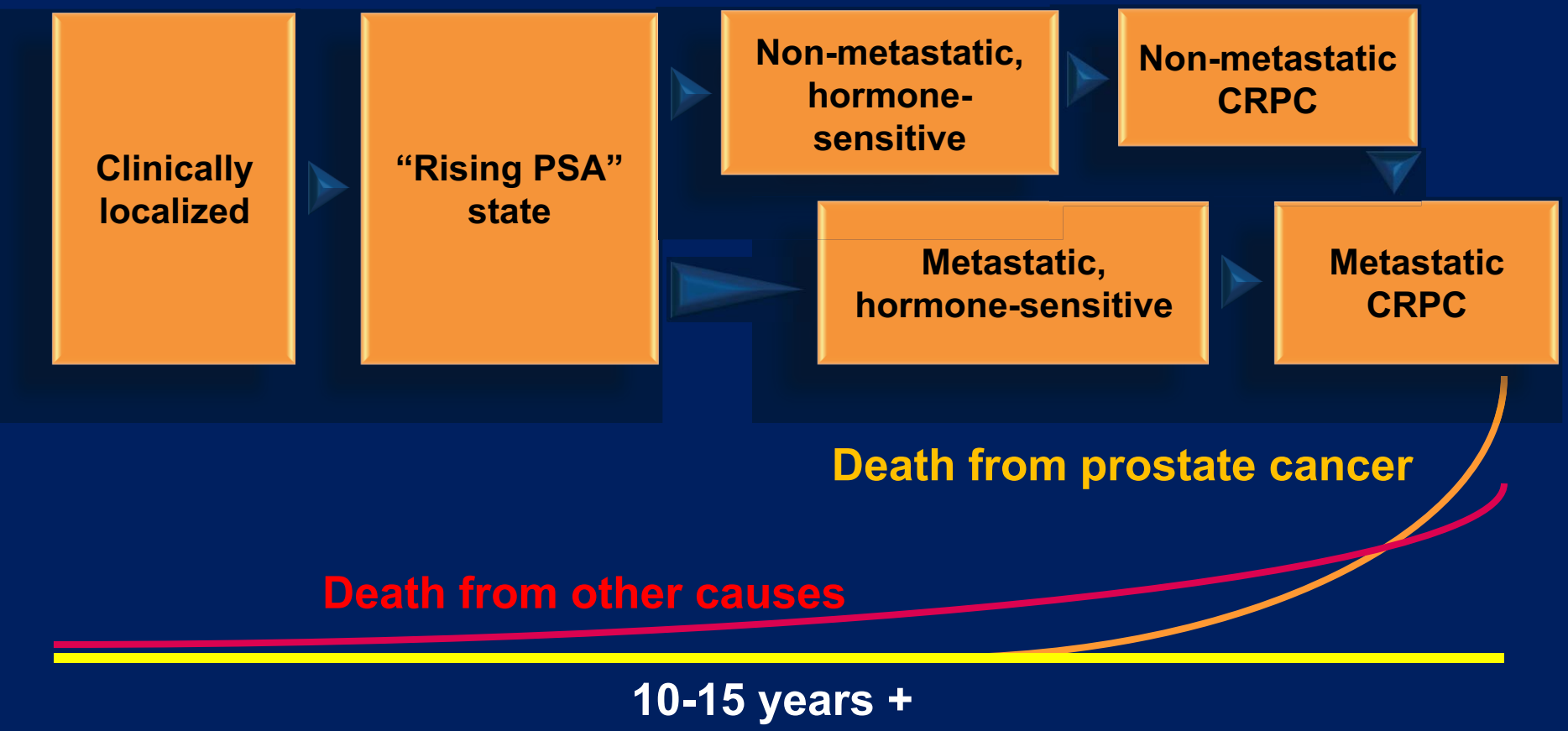
Disclosures

Consulting Agreements	Astellas Pharma Global Development Inc, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Churchill Pharmaceuticals LLC, Inovio Pharmaceuticals Inc, Janssen Biotech Inc, Sanofi Genzyme, Tokai Pharmaceuticals Inc

Clinical States of Prostate Cancer



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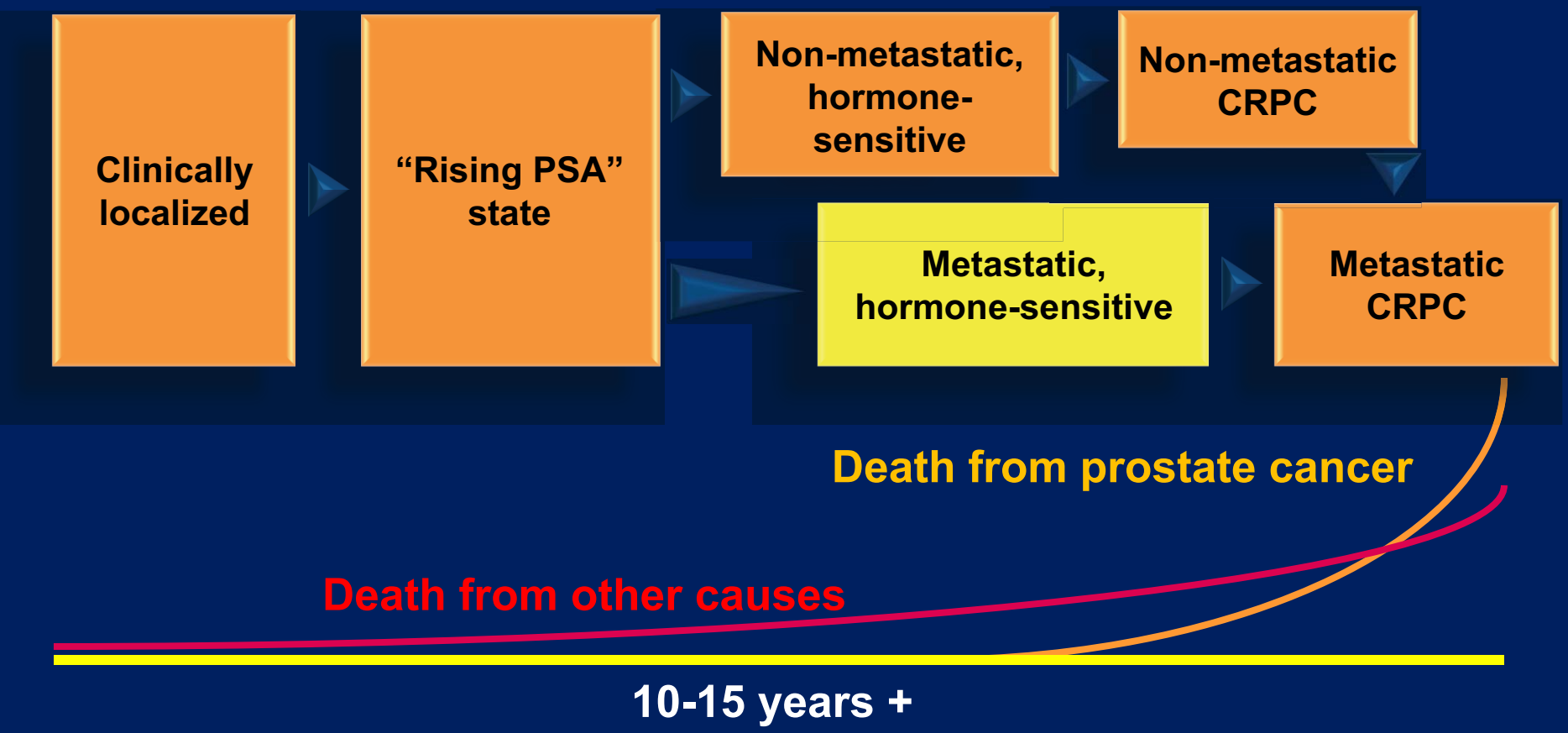
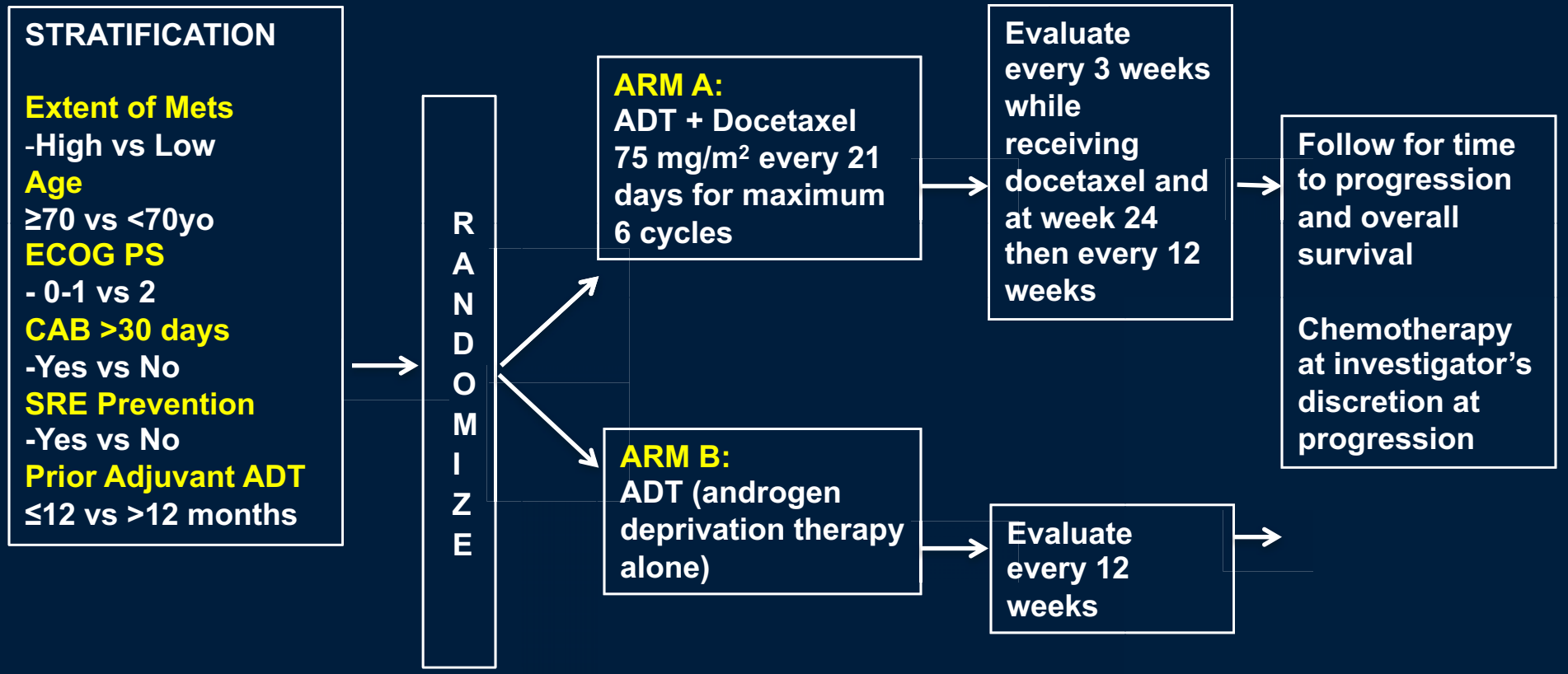


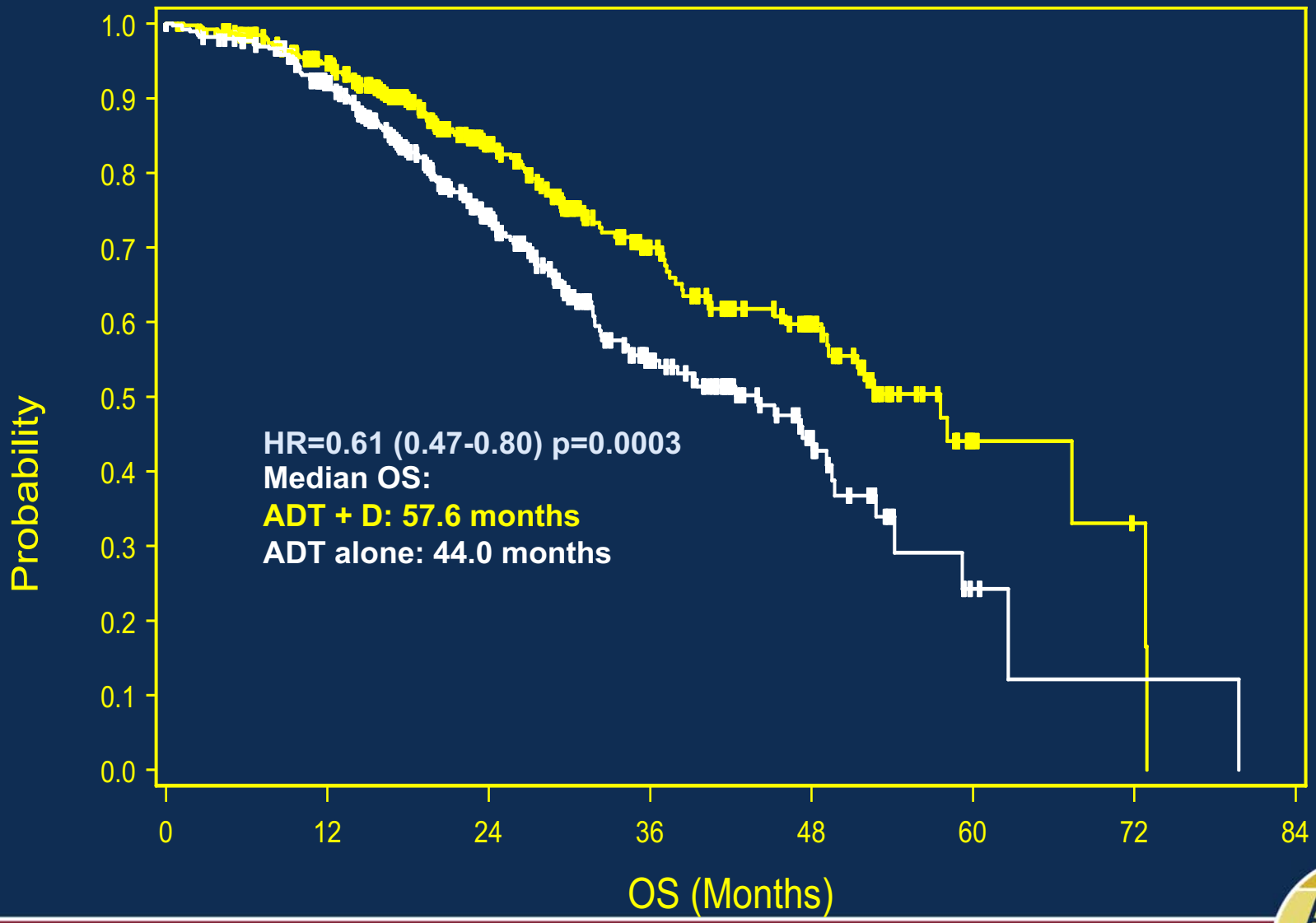
What Is The Role Of Chemotherapy For Newly Diagnosed Metastatic Prostate Cancer?

E3805 – CHAARTED Treatment



- ADT allowed up to 120 days prior to randomization
- Intermittent ADT dosing was not allowed
- Standard dexamethasone premedication but no daily prednisone

Primary endpoint: Overall survival



CHAARTED: Low vs High Volume

Survival	ADT + D	ADT	p-value
LV Deaths / N (%)	51/134 (38.1%)	49/143 (34.3%)	
LV Median OS mos	63.5 (58.3, 78.5)	NR (59.8, -)	0.86
HV Deaths / N (%)	137/263 (52.1%)	162/250 (64.8%)	
HV Median OS mos	51.2 (45.2, 58.1)	34.4 (30.1, 42.1)	<0.0001

Sweeney et al. ESMO 2016

STAMPEDE

Comparison

Open: Oct-2005

Closed: Mar-2013

Accrual: 2962

Number of patients

1184 **A** Standard-of-care (SOC)

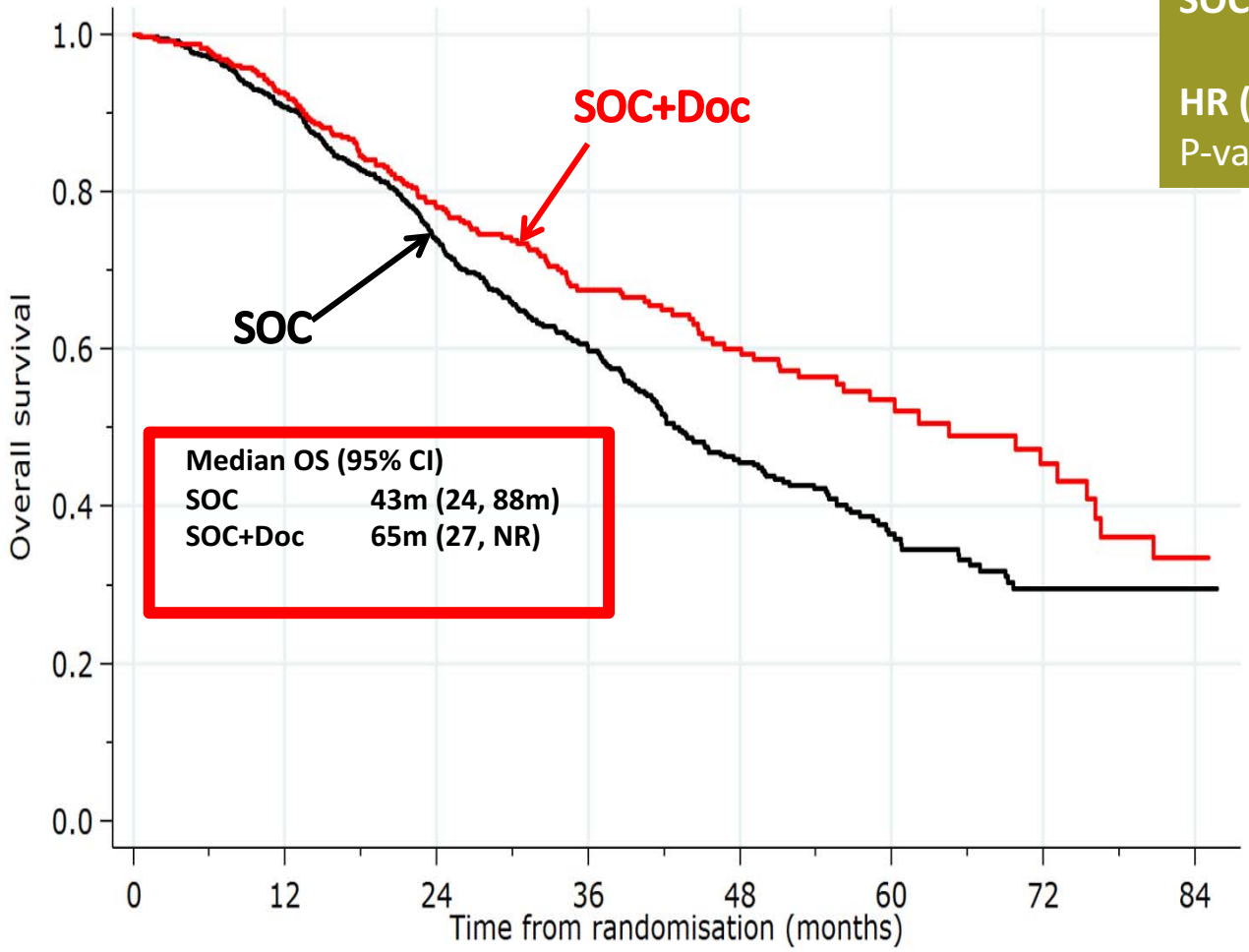
593 **B** SOC + zoledronic acid

592 **C** SOC + docetaxel

593 **E** SOC + zoledronic acid + docetaxel

Docetaxel: Survival – M1 Patients

SOC	**343 deaths**
SOC+Doc	**134 deaths**
HR (95% CI)	**0.73** (0.59, 0.89)
P-value	**0.002**



Median OS (95% CI)

SOC	**43m (24, 88m)**
SOC+Doc	**65m (27, NR)**

Non-PH p-value 0.23

Group
At risk (events)

SOC	725	(66)	645	(117)	469	(75)	254	(52)	134	(21)	58	(10)	24	(0)	10
SOC+Doc	362	(27)	326	(49)	242	(27)	151	(13)	91	(8)	37	(5)	24	(5)	9

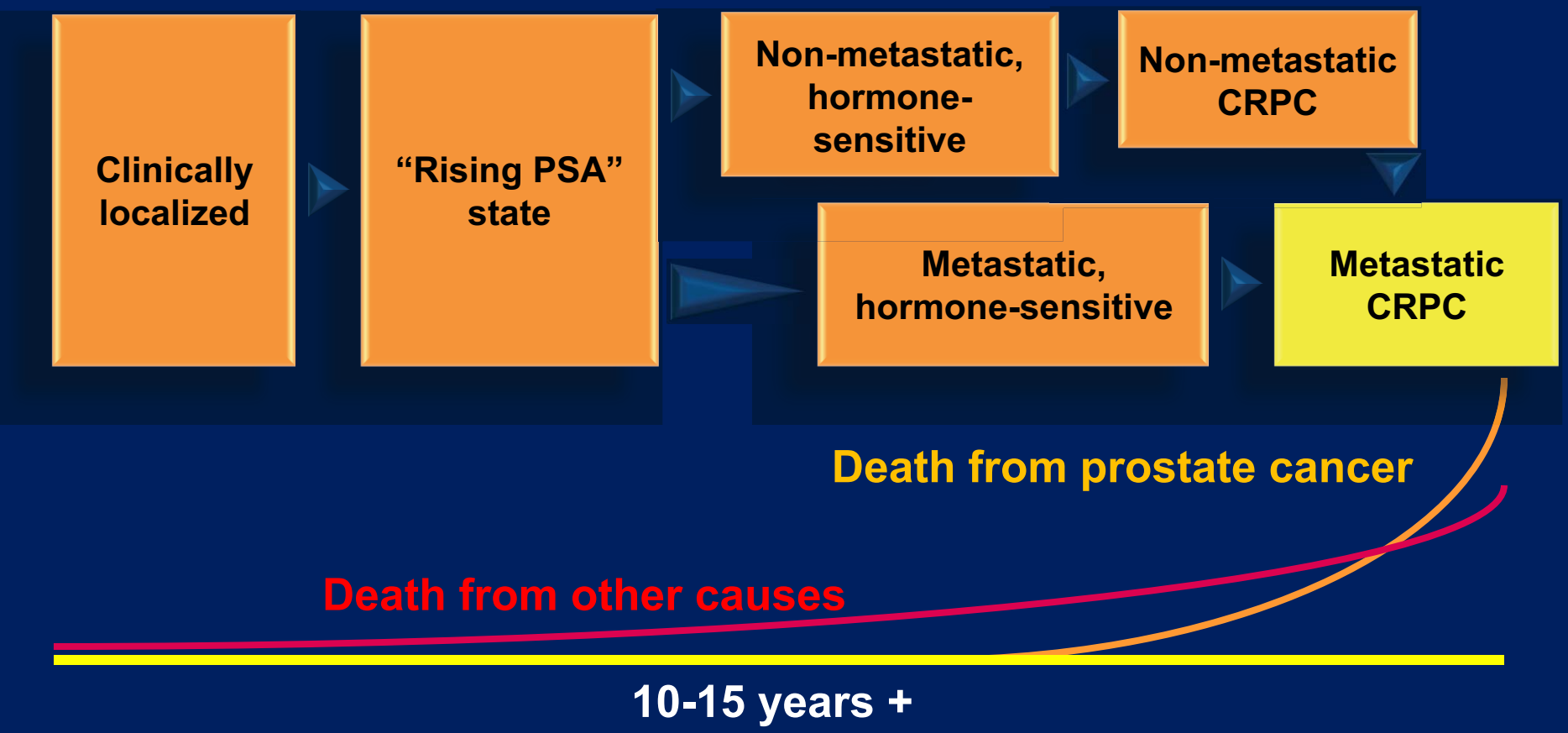
Restricted mean OS time

SOC	49.3m
SOC+Doc	56.1m
Diff (95% CI)	6.8m (2.8, 11.0m)

How do disease volume, symptoms, age factor into chemo decision in mHSPC?

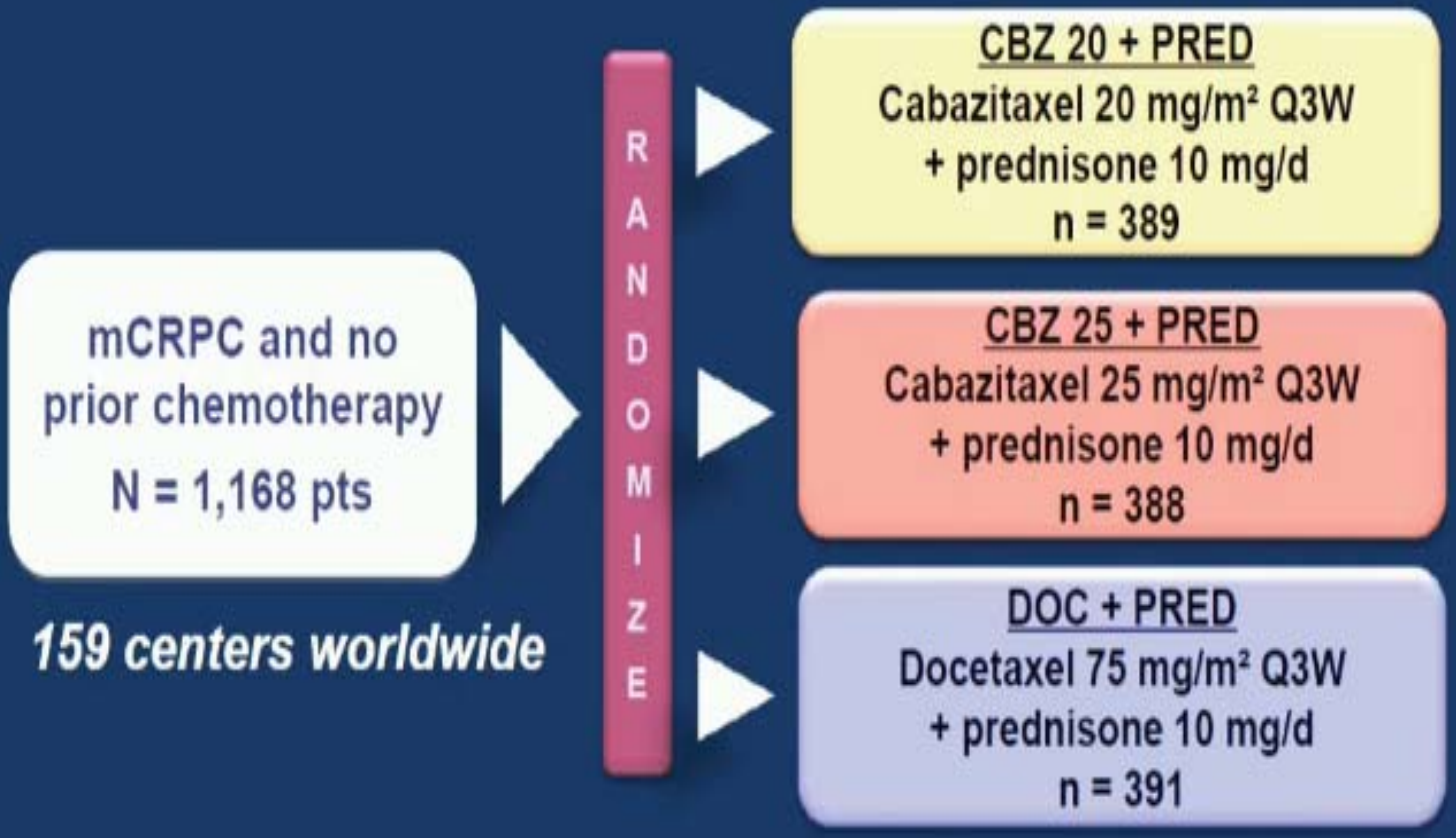
- Low vs high volume is a consideration
- Symptoms are a negative prognostic factor and will push me more towards chemo
- Age has to be a consideration
  - No absolute upper limit for chemo tolerance
  - Dose adjust or add G-CSF, as needed

Clinical States of Prostate Cancer

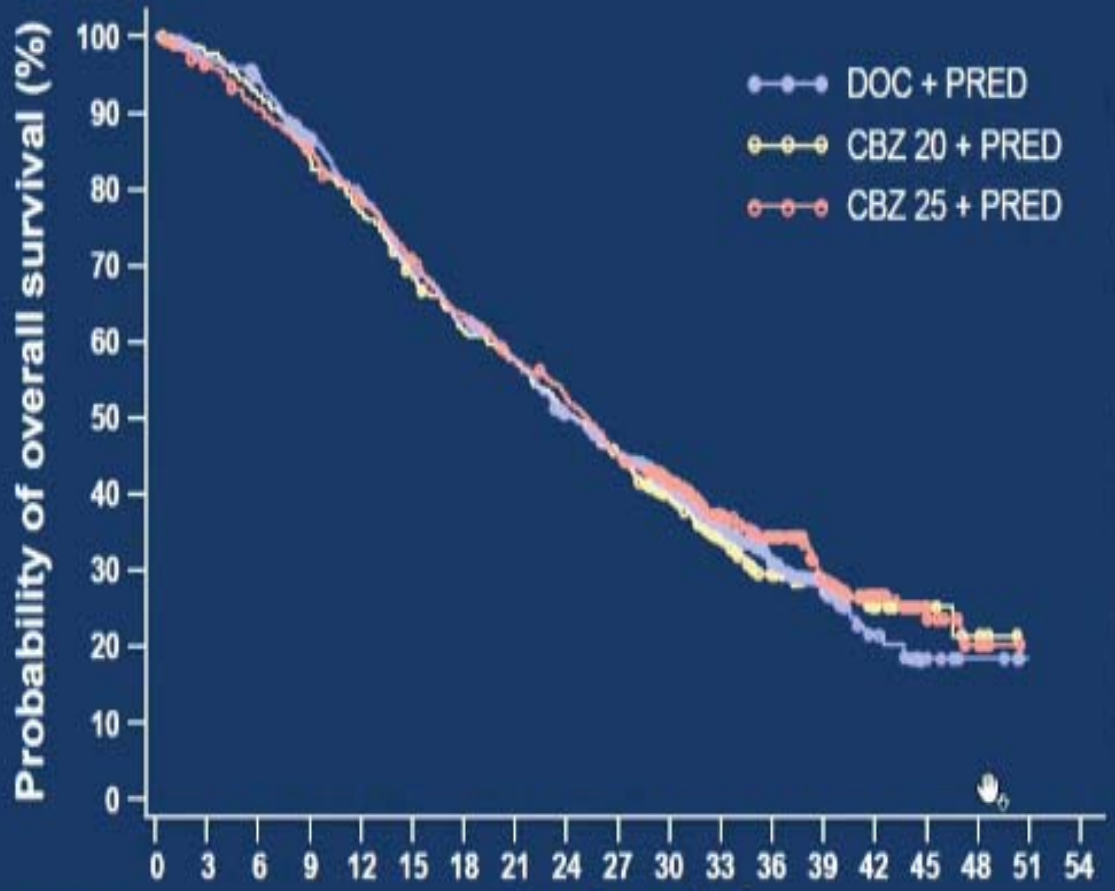


So What Is The Optimal Use Of Chemotherapy for mCRPC?

FIRSTANA: Study Design



FIRSTANA: Overall Survival



Number at risk										
DOC + PRED	391	366	336	307	243	192	133	57	18	3	0
CBZ 20 + PRED	389	356	319	296	234	192	133	49	19	3	0
CBZ 25 + PRED	388	345	325	296	239	197	138	70	28	5	0

Median OS, months (95% CI)

DOC + PRED **24.3** (22.18–27.60)

CBZ 20 + PRED **24.5** (21.75–27.20)

CBZ 25 + PRED **25.2** (22.90–26.97)

CBZ 20 vs DOC

HR 1.009 (0.85–1.197)

P = 0.9967

CBZ 25 vs DOC

HR 0.97 (0.819–1.16)

P = 0.7574

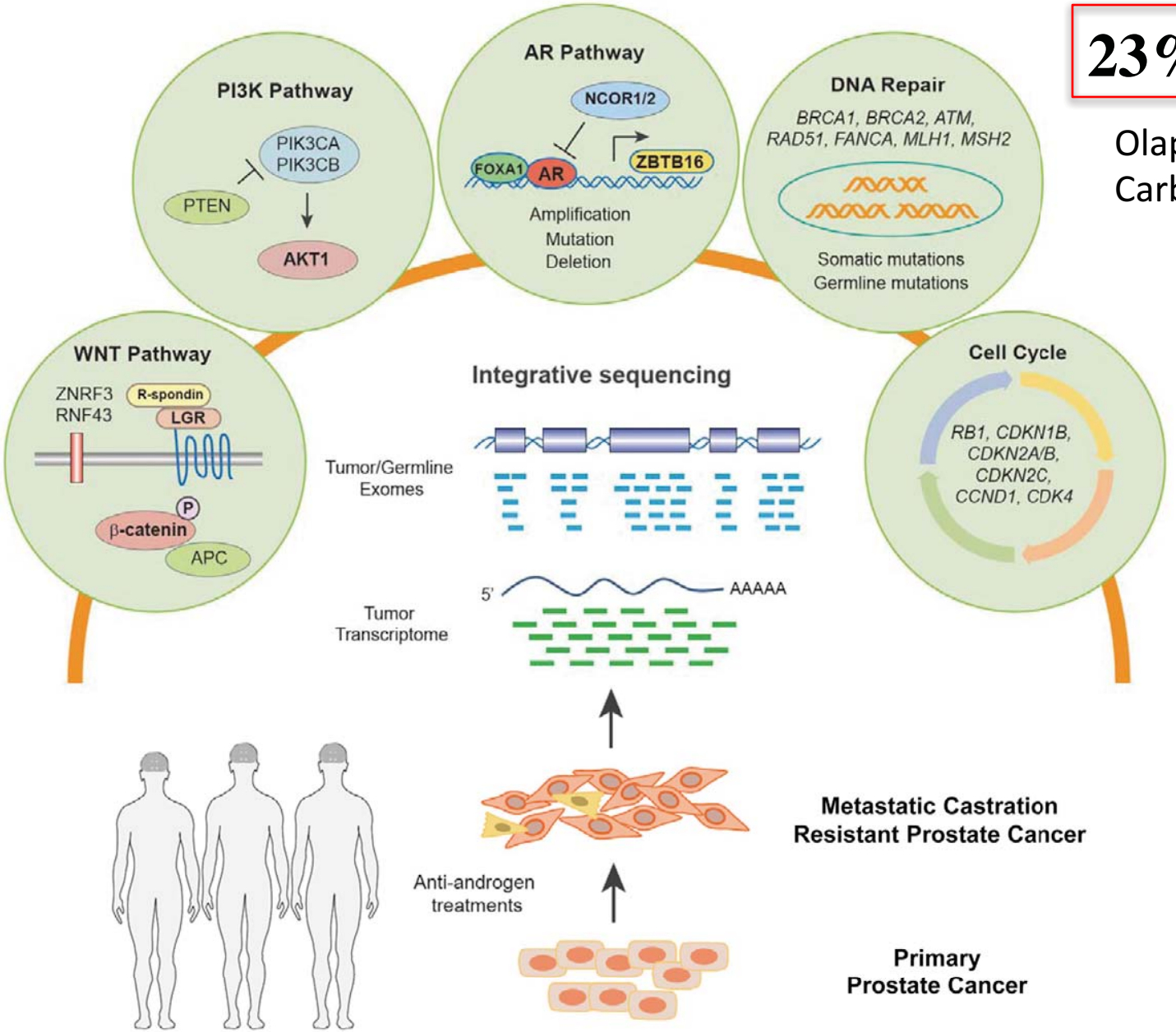
FIRSTANA: Selected Toxicities (%)

TOXICITY	DOC + PRED	CBZ 20 + PRED	CBZ 25 + PRED
Febrile neutropenia	8.3	2.4	12.0
Diarrhea	37.0	32.5	49.9
Hematuria	3.6	20.3	25.1
Peripheral neuropathy	25.1	11.7	12.3
Peripheral edema	20.4	9.8	7.7
Alopecia	39.0	8.9	13.0
Nail disorder	9.0	0.3	0.8

Conclusions

- Therapeutic targeting of tubulins is clinically relevant
  - Docetaxel, cabazitaxel
- Cabazitaxel is equivalent to docetaxel in first line mCRPC
- Should differential toxicity profiles play a role in the selection of a taxane?

Can Molecular Defects in CRPC Drive Therapeutic Choice?

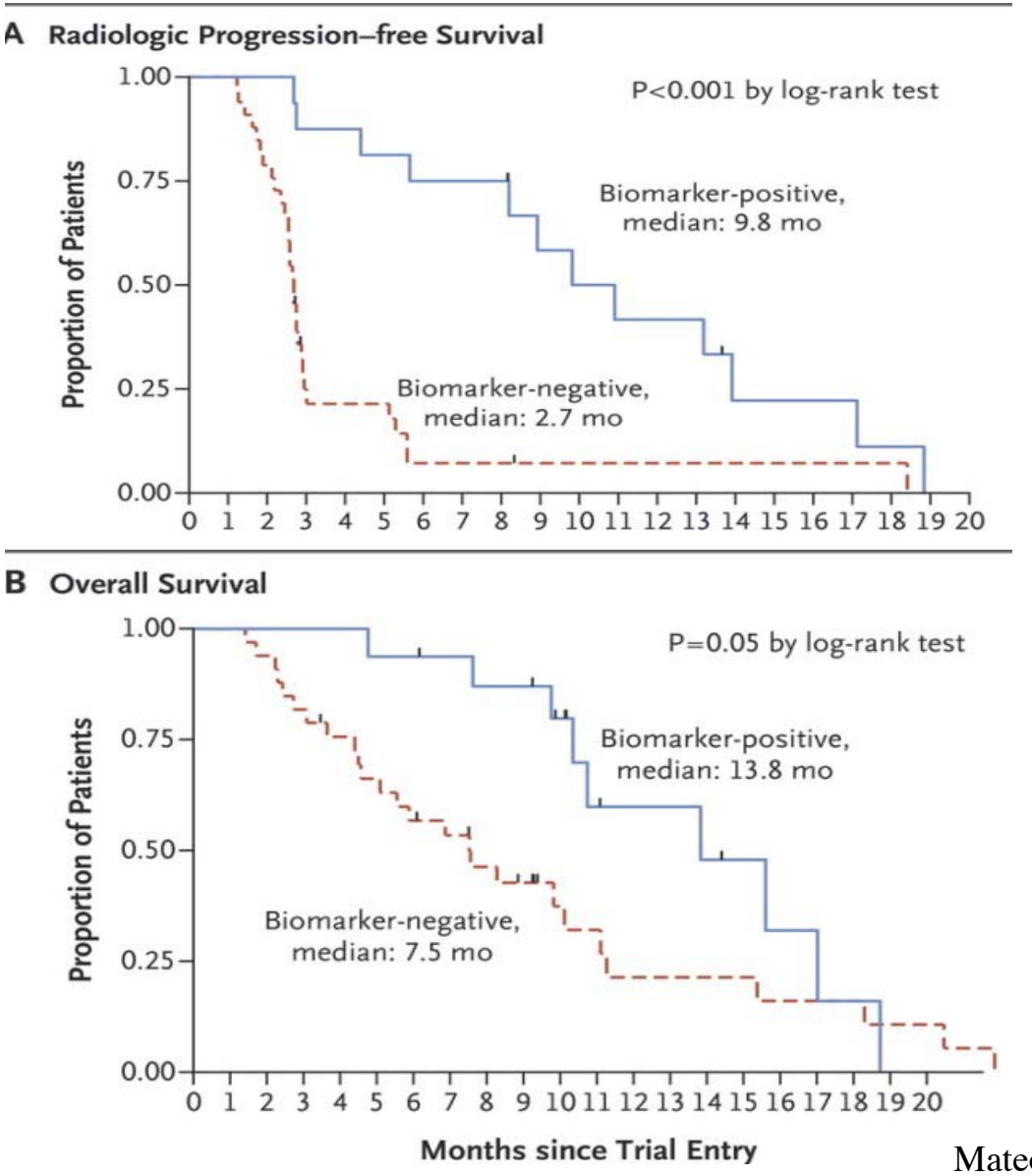


23%

Olaparib
Carboplatin

Robinson Cell 161:1215, 2015

DNA Repair Defects → Olaparib Benefit



Mateo NEJM 373:1697, 2015

Carboplatin in mCRPC

- N = 141 patients rx'd: carbo +/- docetaxel
- 8 (5.7%) with germline BRCA2 mutations
  - 63% had PSA response to carbo
  - 17% of non-BRCA2 carriers
  - p = 0.008
- Should BRCA2 carriers with prostate cancer receive carboplatin?

Pomerantz et al (Submitted)

Treatment Landscape