Prostat Kanserinde Devam Eden Klinik Çalışmalar Gelecek Perspektif

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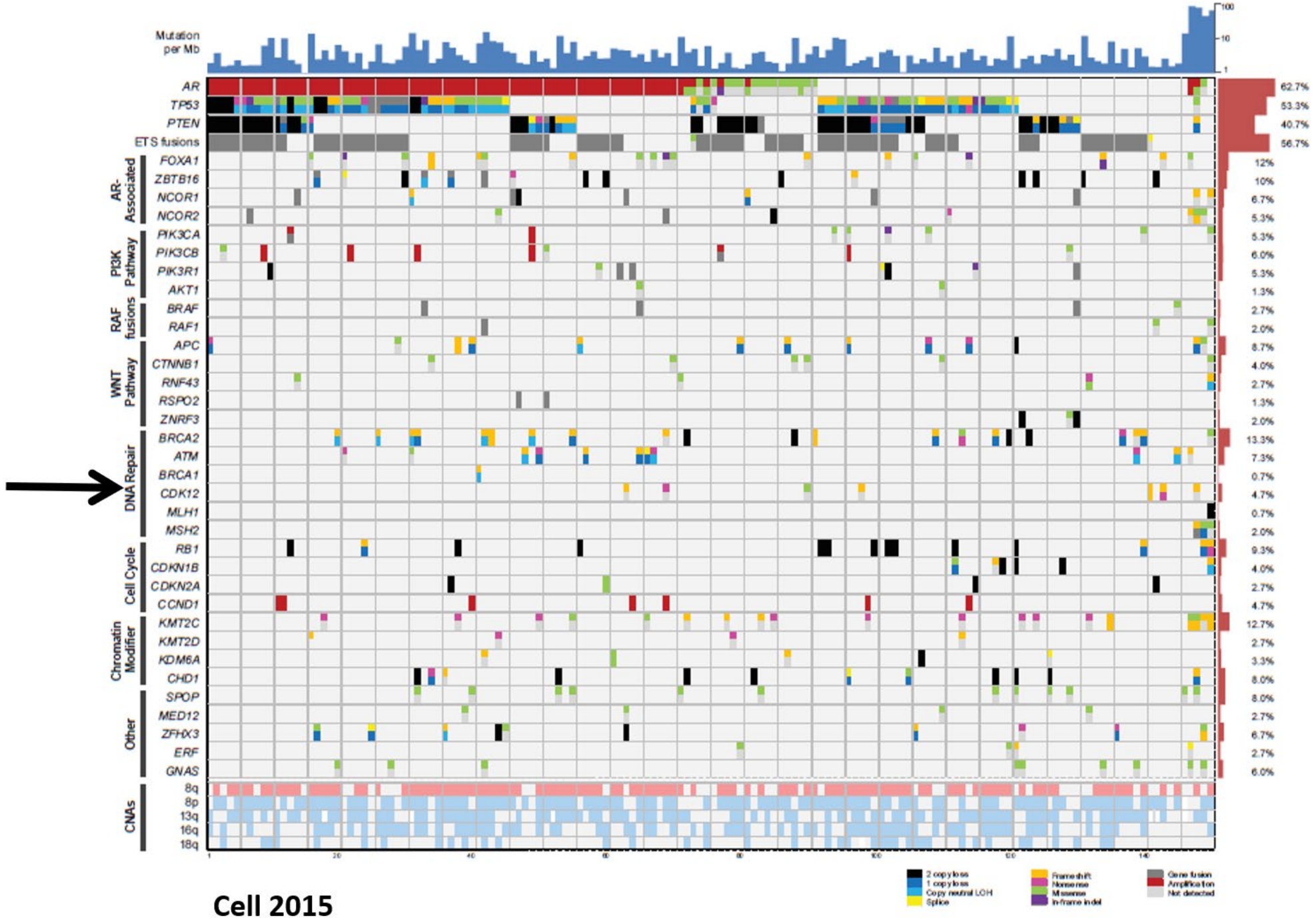
Tıbbi Onkoloji

Ders Planı

- Evre IV kastrasyona Dirençli Prostat Kanserinde Gelecek perspektif
- Evre IV kastrasyona Duyarlı Prostat Kanserinde Gelecek perspektif
- Yüksek Riskli Prostat Kanserinde Gelecek perspektif
- Lokalize Nüks/Biyokimyasal Nükslerde Gelecek Perspektif
- Sonuç

Evre IV kastrasyona Dirençli Prostat Kanserinde Gelecek perspektif

- ❑DNA repair gen mutasyonları
- ❑AR mutasyonları
- ❑PI3K-PTEN-AKT yolağı
- ❑PSMA ekspresyonu
- ❑Mikrosatellit instabilite(MSI)
- ❑Diğer kombinasyonlar


Mutation per Mb
100
10
1
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%
6.0%
5.3%
1.3%
2.7%
2.0%
8.7%
4.0%
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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

Prostat Kanseri Patogenezi

Recent insights into the molecular landscape of advanced PC have identified the following potentially actionable targets:

Molecular alteration	Frequency of expression in advanced PC*
High levels of PSMA expression	**(>80%)[1–5]**
AR pathway mutations/alterations	(63%–71%)[6]
PTEN-PI3K-AKT pathway alterations	(49%)[6]
Cell cycle (CDK) pathway alterations	(21%)[6]
DNA repair pathway alterations	(19%–23%)[6]
WNT pathway alterations	(18%)[6]
MSI-H, dMMR	(~3–5%)[7,8]

PSMA appears to be the most broadly applicable potential biomarker and actionable target in advanced PC[1–6]

**Each figure represents 10% of patients with advanced PC.*

1. Hope TA, et al. J Nucl Med. 2017;58(12):1956–1961; 2. Hupe MC, et al. Front Oncol. 2018;8:623; 3. Pomykala KL, et al. J Nucl Med. 2020;61(3):405–411; 4. Minner S, et al. Prostate. 2011;71(3):281–288; 5. Bostwick DG, et al. Cancer. 1998;82(11):2256–2261; 6. Robinson D, et al. Cell. 2015;161(5):1215–1228; 7. Abida W, et al. JAMA Oncol. 2019; 5(4):471-478; 8. Lindh C, et al. APMIS. 2019; 127(8):554-560.

AKT, protein kinase B; AR, androgen receptor; CDK, cyclin-dependent kinase; PC, prostate cancer; PI3K, phosphoinositide 3-kinase; PSMA, prostate-specific membrane antigen; PTEN, phosphatase and tensin homolog; WNT, wingless int-1.

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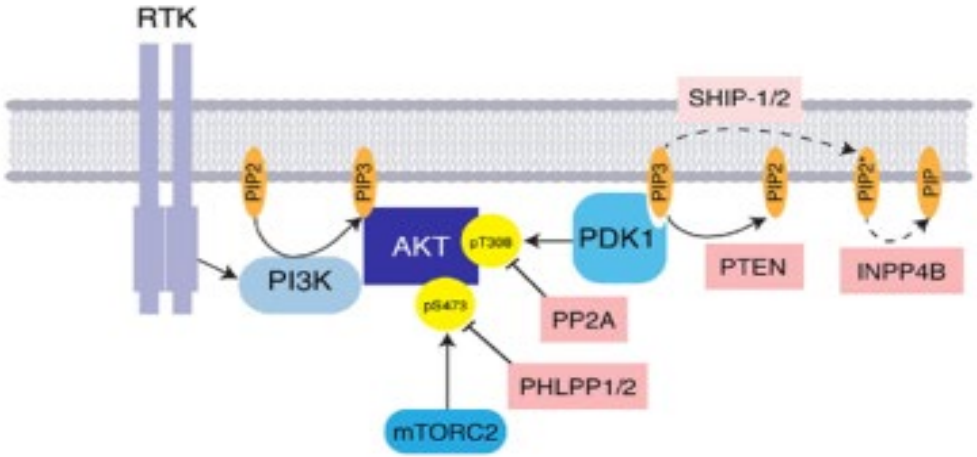
Ipatasertib and the PI3K-AKT Pathway

Presented By Johann De Bono at 2021 Genitourinary Cancers Symposium



J.S. Brown, U. Banerji / Pharmacology & Therapeutics 172 (2017) 101–115

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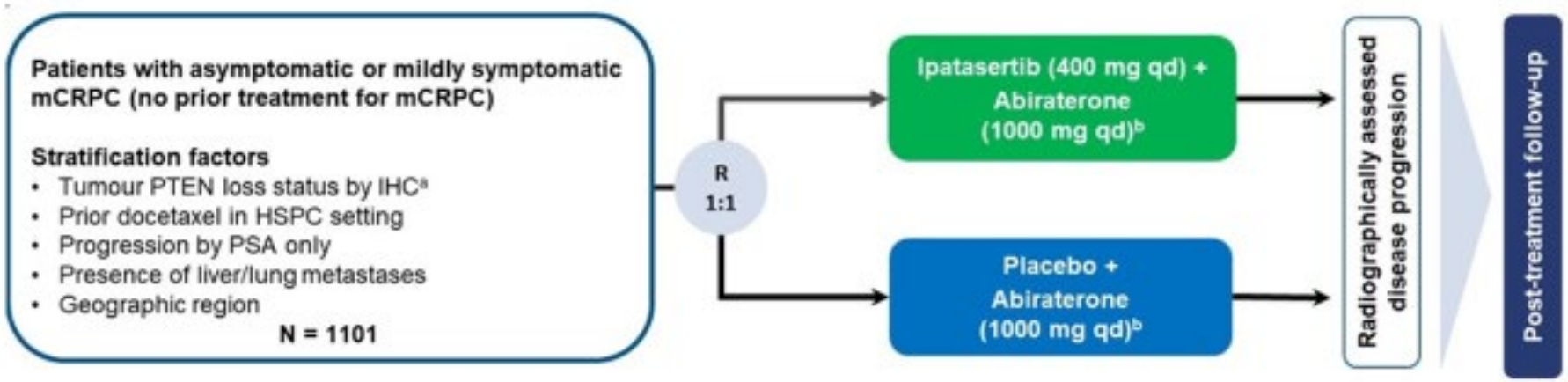
IPATential150 Study Design and Co-primary Endpoint Outcomes



Investigator-assessed rPFS in the PTEN-loss (by IHC) population

	Pbo + abi n = 261	Ipat + abi n = 260
Patients with event, n (%)	154 (59)	124 (48)
1-Year event-free rate (95% CI), %	63.3 (57.3, 69.3)	64.4 (58.3, 70.5)
Stratified HR (95% CI)	**0.77 (0.61, 0.98)**; *P* = 0.0335[c]	

Investigator-assessed rPFS in the ITT population

	Pbo + abi n = 554	Ipat + abi n = 547
Patients with event, n (%)	306 (55)	252 (46)
1-Year event-free rate (95% CI), %	63.0 (58.9, 67.1)	65.3 (61.1, 69.5)
Stratified HR (95% CI)	**0.84 (0.71, 0.99)**; *P* = 0.0431[d]	

HSPC, hormone-sensitive prostate cancer; IHC, immunohistochemistry; NGS, next-generation sequencing; PCWG3, Prostate Cancer Working Group 3; R, randomized.
[a] PTEN loss status was defined as a minimum of 50% of the specimen's tumor area with no detectable PTEN staining (by Ventana PTEN (SP218) Investigational IHC assay using SP218 antibody). [b] Abiraterone s (1000 mg qd) plus prednisone/prednisolone (5 mg bid). [c] Statistically significant at α = 0.05 level. [d] Did not meet statistical significance at α = 0.01 level.

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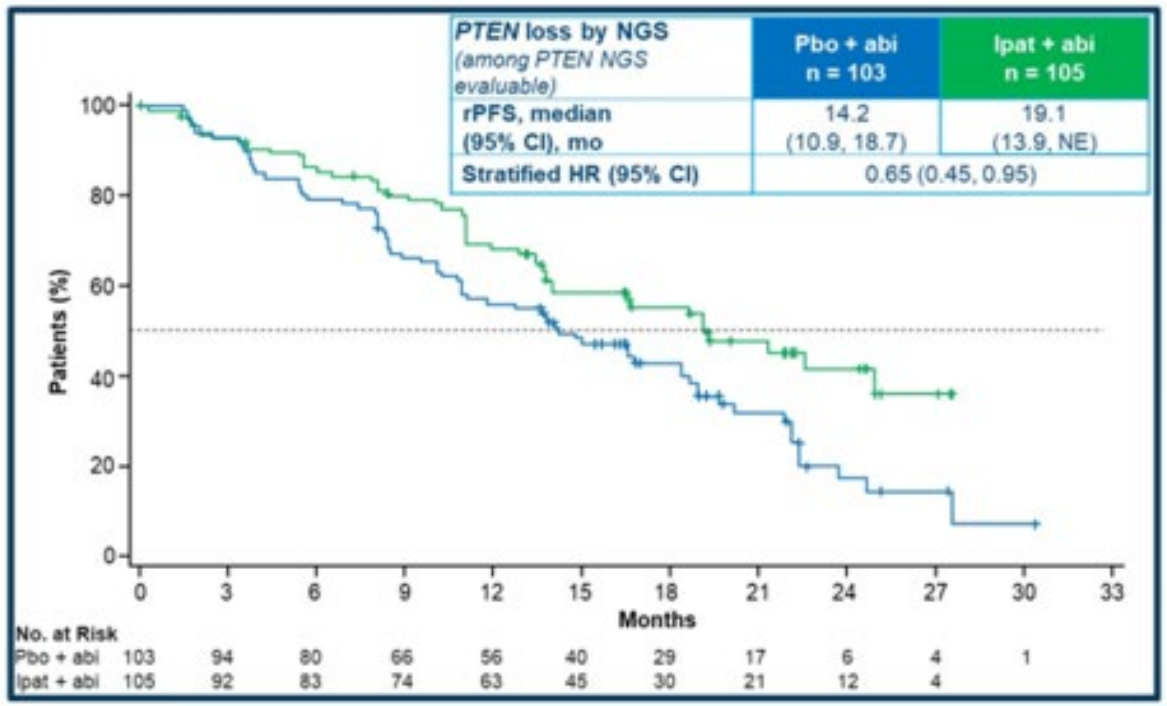
Improvement in rPFS by NGS Population



PTEN WT by NGS (among PTEN NGS evaluable)	Pbo + abi n = 155	Ipat + abi n = 155
rPFS, median (95% CI), mo	16.6 (13.7, 24.9)	20.9 (16.4, NE)
Stratified HR (95% CI)	0.85 (0.62, 1.18)	

PTEN WT + PTEN loss by NGS (among PTEN NGS evaluable)	Pbo + abi n = 258	Ipat + abi n = 260
rPFS, median (95% CI), mo	16.5 (13.7, 19.0)	19.3 (16.7, 24.7)
Stratified HR (95% CI)	0.77 (0.60, 0.99)	

[1]OS data were immature; however, the investigators noted an early trend showing survival favoring the ipatasertib arm in the PTEN-loss group (HR, 0.91) and ITT population (HR, 0.93)

1. de Bono JS, Bracarda S, Sternberg CN, et al. IPATential150: efficacy and safety from the phase III study of ipatasertib plus abiraterone vs placebo plus abiraterone in metastatic castration-resistant prostate cancer. Presented at: 2020 ESMO Virtual Congress; September 19-21, 2020; Virtual. Abstract LBA4.

Presented By Johann De Bono at 2021 Genitourinary Cancers Symposium

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FUTURE PERSPECTIVES

Precision medicine in mHSPC

	Intervention	Control Arm	Column C
TALAPRO-3 NCT04821622	Talazoparib + Enzalutamide	Enzalutamide	DDR gene mutated
CAPItello-281 NCT04493853	Capivasertib + Abi	Abi	PTEN deficiency

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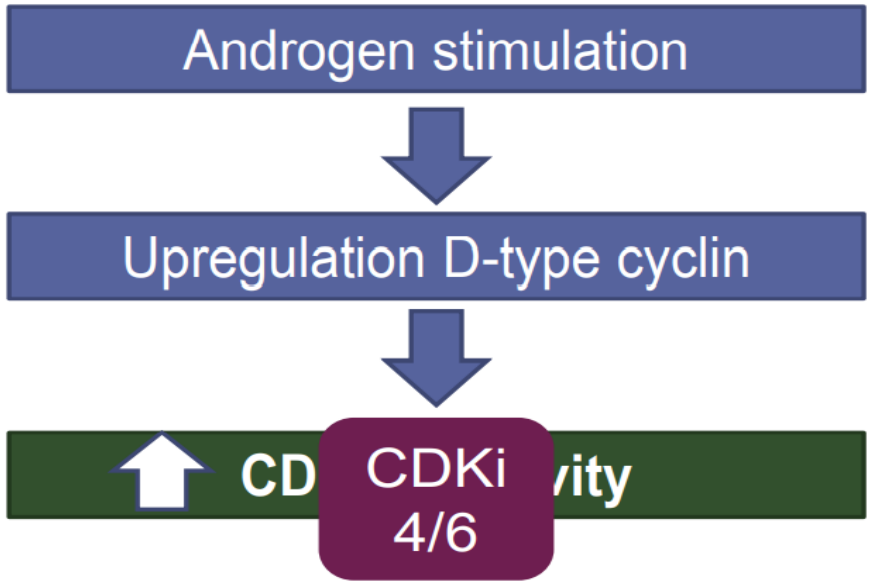
RATIONALE FOR TREATMENT IN PROSTATE CANCER



Cell cycle disruption

Cancer Res (2020) 80 (16_Supplement): 4850

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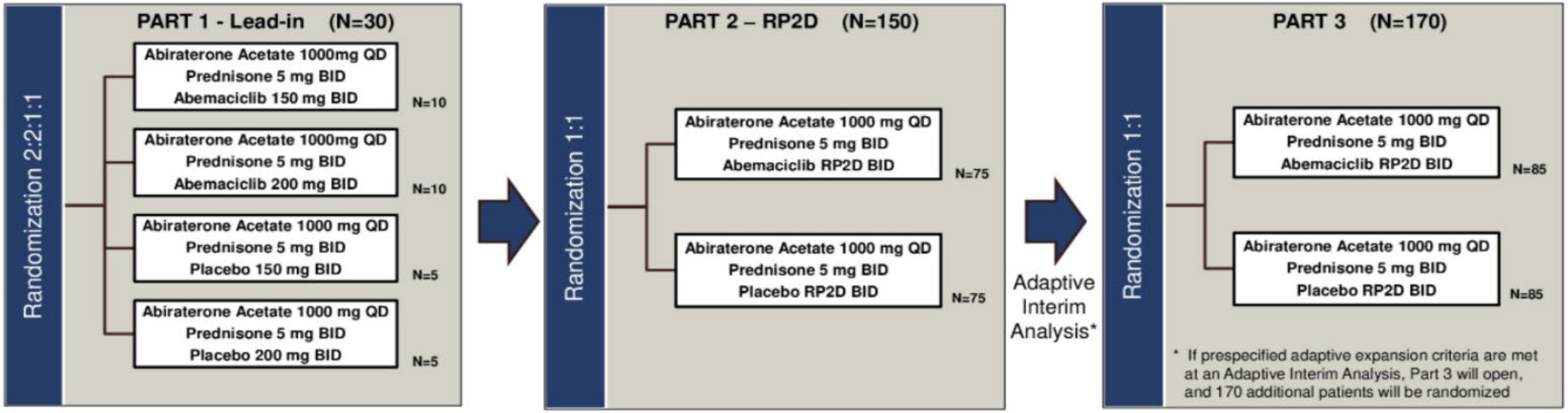
CYCLONE 2

Phase II/III, RCT, placebo controlled



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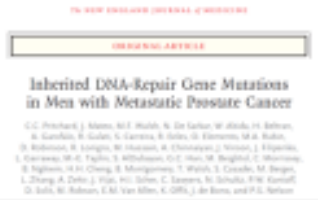
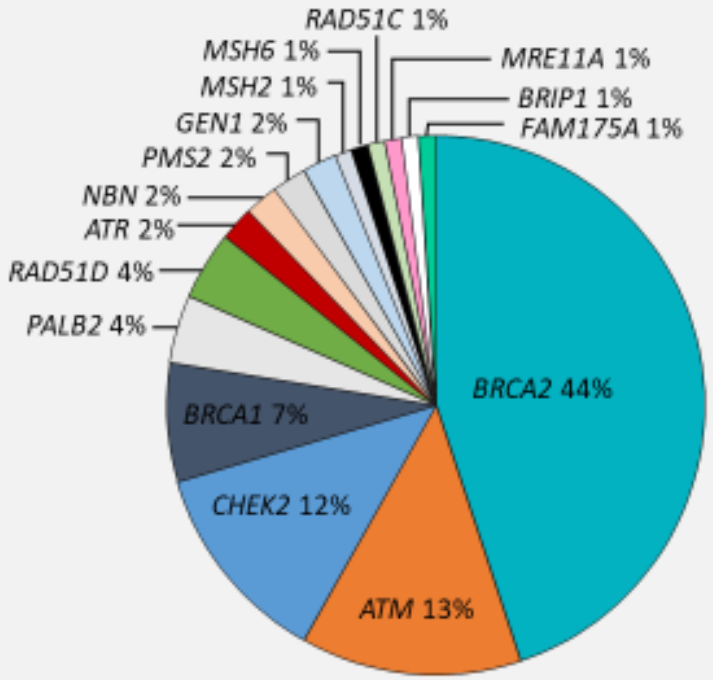
> 1 in 10 Men with mCRPC have Germline Mutations


Inherited DNA-Repair Gene Mutations in Men with Metastatic Prostate Cancer

Distribution of presumed pathogenic germline mutations



- Inherited germline DDR mutations
  - mCRPC: 11.8% (82/692)
  - Localized disease: 4.6% (23/499)

Presumed pathogenic germline mutations in metastatic cases (N = 692)

Gene	No. of Mutations	% of Men
BRCA2	37	5.35
ATM	11	1.59
*CHEK2**	10	1.87
BRCA1	6	0.87

*n = 534; data censored for metastatic cases with inadequate sequencing

Using germline testing alone
~50% of patients with a BRCA1/2, or ATM mutation will be missed

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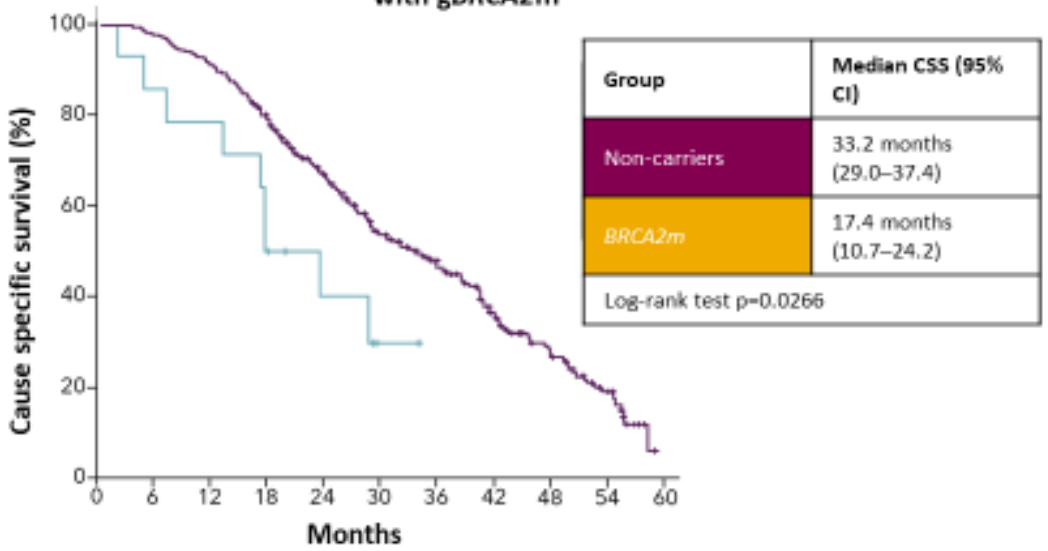
Patients with HRRm including *BRCA2*m are more likely to have poor outcomes on standard of care therapies[1-3]

Patients with **germline HRRm** including *BRCA2*m are more likely to have **poor outcomes** on standard of care therapies[1,2]

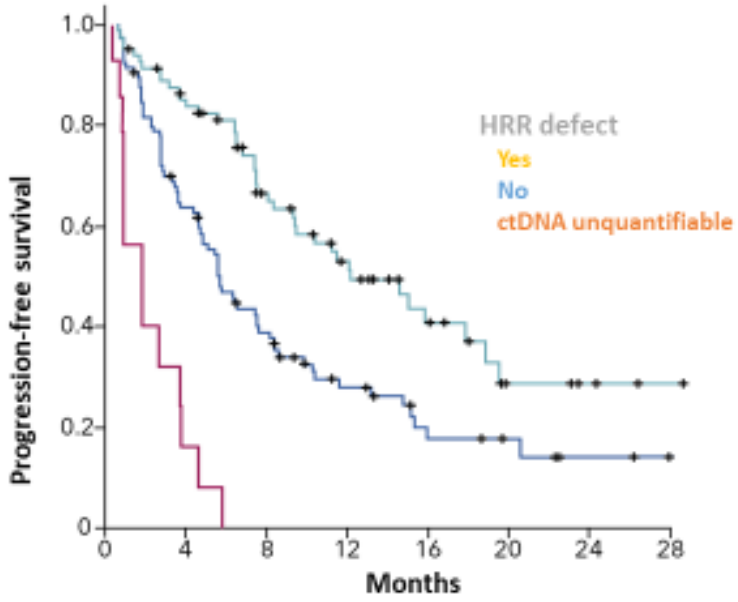
Poor responses to standard therapy also seen for **tumour HRRm**[3]

Cancer specific survival in mCRPC patients with g*BRCA2*m[1]



Group	Median CSS (95% CI)
Non-carriers	33.2 months (29.0–37.4)
BRCA2m	17.4 months (10.7–24.2)
Log-rank test p=0.0266	

Time to progression in mCRPC patients with HRRm[3]



1. Castro E, et al. *J Clin Oncol.* 2019;6:490–503; 2. Annala M, et al. *Eur Urol.* 2017;72:34–42; 3. Annala M, et al. *Cancer Discovery.* 2018;doi:10.1158/2159-8290.CD-17-0937

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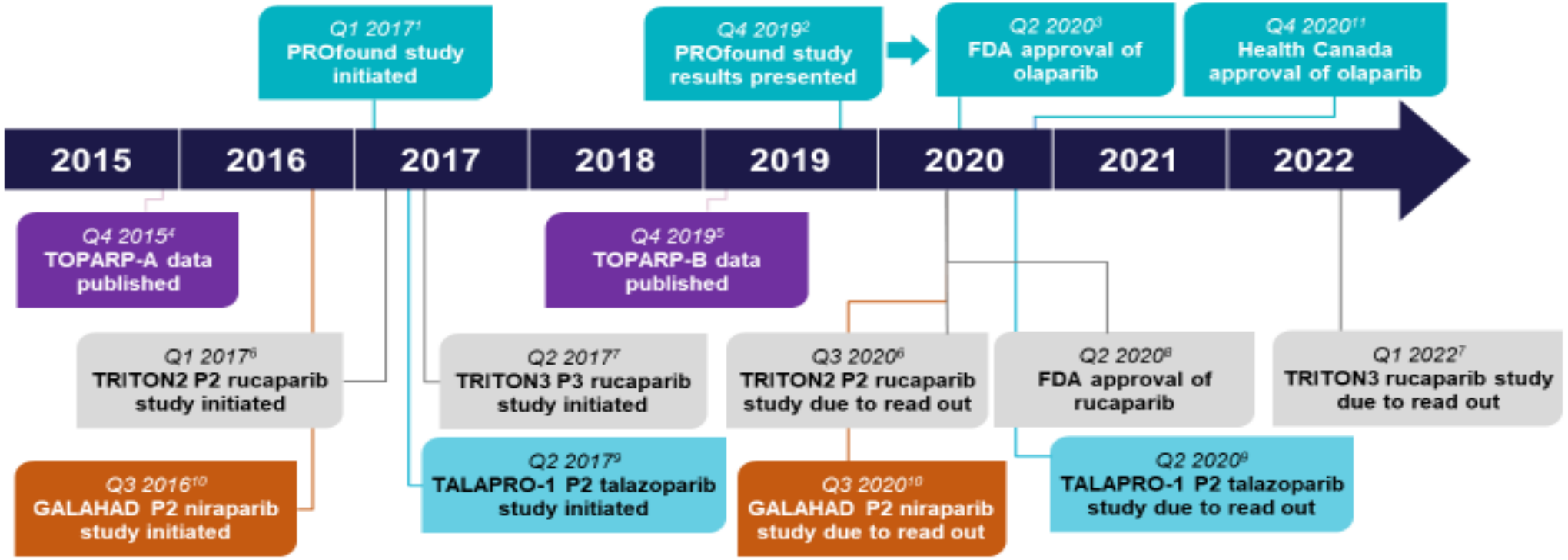
PARP Inhibitor Trials and approvals in mCRPC



HLR, high level results; HRRm, homologous recombination repair; mCRPC, metastatic castration-resistant prostate cancer; PARP, poly(ADP-ribose) polymerase; P, phase
1. de Bono J et al. NEJM 2020;382:2091-102; 2. AstraZeneca press release, 7 August 2019; 3. https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-olaparib-hrr-gene-mutated-metastatic-castration-resistant-prostate-cancer; 4. Mateo J et al. NEJM 2015; 373:1697-708; 5. Mateo J et al. J Clin Oncol 2019;37:Abstr 5005; 6. https://clinicaltrials.gov/ct2/show/NCT02952534
7. https://clinicaltrials.gov/ct2/show/NCT02975934; 8. https://www.fda.gov/drugs/fda-grants-accelerated-approval-rucaparib-brca-mutated-metastatic-castration-resistant-prostate;
9. https://clinicaltrials.gov/ct2/show/NCT03148795; 10. https://clinicaltrials.gov/ct2/show/NCT02854436; 11. Lynparza (olaparib) Canadian Product Monograph.

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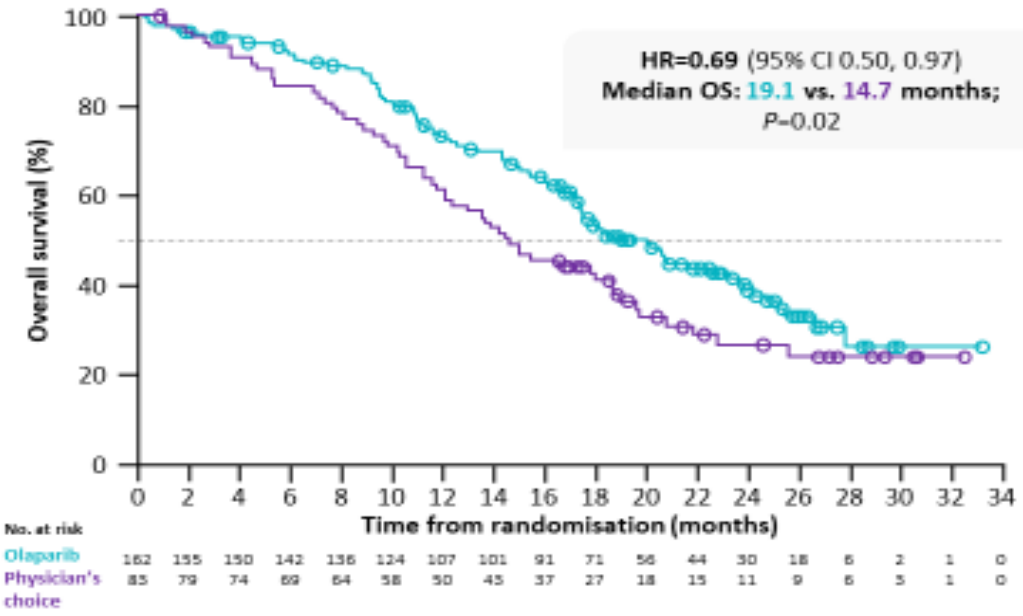
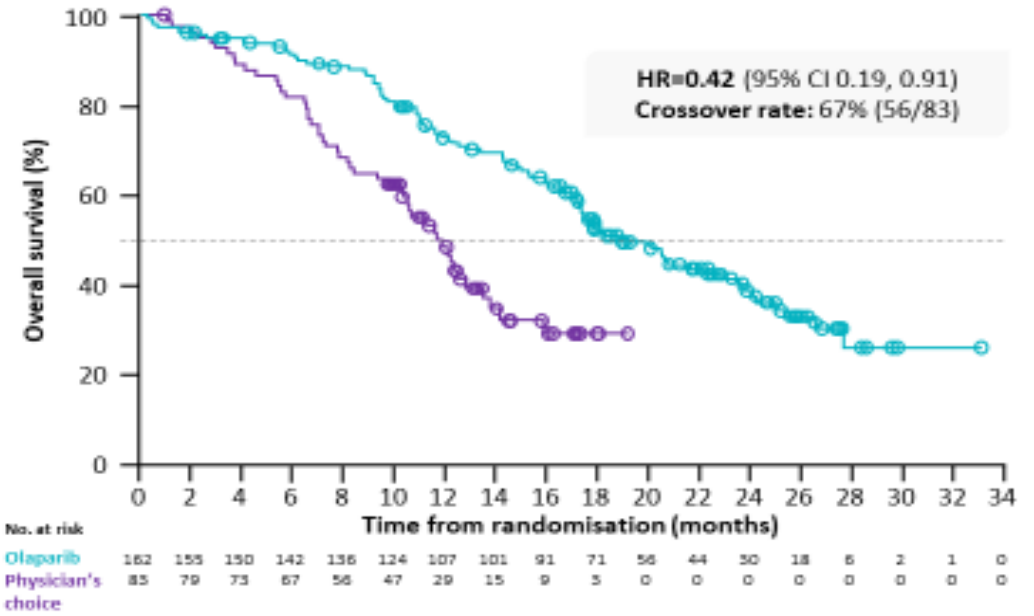
PROfound Secondary Endpoint: Significant Improvement in OS in mCRPC with BRCA1/2 or ATM Mutations (Cohort A)

31% Reduction in Risk Of Death with Olaparib vs. Physician's Choice

Cohort A



Cohort A with adjustment for crossover*



Median follow-up duration for censored patients : olaparib, 21.9 months; control, 21.0 months. *Re-censored; conducted using rank-preserving structural failure time model (RPSFTM) to demonstrate the impact on OS of crossover of patients from the control arm to receive olaparib as a first subsequent anticancer therapy. CI, confidence interval; HR, hazard ratio; OS, overall survival. 1. Hussain M, et al. *NEJM* 2020;Online: doi10.1056/NEJMoa2022485

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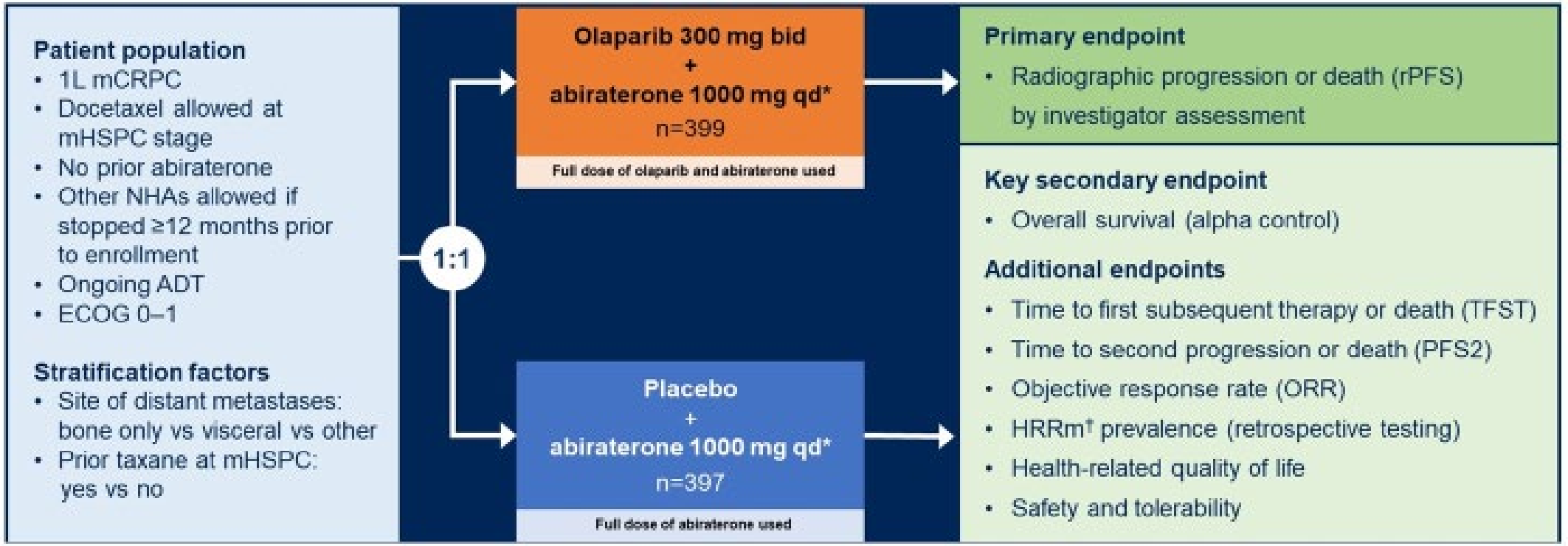
PROpel

Randomized, double-blind, placebo-controlled Phase III trial



Baseline demographics:
HRRm status

HRRm status†		
HRRm	111 (27.8)	115 (28.0)
Non-HRRm	279 (69.9)	273 (68.8)
HRRm unknown	9 (2.3)	9 (2.3)

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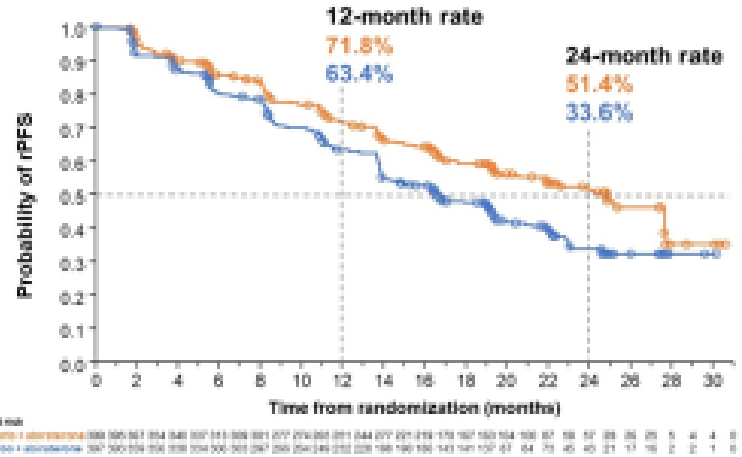
PROpel

Primary endpoint

rPFS by investigator assessment

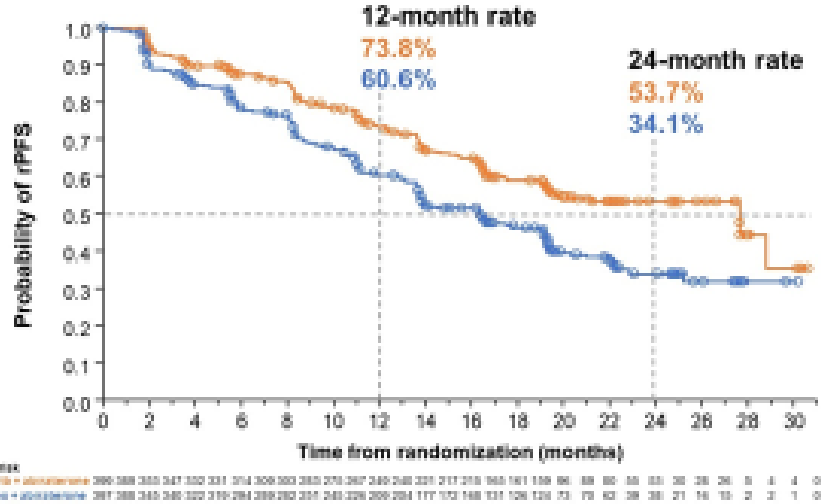


	Olaparib + abiraterone (n=399)	Placebo + abiraterone (n=397)
Events, n (%)	168 (42.1)	226 (56.9)
Median rPFS (months)	24.8	16.6
HR (95% CI)	0.66 (0.54–0.81); *P*<0.0001	

Pre-specified 2-sided alpha: 0.0324

Median rPFS improvement of 8.2 months favors olaparib + abiraterone[1]

rPFS by blinded independent central review^



	Olaparib + abiraterone (n=399)	Placebo + abiraterone (n=397)
Events, n (%)	157 (39.3)	218 (54.9)
Median rPFS (months)	27.6	16.4
HR (95% CI)	0.61 (0.49–0.74) *P*<0.0001[1]	

Median rPFS improvement of 11.2 months favors olaparib + abiraterone[1]

- 34% risk reduction for progression or death with olaparib + abiraterone (HR 0.66; 95% CI 0.54–0.81; *P*<0.0001)

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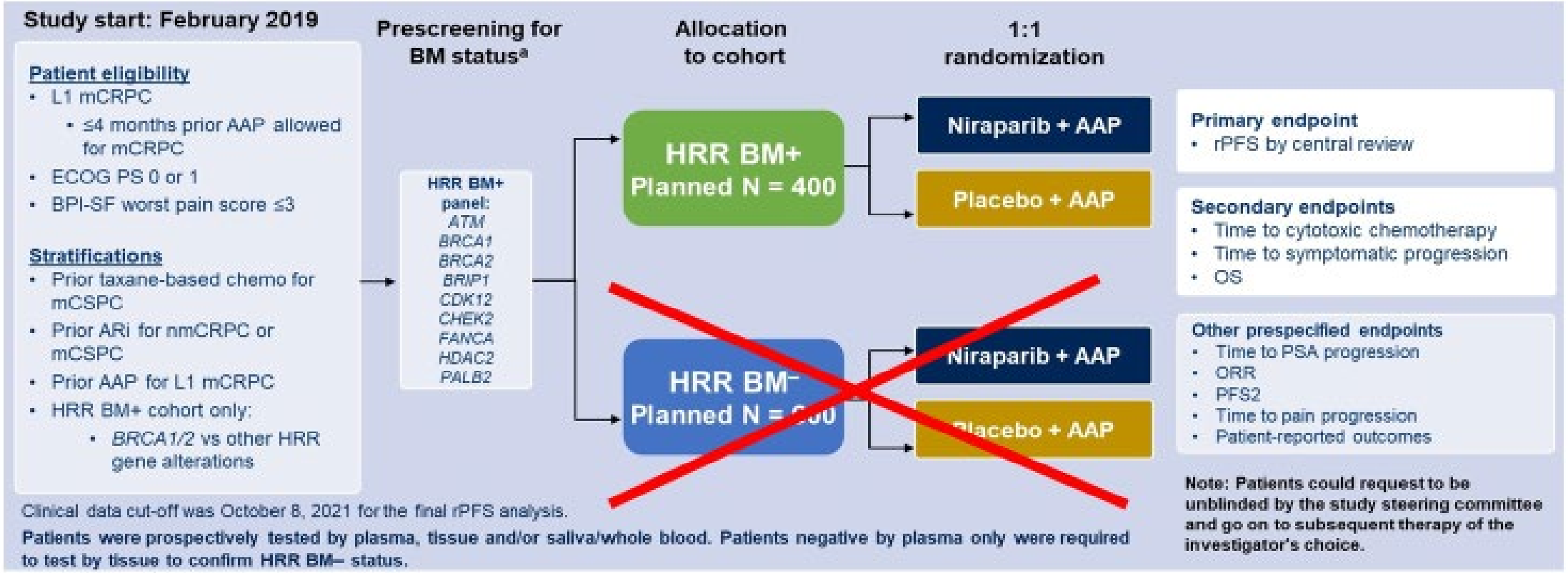
MAGNITUDE

Randomized, double-blind, placebo-controlled Phase III trial



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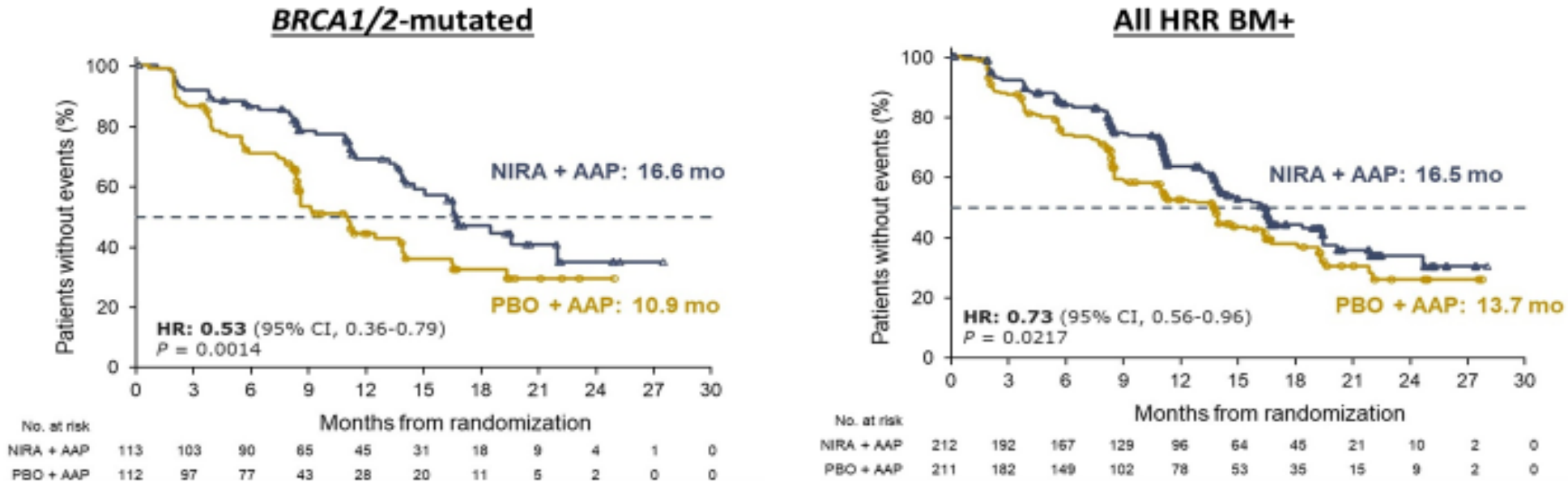
MAGNITUDE

Primary endpoint: rPFS by central review



- 47% improvement in rPFS in patients with *BRCA1/2* alterations (HR 0.53; 95% CI 0.36–0.79; *P*=0.0014)
- 27% improvement in rPFS across all HRR BM+ patients (HR 0.73; 95% CI 0.56–0.96; *P*=0.0217)

Chi KN, et al. Oral presentation at the 2022 ASCO GU Symposium; Feb 17, 2022; Abstract #12

CHUM

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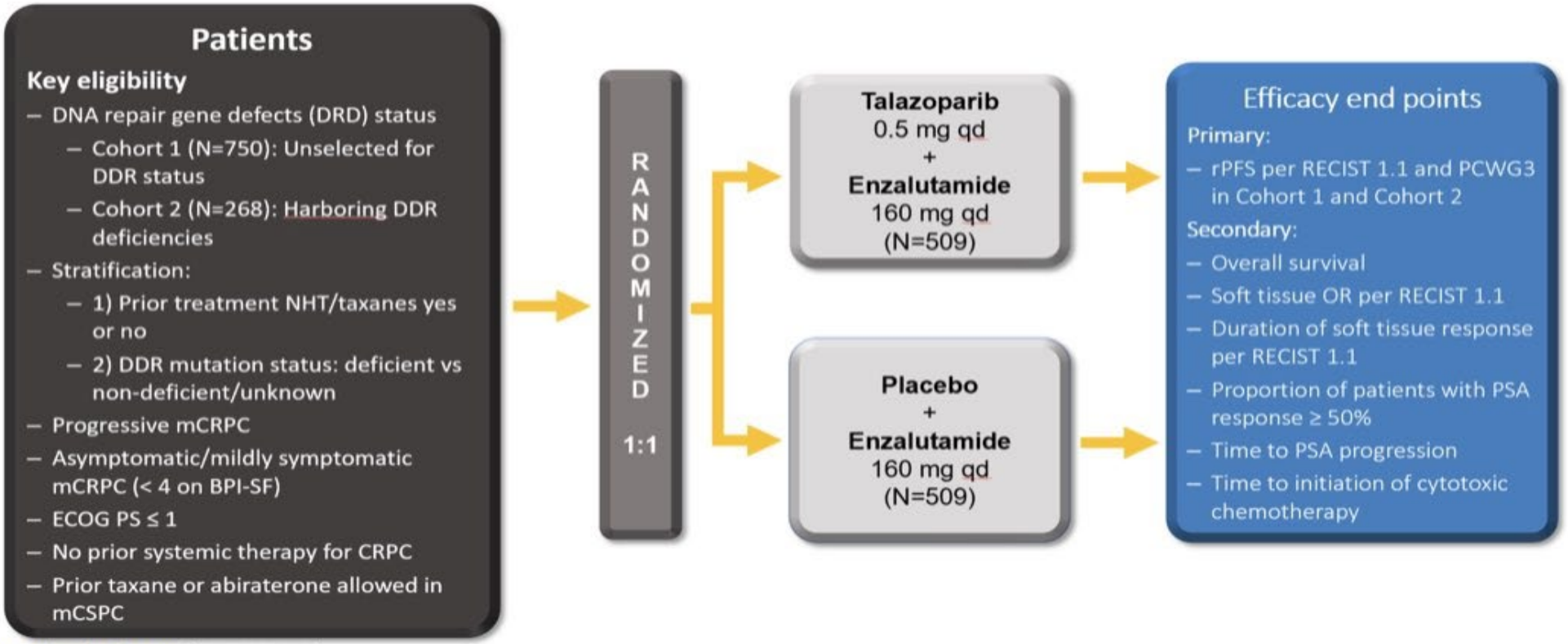
TALAPRO-2: Phase III Trial Design – Talazoparib + Enzalutamide



www.clinicaltrials.gov: (NCT03395197)

Agarwal,..Fizazi. TALAPRO-2 Phase III study design, Future Oncology 2022.

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Pfizer

- *TALZENNA® first PARP inhibitor to demonstrate clinical benefit in combination with XTANDI® in metastatic castration-resistant prostate cancer (mCRPC)*
- *Study achieves primary endpoint of radiographic progression-free survival*
- *Robust, highly consistent efficacy demonstrated in mCRPC both with or withouthomologous recombination repair gene mutations*

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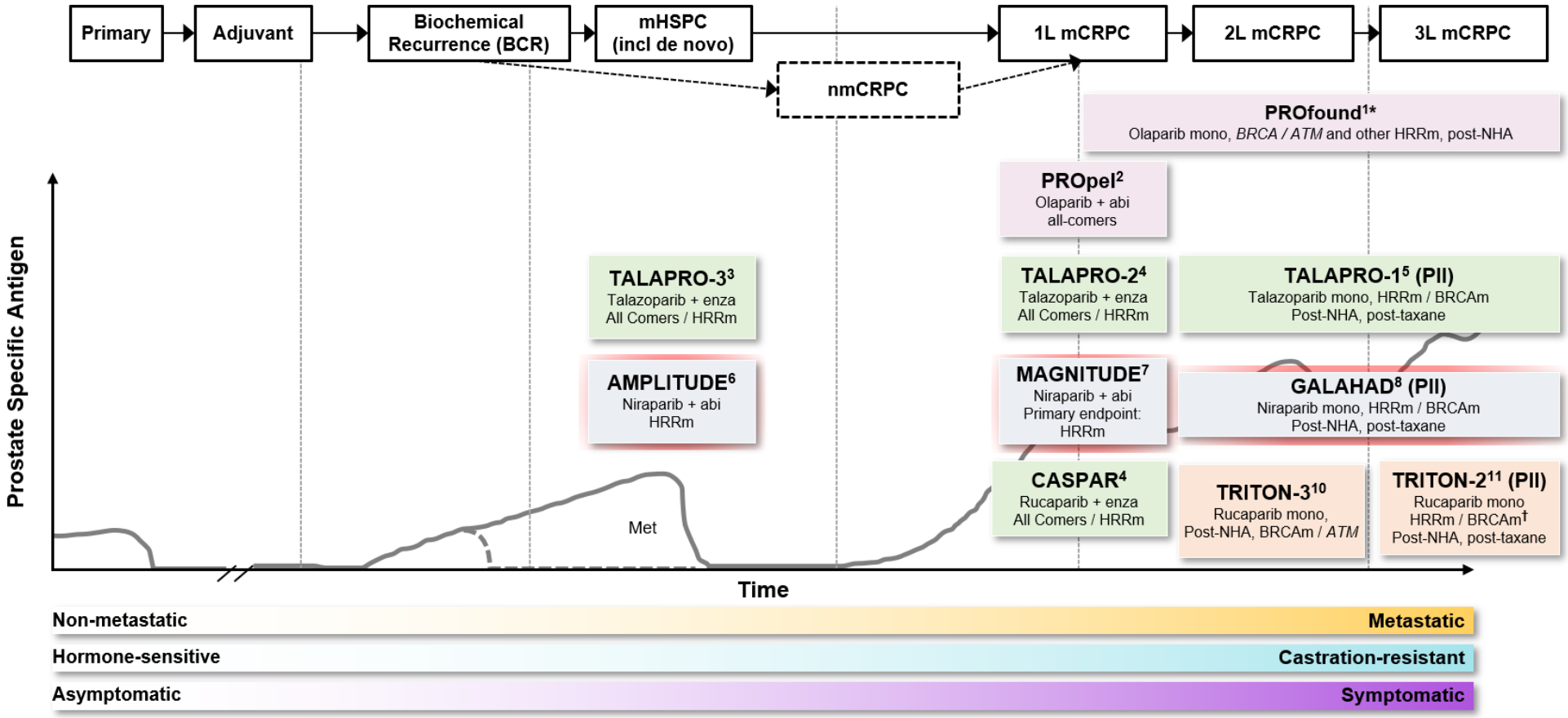
Ongoing trials investigating PARPi in advanced PC



Please see slide notes for references

*As a result of the data from PROfound, olaparib monotherapy was approved for treatment of mCRPC in patients with HRRm (FDA approval) or for patients with mutations in only *BRCA1/2* (EMA approval) after progression on a NHA[12,13]

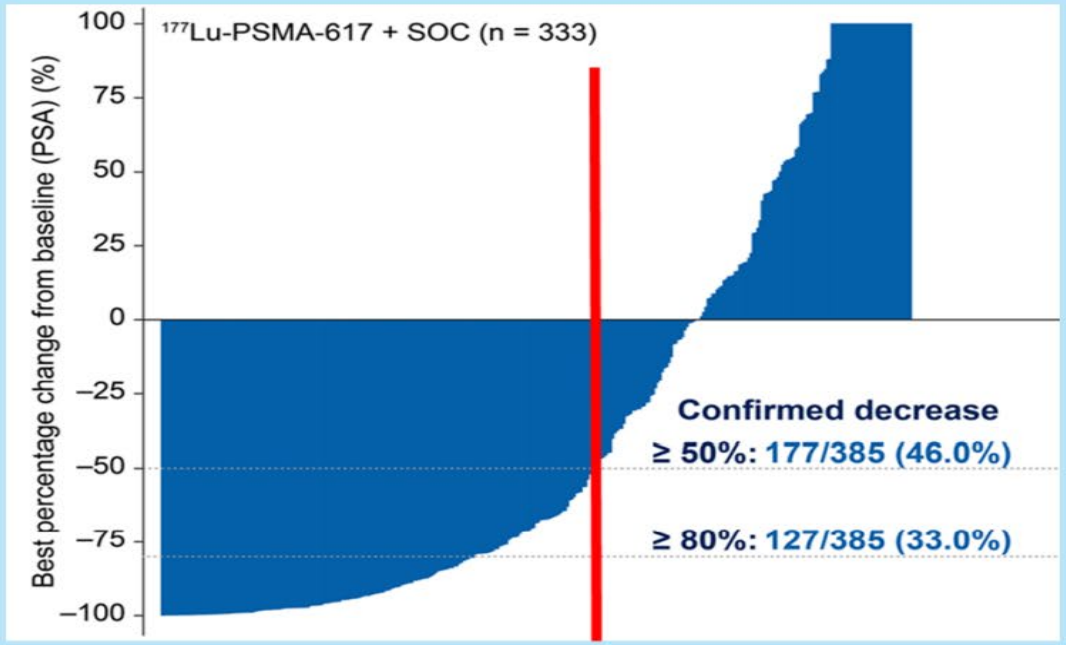
†As a result of the data from TRITON2, rucaparib monotherapy was approved by the FDA only for the treatment of mCRPC in patients with a *BRCA1/2*m who have disease progression after treatment with prior AR-directed therapy and prior taxane[14]

Abi=abiraterone; BCR=biochemical recurrence; enza=enzalutamide; FDA=US Food and Drug Administration; HRRm=homologous recombination repair mutation; mCRPC=metastatic castration-resistant prostate cancer; met=metastasis; mono=monotherapy; mHSPC=metastatic hormone-sensitive prostate cancer; NHA=new hormonal agent; nmCRPC=non-metastatic castration-resistant prostate cancer; P2=Phase II; P3=Phase III.

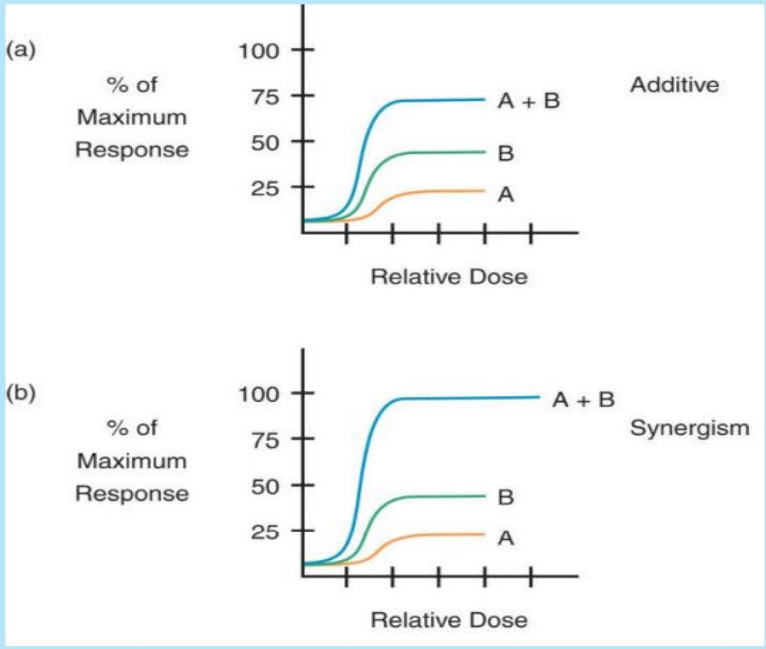
Evre IV Kastrasyona Dirençli Prostat Kanseri PSMA ekspresyonu

EAU22 | AMSTERDAM 1-4 July 2022

Synergism: Holy Grail



Sartor et al., NEJM 2021



https://biology-forums.com/index.php?action=gallery;sa=view;id=28366

1+3 = 4

1+3 > 4

Evre IV Kastrasyona Dirençli Prostat Kanseri PSMA ekspresyonu

EAU22 | AMSTERDAM 1-4 July 2022

Candidates

- Checkpoint Inhibitors
- PARP Inhibitors
- ARDT
- Chemotherapy
- SBRT
- Others?

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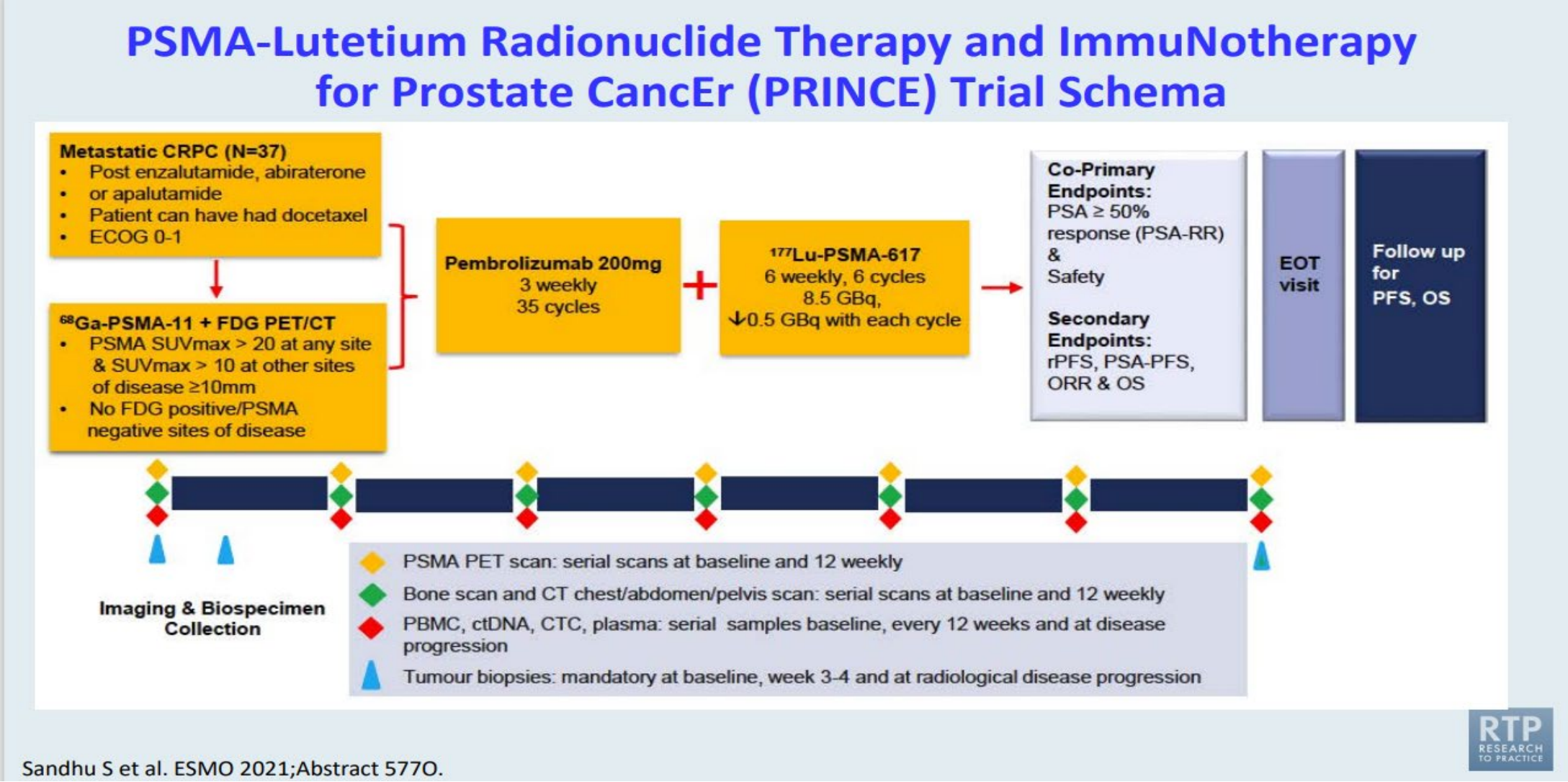
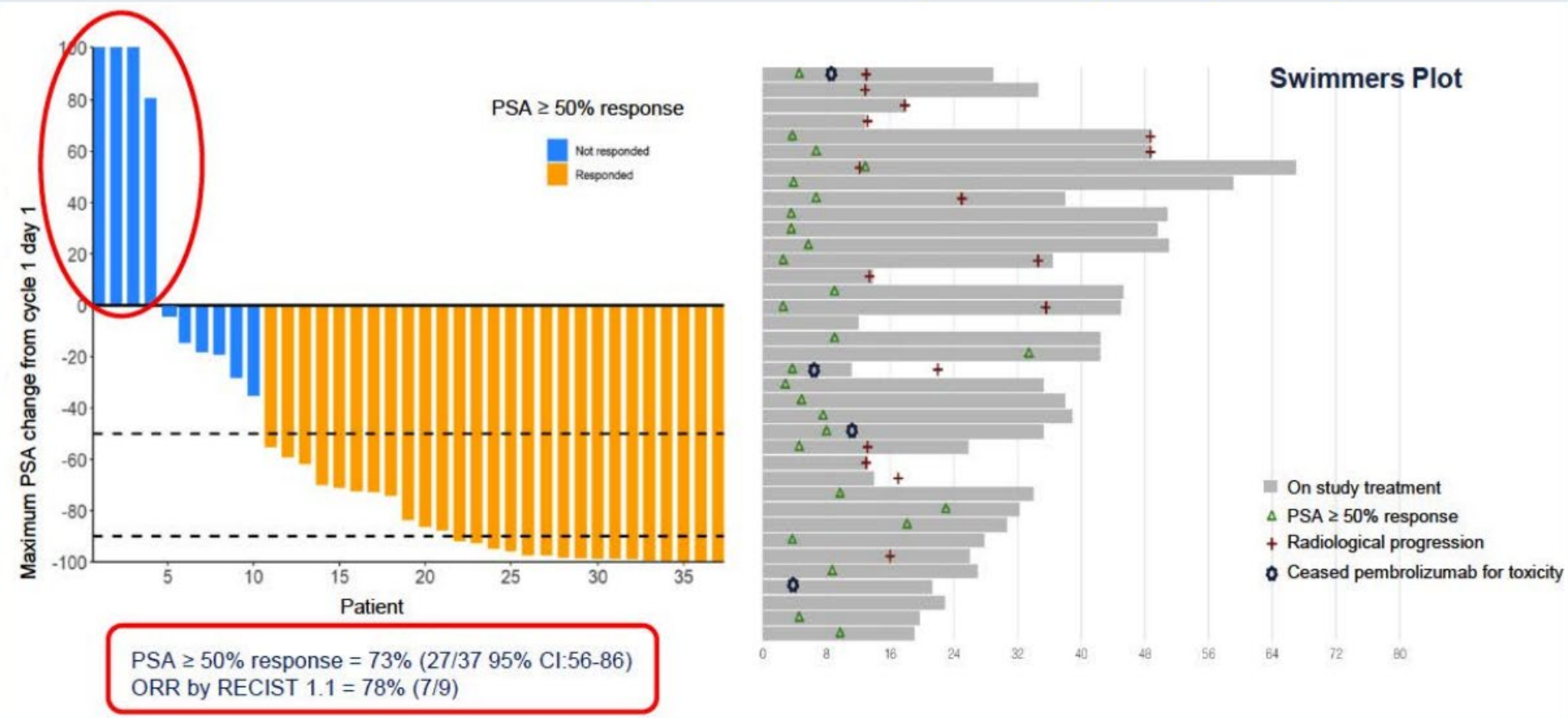


Sandhu S et al. ESMO 2021;Abstract 577O.

Evre IV Kastrasyona Dirençli Prostat Kanseri PSMA ekspresyonu



Sandhu S et al. ESMO 2021;Abstract 577O.

Evre IV Kastrasyona Dirençli Prostat Kanseri PSMA ekspresyonu

EAU22 | AMSTERDAM 1-4 July 2022

PARP Inhibitors

Combination with Olaparib

LuPARP Trial

Phase 1 trial of ^{177}Lu-PSMA-617 therapy and **Olaparib (PARPi)**

- Metastatic CRPC
- Progressed after 2nd generation AR-targeted agent
- Post taxane chemotherapy

↓

PSMA + FDG PET/CT

↓

^{177}Lu-PSMA-617
6 weekly, 4 cycles
7.4 GBq

+

Olaparib day 2-15
3+3 dose escalation design
50mg to 300mg bd
(6 levels of increment)

Prostate Cancer Foundation
Curing Together.
ANSTO
ENDOCYTE
A Novartis Company
BaCT
Centre for Biostatistics and Clinical Trials
PeterMac

Hofman et al., Twitter 2019

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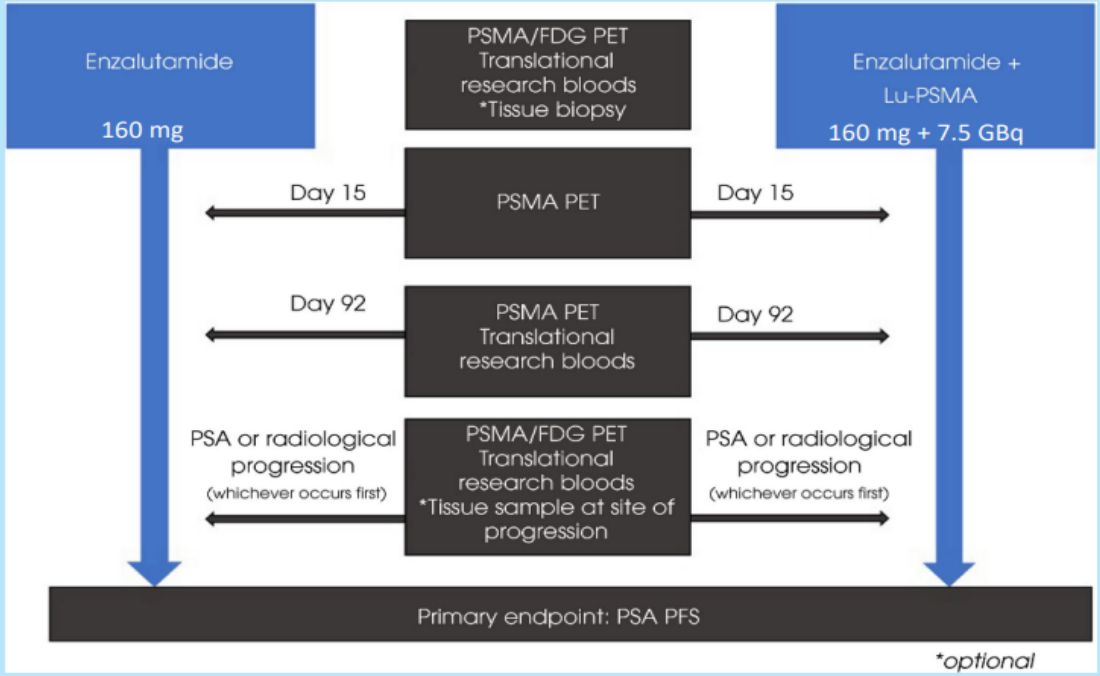
ARDT

ENZA-p Trial

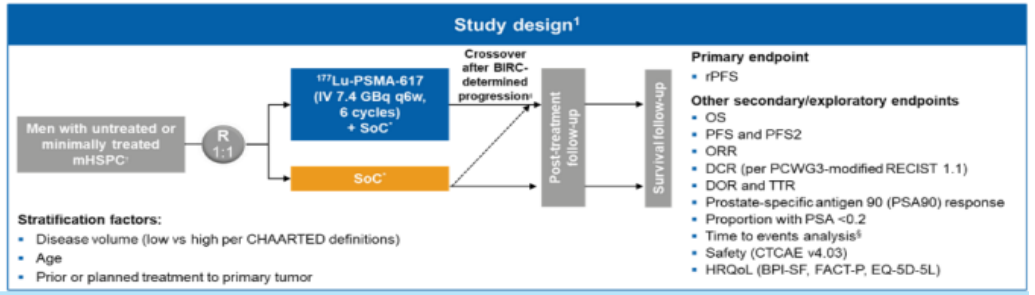


Emmett et al., BJUI 2021

PSMAaddition

PSMAddition: a randomized, phase 3 study of ^{177}Lu-PSMA-617 in patients with untreated or minimally treated mHSPC

- PSMAddition aims to assess the efficacy and safety of ^{177}Lu-PSMA-617 RLT plus SoC* vs SoC in men with untreated/minimally treated mHSPC (NCT04720157)[1]



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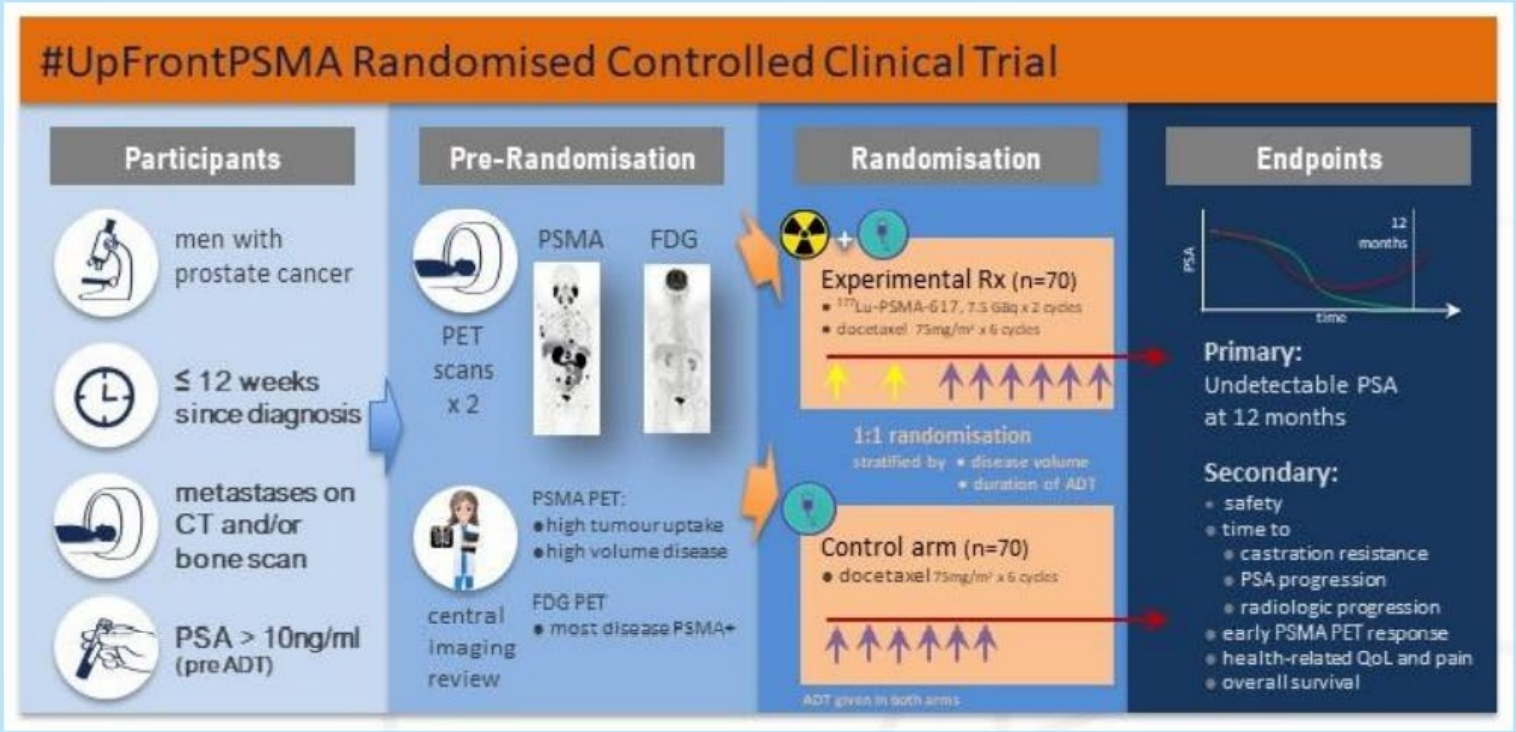
Chemotherapy

UpfrontPSMA (NCT04343885)



Azad et al., ASCO 2021; Azad et al., Twitter 2021; Hofman et al., Twitter 2020

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SBRT

Combining SBRT and PSMA RLT

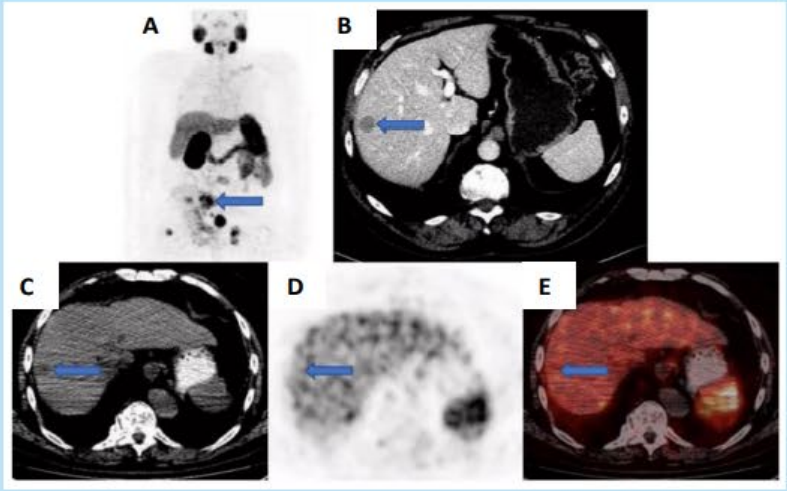
A Study of Stereotactic Body Radiotherapy and 177Lu-PSMA-617 for the Treatment of Prostate Cancer

ClinicalTrials.gov Identifier: NCT05079698

Recruitment Status : Recruiting
First Posted : October 15, 2021
Last Update Posted : June 6, 2022
See Contacts and Locations

Sponsor:
Memorial Sloan Kettering Cancer Center

Collaborator:
Novartis Pharmaceuticals



Rationale of „adding“ SBRT in patients with few, disease dominant but PSMA-negative or PSMA-low uptake lesions very appealing..

Kuo et al., SNMMI 2022

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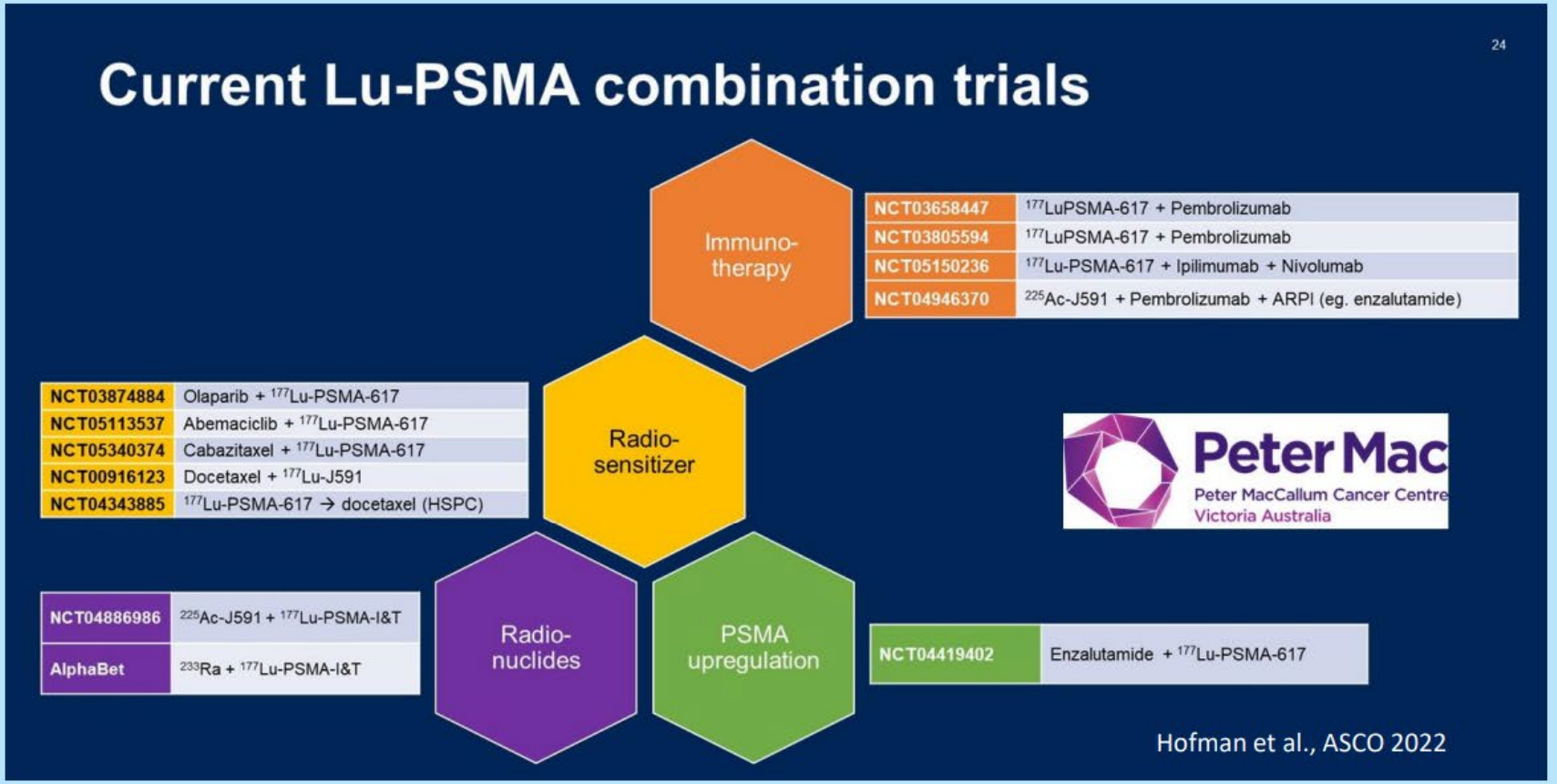
Others



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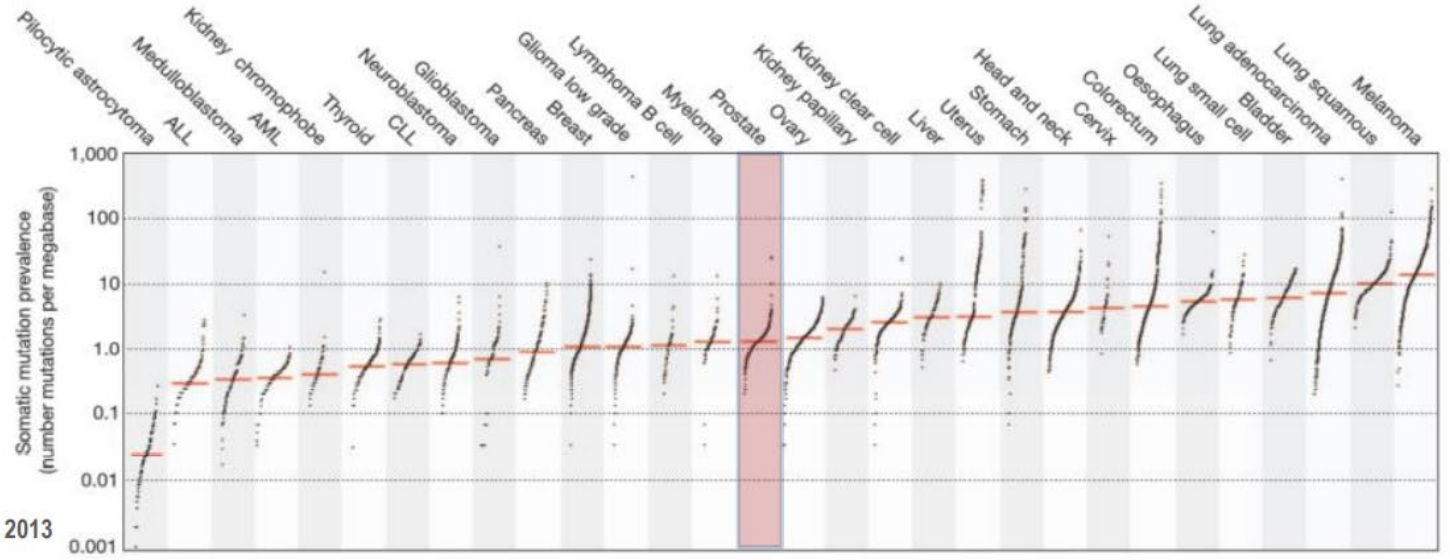
Mikrosatellit instabilite

Immune checkpoint blockade

Limited activity of PD-1/PD-L1 inhibitors in CRPC?
(mutations are rare)



Alexandrov et al, Nature 2013

or re-use.

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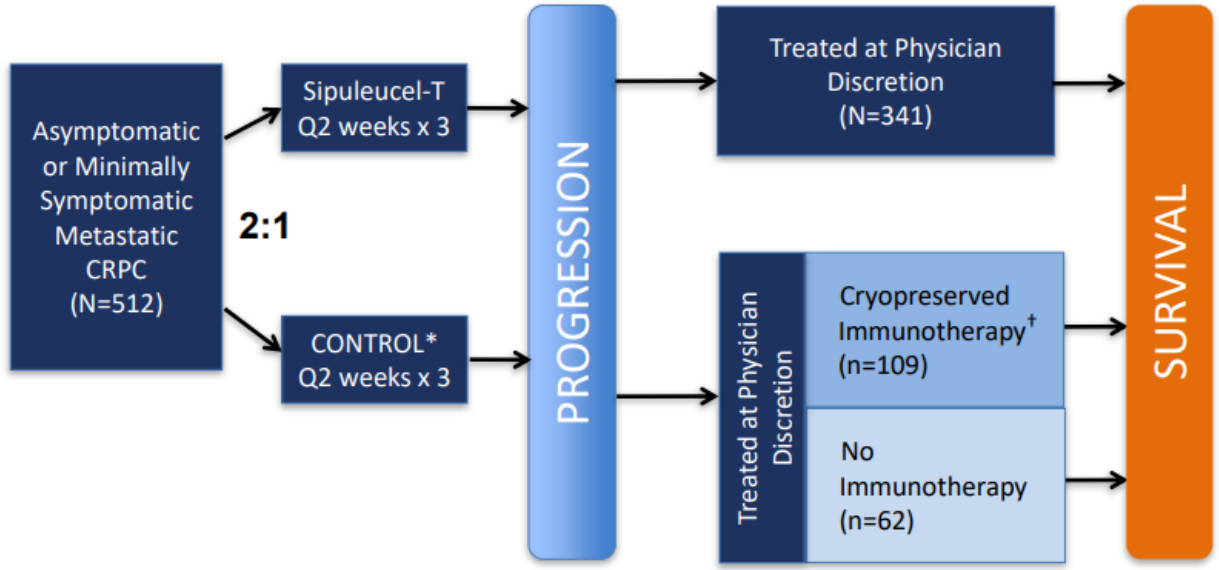
IMPACT: Phase III Trial of Sipuleucel-T



Primary endpoint: Overall survival
Secondary endpoint: Time to objective disease progression

†64% of patients in the control group, following progression, crossed over to receive autologous immunotherapy made from cryopreserved cells.

Kantoff PW et al. *N Engl J Med* 2010;

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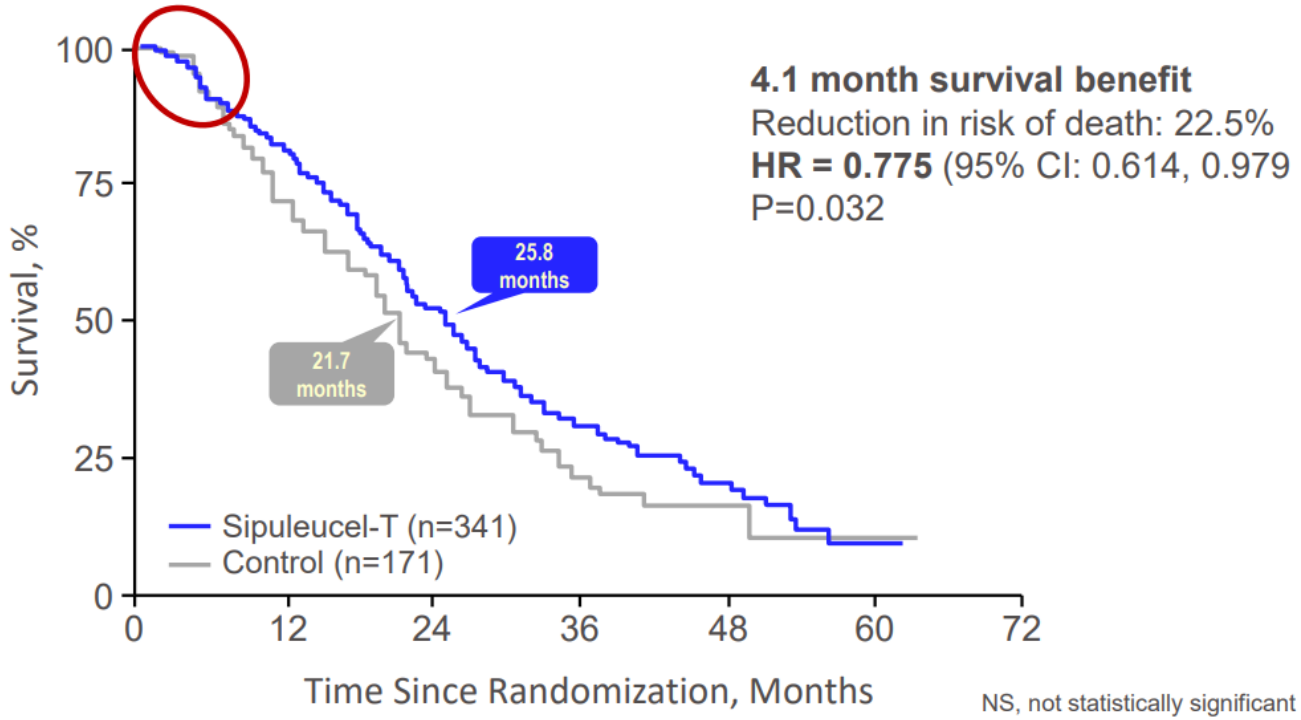
Sipuleucel-T: Impact Phase 3 trial
A first « negative-positive » trial



4.1 month survival benefit
Reduction in risk of death: 22.5%
HR = 0.775 (95% CI: 0.614, 0.979
P=0.032

NS, not statistically significant

Kantoff PW, et al. N Engl J Med 2010;363:411–22

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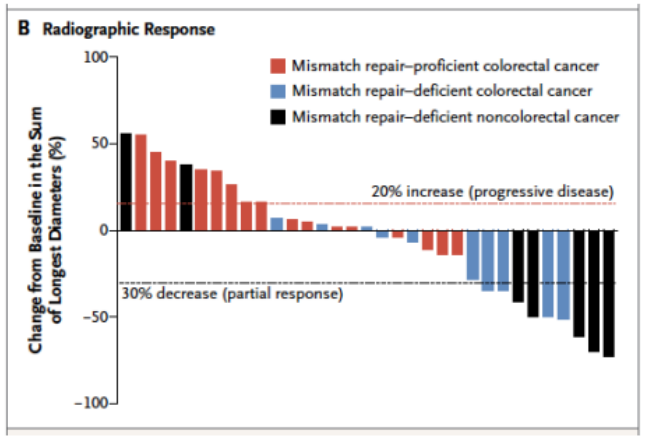
The NEW ENGLAND JOURNAL of MEDICINE

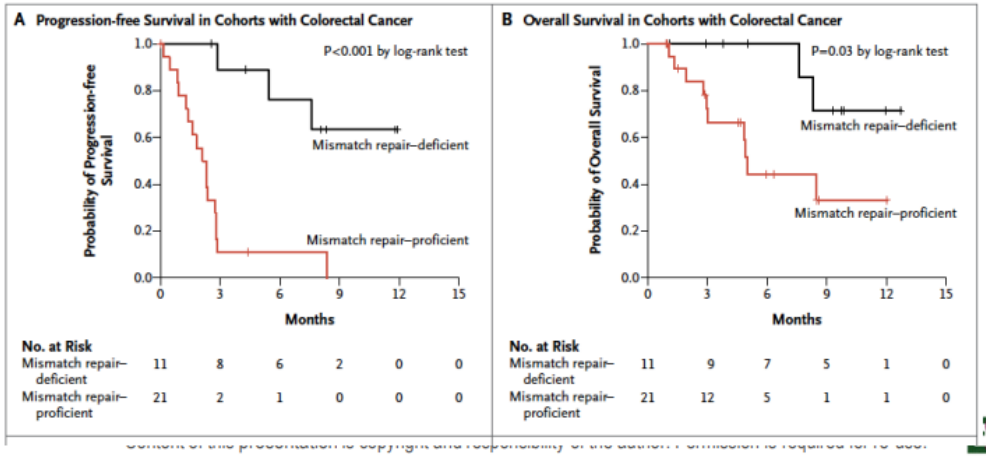
ORIGINAL ARTICLE

PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

D.T. Le, J.N. Uram, H. Wang, B.R. Bartlett, H. Kemberling, A.D. Eyring, A.D. Skora, B.S. Luber, N.S. Azad, D. Laheru, B. Biedrzycki, R.C. Donehower, A. Zaheer, G.A. Fisher, T.S. Crocenzi, J.J. Lee, S.M. Duffy, R.M. Goldberg, A. de la Chapelle, M. Koshiji, F. Bhaijee, T. Huebner, R.H. Hruban, L.D. Wood, N. Cuka, D.M. Pardoll, N. Papadopoulos, K.W. Kinzler, S. Zhou, T.C. Cornish, J.M. Taube, R.A. Anders, J.R. Eshleman, B. Vogelstein, and L.A. Diaz, Jr.

2% of prostate cancers with MMR mutations





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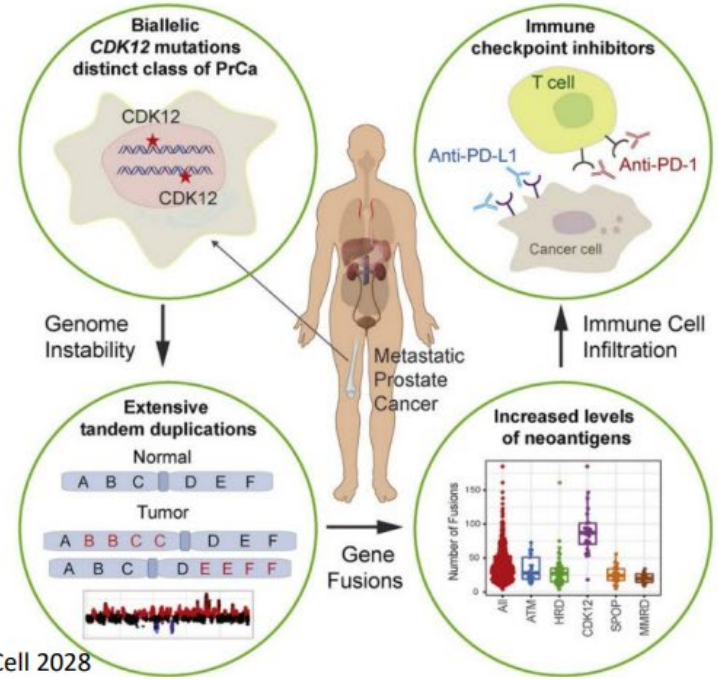
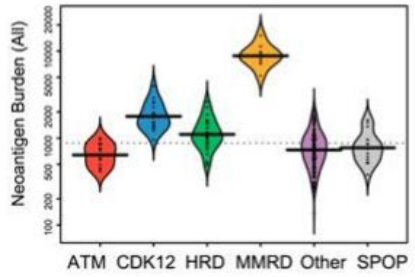
Inactivation of *CDK12* Delineates a Distinct Immunogenic Class of Advanced Prostate Cancer

Yi-Mi Wu,[1,2,20] Marcin Cieślik,[1,2,20] Robert J. Lonigro,[1] Pankaj Vats,[1] Melissa A. Reimers,[3] Xuhong Cao,[1] Yu Ning,[1] Lisha Wang,[1] Lakshmi P. Kunju,[1,2,4] Navonil de Sarkar,[5] Elisabeth I. Heath,[6,7] Jonathan Chou,[8] Felix Y. Feng,[8,9,10,11] Peter S. Nelson,[5,12,13] Johann S. de Bono,[14,15] Weiping Zou,[1,2,16] Bruce Montgomery,[12,17] Ajjai Alva,[1,3] PCF/SU2C International Prostate Cancer Dream Team, Dan R. Robinson,[1,2,*] and Arul M. Chinnaiyan[1,2,4,18,19,21,*]



- 6.9% [4.6%, 10.2%] of mCRPC
- Focal tandem duplications.[1]



Wu et al., Cell 2028

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ESMO

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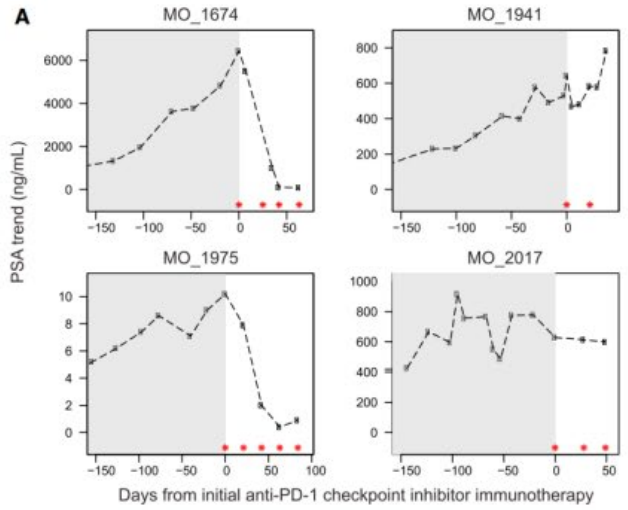
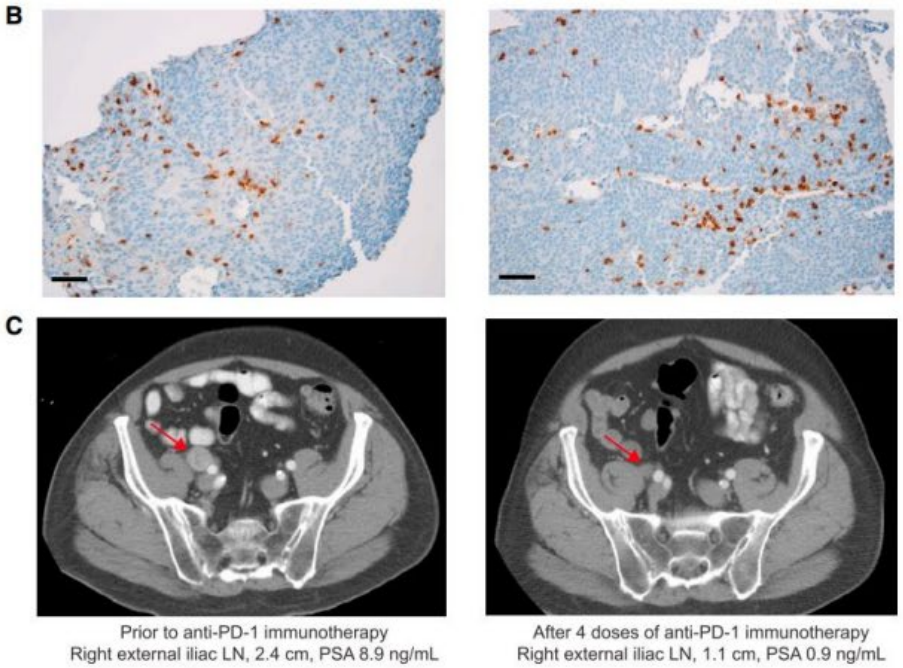
Pilot Clinical Study to Determine CDK12 Mutant Prostate Cancer Response to Checkpoint Inhibitor Immunotherapy

11 pts -5 tt anti PD1

- 1 pt excluded
- 2 pts +++PSA decline





Wu et al., Cell 2028

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Metastatic Castration-resistant **Prostate Cancer**	Drug: Atezolizumab	

Detailed Description:

This is a multi-center, open label Phase II study of patients with metastatic castration resistant prostate cancer (mCRPC) who will be treated with abemaciclib and atezolizumab alone or in combination.

The U.S. Food and Drug Administration (FDA) has not approved abemaciclib or atezolizumab alone or in combination for use in prostate cancer. Abemaciclib is an orally administered molecularly targeted chemotherapy drug called a cyclin-dependent kinase inhibitor, which acts to block the ability of cancer cells to divide and thus prevents tumors from growing. In the laboratory setting, this drug is effective in prostate cancer models that have become resistant to standard hormonal treatments, and this drug is currently being studied for its effectiveness in prostate cancer in other clinical trials. Atezolizumab is an intravenously administered drug called an immune checkpoint inhibitor, which acts to activate the immune system to kill cancer cells. Atezolizumab is ineffective on its own in most patients with prostate cancer, but is being tested in combination with other drugs for prostate cancer in other clinical trials. Multiple research groups have demonstrated in laboratory model systems that abemaciclib can may make immune checkpoint inhibitors more effective.

The research study procedures include screening for eligibility and study treatment including evaluations and follow up visits.

The study design divides study participants into two separate cohorts. The first cohort is a set of subjects whose tumors are not known to have mutations in the CDK12 gene (the "biomarker unselected cohort") - either because tumor tissue never underwent genetic profiling, or because genetic profiling was performed but did not demonstrate a mutation in the CDK12 gene. In this "biomarker unselected cohort," this study will be testing whether abemaciclib alone or in combination with atezolizumab is an effective treatment strategy.

The second cohort of participants is a set of subjects whose tumors are known to have mutations in the CDK12 gene based on genetic profiling of the tumor that occurred prior to enrollment on this study. Prior studies suggest that cancers with mutations in the CDK12 gene can shrink in response to immune checkpoint inhibitors. This study will be testing in study participants whose tumors are known to have mutations in CDK12 whethe atezolizumab alone or in combination with abemaciclib is an effective treatment strategy.

In addition, the trial is testing the safety of the combination of the two drugs in both cohorts.

Participants will receive study treatment for as long as they do not have serious side effects and their disease does not get worse. Participants will be followed after completion of study treatment for up to 24 months

It is expected that about 75 people will take part in this research study.

Eli Lilly and Company is supporting this research study by providing funding for research and the study drug abemaciclib. Genentech, Inc. is supporting the study by providing the study drug atezolizumab.

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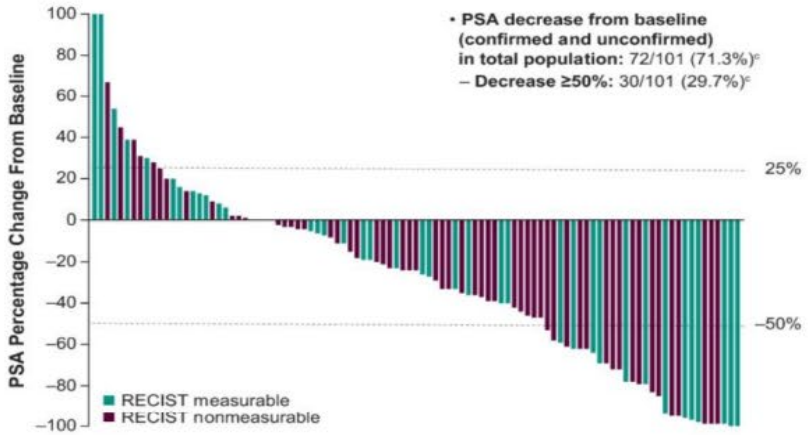
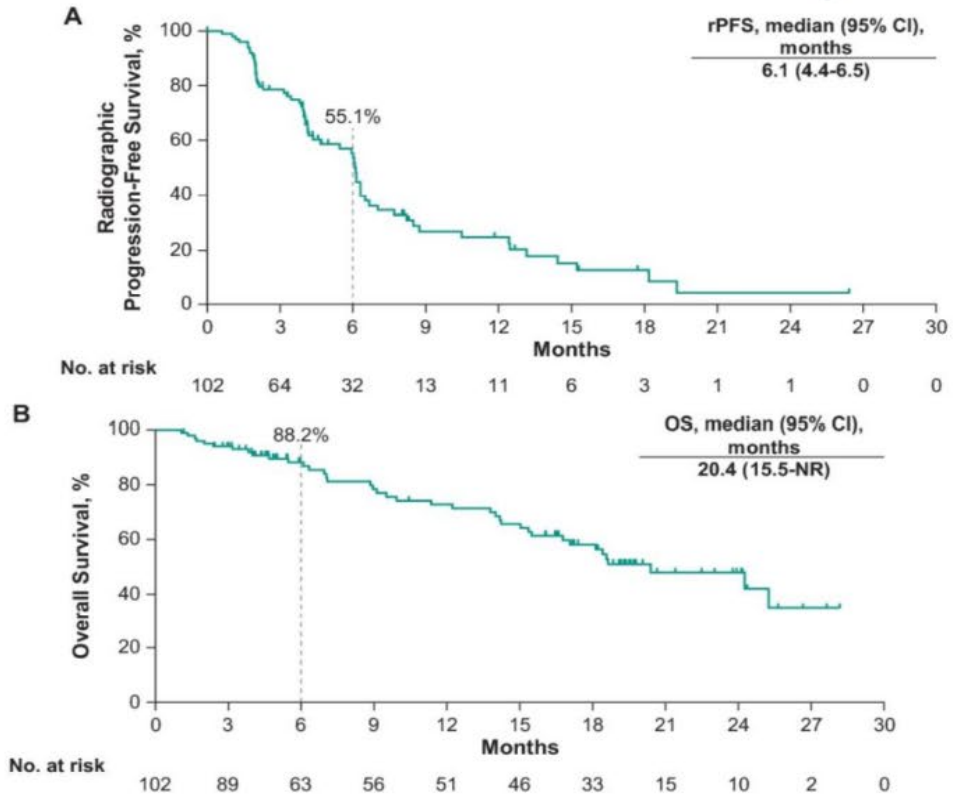
Keynote 365 – Cohort B: Pembrolizumab + Enzalutamide





Conter et al., ASCO 2020

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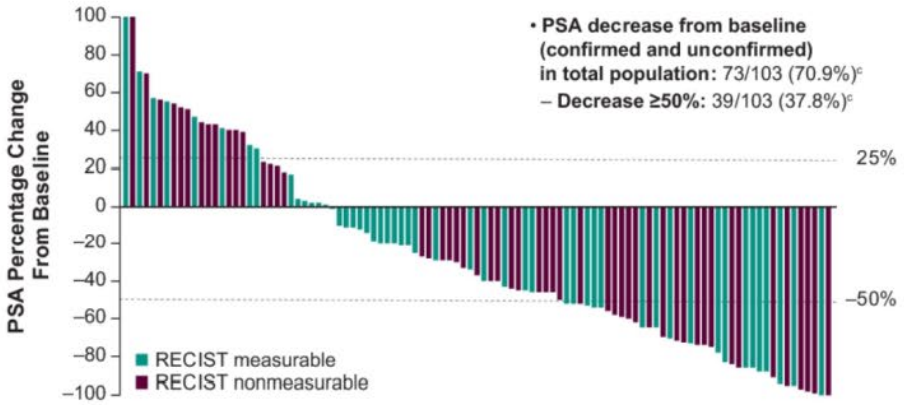
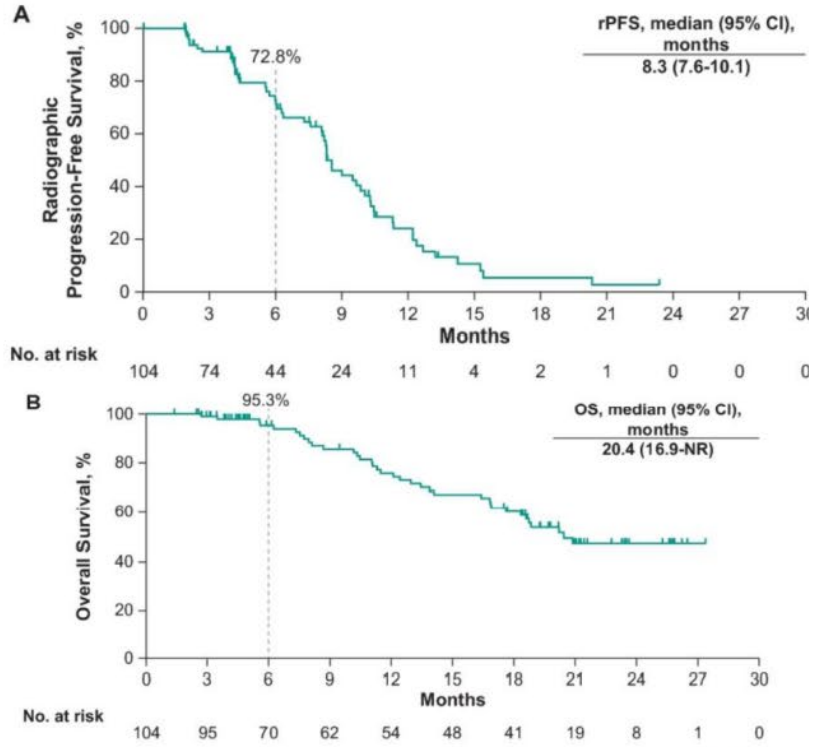
Keynote 365 – Cohort B: Pembrolizumab + Docetaxel





Sridhar et al., ASCO 2020

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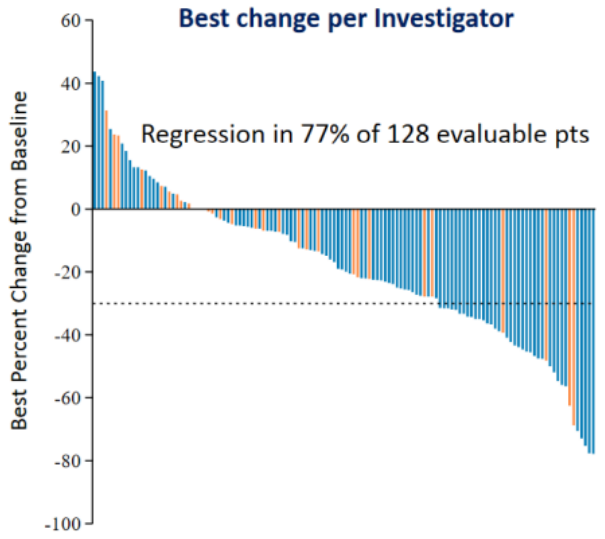
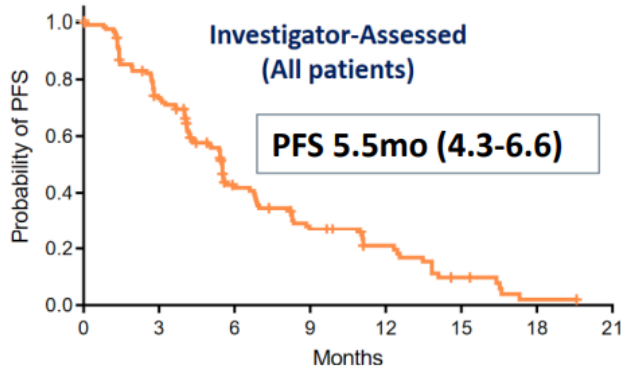
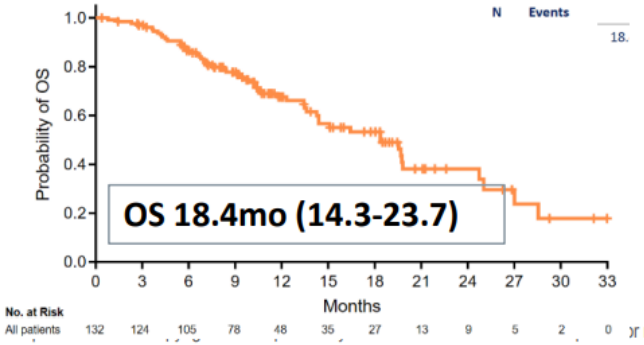
COSMIC-021 phase 1b: Atezolizumab + Cabozantinib







Agarwal et al., ESMO 2021

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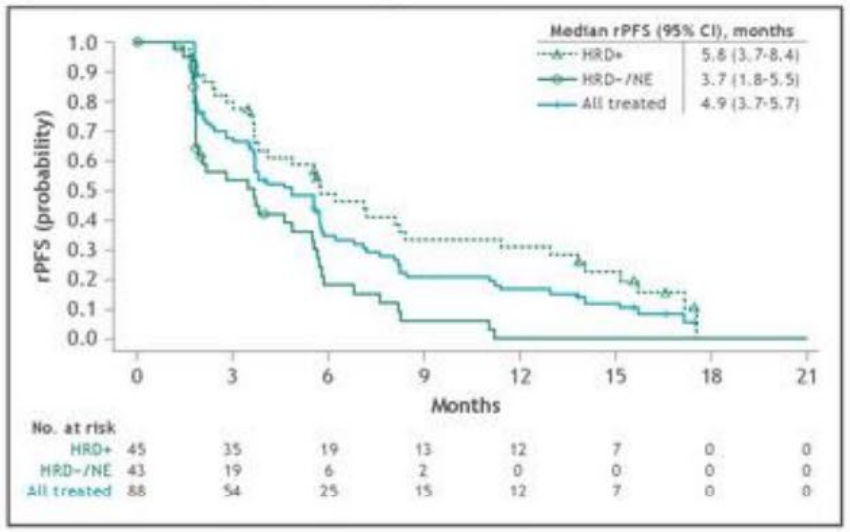
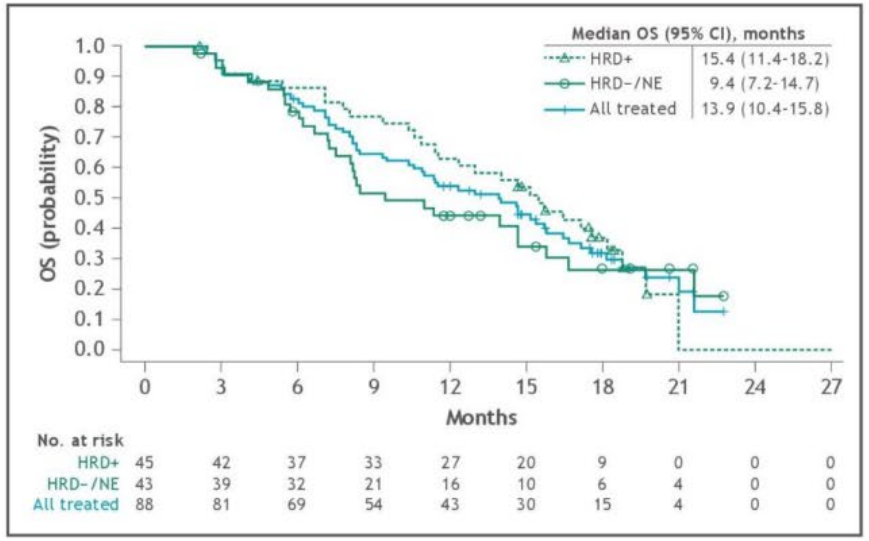
CHECKMATE 9KD: Nivolumab + Rucaparib

Median r PFS



Median OS



Russel K, ASCO 2021

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Immune Checkpoint Inhibitors in mCRPC

Therapy	Disease State	Disease Response
Pembrolizumab monotherapy[a]	Post-chemotherapy	ORR 9% PSA RR 14%
Pembrolizumab + enzalutamide[b]	Pre-chemotherapy progressing on enzalutamide	ORR 12% PSA RR 14%
Atezolizumab + enzalutamide[c]	Pre- and post-chemotherapy, s/p abiraterone	ORR 14% PSA RR 26%
Atezolizumab + cabozantinib[d]	Pre-chemotherapy s/p enzalutamide or abiraterone	ORR 34% PSA RR 29%

[a]JCO 2020: 38(5) 395-405. [b]Presented at the 2021 ASCO Annual Meeting – Virtual; June 4-8, 2021. [c]Sweeney C. AACR 2020. IMbassador250. [d]Agarwal ASCO 2020. COSMIC-021

RTP RESEARCH TO PRACTICE

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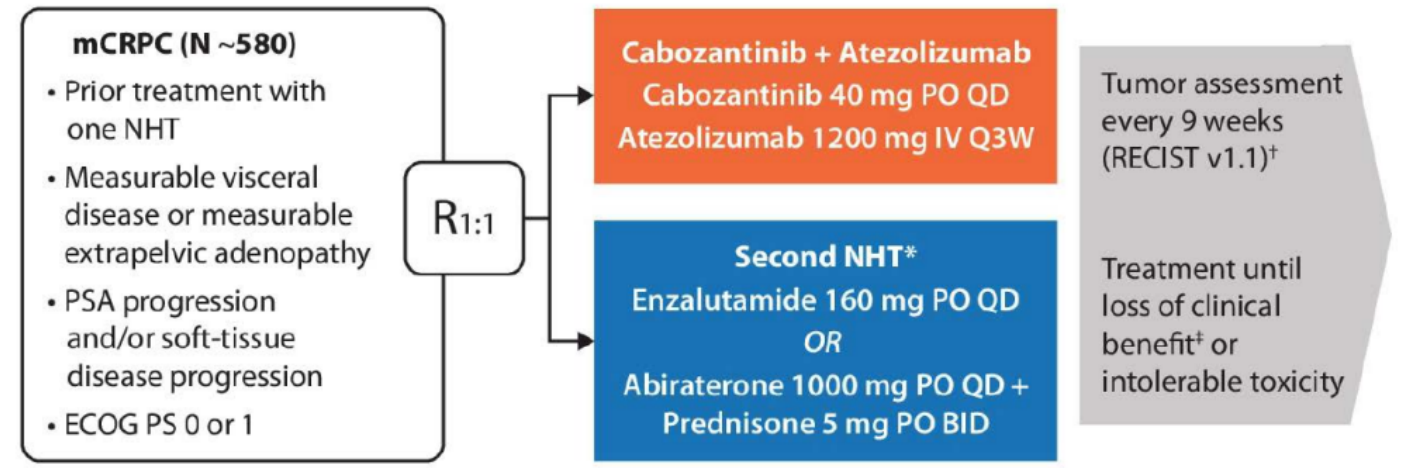
CONTACT-02: Phase III Trial Schema



Primary Endpoints:
- PFS per RECIST v1.1 by BIRC
- OS

Secondary Endpoint:
- ORR per RECIST v1.1 by BIRC

Stratification
- Liver metastasis (yes, no)
- Prior docetaxel treatment for mCSPC (yes, no)
- Disease stage for which the first NHT was given (mCSPC, M0 CRPC, mCRPC)

*Second NHT must differ from previous NHT taken
†Tumor assessment (RECIST v1.1) every 9 weeks for the first 28 weeks then every 12 weeks thereafter
‡Patients may be treated beyond progression if there is a clinical benefit in the opinion of the investigator

Agarwal N et al. Genitourinary Cancers Symposium 2021;Abstract TPS190.

RTP RESEARCH TO PRACTICE

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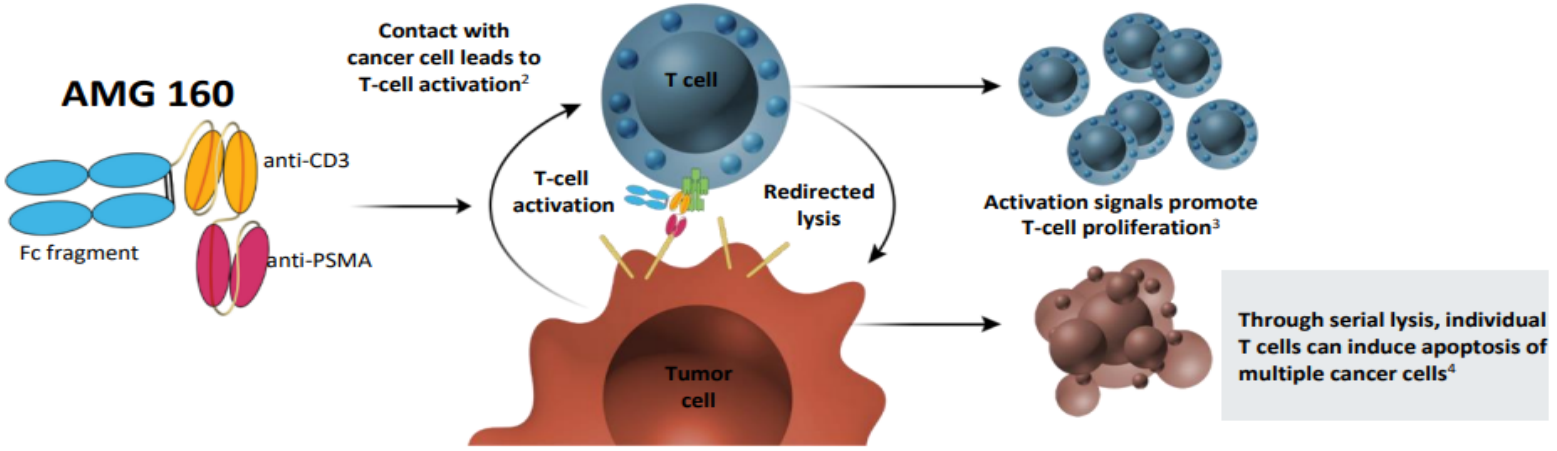
Targeting PSMA: PSMA BiTE



BiTE molecules engage a patient's own T cells to attack and eradicate cancer cells

– T-cell activation induces transient cytokine release and tumor killing

1. Baeuerle PA, et al. *Cancer Res.* 2009; 2. Klinger M, et al. *Immun Rev.* 2016; 3. Bargou R, et al. *Science.* 2008;
4. Stieglmaier J, et al. *Expert Opin Biol Ther.* 2015;15(8):1093-9.

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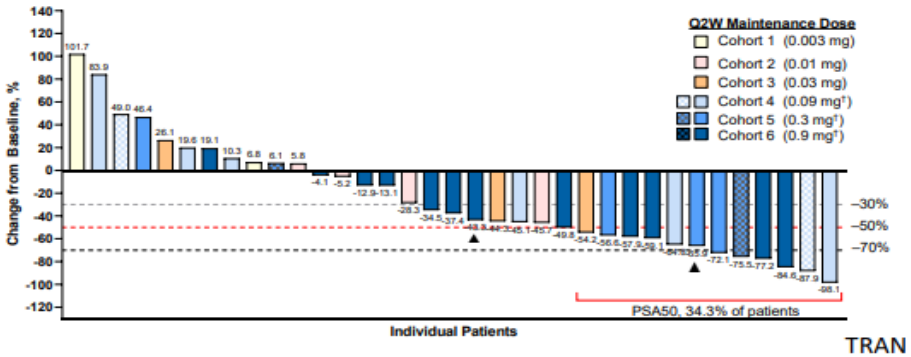
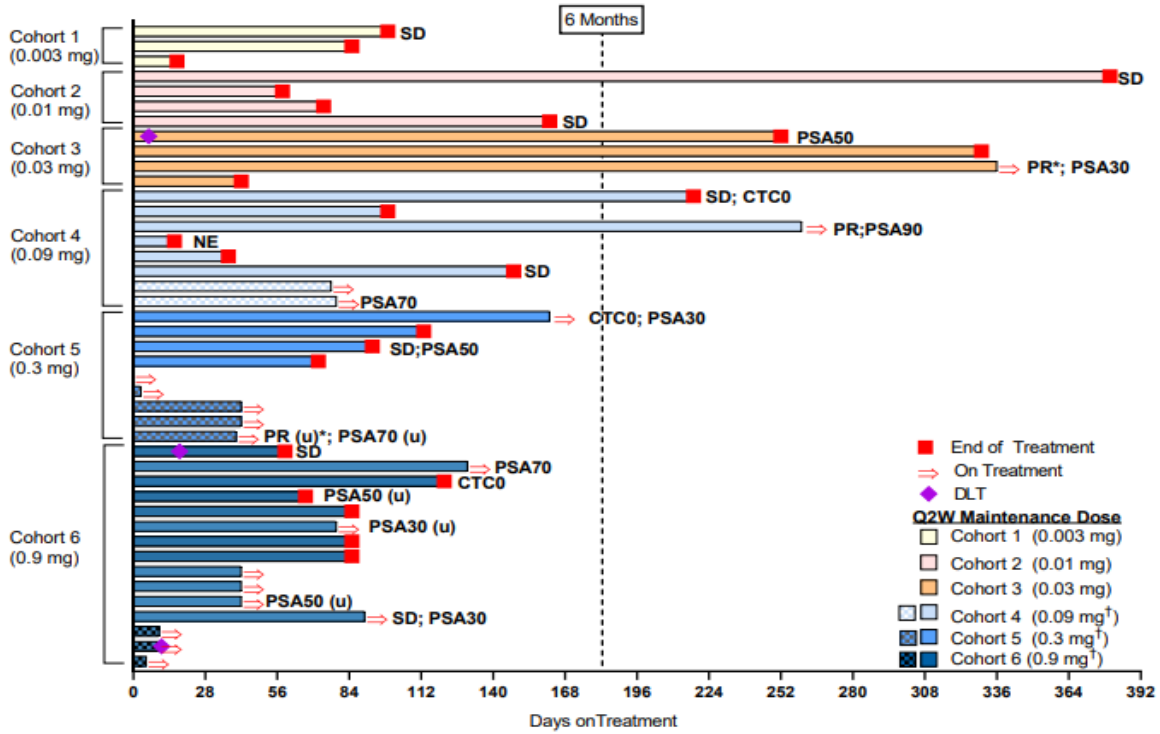
Evre IV Kastrasyona Dirençli Prostat Kanseri PSMA BİTE

AMG 160 monotherapy: Results

PSA/CTC Responses (n = 13–35)	
Response	**All, n (%)**
PSA response, confirmed*	8 (27.6)
PSA response, unconfirmed†	4 (11.4)
CTC0 response‡	3 (23.1)

RECIST Responses (n = 15)	
Response	**All, n (%)**
Partial response, confirmed	2§ (13.3)
Partial response, unconfirmed	1§ (6.7)
Stable disease	8 (53.3)





CTC = circulating tumor cell; DLT = dose-limiting toxicities; NE = not evaluable; PSA = prostate-specific antigen; PR = partial response; Q2W = every 2 weeks; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease; (u) = unconfirmed

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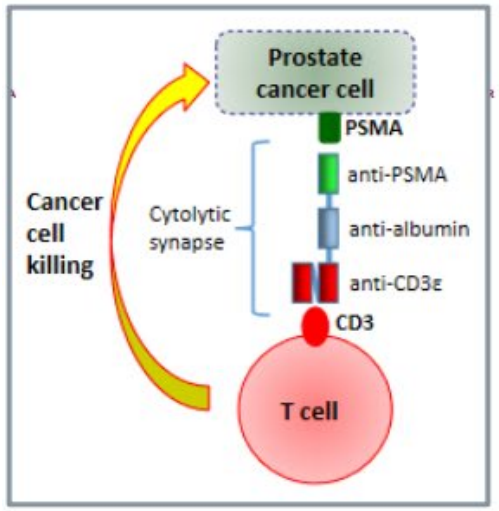
TRAN B, ESMO 2020

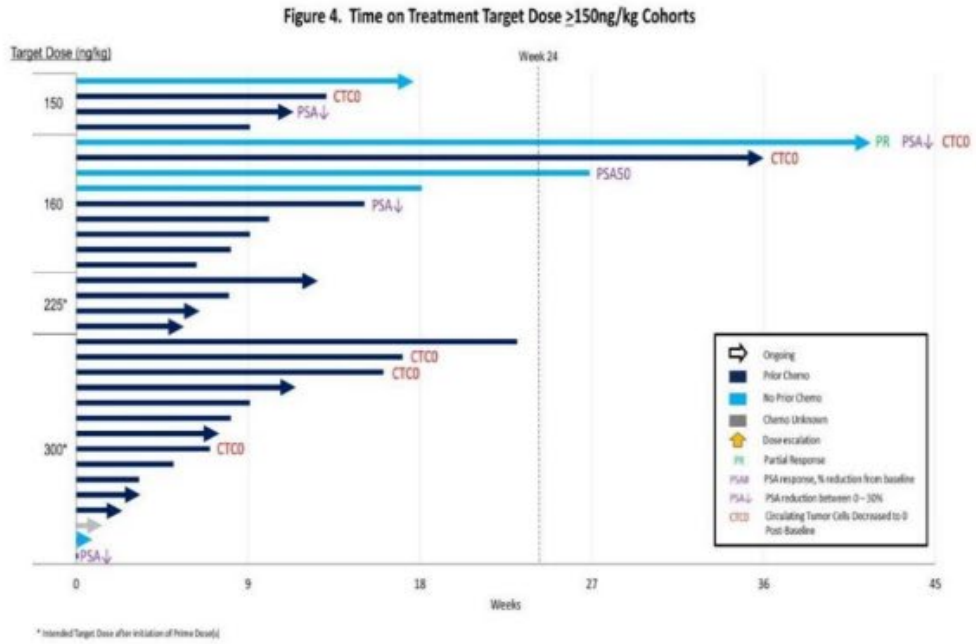
Evre IV Kastrasyona Dirençli Prostat Kanseri
PSMA BİTE

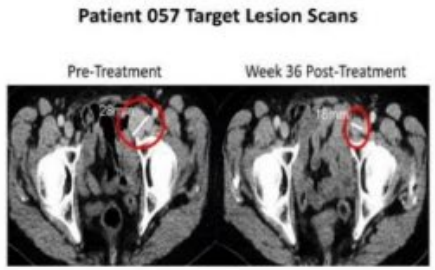
HPN424: “Trispecific T-cell Activating Constructs” (TriTACs)

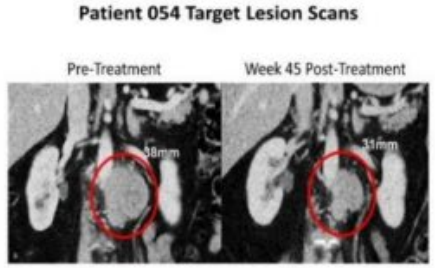


Anti-Tumor Activity

Treatment duration of >24 weeks in 20% of patients, Confirmed RECIST PR, PSA declines and CTC reductions observed across cohorts



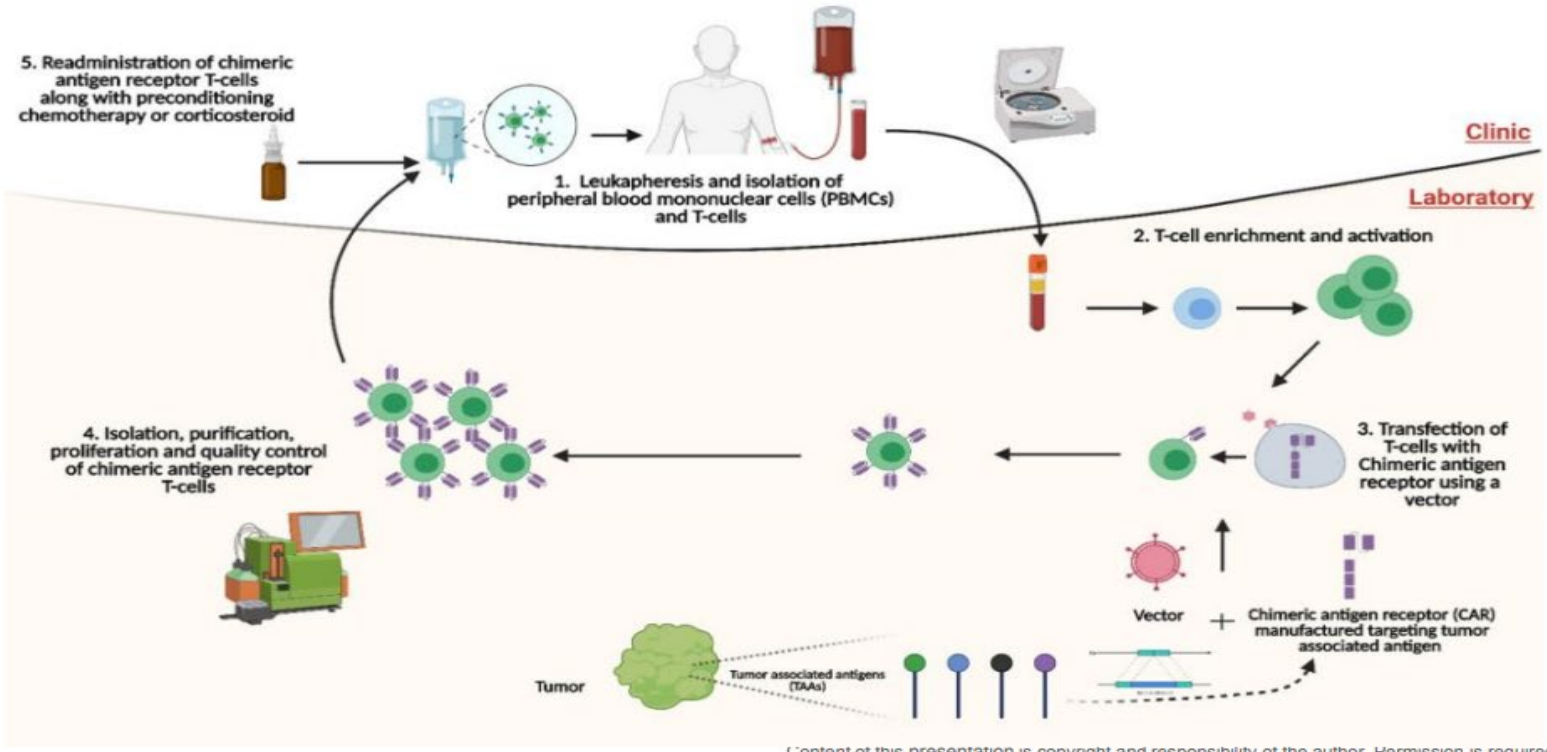




De Bono JS, ASCO 2021

Evre IV Kastrasyona Dirençli Prostat Kanseri

CAR T Cells



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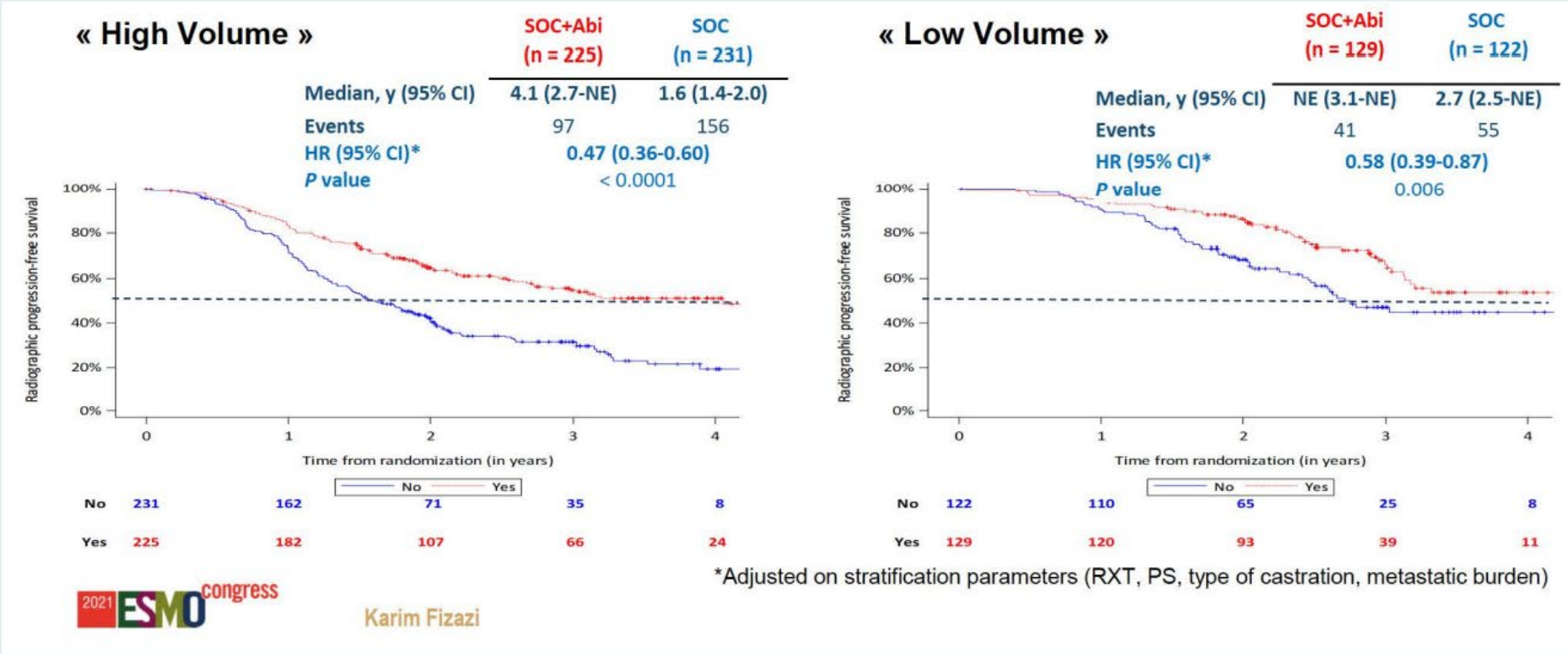
ESMO

Evre IV Kastrasyona Duyarlı Prostat Kanseri
Üçlü Kombinasyonlar

RTP RESEARCH TO PRACTICE

Evre IV Kastrasyona Duyarlı Prostat Kanseri
Üçlü Kombinasyonlar

PEACE-1: Radiographic PFS (rPFS) by Metastatic Burden



Fizazi K et al. ESMO 2021;Abstract LBA5.

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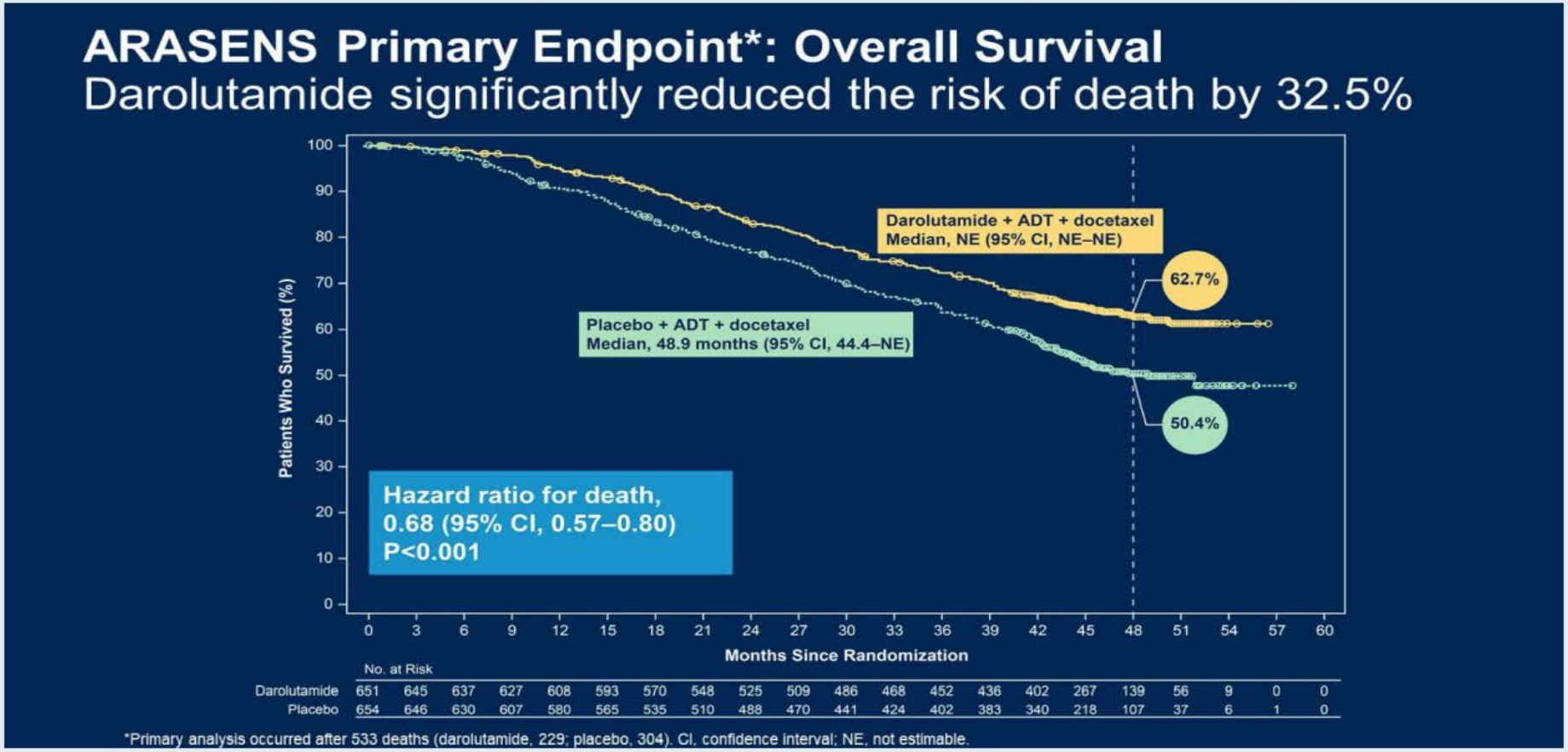
Evre IV Kastrasyona Duyarlı Prostat Kanseri
Üçlü Kombinasyonlar



Smith MR et al. Genitourinary Cancers Symposium 2022;Abstract 13.

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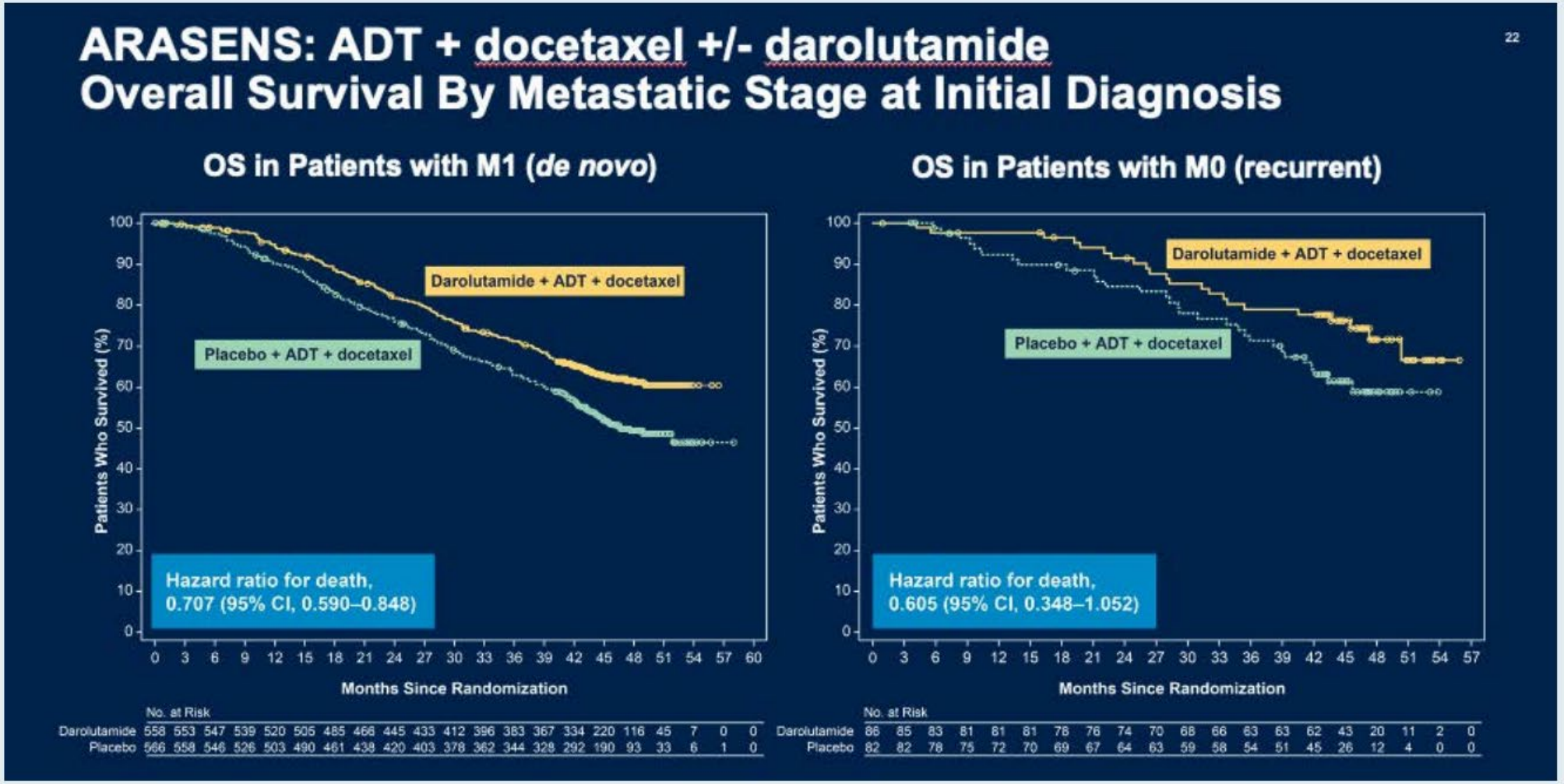
Evre IV Kastrasyona Duyarlı Prostat Kanseri
Üçlü Kombinasyonlar



Smith MR et al. Genitourinary Cancers Symposium 2022;Abstract 13.

RTP RESEARCH TO PRACTICE

Evre IV Kastrasyona Duyarlı Prostat Kanseri
İkili Kombinasyonlar

Doublet Therapy Trials in mHSPC: Results

Trial	Patients Enrolled	Intervention Arm	Control Arm	Prior/ Concurrent Docetaxel	Median Follow-up (mo)	Median OS in Interventional Arm (mo)	Median OS in Control Arm (mo)
CHAARTED[1]	790	ADT + Docetaxel		Not allowed	53.7	57.6	47.2
STAMPEDE[2]	2962	ADT + Docetaxel		Not allowed	78.2	59.1	43.1
LATITUDE[3]	1199	ADT + Abiraterone + Prednisone		Not allowed	51.8	53.3	36.5
STAMPEDE[4]	1917	ADT + Abiraterone + Prednisone		Not allowed	40	HR, 0.61 (P <0.001)	
ENZAMET[5]	1125	ADT+Enzalutamide	ADT + Placebo	Allowed	68	NR	73.2
ARCHES[6]	1150	ADT+Enzalutamide	ADT + Placebo	Allowed	44.6	HR, 0.66 (P <.0001) (median not reached in either group)	
TITAN[7]	1052	ADT + Apalutamide	ADT + Placebo	Allowed	44	NR	52.2

1.Kyriakopoulos et al. J Clin Oncol 2018; 2.Clarke et al. Ann Oncol 2019; 3-Fizazi et al. Lancet Oncol 2019; 4-James et al. N Engl J Med 2017; 5-Davis et al. ASCO Annual Meeting 2022; 6-Armstrong et al. J Clin Oncol 2022; 7-Chi et al. J Clin Oncol 2021

Evre IV Kastrasyona Duyarlı Prostat Kanseri
Tripler kombinasyonlar

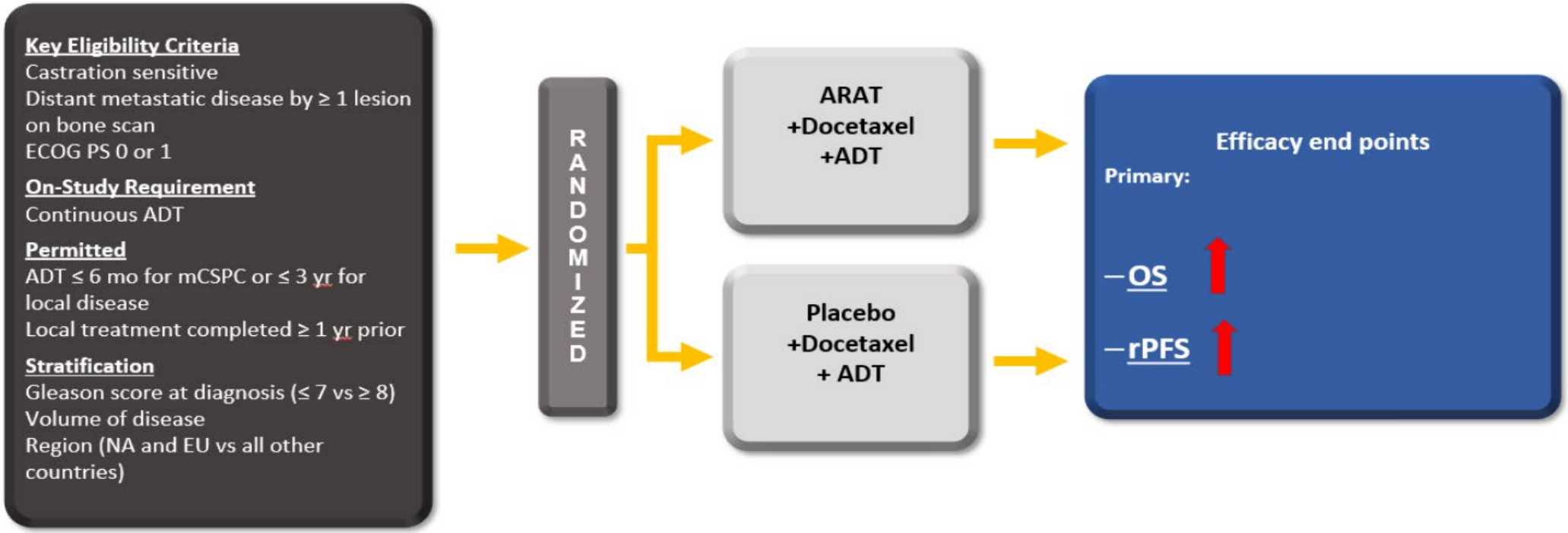
Trials with Triplet Therapy in mHSPC: Results

Trial	Patients Enrolled	Intervention Arm	Control Arm	% De-novo	%High Volume	Median Follow-up (mo)	Median OS in Interventional Arm (mo)	Median OS in Control Arm (mo)
ARASENS[1]	1306	ADT + Docetaxel + Darolutamide	ADT + Docetaxel + Placebo	86		43.7	NR	48.9
PEACE-1[2]	710	ADT + Docetaxel + Abiraterone	ADT + Docetaxel	100	64	45.6	NR	52.8
PEACE-1 Subgroup analysis : De-novo High volume of disease →							61	42

1.Smith et al. N Engl J Med 2022; 2.Fizazi et al. Lancet 2022.

Evre IV Kastrasyona Duyarlı Prostat Kanseri
Üçlü Kombinasyonlar

Phase III Trial: Triplets (ARAT+ Docetaxel + ADT) vs. Docetaxel + ADT



ECOG PS, Eastern Cooperative Oncology Group performance status; ART, Androgen receptor targeted therapy; NA, North America; PSA, prostate-specific antigen; OS, Overall survival; rPFS, radiographic progression-free survival.

Evre IV Kastrasyona Duyarlı Prostat Kanseri
Üçlü Kombinasyonlar

This trial has not been done yet:

Triplet (Docetaxel + ARAT + ADT) versus ARAT + ADT

Key Eligibility Criteria
Castration sensitive
Distant metastatic disease by ≥ 1 lesion on bone scan
ECOG PS 0 or 1

On-Study Requirement
Continuous ADT

Permitted
ADT ≤ 6 mo for mCSPC or ≤ 3 yr. for local disease
Local treatment completed ≥ 1 yr. prior

Stratification
Gleason score at diagnosis (≤ 7 vs ≥ 8)
Volume of disease
Region (NA and EU vs all other countries)

RANDOMIZED

Docetaxel
+ARAT
+ADT

Placebo
+ARAT
+ ADT

Efficacy end points

Primary:

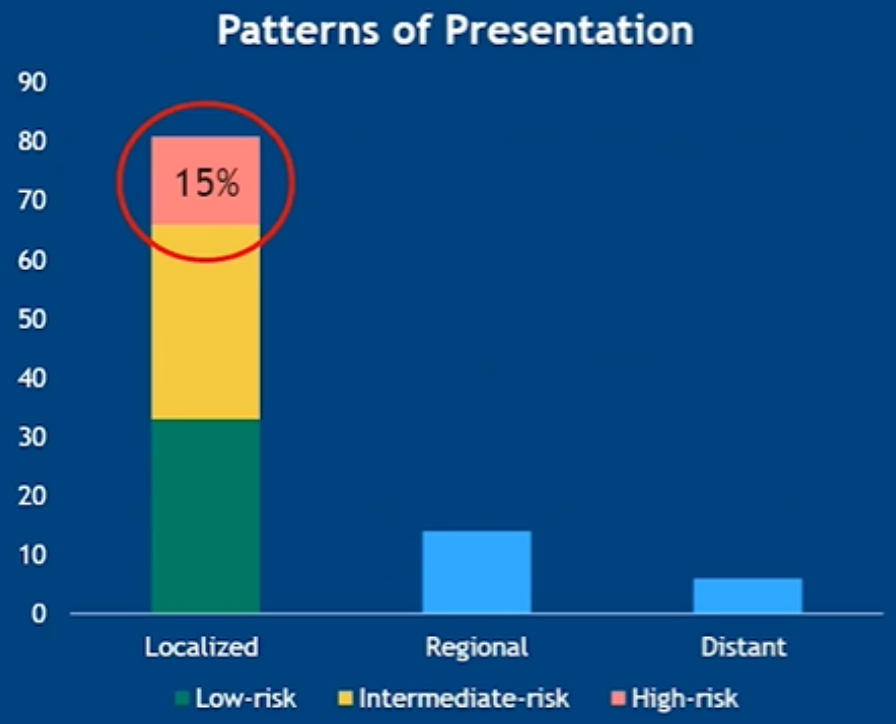
– OS ?

– rPFS ?

ECOG PS, Eastern Cooperative Oncology Group performance status; ART, Androgen receptor targeted therapy; NA, North America; PSA, prostate-specific antigen; OS, Overall survival; rPFS, radiographic progression-free survival.

Lokalize Yüksek Riskli Prostat Kanseri

Localized High-Risk Prostate Cancer



Increased Mortality in High-Risk Prostate Cancer

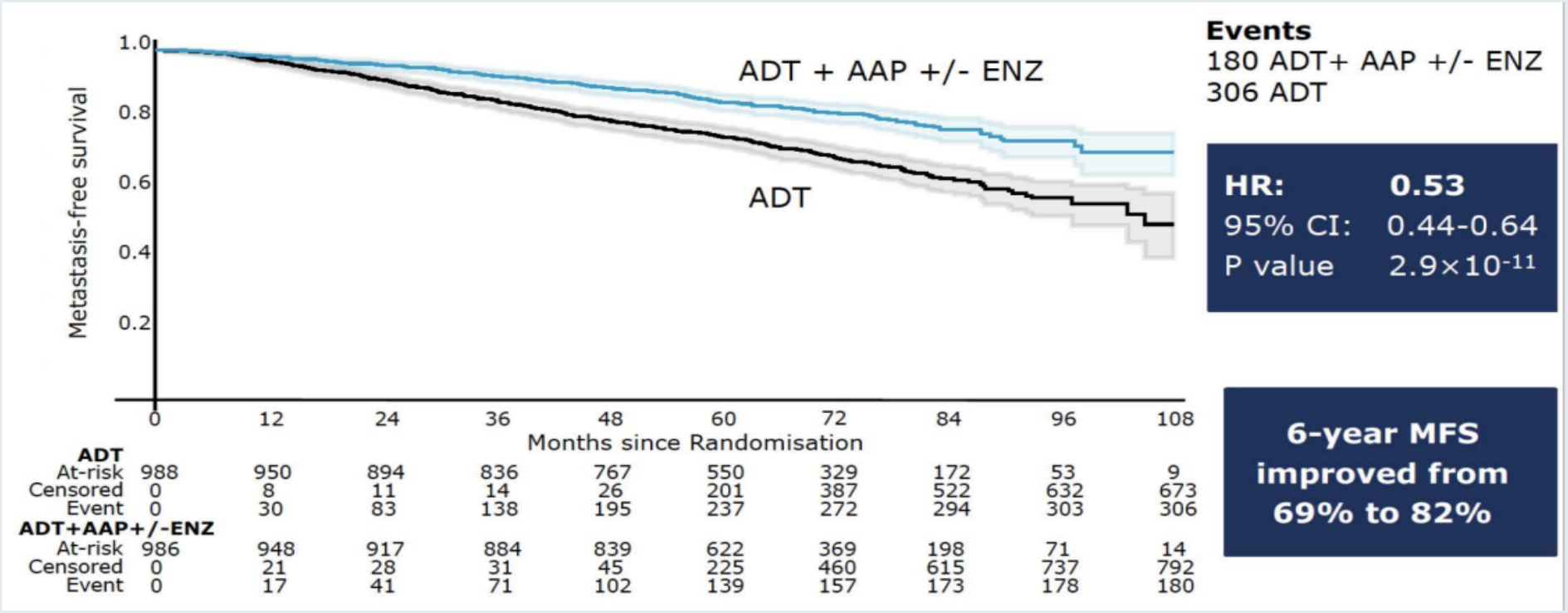
High-Risk Feature	15-Year PCSM
PSA > 20 ng/mL	22%
Gleason 8-10	34%
cT3	38%
High-risk Disease*	19%

PCSM=Prostate cancer specific mortality; PSA=Prostate specific antigen. *Defined by D'Amico criteria: PSA > 20 ng/mL, Gleason 8-10, or cT2c-T3.

Cooperberg, JCO, 2010; Eggener, J Urol, 2011

Lokalize Yüksek Riskli Prostat Kanseri

Metastasis-Free Survival with the Addition of Abiraterone Acetate and Prednisolone with or without Enzalutamide to ADT for High-Risk M0 Prostate Cancer



ADT										
At-risk	988	950	894	836	767	550	329	172	53	9
Censored	0	8	11	14	26	201	387	522	632	673
Event	0	30	83	138	195	237	272	294	303	306
ADT+AAP+/-ENZ										
At-risk	986	948	917	884	839	622	369	198	71	14
Censored	0	21	28	31	45	225	460	615	737	792
Event	0	17	41	71	102	139	157	173	178	180

Events
180 ADT+ AAP +/- ENZ
306 ADT

HR:	**0.53**
95% CI:	0.44-0.64
P value	2.9×10^{-11}

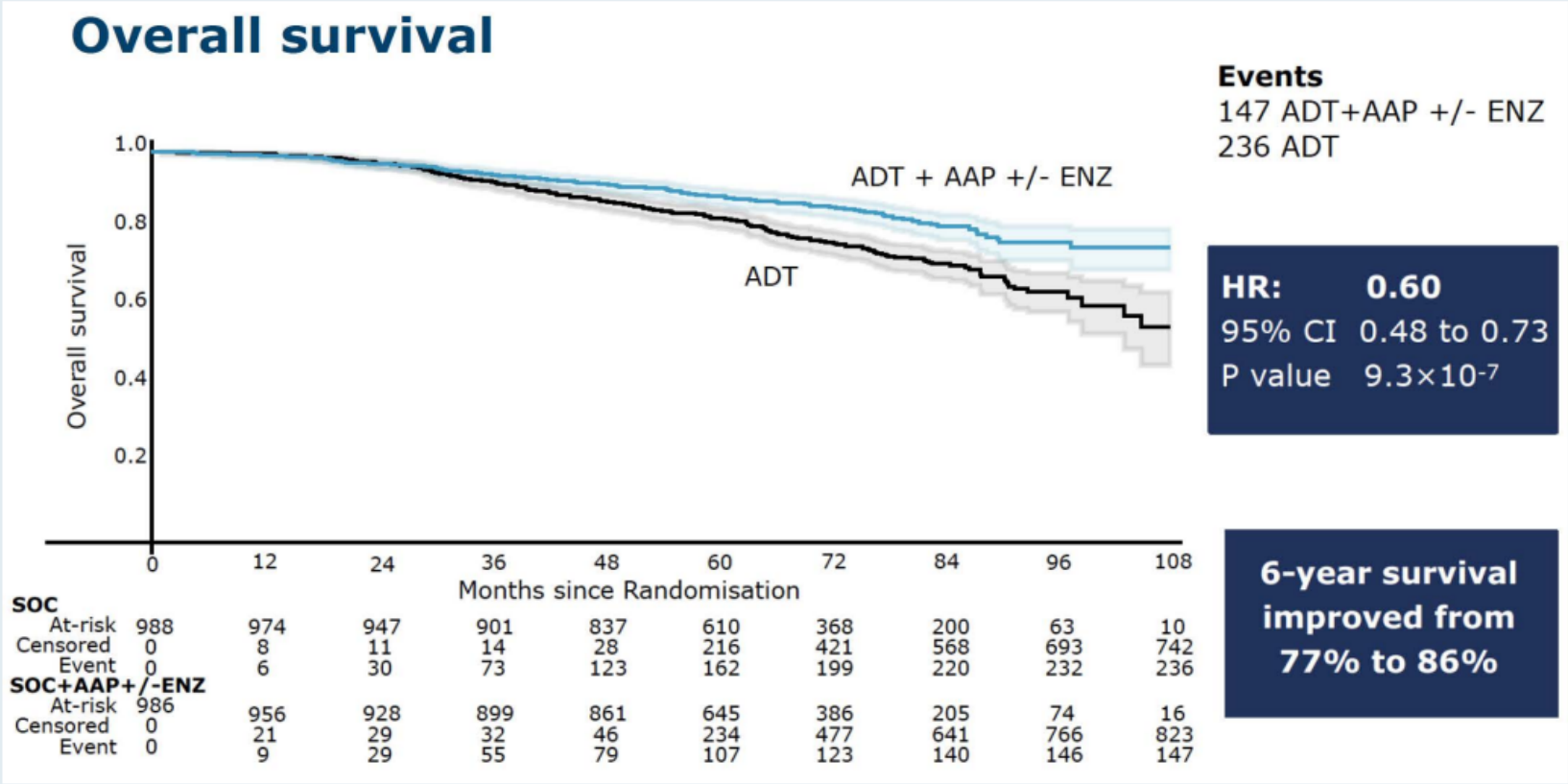
6-year MFS improved from 69% to 82%

Attard G et al. ESMO 2021;Abstract LBA4_PR.

RTP RESEARCH TO PRACTICE

Lokalize Yüksek Riskli Prostat Kanseri

Overall Survival with the Addition of Abiraterone Acetate and Prednisolone with or without Enzalutamide to ADT for High-Risk M0 Prostate Cancer



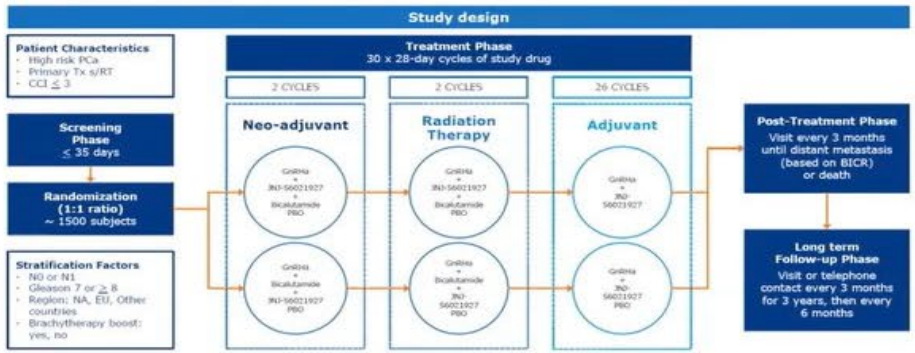
Attard G et al. ESMO 2021;Abstract LBA4_PR.

RTP RESEARCH TO PRACTICE

Definitif RT+ADT+ Yeni Nesil AR-yolağı İnhibitörleri

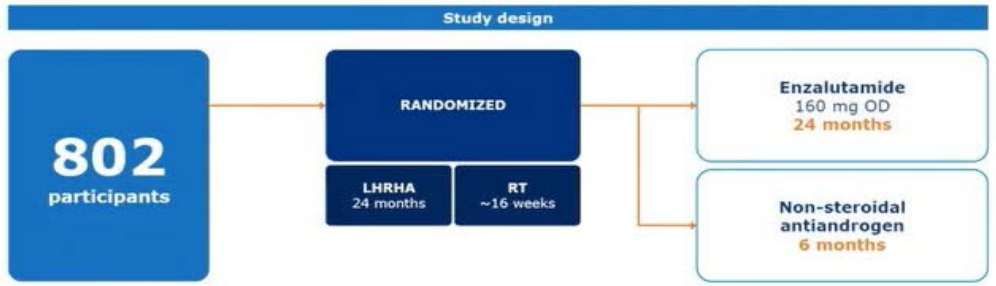
Apalutamide

ATLAS: Apalutamide in high-risk, localized or locally advanced PC patients receiving primary RT



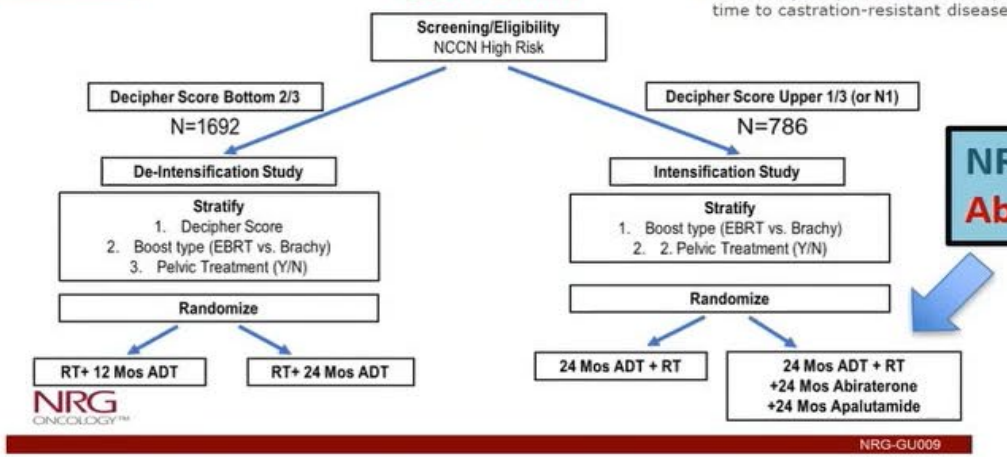
Enzalutamide

ENZARAD: Enzalutamide in ADT with RT for high-risk, clinically localized PC



- Primary endpoint is OS
- Secondary endpoints include CSS, PSA PFS, clinical PFS, time to subsequent hormonal therapy, time to castration-resistant disease (PCWG2 criteria), MFS, AEs and HRQOL

SCHEMA

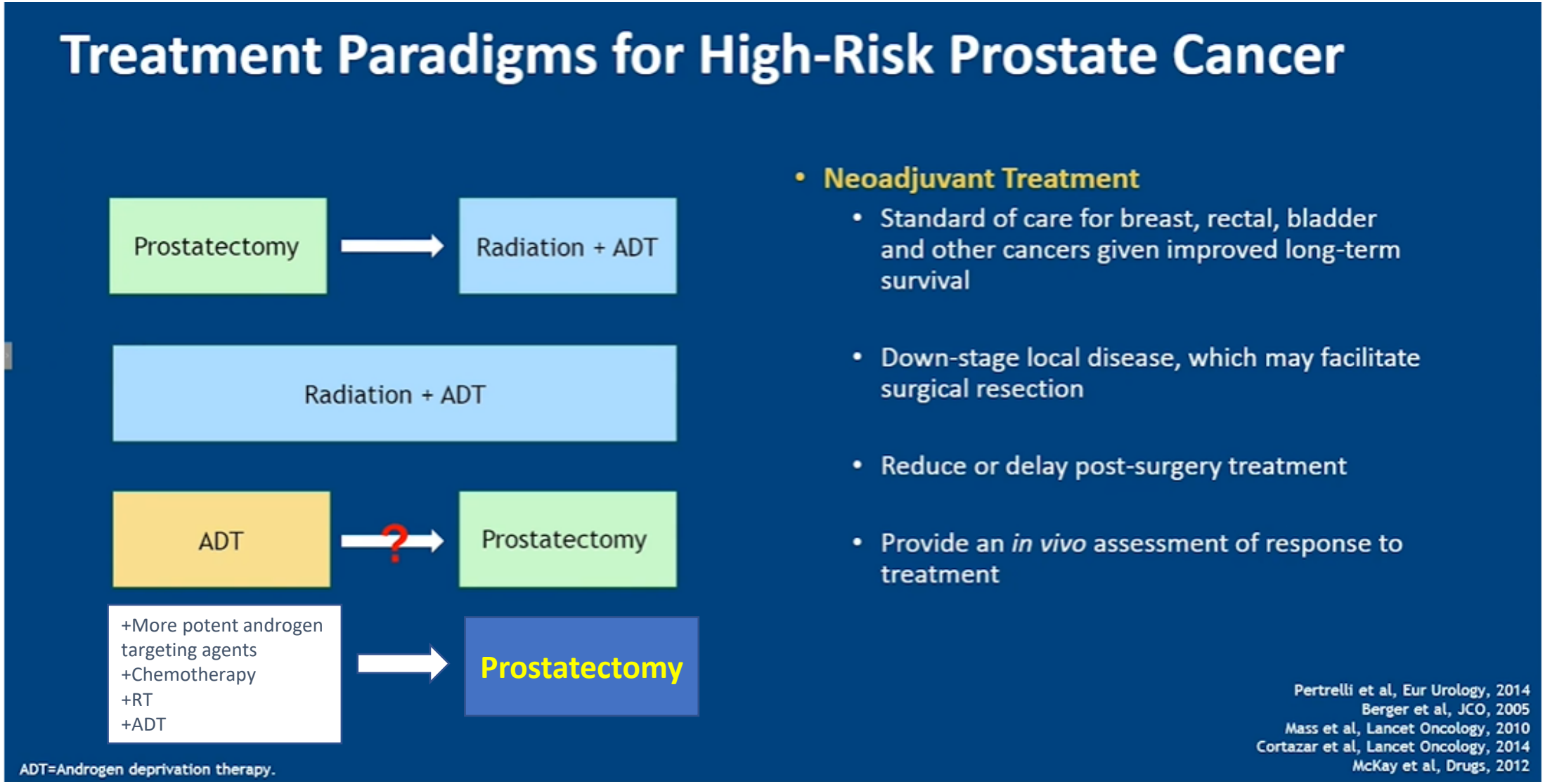


NRG GU009
Abiraterone + Apalutamide

Clinical Trial Information:
NCT02531516; NCT02446444; NCT04513717

This presentation is for scientific discussion only – Please do not distribute following this meeting.

Neoadjuan Tedavi Gerekçesi



Neoadjuvan Yeni Nesil AR-yolağı İnhibötörleri

Pathologic Responses from Potent Neoadjuvant Therapy

Conducted a series of neoadjuvant trials over the last 10 years

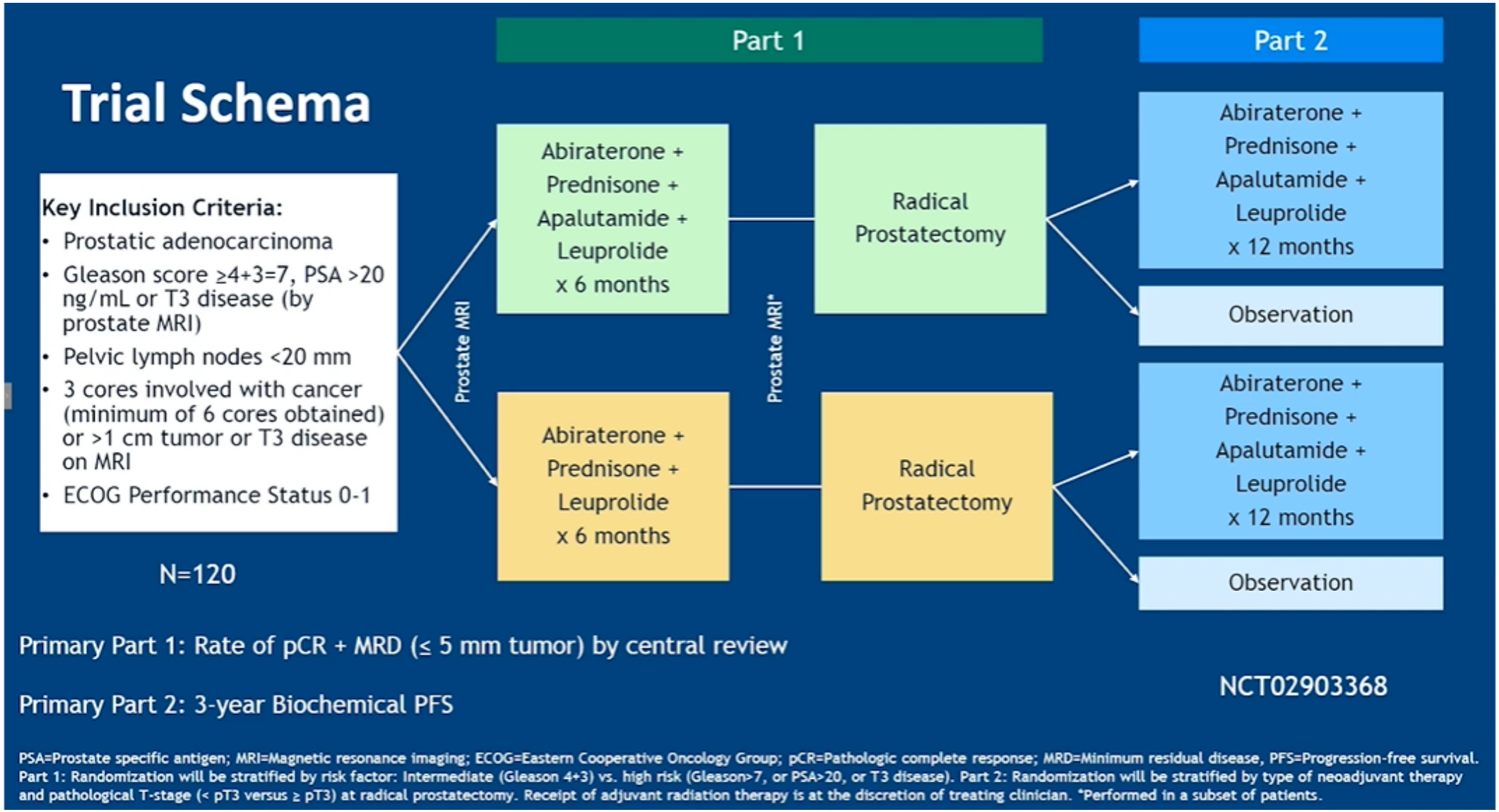
Phase 2 biomarker integrated trials evaluating potent neoadjuvant hormone therapy

	NeoAbi (n=58)	NeoEnza (n=40)	NeoAbiEnza (n=75)
Arms	12wAbi vs. 24wAbi	Enza vs. EDL	EL vs. APEL
CR	4% vs. 10%	0% vs. 4%	8 vs. 12%
MRD*	0% vs. 14%	0% vs. 13%	11% vs. 18%
CR + MRD	4% vs. 24%	0% vs. 17%	19% vs. 30%

Abi=Abiraterone; Enza=Enzalutamide; EDL=Enzalutamide, dutasteride, leuprolide; APEL=Abiraterone, prednisone, enzalutamide, leuprolide; EL=Enzalutamide, leuprolide; CR=Complete response; MRD=Minimum residual disease. *Defined as residual tumor with largest cross section dimension ≤ 0.3-0.5 cm.

Taplin et al, JCO, 2014
Montgomery et al, CCR, 2016
McKay et al, JCO, 2019

Neoadjuvan Yeni Nesil AR-yolağı İnhibötörleri



Neoadjuvan Yeni Nesil AR-yolağı İnhibötörleri

Pathologic Outcomes

		APL (n=59)	APAL (n=55)
Pathologic Response	pCR	6 (10%)	7 (13%)
	MRD (≤5 mm)*	6 (10%)	5 (9%)
	pCR or MRD	12 (20%)	12 (22%)
ypT stage, n (%)	T0	6 (10%)	7 (13%)
	T2	19 (32%)	21 (38%)
	T3	34 (58%)	27 (49%)
pN1, n (%)		10 (17%)	4 (7%)
Positive surgical margins, n (%)		7 (12%)	4 (7%)
Seminal vesicle invasion, n (%)		16 (27%)	15 (27%)
Percent cellularity, % (range)**		5% (0-50%)	5% (0-80%)
RCB (cm^3)		0.07 (0-6.8)	0.02 (0-7.8)

APAL=Abiraterone, prednisone, apalutamide, leuprolide; APL=Abiraterone, prednisone, leuprolide; pCR=Pathologic complete response; MRD=Minimum residual disease; RCB=Residual cancer burden. *Minimum residual disease was defined as residual tumor in the radical prostatectomy specimen measuring ≤5 mm. **Residual cancer burden calculated as tumor volume (cm3) x percent cellularity.

Neoadjuvan Yeni Nesil AR-yolağı İnhibitörleri

Neoadjuvant Novel Hormonal Therapy Followed by Prostatectomy versus Up-Front Prostatectomy for High-Risk Prostate Cancer: A Comparative Analysis

Praful Ravi,[1] Lucia Kwak,[1] Wanling Xie,[1] Kaitlin Kelleher,[1] Andres M. Acosta,[1] Rana R. McKay,[2] Adam S. Kibel,[1] and Mary-Ellen Taplin[1]*

[1]*Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts*
[2]*Department of Medicine, Division of Hematology-Oncology, University of California, San Diego, La Jolla, California*

Purpose: We sought to compare outcomes between neoadjuvant therapy with a novel hormonal agent (NHA) prior to radical prostatectomy (neo-RP) and up-front radical prostatectomy (RP) in patients with high-risk prostate cancer (HRPC).

Materials and Methods: HRPC patients treated on 3 trials of neoadjuvant NHA followed by RP formed the neo-RP cohort (112). The RP group (259) comprised an observational cohort of HRPC patients undergoing RP without neoadjuvant therapy between 2010—2016 at our institution who met key eligibility criteria for the neoadjuvant trials (ie ≥3 positive biopsy cores and Gleason ≥4+3=7). Inverse probability of treatment weighting (IPTW) was used to minimize potential confounding factors when estimating treatment effects. The primary outcomes were time to biochemical recurrence (BCR) and metastasis-free survival (MFS).

Results: Before IPTW, the neo-RP cohort had higher rates of Gleason 9-10 cancer (46% vs 24%), cT3 disease (22% vs 5%), and PSA ≥20 ng/ml (14% vs 7%); after IPTW, the 2 cohorts were balanced. Overall, after IPTW, time to BCR (HR=0.25 [95% CI 0.18—0.37]) and MFS (HR=0.26 [0.15—0.46]) were significantly longer in the neo-RP compared to the RP cohort. Rates of adjuvant (7% vs 24%) and salvage therapy (34% vs 46%) were lower in the neo-RP cohort.

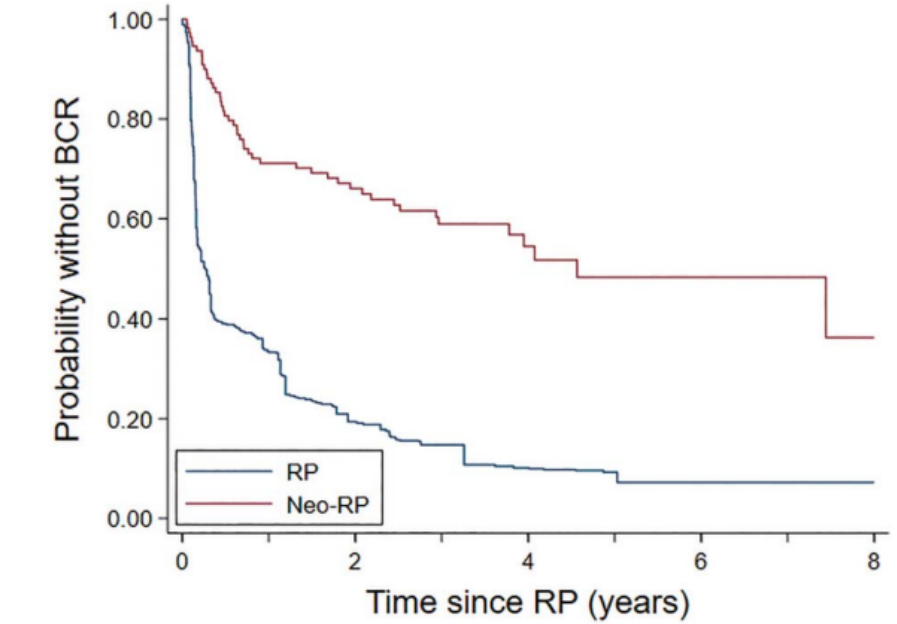
Conclusions: Neoadjuvant therapy with an NHA prior to RP was associated with longer time to BCR and superior MFS compared to up-front RP in men with HRPC. These findings are hypothesis-generating but suggest benefit with neoadjuvant therapy with an NHA in HRPC, an approach which is currently being studied in the phase 3 PROTEUS trial (NCT03767244).

Key Words: neoadjuvant therapy, prostatic neoplasms, general surgery

Abbreviations and Acronyms

ADT = androgen deprivation therapy
BCR = biochemical recurrence
HRPC = high-risk prostate cancer
IPTW = inverse probability of treatment weighting
MFS = metastasis-free survival
MRD = minimal residual disease
NHA = novel hormonal agent
OS = overall survival
pCR = pathological complete response
RP = radical prostatectomy

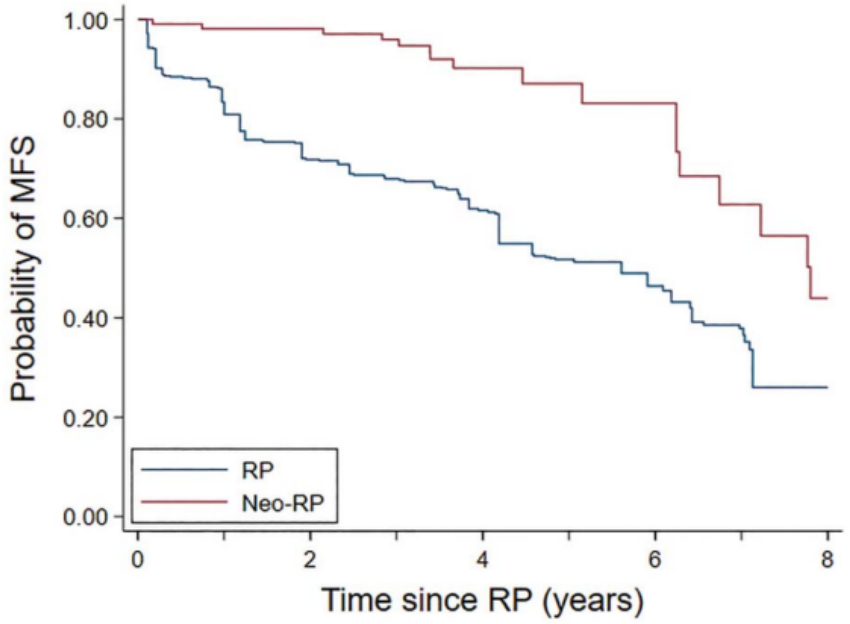
Neoadjuvan Yeni Nesil AR-yolağı İnhibitörleri



Number at risk

RP	257	41	17	6	1
Neo-RP	112	61	22	9	3

Figure 1. Time to BCR in the neo-RP and RP cohorts after IPTW. The number of participants at risk are based on unweighted population.

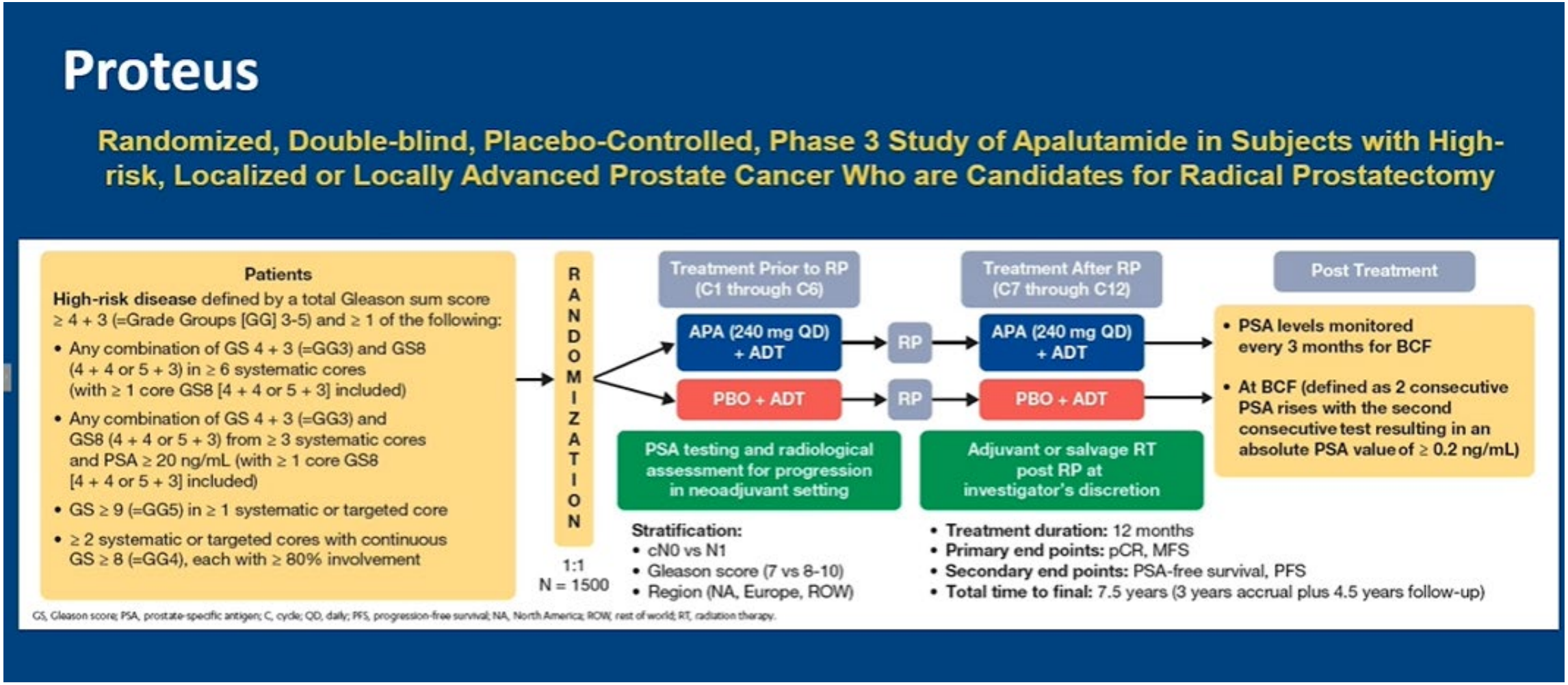


Number at risk

RP	259	155	97	43	6
Neo-RP	112	95	41	20	7

Figure 2. MFS in the neo-RP and RP cohorts after IPTW. The number of participants at risk are based on unweighted population.

Devam Eden Çalışmalar

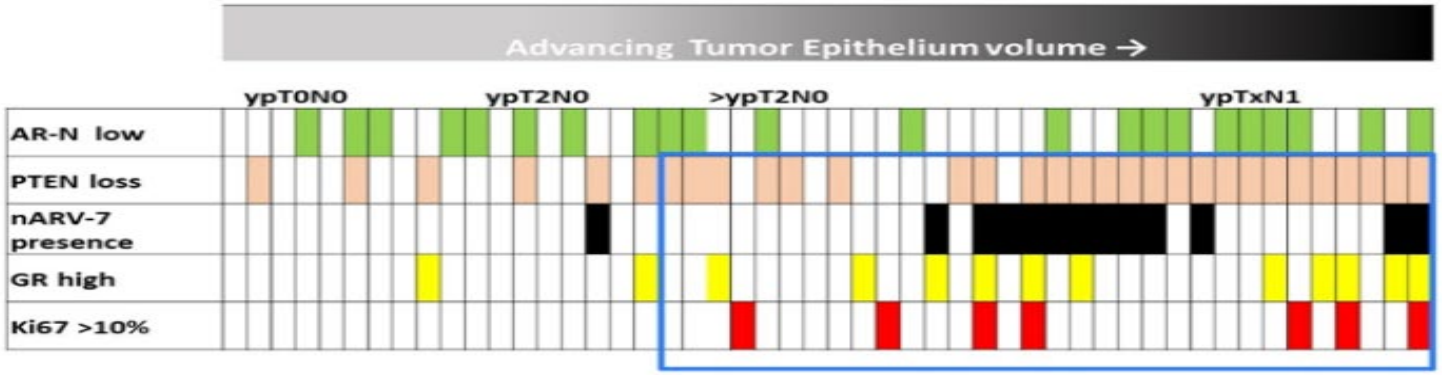


Neoadjuvan Yeni Nesil AR-yolağı İnhibitörleri

Tumor volume and tumor cellularity varied significantly. The finding of ≤ypT2N0 did not correlate with Gleason score, but did correlate with a pre-specified molecular signature, PTEN expression, and absence of cribriform/intraductal spread.

A 4-marker candidate signature (PTEN loss, nARV-7 presence, Glucocorticoid receptor (GR) high, or Ki67>10%) was predictive of resistance.

Univariate Analyses for association of pretreatment tumor characteristics with therapy effect



Marker		Pathology Stage >ypT2N0 N(%)	Pathology Stage ≤ypT2N0 N(%)	Fisher exact test p-value
AR-N	Low	13(42)	9(47)	0.77
	High	18(58)	10(53)	
PTEN	Loss	**24(77)**	**7(37)**	**0.007**
	Intact	**7(23)**	**12(63)**	
ARV7 nuclear	absence	**19(61)**	**18(95)**	**0.009**
	presence	**12(39)**	**1(5)**	
GR	Low	20(65)	17(89)	**0.091**
	High	11(35)	**2(11)**	
Ki67	≤10%	24(77)	19(100)	**0.035**
	>10%	7(23)	**0(0)**	
Clinical Stage	cT2	6(16)	**11(44)**	**0.02**
	cT3/4	**32(84)**	14(56)	
Biopsy Gleason	7	10(26)	8(32)	0.77
	8-10	28(73)	17(68)	
Diagnostic PSA	>10ng/ml	26 (68)	16 964)	0.23

Diagnostic Biopsy Markers:

- ✓ **PTEN loss** enriched in persistent cancers
- ✓ **Nuclear ARV7 presence, GR high (>10%), Ki67 >10%,** correlate with persistent cancers

Devam Eden Neoadjuvan Çalışmaları

Name (trial number)	Location	Phase	Abbreviated Oncologic Eligibility	Treatment arms
Neoadjuvant Degarelix With or Without Apalutamide Followed by Radical Prostatectomy (ARNEO) (NCT03080116)	Leuven, Belgium	II	-Intermediate risk: at least 2 of the following factors: cT2b, biopsy GS 7, PSA 10-20ng/ml -High risk: cT≥2c and/or biopsy GS≥8 and/or PSA>20ng/ml -cN0-cN1, cM0	-Apalutamide + Degarelix -Placebo + Degarelix
Neoadjuvant Pembrolizumab Plus Androgen Axis Blockade Prior to Prostatectomy for High Risk Localized Prostate Cancer (NCT03753243)	Portland, OR, USA	II	- Any one of the following three high risk features: Gleason grade > 8-10, PSA > 20 ng/ml, cT3a -cM0	-Pembrolizumab + Enzalutamide + GNRH agonist (Single arm)
Neoadjuvant Atezolizumab-Based Combination Therapy in Men With Localized Prostate Cancer Prior to Radical Prostatectomy (NCT03821246)	San Francisco, CA, USA	II	-Only high risk patients in the safety-lead in for each cohort -Intermediate risk patients eligible once safety confirmed on interim analysis -cM0	-Atezolizumab +/- either Tocilizumab OR Etrumadenant (Non-randomized, sequential cohorts)
A Study of Neoadjuvant Hormone Therapy in Patient With Advanced Prostate Cancer Undergoing Radical Prostatectomy. (NCT03971110)	Guangzhou, China	IV	-cT3/4, cN0/1, cM0/1 (with five or fewer extra-pelvic lesions)	-Zoladex + Casodex (Single Arm)
Ibrutinib as Neoadjuvant Therapy in Localized Prostate Cancer (NCT02643667)	San Francisco, CA, USA	II	-Suitable for radical prostatectomy -cM0	-Ibrutinib (Single Arm)
Biomarkers for Neoadjuvant Pembrolizumab in Non-Metastatic Prostate Cancer Positive by 18FDG-PET Scanning (NCT04009967)	Laval, Québec, Canada	II	-Gleason Score ≥ 8, cM0 -Intraprostatic maximum standardized uptake value (SUVmax) ≥4 at 18-FDG-PET/CT exam	-Pembrolizumab (Single arm)
Neoadjuvant Hiltonol® (PolyICLC) for Prostate Cancer (NCT03262103)	New York, NY, USA	I	-Gleason 7 – 10, cT2a - cT3b adenocarcinoma of the prostate with plans for radical prostatectomy and PSA ≥ 4 ng/ml -Tumor visible on multiparametric MRI	Intratumoral injection of Poly-ICLC
177Lu-PSMA-I&T Prior to Radical Prostatectomy for Locally Advanced Disease (NCT04297410)	Petach Tikva, Israel	NA	-cT3/4 and/or Gleason score ≥8 and/or PSA ≥ 20 ng/dl) -Loco-regional prostate cancer (pelvic lymphadenopathy of ≥2 cm on axial imaging) -High PSMA expression: with tracer uptake greater than normal liver (maximal SUV ≥1.5 of liver)	- 177Lu-PSMA-I&T Radionuclide (Single arm)
Neoadjuvant Therapy With Proxalutamide Combined With Androgen Deprivation Therapy (ADT) for High Risk Prostate Cancer (NCT05076851)	Nanjing, Jiangsu, China	II	- High-risk prostate cancer (cT≥2c or Gleason score ≥8 or PSA≥20ng/ml) -cM0	-Proxalutamide +ADT -Placebo + ADT

PSA Nüksü Olan Hastalarda Salvage Tedaviler

THE SALV-ENZA TRIAL (#5012)

A Phase II, Double-blind, Randomized Study of Salvage Radiation Therapy Plus Enzalutamide or Placebo for High-Risk PSA-Recurrent Prostate Cancer after Radical Prostatectomy

Phuoc T. Tran, Kathryn Lowe, Hao Wang, Hua-Ling Tsai, Daniel Y. Song, Arthur Y. Hung, Jason W.D. Hearn, Tamara Lotan, Channing Paller, Mark Markowski, Samuel Denmeade, Michael Carducci, Mario Eisenberger, Matthew Orton, Curtiland Deville, Stanley L. Liauw, Elisabeth I. Heath, Neil B. Desai, Tomasz M. Beer, Emmanuel S. Antonarakis

Salvage radiation (SRT) + ENZA monotherapy for 6 months in men with PSA-recurrent high-risk prostate cancer following prostatectomy is safe and delays PSA progression relative to SRT alone

BACKGROUND:

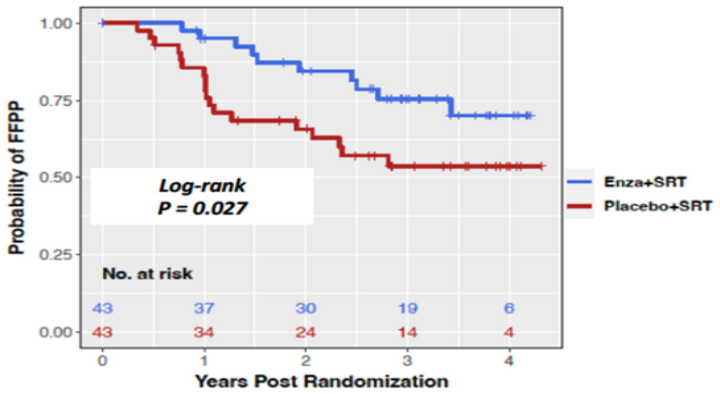
Does enzalutamide (ENZA) treatment without androgen deprivation therapy increase freedom-from-PSA-progression (FFPP) when combined with salvage radiation therapy (SRT) in men with recurrent prostate cancer (PCa) post-radical prostatectomy (RP)?

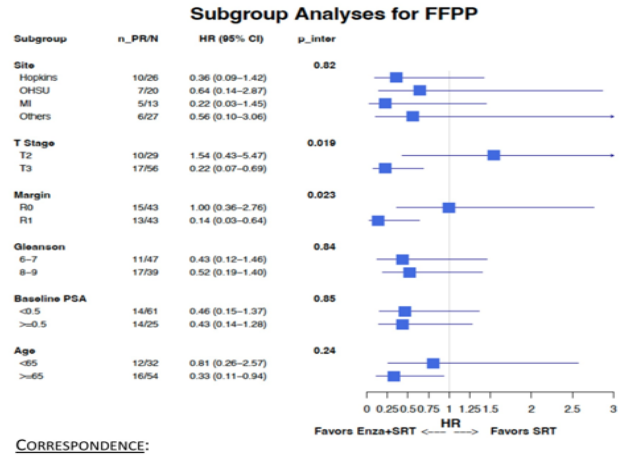
METHODS:

- Men with biochemically recurrent PCa after RP were randomized onto either placebo or ENZA 160 mg PO once daily for 6 months and then prostate bed radiotherapy (66.6-70.2 Gy)
- Randomization (1:1) was stratified by center, surgical margin status (R0 vs R1), PSA prior to salvage treatment (PSA ≥0.5 vs <0.5 ng/mL), and pathologic Gleason sum (7 vs 8-10)
- Powered for hazard ratio (HR) 0.44 FFPP benefit with enrollment of 96 subjects
- 86 men were randomized; 43 per arm
- Median follow-up of 34 months (range 0-52)

RESULTS:

- **FFPP was significantly improved with ENZA vs placebo (HR 0.42, 95% CI 0.19-0.92, P=0.031)**
- **There was differential benefit of ENZA in men with pT3 vs pT2 disease (Pinter=0.019); and R1 vs R0 (Pinter=0.023)**
- Common AEs were grade 1-2 fatigue (65% ENZA vs 53% placebo) and urinary frequency (40% ENZA vs 49% placebo)





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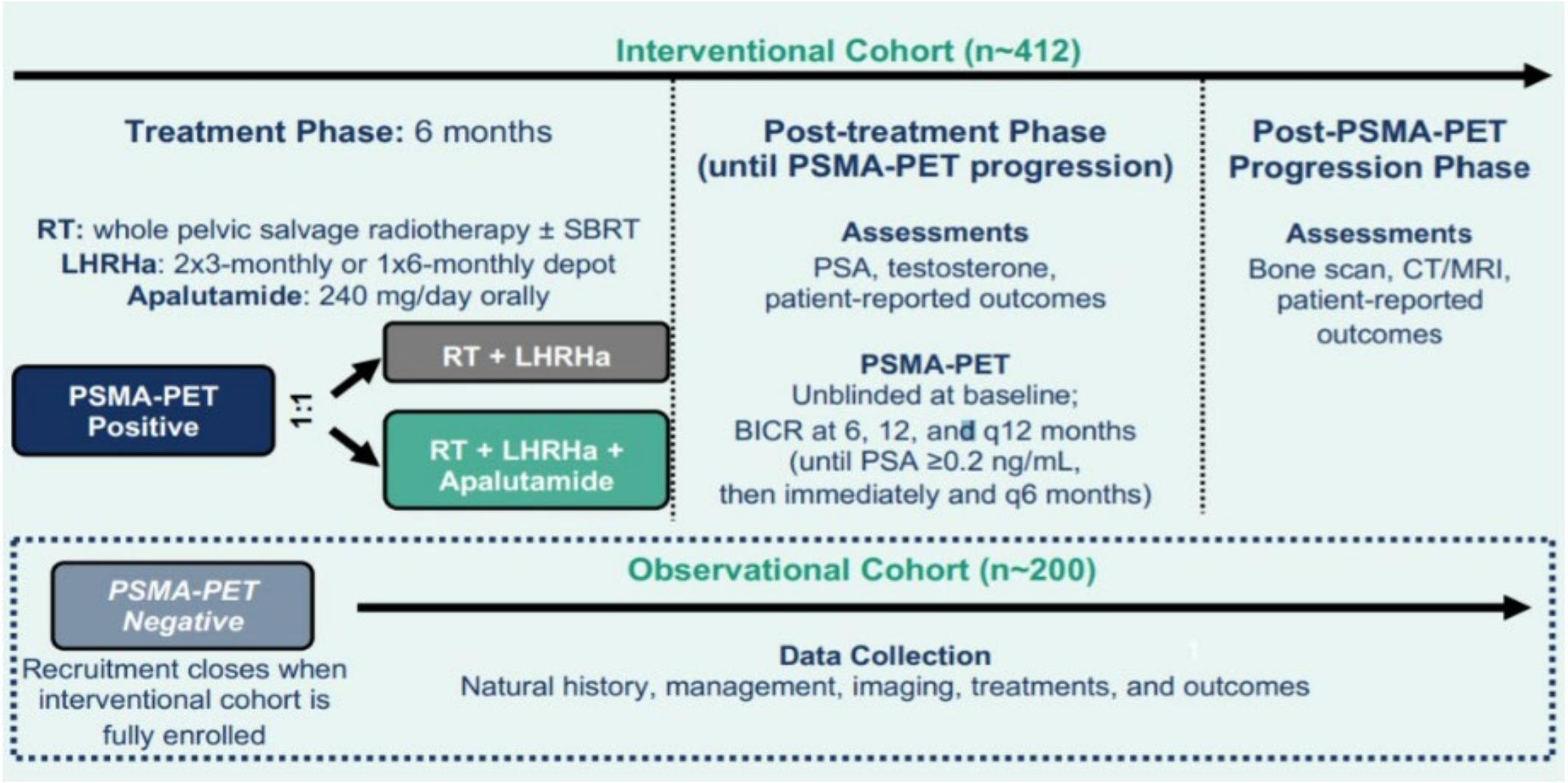
PSA Nüksü Olan Hastalarda Salvage Tedaviler



Sonuç

- DNA repair gen mutasyonu +, PARP inhibitörlerin kombinasyon olarak erken aşamada kullanımı
- PI3K-PTEN-AKT yolağı ilgili kombinasyon tedavileri
- PSMA ekspresyonu olanlarda Lutesyum vb +kombinasyon tedavileri daha erken aşamalarda kullanımı
- PSMA-BİTE tedavileri çoklu tedavi almış hastalarda kullanımı
- Mikrosatellit instabilite(MSI) olanlarda Checkpoint inhibitörlerin daha erken aşamada kullanımı
- Checkpoint inhibitörlerin kombinasyon(Cabozantinib vb.) olarak kastrasyona dirençli aşamada kullanımı
- Lokalize yüksek riskli ve biyokimyasal nükslerde yeni nesil AR inbitörlerin kullanılması