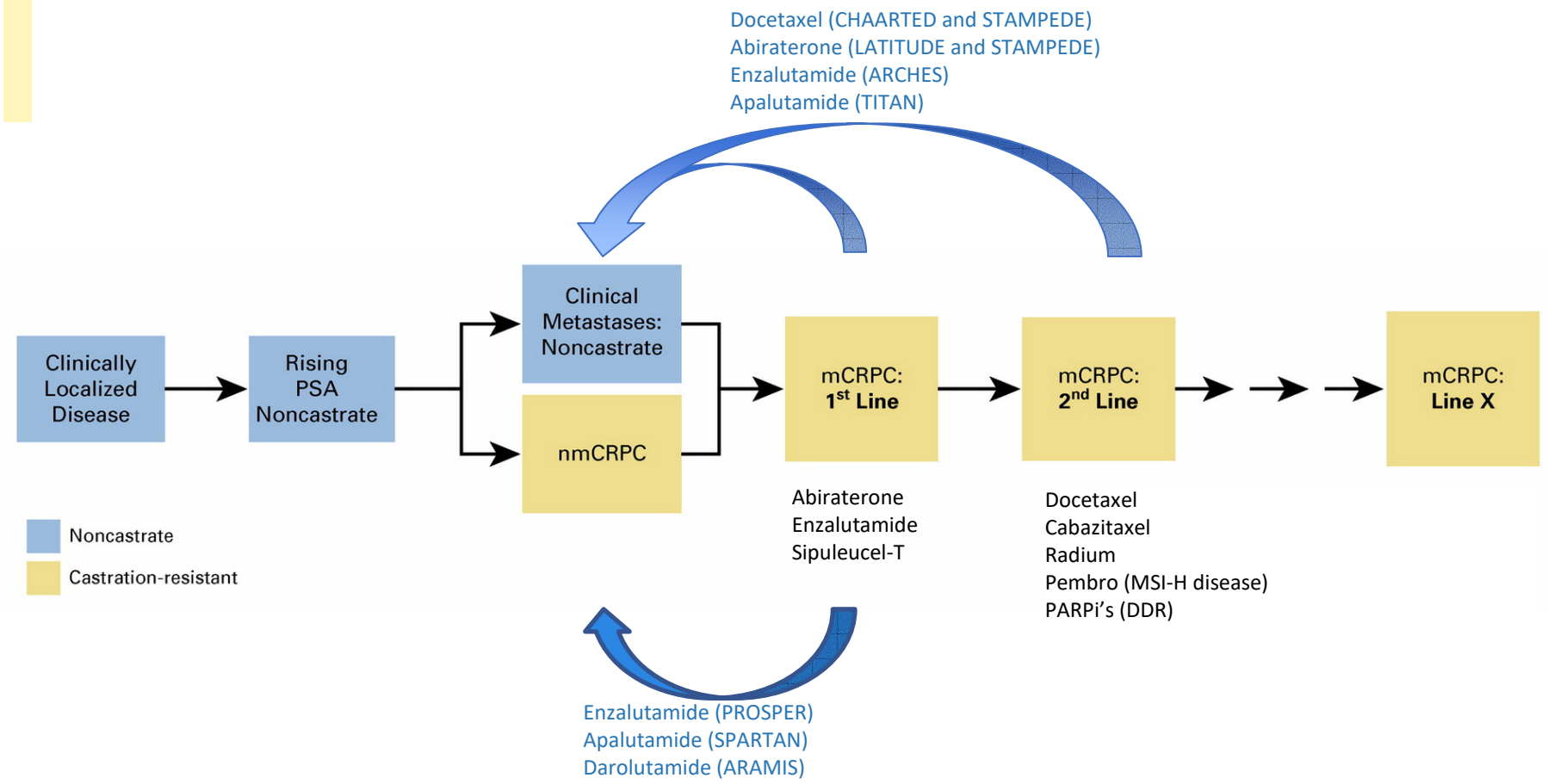
New Insights Into The Biology And Treatment Of Advanced Prostate Cancer

Philip Kantoff, MD
Chairman of Medicine
Memorial Sloan Kettering Cancer Center

10 Major Changes Since 2010

- Increased basic science understanding of PC
- Improved understanding genetics/genomics of PC
- Magnetic Resonance Imaging (MRI) targeted imaging of the prostate
- Acceptance of active surveillance as treatment option
- Robotic prostatectomy
- IMRT/Image-guided radiation
- Improved targeting of androgen receptor (AR)
- Intensified treatment of hormone-sensitive metastatic PC
- Numerous approvals of agents and strategies for castration resistant PC (CRPC)
- Radiopharmaceutical imaging and targeted therapies

The Landscape of Prostate Cancer Treatment



Classes of Agents

- Hormonal
  - Abiraterone, enzalutamide, apalutamide, darolutamide
- Cytotoxic
  - Docetaxel, cabazitaxel
- DNA Damage
  - Rad-223
  - PSMA directed therapy
  - Olaparib, rucaparib
- Immunotherapeutic
  - Sipuleucel-T
  - Pembrolizumab MSI high
  - CPIs

Factors that determine how we sequence these agents in mCRPC?

- Clinical Characteristics
  - How did the patient progress to mCRPC?
    - If progressed from nmCRPC to mCRPC, likely to be more indolent disease
    - If progressed from mHSPC to mCRPC, likely to be more aggressive
  - What if any additional therapy was given with ADT?
  - Asymptomatic/mildly symptomatic vs Asymptomatic
  - Visceral (Liver) vs Non-Visceral
  - Pre vs Post Docetaxel
  - Comorbidities
- Biological Factors
  - Germline abnormalities eg *BRCA2*
  - Other DNA Repair abnormalities (germline or somatic)
  - MSI-high, TMB high
  - *RB1*/P53/*PTEN* loss or mutated
  - AR markers-AR amplified/AR V7
  - PTEN loss

Peter Nelson, MD
Dream Team Principal
University of Washington /

FRED HUTCHINSON CANCER RESEARCH CENTER

rul Chinnaiyan, MD, PhD
Dream Team Co-Leader
University of Michigan

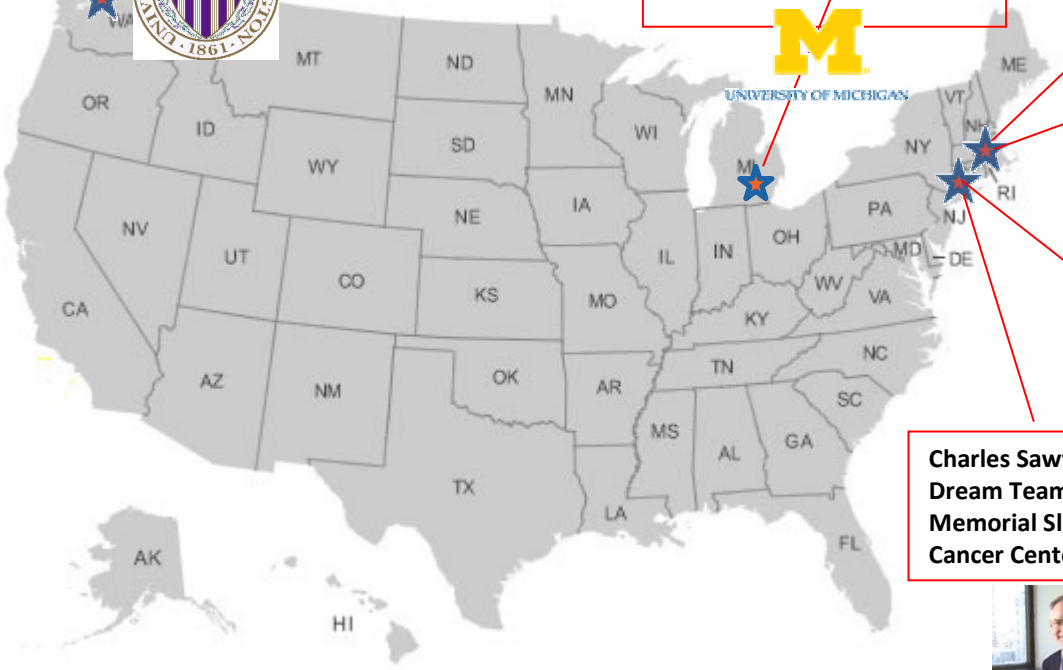
UNIVERSITY OF MICHIGAN

Levi Garraway, MD, PhD
Dream Team Principal
The Broad Institute

BROAD INSTITUTE

DANA-FARBER CANCER INSTITUTE

Philip Kantoff, MD
Dream Team Principal
Dana Farber Cancer Institute



Mark Rubin, MD
Dream Team Principal
Weill Cornell

Johann de Bono, MD, PhD
Institute of Cancer Research/
Royal Marsden Hospital

Charles Sawyers, MD
Dream Team Co-Leader
Memorial Sloan Kettering
Cancer Center

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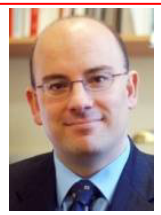

ICR The Institute of Cancer Research

THE ROYAL MARSDEN

SU2C/PCF International Prostate Cancer Team

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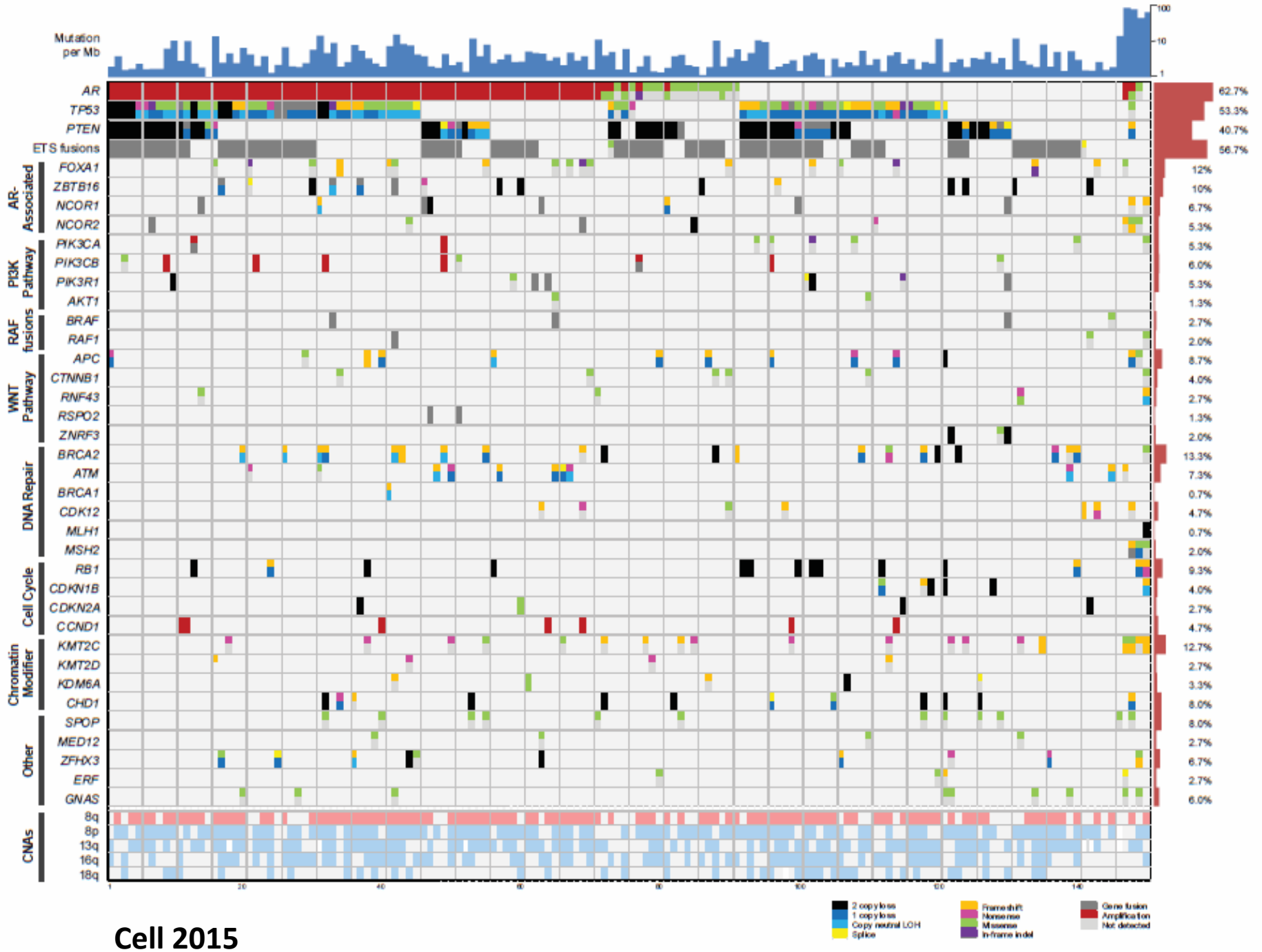
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RAF fusions
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WNT Pathway
APC
CTNNB1
RNF43
RSPO2
ZNRF3
DNA Repair
BRCA2
ATM
BRCA1
CDK12
MLH1
MSH2
Cell Cycle
RB1
CDKN1B
CDKN2A
CCND1
Chromatin Modifier
KMT2C
KMT2D
KDM6A
CHD1
Other
SPOP
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Splice
Frameshift
Nonsense
Missense
In-frame indel
Gene fusion
Amplification
Not detected

Cell 2015

Classes of Agents

- Hormonal
  - Abiraterone, enzalutamide, apalutamide, darolutamide

J Natl Cancer Inst. 2020 Aug 28;djaa134. doi: 10.1093/jnci/djaa134. Online ahead of print.

Inferences about drug safety in phase 3 trials in oncology: Examples from advanced prostate cancer

Joshua Z Drago [1], Mithat Gönen [2], Gita Thanarajasingam [3], Chana A Sacks [4], Michael J Morris [1] [5], Philip W Kantoff [1] [5], Konrad H Stopsack [1]

Affiliations + expand

PMID: 32857839 DOI: 10.1093/jnci/djaa134

Classes of Agents

- Hormonal
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Classes of Agents

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  - Rad-223
  - PSMA directed therapies
  - Olaparib, rucaparib

Radium-223-Conclusions

- Radium-223:
  - Significantly prolonged median OS
  - Significantly prolonged median time to first SRE by 5.5 months
  - Benefit to pre and post chemotherapy patients
  - It has not been widely used

Radium-223-Questions

- Radium-223:
  - Rare declines in PSA
  - Given over 6 months
  - Optimal timing
  - Can it be used earlier successfully and safely
  - Can it be successfully combined with other agents

Ra-223 PLUS

ERA 223

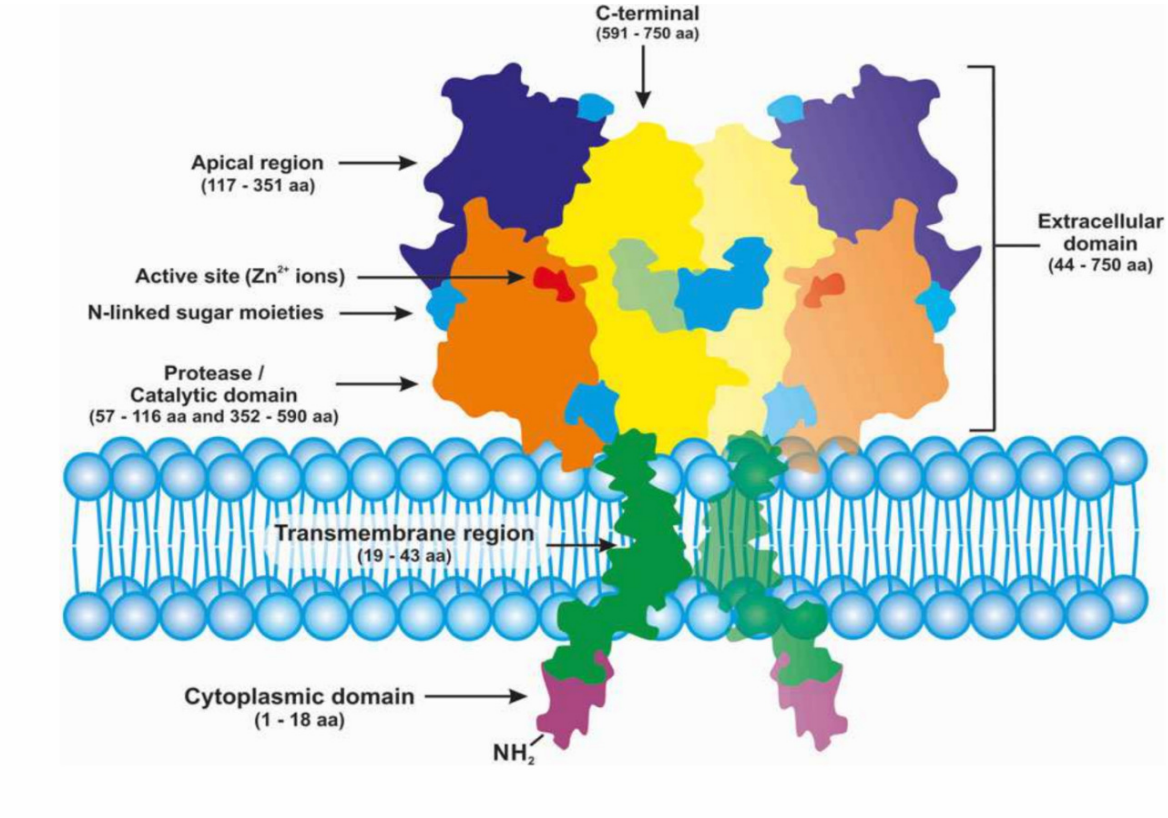
- Phase 3 trial, 1:1 randomization abiraterone plus Ra-223 versus abiraterone alone, 806 patients
- Primary endpoint: symptomatic skeletal event-free survival
  - 22.3 mos vs 26 mos, HR:1.122, p=0.26
- Secondary endpoints: OS, rPFS, time to opiate use for cancer pain, time to cytotoxic chemotherapy
  - OS: 30.7 mos vs 33.3 mos
- Combination increased bone fragility (fractures 28.6% vs 11.4%) and deaths (38.5% vs 35.5%)

PEACE-3

- Phase 3, 1:1 randomization enzalutamide plus Ra-223 versus enzalutamide alone, 560 patients
- Primary endpoint: rPFS
- Secondary endpoints: OS, first symptomatic skeletal event, time to initiation of next systemic therapy
- Combination increased fracture risk to 33% (from 13%)
- Use of mandatory continuous bone protecting agents starting at least 6 weeks prior to first injection reduced risk to almost zero

Smith M et al. Lancet Oncol 20:408-419. Tombal B et al. J Clin Oncol.37:suppl_abs 5007 (oral presentation).

Targeting PSMA: Transmembrane Protein



Evans JC et al, Br J Pharmacol. 2016;173(21):3041-3079.

Component Options
Radionuclide pharmacy

Two clinically validated *Targeting* options for PSMA

- Small molecule ligands (SML) that bind the enzymatic pocket
  - PSMA-617
  - PSMA-I&T
- Antibodies
  - e.g. J591

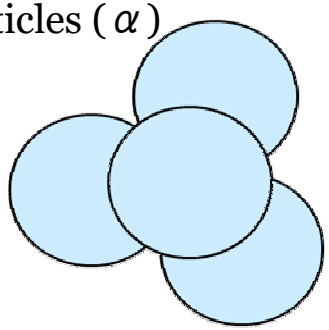
Two clinically validated *Payload* (radionuclide) options

- Beta particles (β)

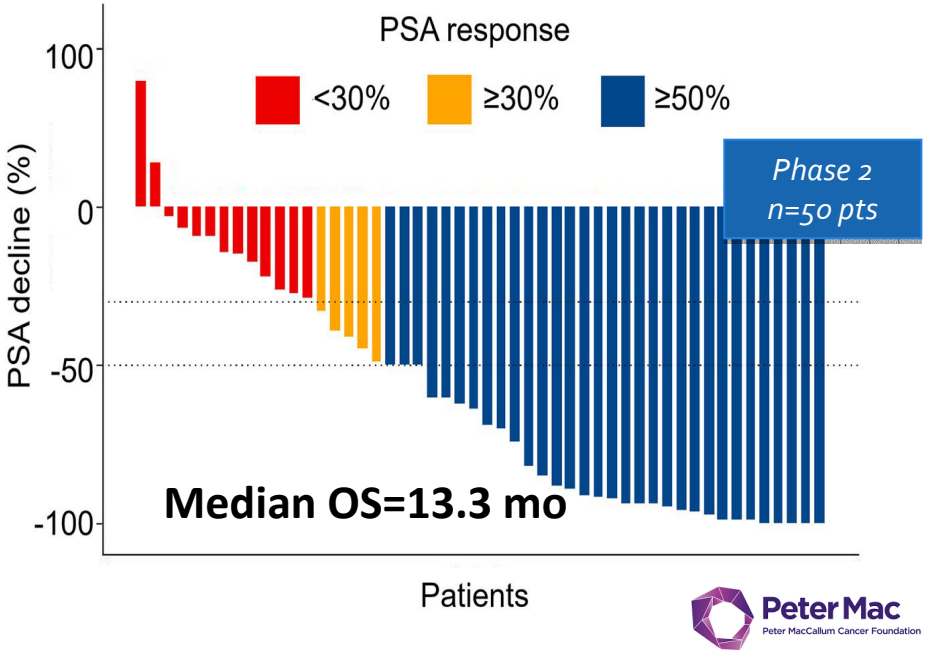
e.g. Lu^{177}

- Alpha particles (α)

e.g. Ac^{225}



SML RNT in advanced prostate cancer
PSMA-617 $Lu^{177}(\beta)$: Phase 2 results



Heavily pre-treated patients

Highly selected [FDG-, PSMA+ PET]—30% rejected

Dose every 6 weeks x 4 (47% of subjects got 4 doses)

Toxicity= grade 1-2 dry mouth in 87%

Phase 3 registration trial by Novartis awaiting data release

Source: 1.) Hofman M et al. *Lancet Oncol*. 2018;19(6):825-833.; 2.) Violet J et al. *J Nucl Med.* 2020;61(6):857-865.

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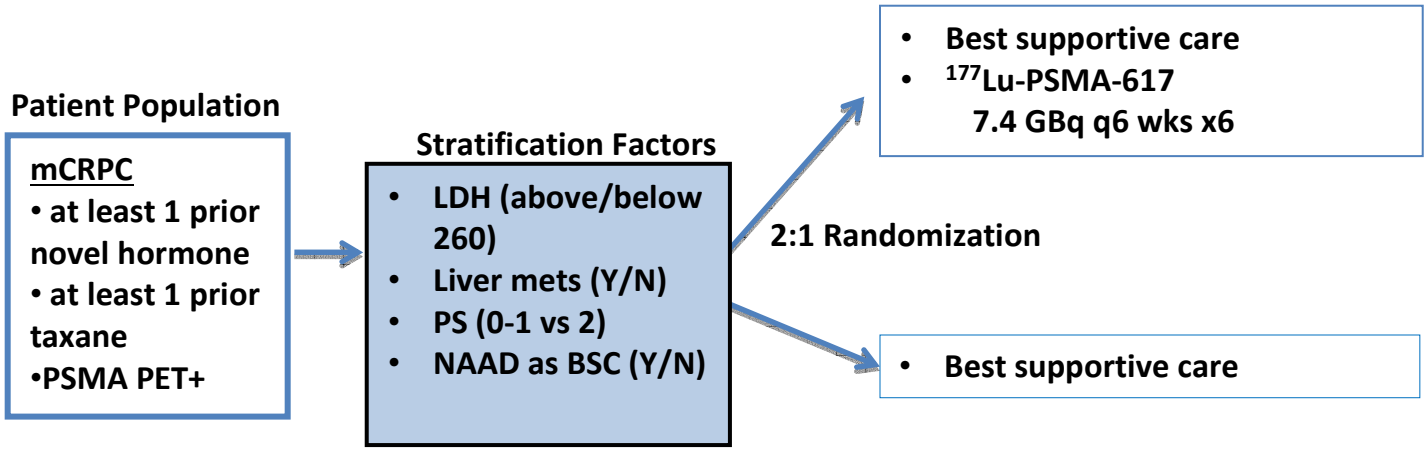
PSMA-Lu-177 Pivotal Phase III VISION Trial



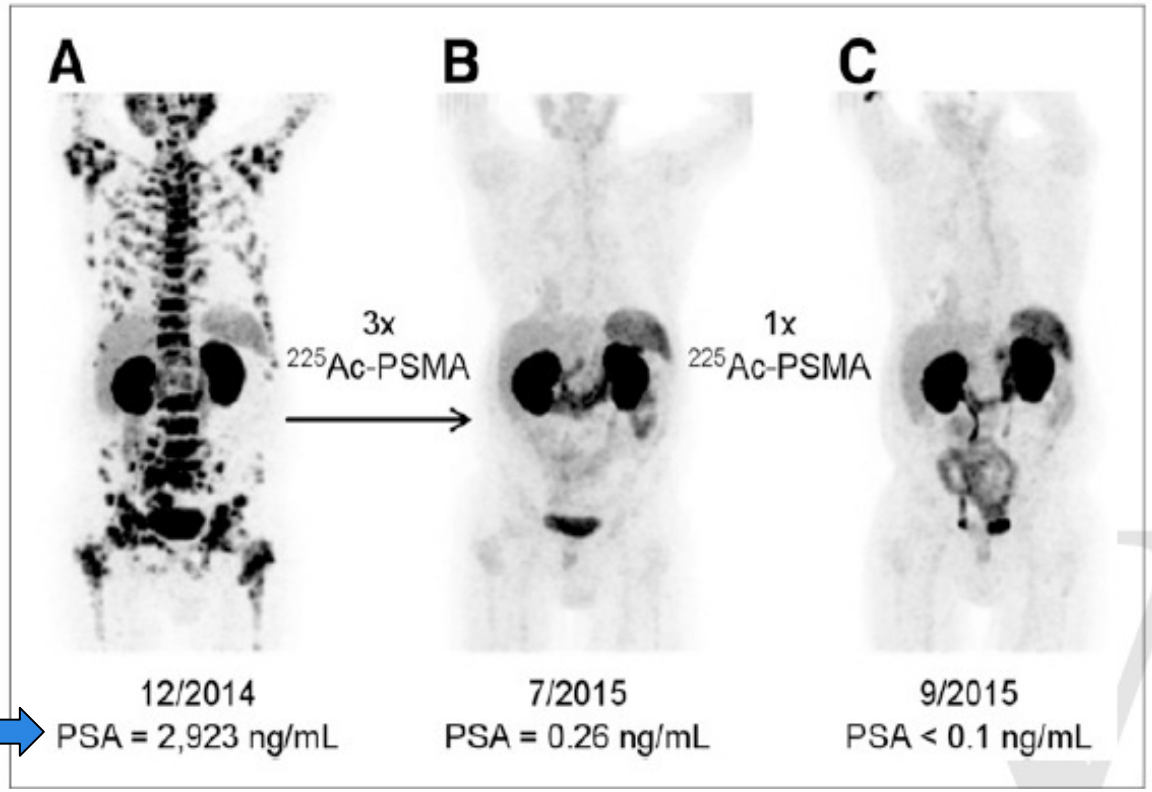
N=750
Alternative 1° endpoint:
rPFS or OS

Are Alpha-Particles Better than Betas?

Radio-conjugates: PSMA targeted alpha emitters (Actinium-225) as 9th line treatment

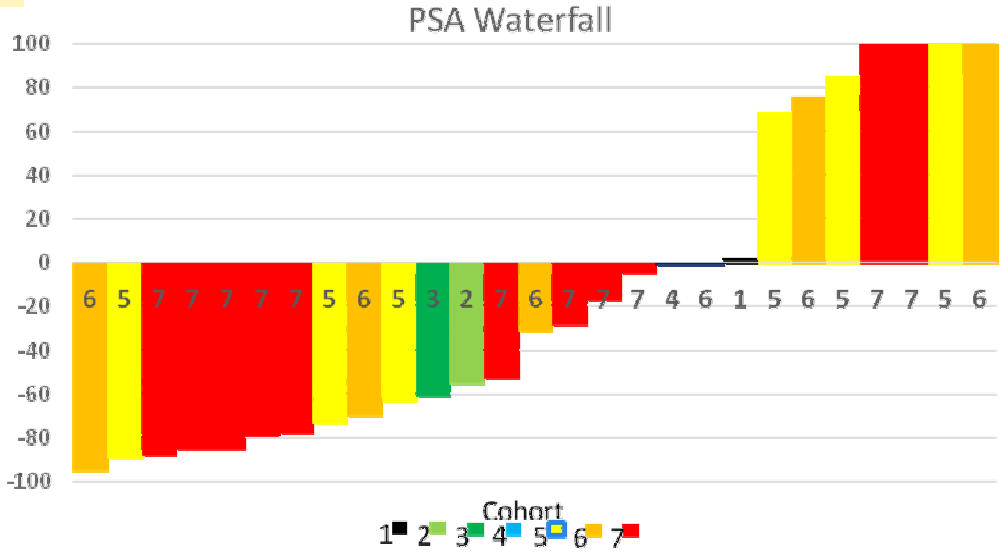
Patient A

- Leuprorelin
- Zoledronate
- Docetaxel (50 cycles)
- Carmustine/epirubicin in hyperthermia
- Abiraterone
- Enzalutamide
- ^{223}Ra (6 cycles)
- Abiraterone reexposition
- Estramustine



Kratochwil et a. J Nucl Med. 2016;57(12):1941-1944.

Antibody RNT in advanced prostate cancer
J591-Ac^{225}: Phase 1 single dose



Weill Cornell Medicine

Design:
- 27 patients; **NO** PSMA imaging pre-selection used
- One dose only; 7 escalating dose levels
- Heavily Pre-treated patients (eg, ARi, chemo)
- **48% relapsed/refractory to prior PSMA-617-Lu^{177}**
- 19% relapsed/refractory to prior Ra^{223}

Results:
- Well tolerated
- **PSA$_{50}$ response = 13/27 (48%)**
- 1 DLT (platelets), MTD not reached
- 6 grade 1 xerostomia, 5 of 6 had prior 617-Lu^{177}
- Multi-dose trial underway (Aug, 2020)

Source: Updated from Tagawa S, Bander N et al. *J Clin Oncol.* 38:2020 (suppl; abstr 5560)

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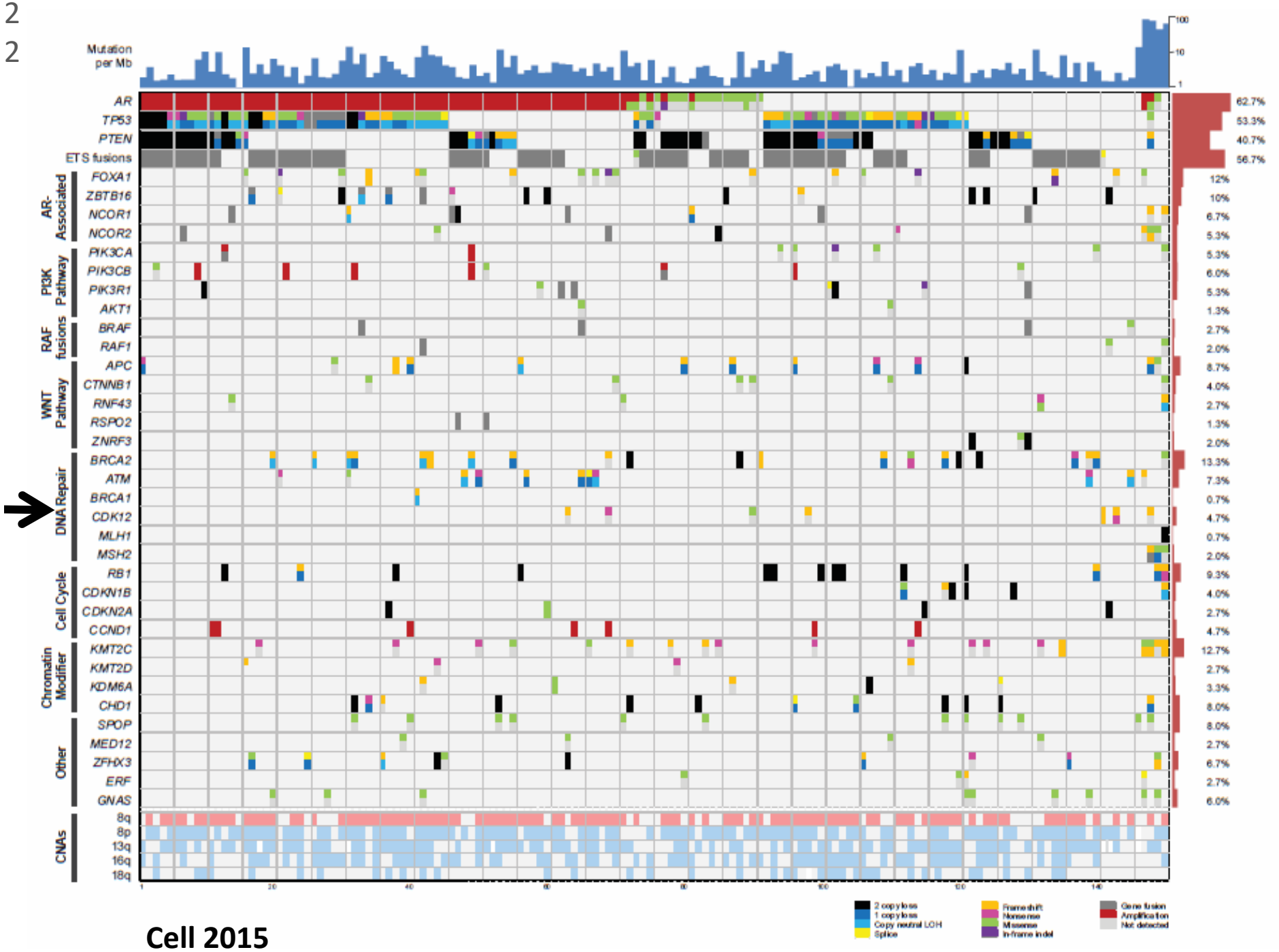
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WNT Pathway
APC
CTNNB1
RNF43
RSPO2
ZNRF3
DNA Repair
BRCA2
ATM
BRCA1
CDK12
MLH1
MSH2
Cell Cycle
RB1
CDKN1B
CDKN2A
CCND1
Chromatin Modifier
KMT2C
KMT2D
KDM6A
CHD1
Other
SPOP
MED12
ZFHX3
ERF
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CNAs
8q
8p
13q
16q
18q
62.7%
53.3%
40.7%
56.7%
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In-frame indel
Gene fusion
Amplification
Not detected

Cell 2015

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer

Joaquin Mateo, M.D., Suzanne Carreira, Ph.D., Shahneen Sandhu, M.D., Susana Miranda, B.Sc., Helen Mossop, M.Math.Stat., Raquel Perez-Lopez, M.D., Daniel Nava Rodrigues, M.D., Dan Robinson, Ph.D., Aurelius Omlin, M.D., Nina Tunariu, M.D.Res., Gunther Boysen, Ph.D., Nuria Porta, Ph.D., Penny Flohr, B.Sc., Alexa Gillman, B.Sc., Ines Figueiredo, B.Sc., Claire Paulding, B.Sc., George Seed, M.Sc., Sunell Jain, M.D., Christy Ralph, M.D., Andrew Protheroe, M.D., Ph.D., Syed Hussain, M.D., Robert Jones, M.D., Ph.D., Tony Elliott, M.D., Ph.D., Ursula McGovern, M.D., Ph.D., Diletta Bianchini, M.D., Jane Goodall, B.Sc., Zafeiris Zafeiriou, M.D., Chris T. Williamson, Ph.D., Roberta Ferraldeschi, M.D., Ph.D., Ruth Riisnaes, F.I.B.M.S., Bernardette Ebbs, B.T.E.C., Gemma Fowler, B.Sc., Desamparados Roda, M.D., Wei Yuan, Ph.D., Yi-Mi Wu, Ph.D., Xuhong Cao, M.S., Rachel Brough, Ph.D., Helen Pemberton, Ph.D., Roger A'Hern, Ph.D., Amanda Swain, Ph.D., Lakshmi P. Kunju, M.D., Rosalind Eeles, M.D., Ph.D., Gerhardt Attard, M.D., Ph.D., Christopher J. Lord, Ph.D., Alan Ashworth, Ph.D., Mark A. Rubin, M.D., Karen E. Knudsen, Ph.D., Felix Y. Feng, M.D., Ph.D., Arul M. Chinnaiyan, M.D., Ph.D., Emma Hall, Ph.D., and Johann S. de Bono, M.B., Ch.B., Ph.D.

N Engl J Med 2015; 373:1697-1708 | October 29, 2015 | DOI: 10.1056/NEJMoa1506859

N Engl J Med. 2020 Sep 20. doi: 10.1056/NEJMoa2022485. Online ahead of print.

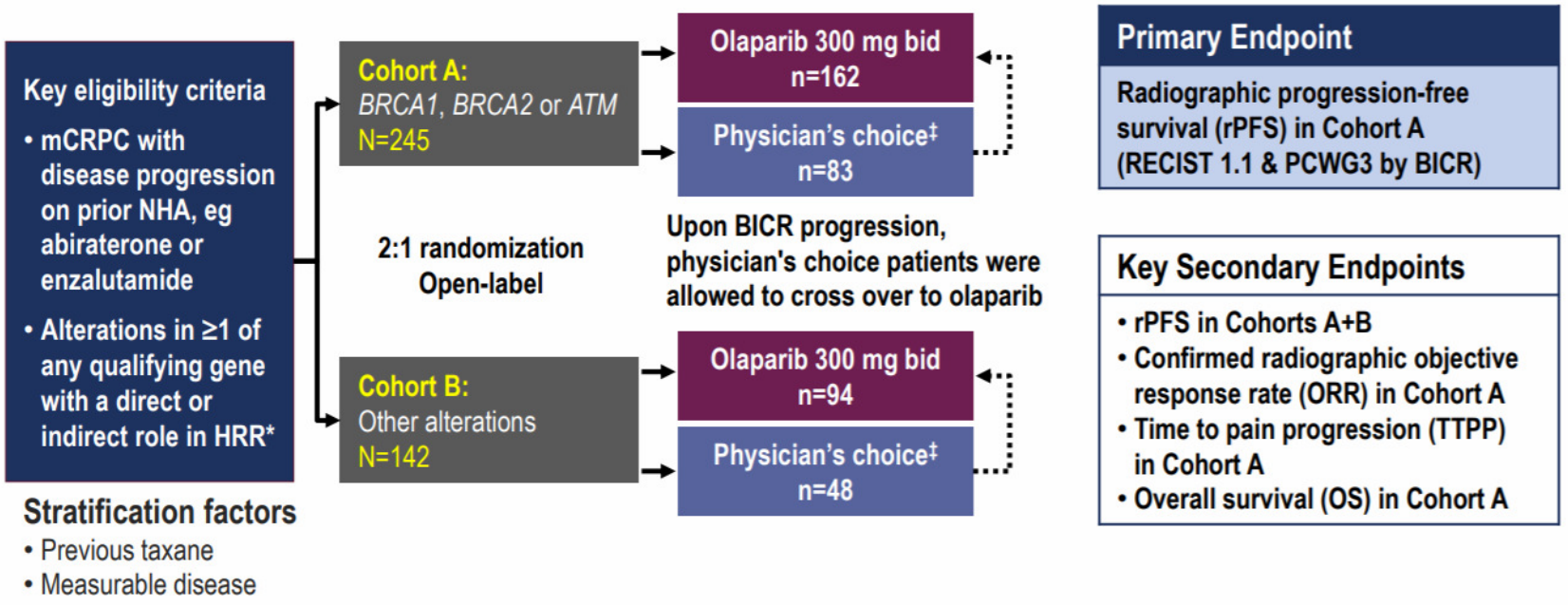
Survival with Olaparib in Metastatic Castration-Resistant Prostate Cancer

Maha Hussain [1], Joaquin Mateo [1], Karim Fizazi [1], Fred Saad [1], Neal Shore [1], Shahneen Sandhu [1], Kim N Chi [1], Oliver Sartor [1], Neeraj Agarwal [1], David Olmos [1], Antoine Thiery-Vuillemin [1], Przemyslaw Twardowski [1], Guilhem Roubaud [1], Mustafa Özgüroğlu [1], Jinyu Kang [1], Joseph Burgents [1], Christopher Gresty [1], Claire Corcoran [1], Carrie A Adelman [1], Johann de Bono [1], PROfound Trial Investigators

Affiliations + expand

PMID: 32955174 DOI: 10.1056/NEJMoa2022485

Phase III PROfound Study: Study Design

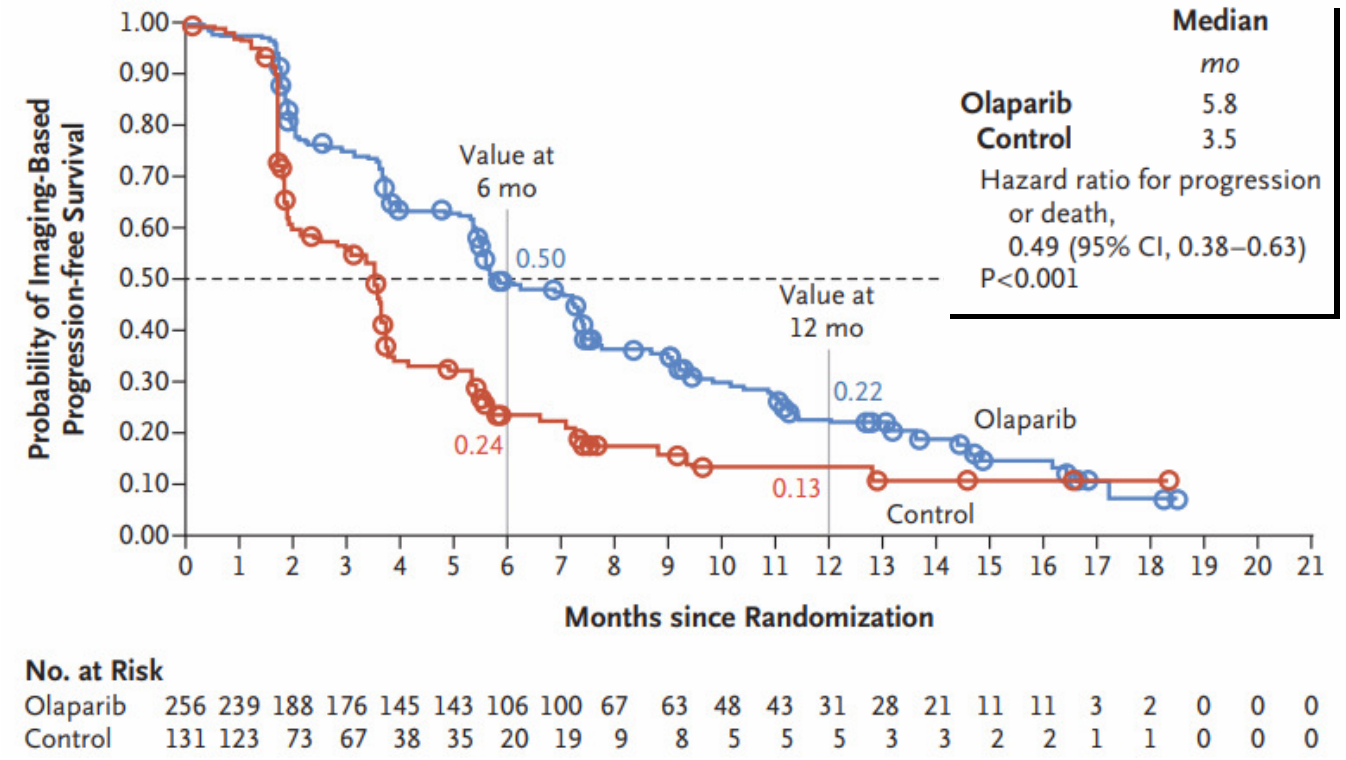


*An investigational Clinical Trial Assay, based on the FoundationOne® CDx next-generation sequencing test

Developed in partnership with Foundation Medicine Inc, and used to prospectively select patients harboring alterations in *BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D* and/ or *RAD54L* in their tumor tissue

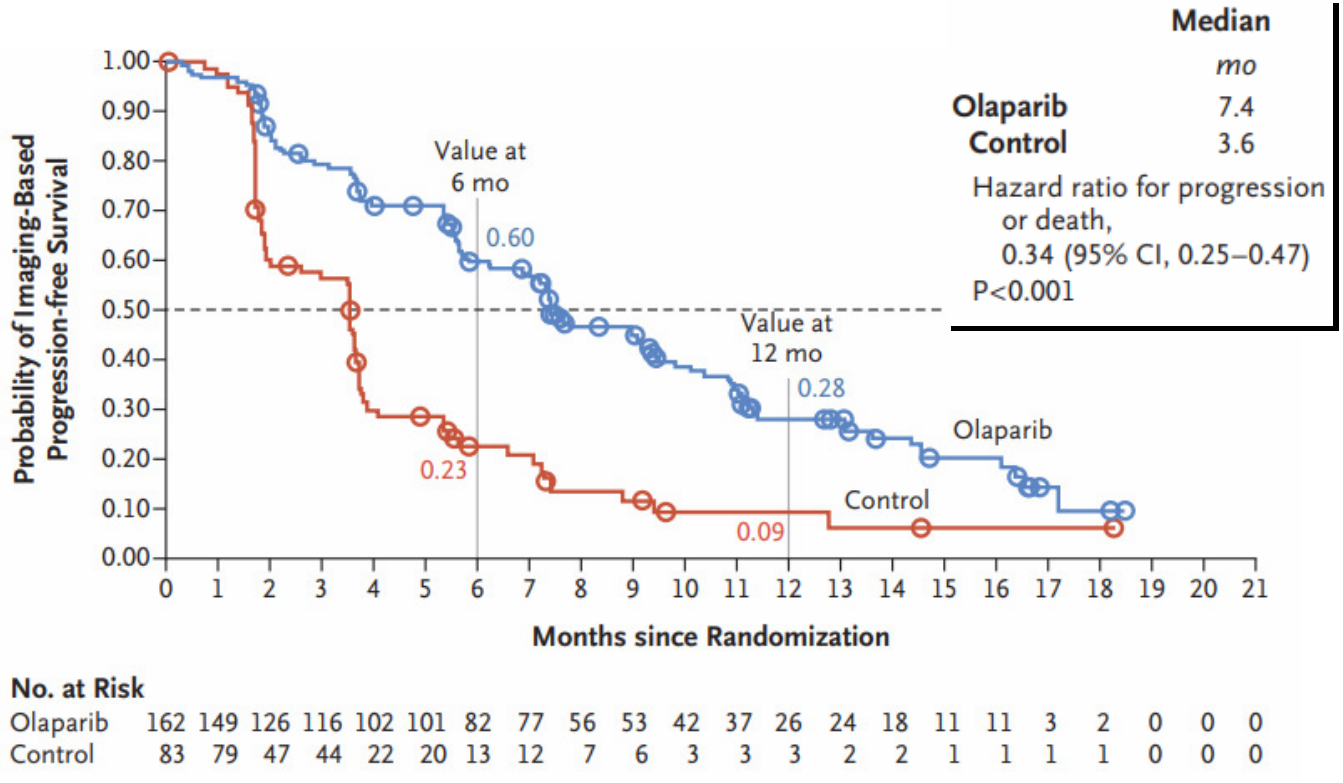
Hussain M et al. NEJM 2020.

Phase III PROfound Study: rPFS in Cohorts A + B (Overall Population)



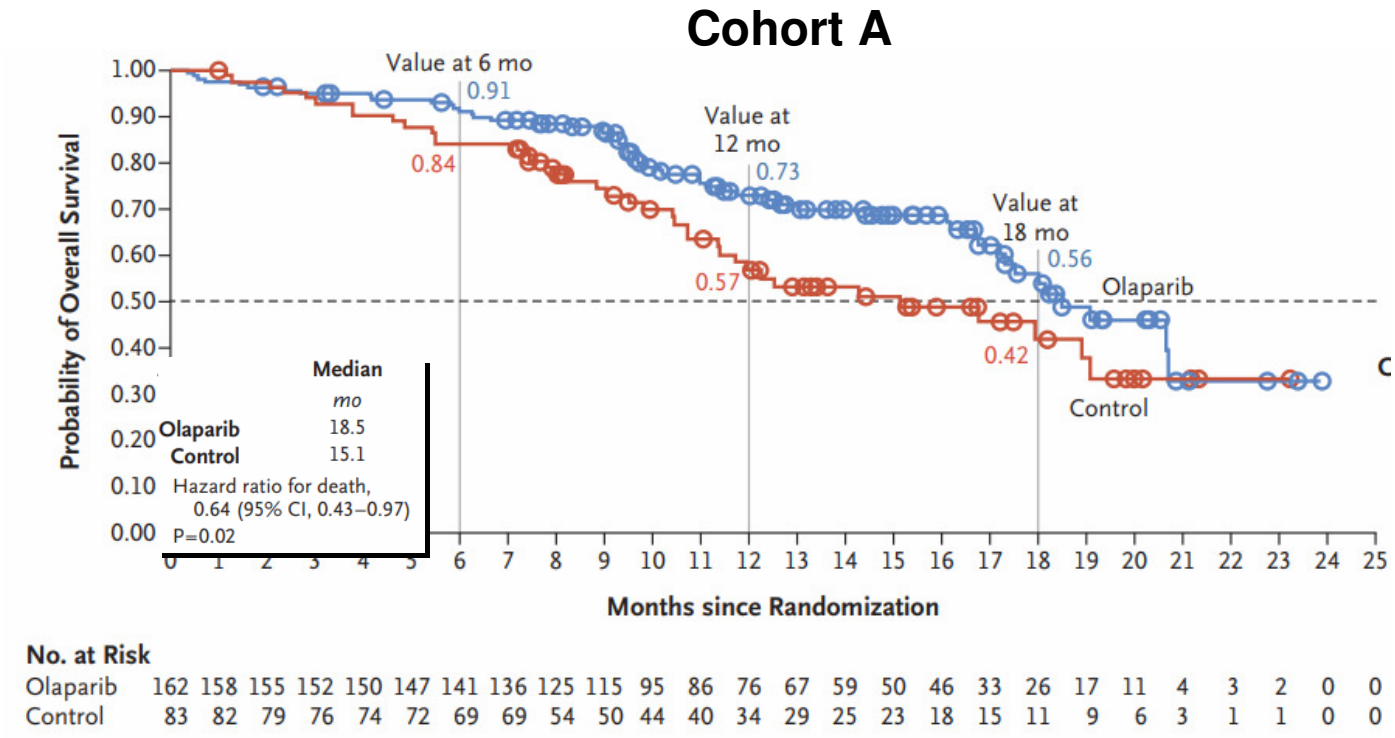
Hussain M et al. NEJM 2020.

Phase III PROfound Study: rPFS in Cohort A (Patients With *BRCA1/2* or *ATM* Alterations)



Hussain M et al. NEJM 2020.

Phase III PROfound Study: Interim OS



Overall population, median OS: 17.5 mo vs 14.3 mo (HR, 0.67; 95% CI, 0.49-0.93; *P* =.0063)

Hussain M et al. 2019 ESMO Congress. Abstract LBA12_PR.

FDA approves olaparib for HRR gene-mutated metastatic castration-resistant prostate cancer

On May 19, 2020, the Food and Drug Administration approved olaparib (LYNPARZA, AstraZeneca Pharmaceuticals, LP) for adult patients with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (mCRPC), who have progressed following prior treatment with enzalutamide or abiraterone.

Today, the FDA also approved FoundationOne CDx (Foundation Medicine, Inc.) for selection of patients with mCRPC carrying HRR gene alterations and BRACAnalysis CDx test (Myriad Genetic Laboratories, Inc.) for selection of patients with mCRPC carrying germline *BRCA1/2* alterations as companion diagnostic devices for treatment with olaparib.

J Clin Oncol. 2020 Nov 10;38(32):3763-3772. doi: 10.1200/JCO.20.01035. Epub 2020 Aug 14.

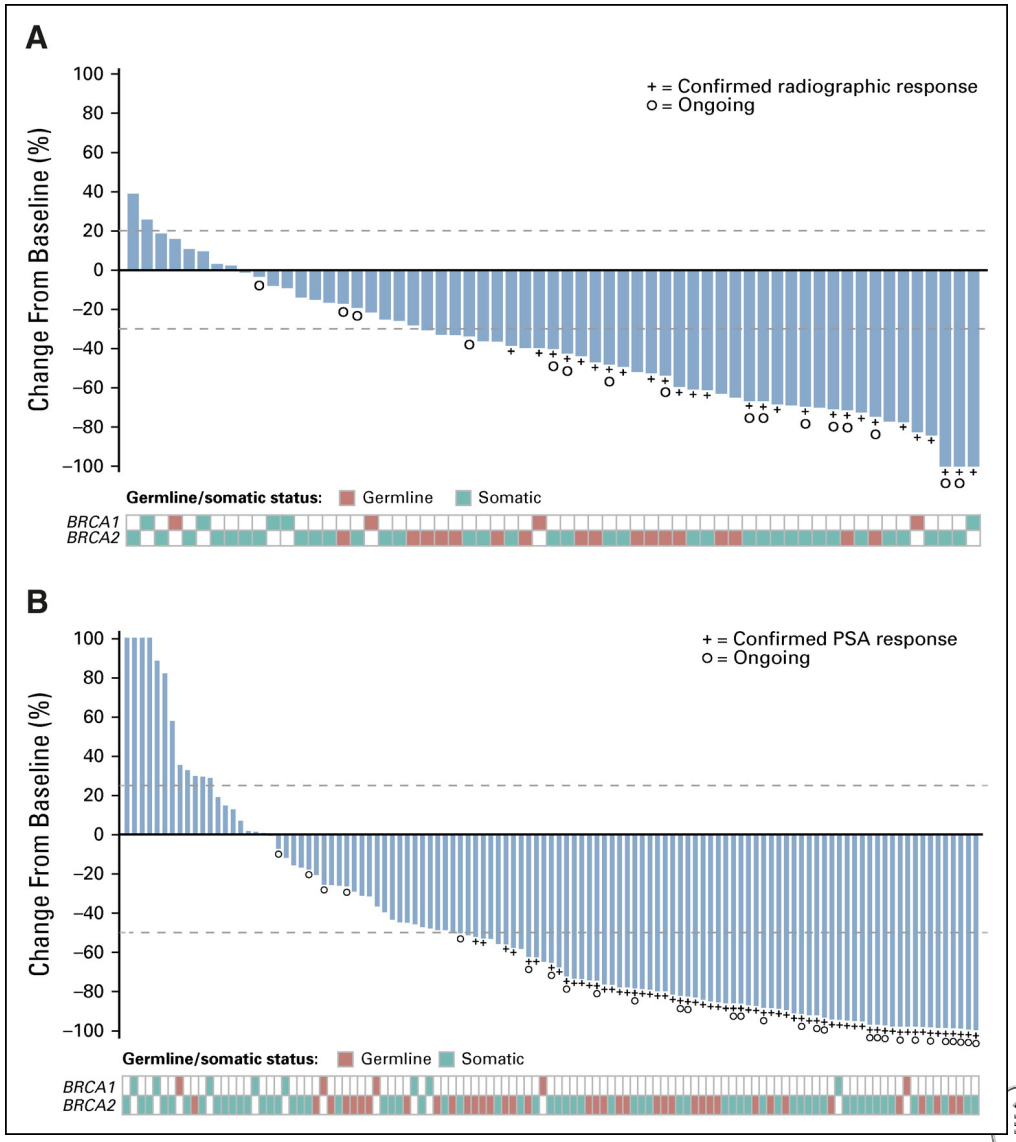
Rucaparib in Men With Metastatic Castration-Resistant Prostate Cancer Harboring a *BRCA1* or *BRCA2* Gene Alteration

Wassim Abida [1], Akash Patnaik [2], David Campbell [3], Jeremy Shapiro [4], Alan H Bryce [5], Ray McDermott [6], Brieuc Sautois [7], Nicholas J Vogelzang [8], Richard M Bambury [9], Eric Voog [10], Jingsong Zhang [11], Josep M Piulats [12], Charles J Ryan [13], Axel S Merseburger [14], Gedske Daugaard [15], Axel Heidenreich [16], Karim Fizazi [17], Celestia S Higano [18], Laurence E Krieger [19], Cora N Sternberg [20], Simon P Watkins [21], Darrin Despain [22], Andrew D Simmons [23], Andrea Loehr [23], Melanie Dowson [24], Tony Golsorkhi [25], Simon Chowdhury [26 27], TRITON2 investigators

Affiliations + expand

PMID: 32795228 PMCID: PMC7655021 DOI: 10.1200/JCO.20.01035

TRITON 2-Rucaparib in *BRCA1* and 2 and *ATM* patients



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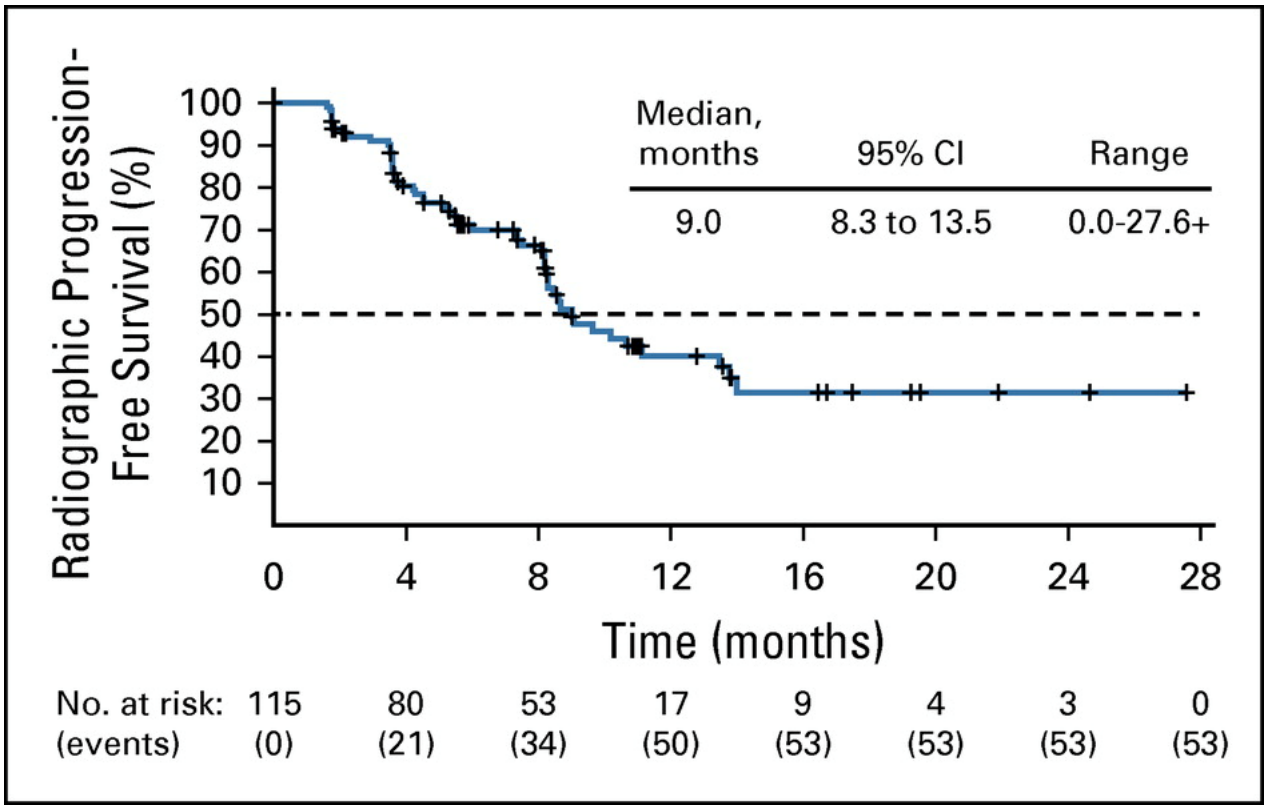
Rucaparib-rPFS in *BRCA* mutated patients



FDA grants accelerated approval to rucaparib for BRCA-mutated metastatic castration-resistant prostate cancer

On May 15, 2020, the Food and Drug Administration granted accelerated approval to rucaparib (RUBRACA, Clovis Oncology, Inc.) for patients with deleterious *BRCA* mutation (germline and/or somatic)-associated metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor-directed therapy and a taxane-based chemotherapy.

Efficacy was investigated in TRITON2 (NCT02952534), an ongoing, multi-center, single arm clinical trial in 115 patients with *BRCA*-mutated (germline and/or somatic) mCRPC who had been treated with androgen receptor-directed therapy and taxane-based chemotherapy. Patients received rucaparib 600 mg orally twice daily and concomitant GnRH analog or had prior bilateral orchiectomy.

PARP Conclusions and Clinical Implications

- PARP inhibition is effective in patients with DNA repair mutations
- PARP inhibition appears to be less effective in those patients with ATM mutations
- Olaparib is FDA approved in CRPC patients with HRR gene mutations who have been treated with enzalutamide or abiraterone
- Rucaparib is FDA approved in BRCA mutated patients who have received abiraterone or enzalutamide and docetaxel chemotherapy

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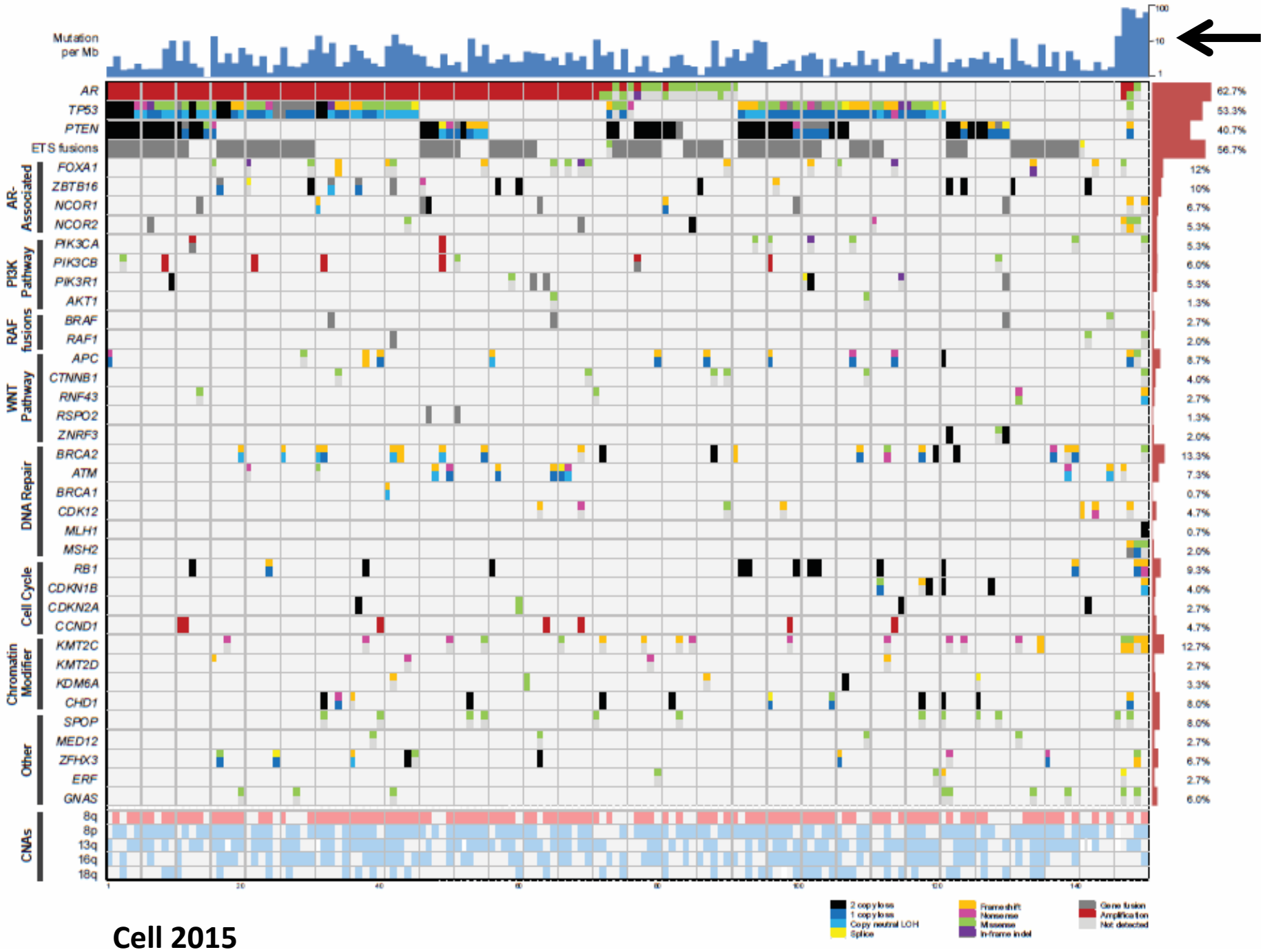
- Immunotherapeutic
  - Sipuleucel T
  - Pembrolizumab MSI high
  - CPIs

Sipuleucel T-Questions

- While this was a breakthrough in terms of validating a new MOA and validating the principles of immunotherapy, it has not been widely used:
  - Controversial MOA-does it really work the way we thought?
  - Few PSA declines
  - No measurable prolongation in TTP (NB-time to first progression)
  - Other agents with more “straightforward” MOAs were developed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RAF fusions
BRAF
RAF1
WNT Pathway
APC
CTNNB1
RNF43
RSPO2
ZNRF3
DNA Repair
BRCA2
ATM
BRCA1
CDK12
MLH1
MSH2
Cell Cycle
RB1
CDKN1B
CDKN2A
CCND1
Chromatin Modifier
KMT2C
KMT2D
KDM6A
CHD1
Other
SPOP
MED12
ZFHX3
ERF
GNAS
CNAs
8q
8p
13q
16q
18q
62.7%
53.3%
40.7%
56.7%
12%
10%
6.7%
5.3%
5.3%
6.0%
5.3%
1.3%
2.7%
2.0%
8.7%
4.0%
2.7%
1.3%
2.0%
13.3%
7.3%
0.7%
4.7%
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2.0%
9.3%
4.0%
2.7%
4.7%
12.7%
2.7%
3.3%
8.0%
8.0%
2.7%
6.7%
2.7%
6.0%
1
20
40
60
80
100
120
140
2 copy loss
1 copy loss
Copy neutral LOH
Splice
Frameshift
Nonsense
Missense
In-frame indel
Gene fusion
Amplification
Not detected

Cell 2015

REPORT

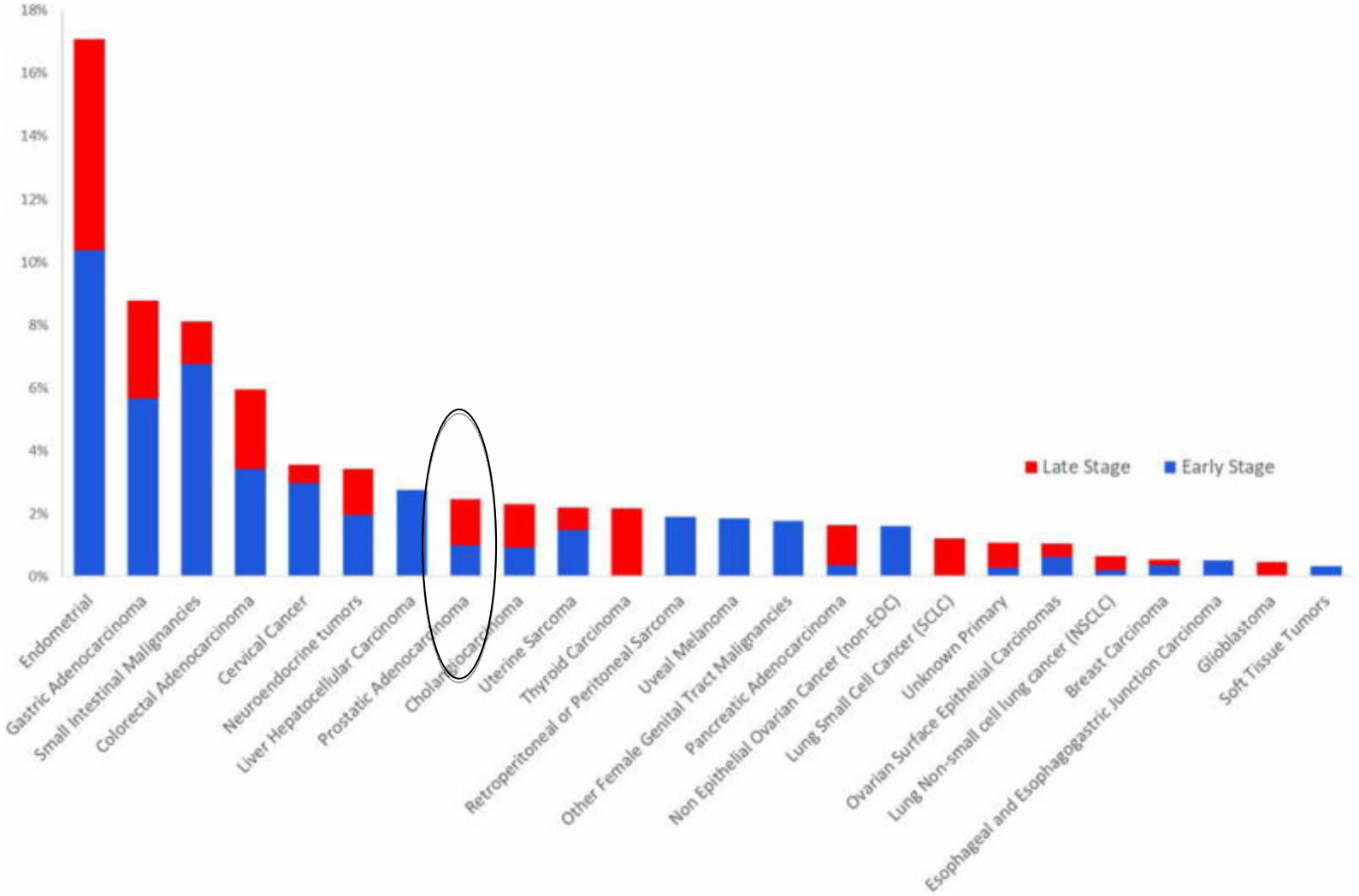
Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade

Dung T. Le[1,2,3], Jennifer N. Durham[1,2,3,*], Kellie N. Smith[1,3,*], Hao Wang[3,*], Bjarne R. Bartlett[2,4,*], Laveet...

+ See all authors and affiliations

Science 28 Jul 2017:
Vol. 357, Issue 6349, pp. 409-413
DOI: 10.1126/science.aan6733

Mismatch Repair Deficiency



Le et al. Science 2017

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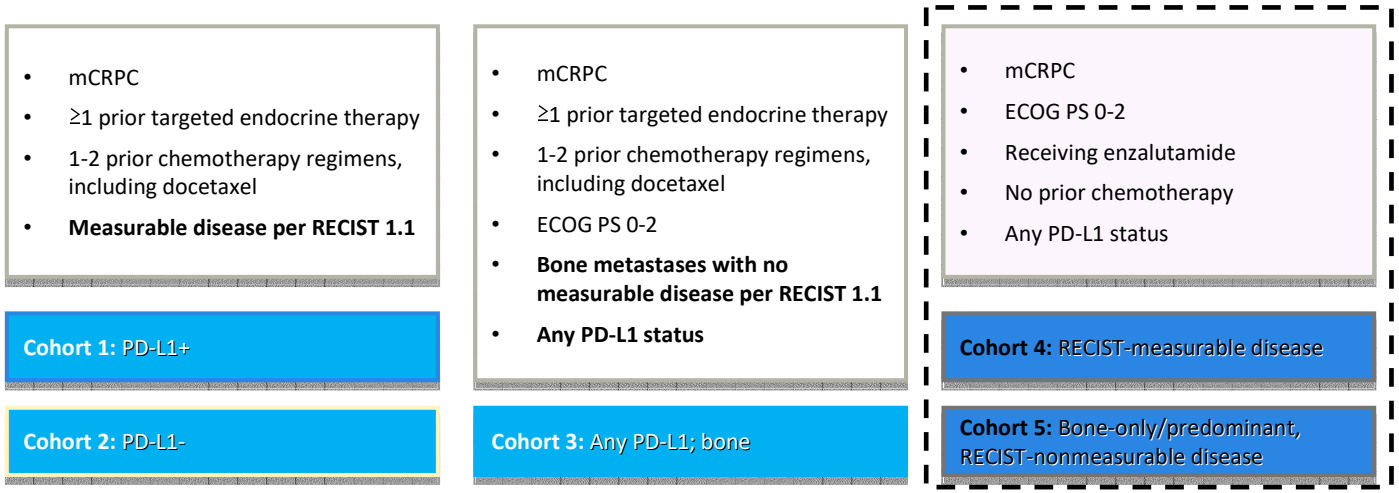
MSI-H and MRD

- 1346 patients with PC underwent paired tumor and germline sequencing
- 32 of 1033 (3.1%) had microsatellite instability–high or mismatch repair deficient disease
- 7/32 (21.9%) carried a germline mutation in a Lynch syndrome–associated gene.
- Five of 11 patients who received an anti–PD-1/PD-L1 agent had durable clinical benefit.

Abida et al, JAMA Onc 2018

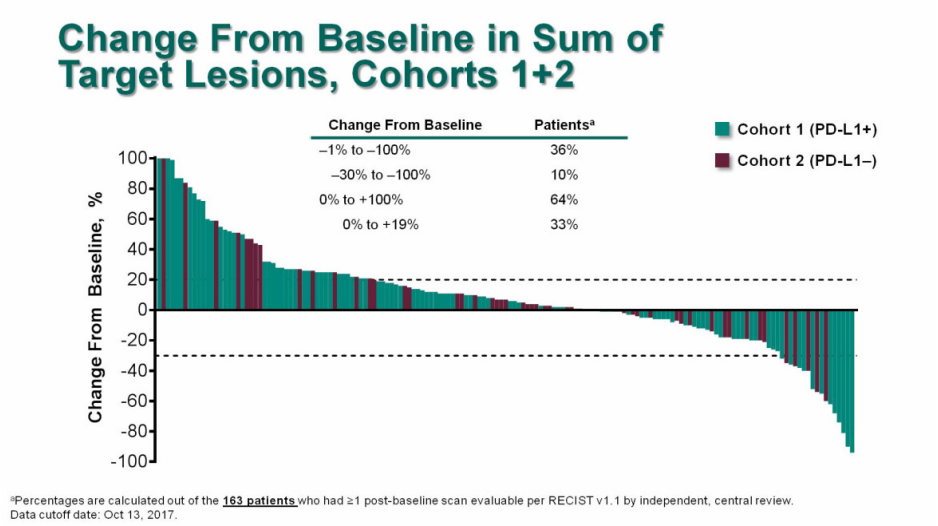
KEYNOTE-199: Study Design



- **Treatment in all cohorts:** Pembrolizumab 200 mg every 3 weeks for 35 cycles or until confirmed PD, intolerable toxicity, investigator decision, or patient withdrawal

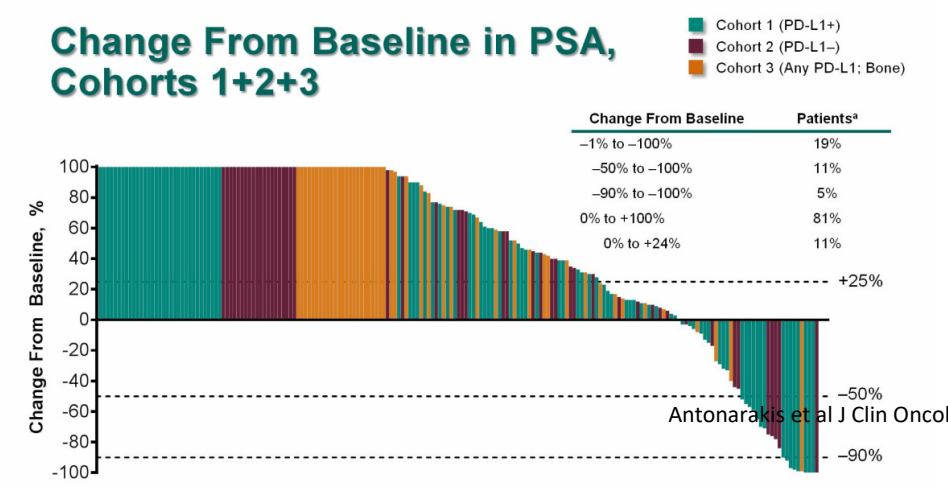
Antonarakis et al J Clin Oncol. 2020 Feb 10;38(5):395-405.

Pembrolizumab in mCRPC



[a]Percentages are calculated out of the **163 patients** who had ≥1 post-baseline scan evaluable per RECIST v1.1 by independent, central review.
Data cutoff date: Oct 13, 2017.

10% RR



[a]Percentages are calculated out of the **193 patients** who had ≥1 post-baseline PSA assessment.
Data cutoff date: Oct 13, 2017.

11% PSA declines

Antonarakis et al J Clin Oncol. 2020 Feb 10;38(5):395-405.

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KEYNOTE-199: Update Cohorts 4 and 5[1]

ASCO Abstract 5543

n (%)	Cohort 4 (n = 81)	Cohort 5 (n = 45)
ORR	10 (12)	NA
CR	2 (2)	NA
PR	8 (10)	NA
SD of any duration	31 (38)	0 (0)
Non-CR/non-PD of any duration	0 (0)	23 (51)
DCR (CR + PR + SD or non-CR/non-PD)	41 (51)	23 (51)
PD	31 (38)	20 (44)
NE[a]	2 (2)	1 (2)
No assessment[b]	7 (9)	1 (2)

1. Hoimes CJ et al. ASCO 2020. Abstract 5543.

KEYNOTE-365

Pembrolizumab + olaparib

Cohort A[1]

Median follow-up:
3.6 mo for all pts (n = 84)
26.7 mo for pts with ≥27 wks' follow-up (n = 41)

Efficacy
PSA response: 7/82 (9%) pts
Time to PSA progression: 3.8 mo
ORR: 2/24 (8%) pts; both PR
DCR: 22%
DOR: Not reached

Median rPFS: 4.3 mo;
12mo rPFS rate: 23.3%

Median OS: 14.4 mo
12mo OS rate: 58.2%

Pembrolizumab + docetaxel/prednisone

Cohort B[2]

Median follow-up:
19.9 mo for all pts (n = 104)
21.8 mo for pts with ≥27 wks' follow up (n = 72)

Efficacy
PSA response: 29/103 (28%) pts
Time to PSA progression: 6.2 mo
ORR: 7/39 (18%) pts; all PRs
DCR: 51%
DOR: 6.7 mo

Median rPFS: 8.3 mo
12mo rPFS rate: 24.0%

Median OS: 20.4 mo
12mo OS rate: 75.8%

Pembrolizumab + enzalutamide

Cohort C[3]

Median follow-up:
19.1 mo for all pts (n = 102)
21.4 mo for pts with ≥ 27 wks' follow-up (n = 69)

Efficacy
PSA response: 22/101 (22%) pts
Time to PSA progression: 3.5 mo
ORR: 3/25 (12%) pts; 2 CR and 1 PR
DCR: 35%
DOR: Not reached

Median rPFS: 6.1 mo
12mo rPFS rate: 24.6%

Median OS: 20.4 mo
12mo OS rate: 72.8%

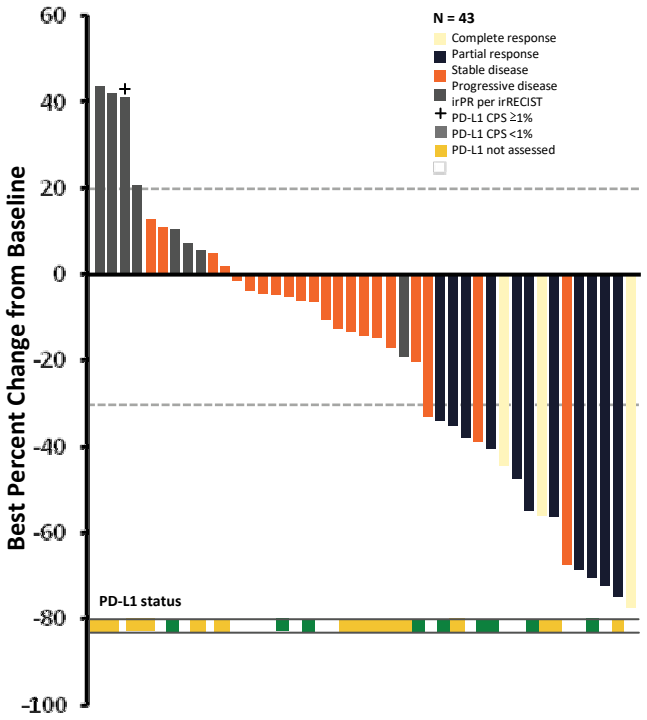
Phase 1b COSMIC-021

- Radiographic progression after prior enzalutamide and/or prior abiraterone
- ECOG-PS 0-1
- Prior chemotherapy not permitted except docetaxel for mCSPC

Cohort 6:
CRPC expansion

cabozantinib 40 mg PO orally + atezolizumab 1,200 mg IV q3w

	CRPC Cohort (N = 44)
ORR, (80% CI), %	32 (23-42)
CR, n (%)	3 (6.8)
PR, n (%)	11 (25)
SD, n (%)	21 (48)
PD, n (%)	8 (18)[a]
Missing, n (%)	1 (2.3)
DCR (CR + PC + SD), n (%)	35 (80)
DOR, median (range), mo	8.3 (2.8-12.5+)
Time to OR, median (range), mo	1.6 (1-7)



1. Agarwal N et al. ASCO 2020. Abstract 5564.

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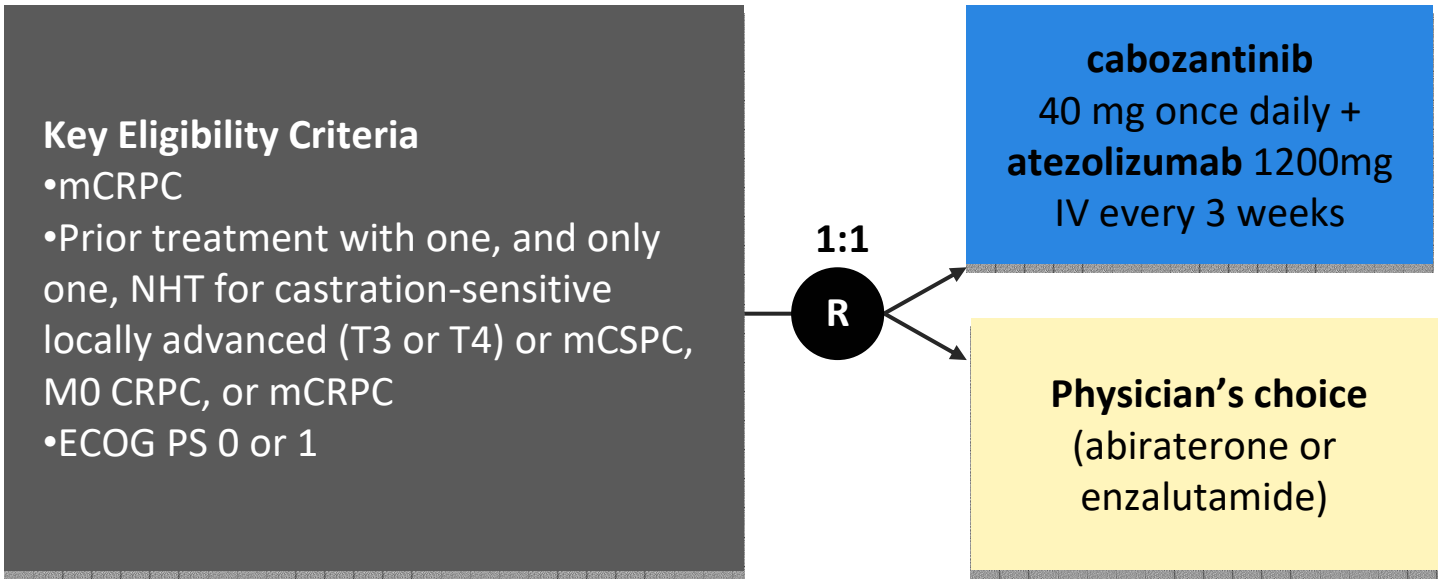
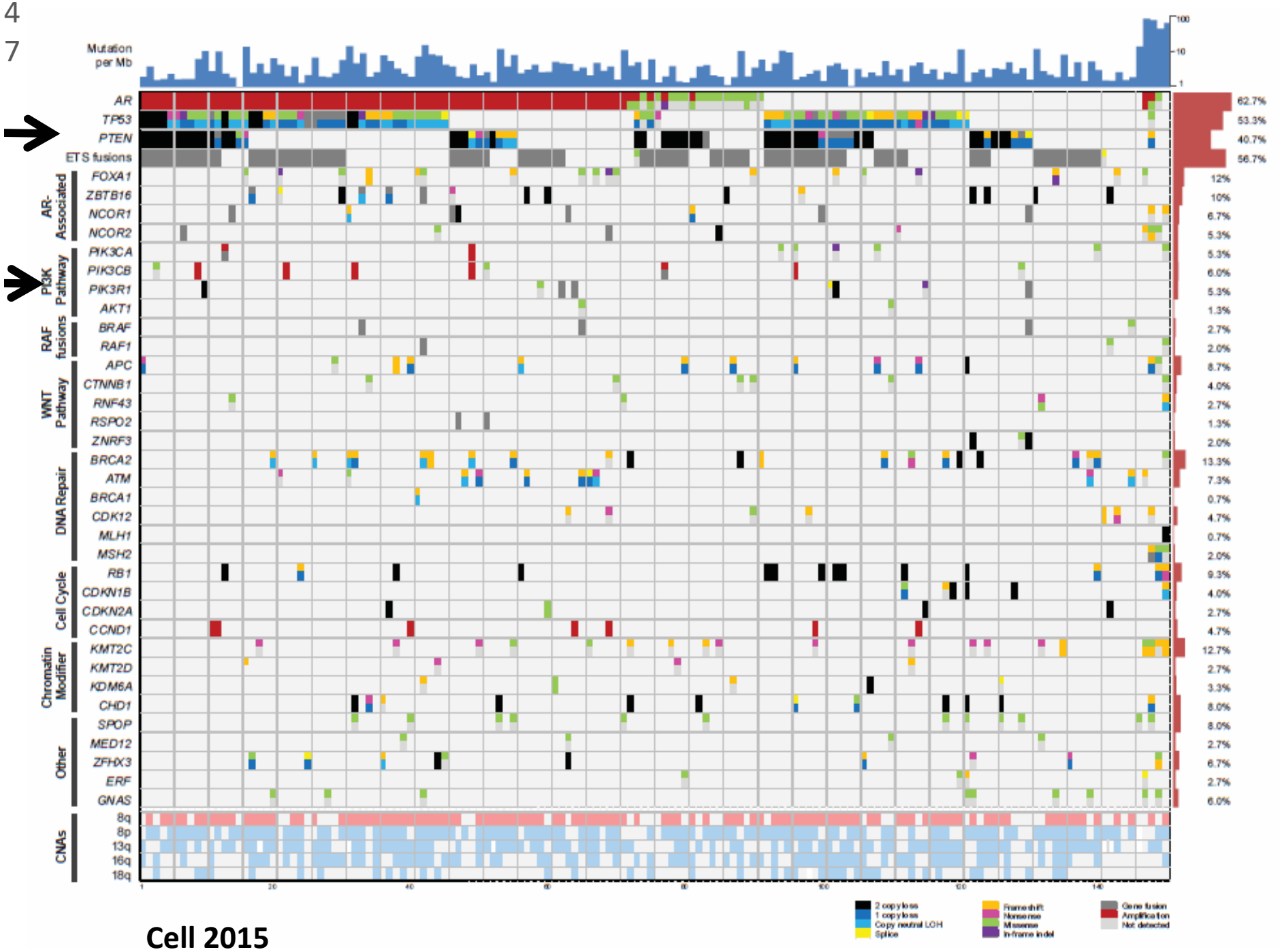
Phase 3 CONTACT-02



Primary endpoints: PFS, OS
Secondary endpoint: ORR

https://clinicaltrials.gov/ct2/show/NCT04446117


Mutation per Mb
AR
TP53
PTEN
ETS fusions
AR-Associated
FOXA1
ZBTB16
NCOR1
NCOR2
PI3K Pathway
PIK3CA
PIK3CB
PIK3R1
AKT1
RAF fusions
BRAF
RAF1
WNT Pathway
APC
CTNNB1
RNF43
RSPO2
ZNRF3
DNA Repair
BRCA2
ATM
BRCA1
CDK12
MLH1
MSH2
Cell Cycle
RB1
CDKN1B
CDKN2A
CCND1
Chromatin Modifier
KMT2C
KMT2D
KDM6A
CHD1
Other
SPOP
MED12
ZFHX3
ERF
GNAS
CNAs
8q
8p
13q
16q
18q
62.7%
53.3%
40.7%
56.7%
12%
10%
6.7%
5.3%
5.3%
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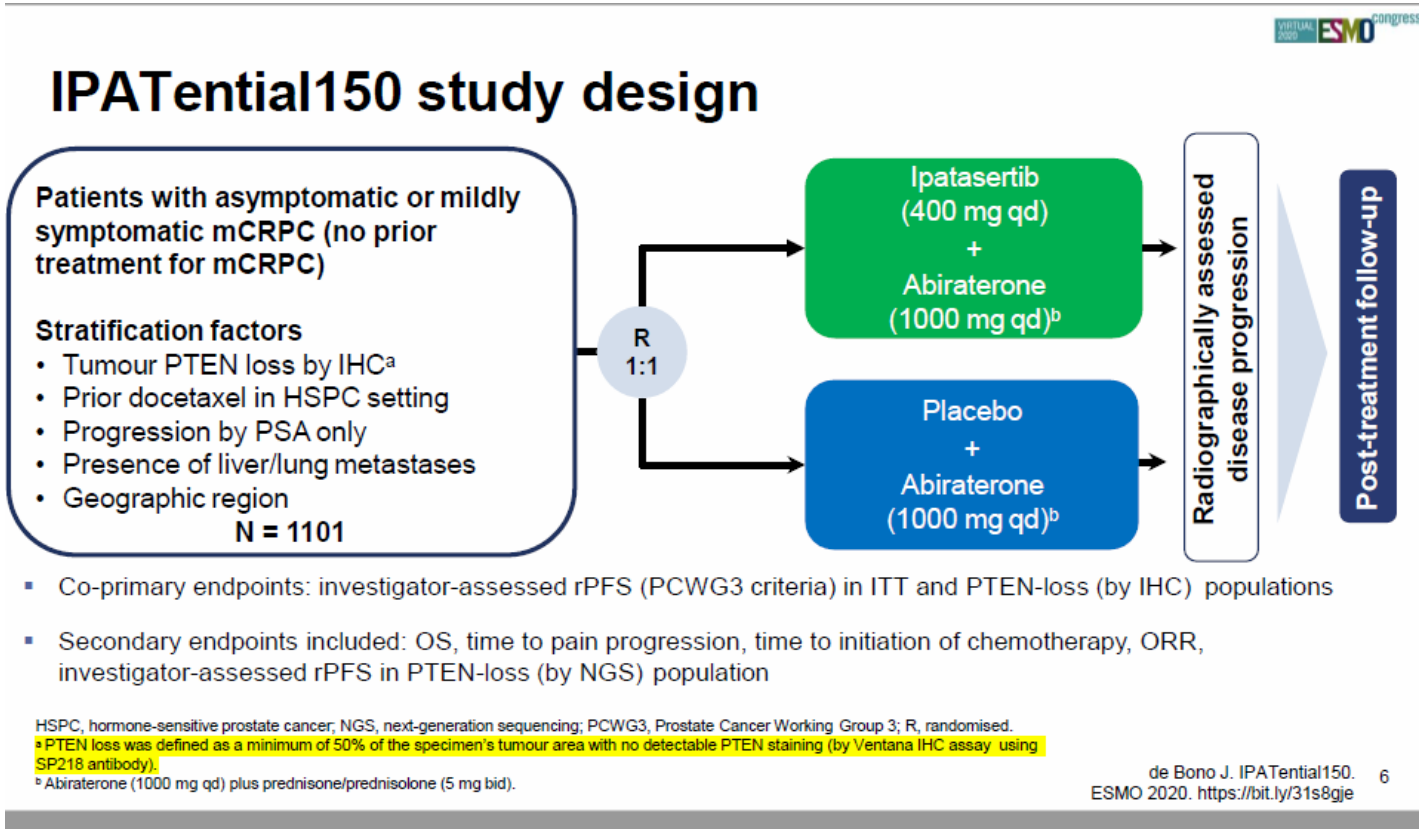
Copy neutral LOH
Splice
Frameshift
Nonsense
Missense
In-frame indel
Gene fusion
Amplification
Not detected

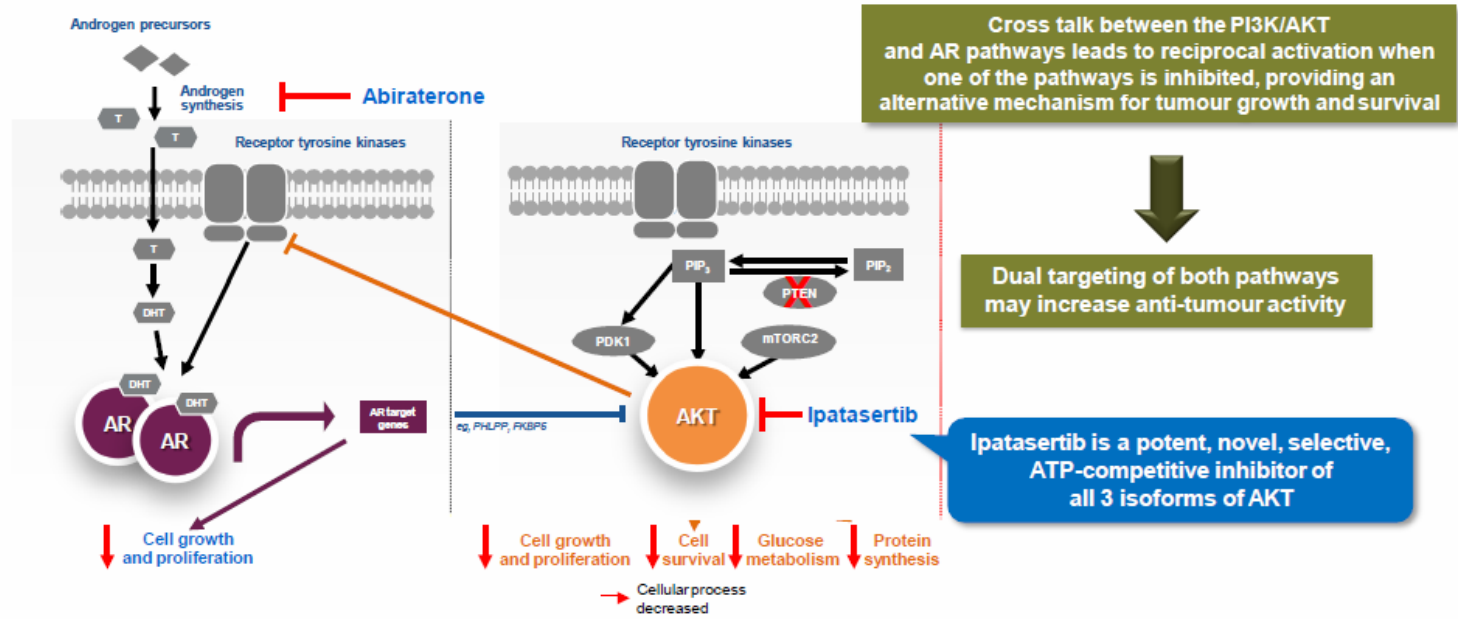
Cell 2015

IPATential150



IPATential150

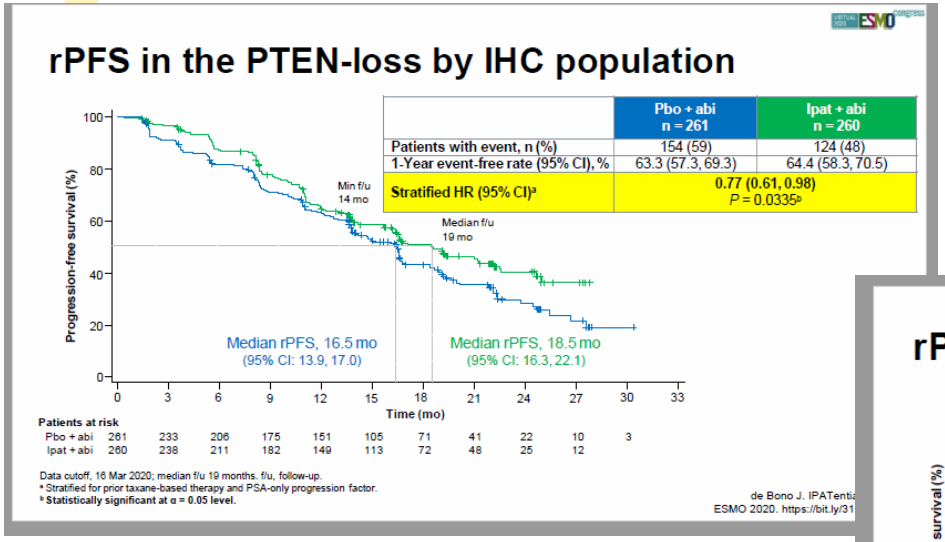
Rationale for dual pathway inhibition

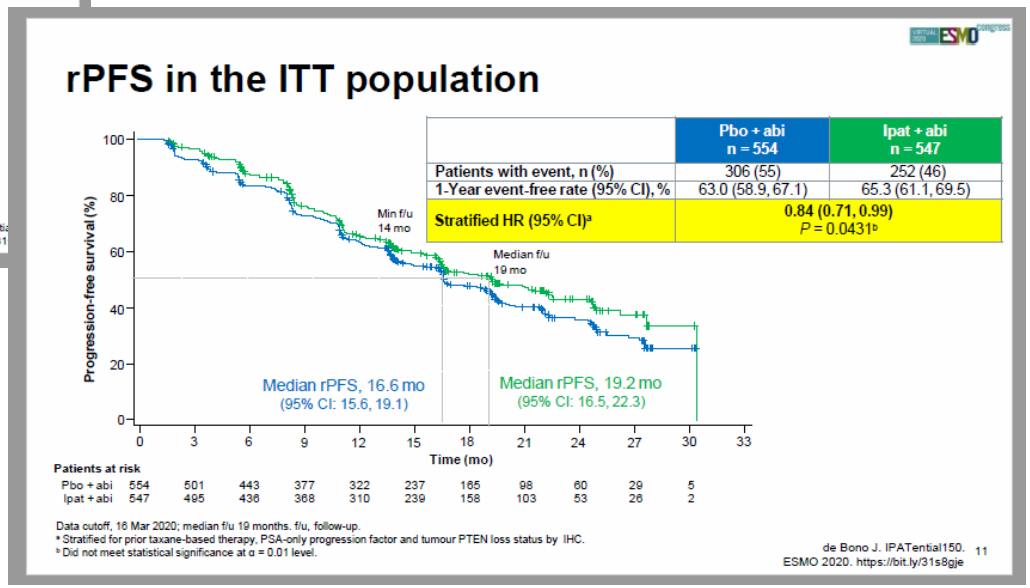


1. Lin J, et al. *Clin Cancer Res.* 2013; 2. Carver BS, et al. *Cancer Cell.* 2011; 3. Bitting RL, Armstrong AJ. *Endocr Relat Cancer.* 2013; 4. Hodgson MC, et al. *Cancer Res.* 2011; 5. Mulholland DJ, et al. *Cancer Cell.* 2011; 6. Jamaspishvili T, et al. *Nat Rev Urol.* 2018.

de Bono J. IPATential150. ESMO 2020. https://bit.ly/31s8gje

IPATential150





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Conclusions

- Multiple ARSIs with different toxicity profiles but hard to compare
- Second line ARSIs are largely unsuccessful so go to other therapies including Rad-223, chemo and Sip-T
- Screen for DNA repair abnormalities and MSI-high and TMB-high since PARPi and CPIs work in these patients
- Screen for PTEN and PI3K abnormalities since Akt inhibition works