



Multidisciplinary Approaches to Cancer Symposium

Sequencing Therapies in Metastatic Prostate Cancer

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Disclosures

- Consultant for AstraZeneca, Aveo, Bayer, Caremark/CVS, EMD Serano, Fortress Biotech, Merck, Pfizer, Treadwell Therapeutics (DSMB), and XenCor
- Grant/Research Support from Abbvie, Amgen, AstraZeneca, Astellas (Medivation), Bayer, Bristol Myers Squibb, Boehringer-Ingelheim, Calithera, Corvus, Eisai, Exelixis, Genentech (Roche), GlaxoSmithKline, Johnson & Johnson (Janssen), Merck, Novartis, Pfizer, Seattle Genetics, X4Pharmaceuticals, Xencor
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This presentation has been peer-reviewed and no conflicts were noted.

The off-label/investigational use of PSMA-targeted actinium-225; ABBV-969, Xaluritamig (AMG 509), ARV-766, possibly other investigational agents will be addressed.



Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:

Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

The following CLC & IB components will be addressed in this presentation:

- *Complexities of care for underserved populations, especially Hispanic individuals and Blacks*
- *Implicit bias regarding health literacy for underserved patients*



Systemic Disease – Nomenclature (PCWG4)

Androgen Pathway Modulation Terminology

- Changes “castration-sensitive” and “castration-resistant” nomenclature
- Uses patient-centric indication model with androgen pathway modulation terms
 - Androgen Pathway Modulation Naïve (**APMN**) or Sensitive (**APMS**): hormone/castration naïve/sensitive equivalents
 - Androgen Pathway Modulation Resistant (**APMR**): resistant equivalents

A patient is classified as APMR when disease progresses despite ongoing androgen pathway modulation (ADT ± ARPI)

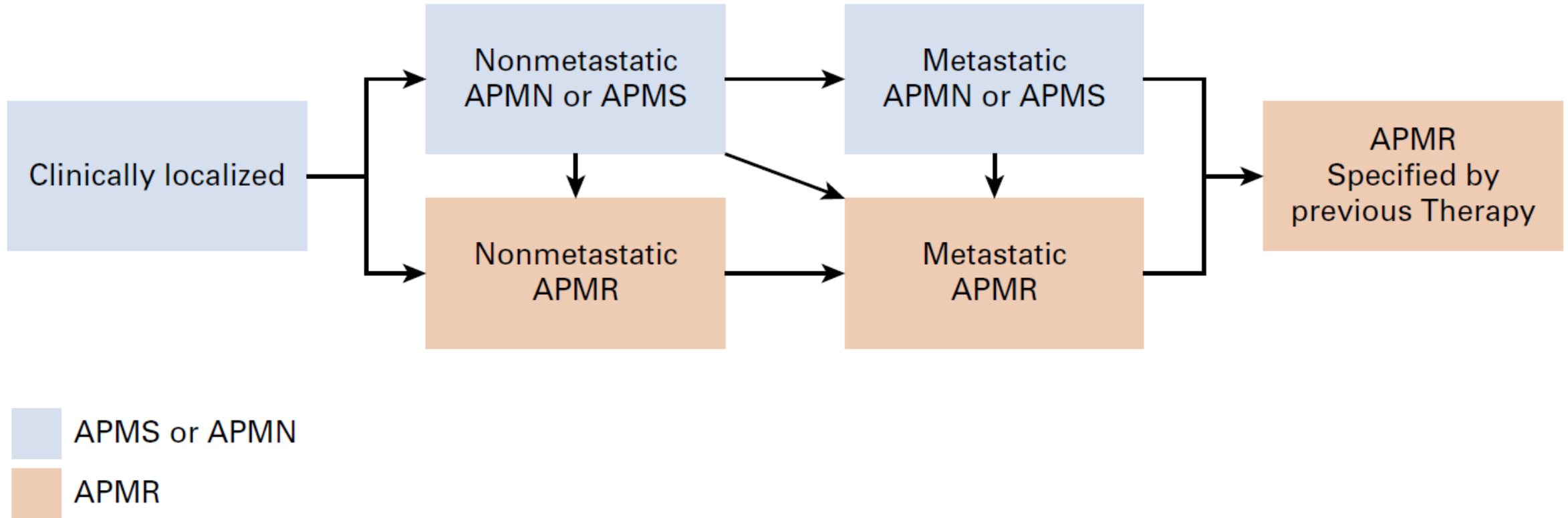
Progression may be defined by any of the following:

- PSA progression (per PCWG2/3 criteria)
- Radiographic progression (new lesions or measurable disease growth by CT/MRI, bone scan, or PSMA-PET — specifying modality)
- Clinical progression (symptomatic deterioration not attributable to other causes)



Prostate Cancer Clinical States Model

A Framework for Patient Treatment and Drug Development, Updated for the PCWG4



Combination therapy is considered one line of therapy. Androgen Pathway Modulation includes ADT, androgen deprivation therapy, and ARPI, androgen receptor pathway inhibitor. Within each state, specify where relevant: 1) genotype (germline, somatic), 2) imaging modality used to define metastasis (PET, CT/MRI/bone scan), 3) disease characteristics and biomarkers critical for risk stratification, and 4) prior therapies.

Practical Applications and Pitfalls

Define state/indication using:

APM exposure/response (naïve vs. sensitive vs. resistant)

Metastatic status by modality (CT/MRI/bone scan vs. PSMA-PET)

Symptoms and pattern of spread (bone-only, visceral, lymph node, prostate bed)

Genotype examples: BRCA2, ATM, CDK12, MSI-high, SPOP mutations, AR amplification/mutations, RB1/TP53 loss

Phenotype examples: adenocarcinoma vs. neuroendocrine/small cell, AR-positive vs. AR-low/negative (double-negative), intraductal carcinoma, high proliferation index, PSMA-avid vs. PSMA-non-avid on PET

Pitfall: Mixing positron emission tomography- (PET-) defined “metastatic” with conventional imaging-defined “non-metastatic” without accounting for modality



Systemic Disease – Androgen Pathway Modulator Therapy

“Non-Metastatic” Disease

- A diagnosis of technology and not biology
 - Plain x-ray < Tc bone scan < Fluciclivone PET < PSMA PET <
- Metastasis-free Survival
 - Reasonable intermediate endpoint for a *controlled clinical trial*
 - Good correlation with clinically relevant outcomes
 - Not necessarily important for patients
 - Not necessarily a physician trigger for altering therapy in practice
- FDA approval based on
 - Studies performed
 - FDA acceptance of intermediate endpoints
 - Lack of FDA approval ≠ lack of efficacy



Hormone Therapy: Some Simple Pharmacology

- LHRH agonists = orchiectomy
 - Orchiectomy is most cost effective
- LHRH antagonists ≈ agonists
 - No clear advantage of oral vs parenteral route
 - No testosterone flair w antagonists
 - Clinically relevant for metastatic disease
 - Unclear clinical relevance for non-metastatic disease
 - Incomplete but provocative data on prevention of early CV events
- ARPI potency matters, to a point.
 - Low: Flutamide = Bicalutamide = Nilutamide
 - Low potency tends to lead to rapid resistance
 - Clinical value rapidly declining, but cheap
 - High: Enzalutamide ≈ Apalutamide ≈ Darolutamide
 - Clinical value demonstrated
 - Expensive
 - Lack of brain penetration by darolutamide may be important
- Androgen synthesis (CYP17) inhibitors ≈ Potent AR antagonists



Phase 3 Trials in Untreated Metastatic PCa

TRIAL	ARPI	Docetaxel	PFS	OS
LATITUDE	abiraterone	No	HR = 0.47; p < 0.001	HR = 0.66; p < 0.0001
TITAN	apalutamide	11%	HR = 0.48; p < 0.001	HR = 0.65; p < 0.0001
ARCHES	enzalutamide	18%	HR = 0.39; p < 0.001	HR = 0.66; p < 0.0001
STAMPEDE	abiraterone	No	HR = 0.29; p < 0.001	HR = 0.63; p < 0.0001
ARASENS	darolutamide	100%	HR = 0.36; p < 0.001	HR = 0.68; p < 0.001
ARANOTE	darolutamide	No	HR = 0.54; p < .0001	HR = 0.81 [95% CI, 0.59 to 1.12]
CHAARTED	None	50% (exptl arm)	HR = 0.61; p < 0.001	HR = 0.72; p = .0018

What About Biochemical Recurrence?

A (mostly) Data-Free Zone

What I tend to do

- “Slow” PSA doubling time and PSMA-PET negative ➡ Surveillance
- “Slow” PSA doubling time and “oligometastatic” PSMA-PET ➡ focal/pelvic radiotherapy only
- “Fast” PSA doubling time and PSMA-PET negative ➡ pelvic radiotherapy
- “Fast” PSA doubling time and “oligometastatic” PSMA-PET ➡ focal/pelvic radiotherapy + ADT + (ARPI?) 6-12 mo
- But sometimes continuous (or intermittent) ADT with or without ARPI is reasonable
- Goals of care: chance of cure, delay use of hormonal therapy, maximize survival

AR Targeted Therapy Toxicity

- **Financial:**
 - o Orchiectomy vs chemical castration
 - o Brand name vs generic vs pharmacology guided dosing
- **Fatigue**
- **Neuropsychiatric**
 - o At extreme with rare seizures (enzalutamide, apalutamide)
 - o Depression vs neurocognitive vs fatigue/activation
 - o Benefit with low-brain penetration darolutamide
- **Libido/sexual function** (we are ignoring the partner)
- **Osteopenia/Osteoporosis**
 - o Role of exercise, calcium, Vitamin D
 - o Role for denosumab, zoledronate
- **Sarcopenia**
 - o Fatigue syndrome
 - o Role of exercise
- **Frailty**
- **Metabolic syndrome**
 - o Diabetes
 - o Hyperlipidemia

All these are much more impactful and tend to be under-recognized in elderly and underserved patients!



Mitigating ARP Targeting Toxicity

- Exercise and Physical Therapy
- Oxybutinin for hot flashes
- Darolutamide has fewer neurocognitive toxicity compared to enzalutamide
- Combined hormonal therapy may not always be necessary
- Intermittent therapy is feasible, and may allow testosterone recovery, but this is variable
- LHRH antagonists may have less initial CV morbidity than agonists

Systemic Disease – Non-AR Targeted Therapy

Taxanes & Misc Agents

■ Docetaxel vs Cabazitaxel

- No difference in taxane naïve patients
- Cabazitaxel more toxic and more expensive
- Sequential docetaxel -> cabazitaxel useful

■ Taxane vs ARPI in ARPI naïve patients

- No data as to which to do first
- Community tends to favor AR targeting first
- Population is going away since most receive combination hormonal therapy initially

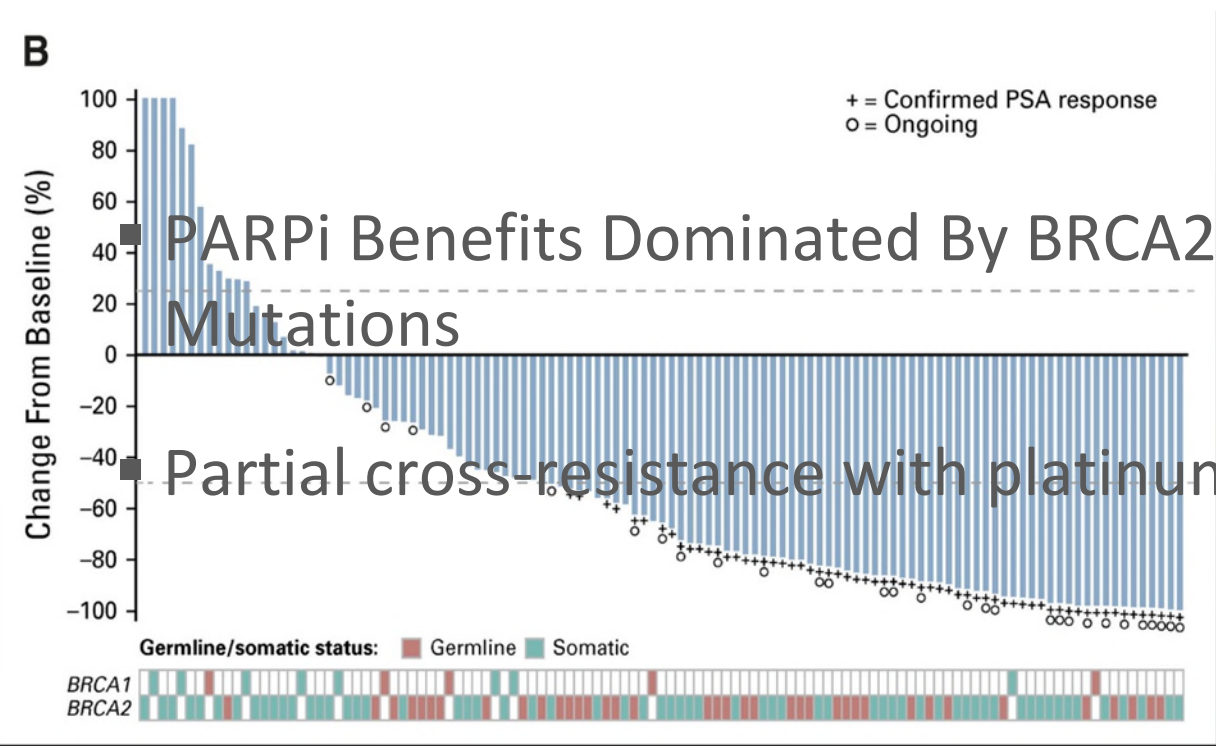
■ Taxane vs ARPI in ARPI treated patients

- Very limited value of sequential ARPI
- Occasional long term responses
- Combination abiraterone AR antagonist not useful

■ Miscellaneous:

- Mitoxantrone (never evaluated in the modern era)
- Sipuleucel-T (minimal value)
- Ra223 (bone mets only)
Survival advantage post-docetaxel vs BSC
No PSA impact
May have palliative impact

PARPi Therapy: The Rucaparib Example



Response by DDR gene alteration.

	By DDR gene group		
	ATM (n = 49)	CDK12 (n = 15)	CHEK2 (n = 12)
Confirmed investigator-assessed objective response ^b	2/19 (10.5)	0/10 (0)	1/9 (11.1)
Confirmed PSA response ^e	2/49 (4.1)	1/15 (6.7)	2/12 (16.7)
Median time to PSA progression, mo (95% CI)	3.1 (2.8–4.6)	3.2 (2.8–4.6)	7.4 (2.8–7.4)

LU-PSMA Therapy

■ Definitive Trial Selection

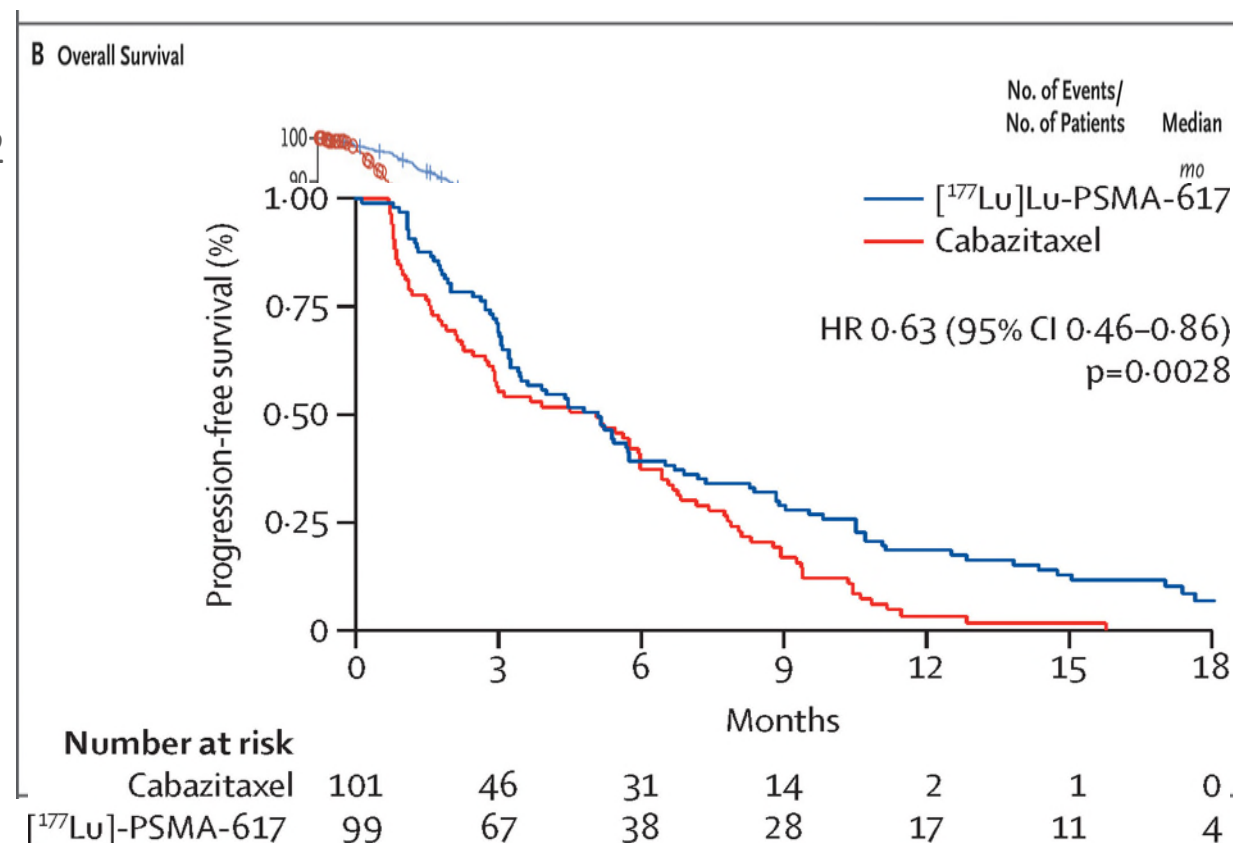
- PSMA-positivity with ^{68}Ga -PSMA-11
- Prior ARPI and at least 1 taxane (only 40% with 2 taxanes)

■ Treatment

- Up to 6 doses, every 4 weeks
- Less therapy being investigated

■ Issues

- Coordination with Nuclear Medicine
- Anemia, ? Long-term myelosuppression, especially with earlier therapy
- Risk/benefit of earlier therapy controversial
- Other PSMA targeted therapies emerging



Should more Aggressive Therapy be Utilized for High Risk APMN Disease?

- We can identify high risk patients with simple clinical metrics
 - High PSA and Gleason score
 - Extensive disease on imaging, especially visceral disease
- ADT/ARPI/docetaxel
 - Encouraging Phase II data
 - No phase III data, but trial in process
 - Decipher score may be predictive for benefit (ASCO abstract 5001, Sweeney et al)
- ADT/ARPI/PARPi (in pts with HRR mutation tumors)
 - Positive phase III data with talazoparib (TALAPRO-3)
 - Supportive data in APMR disease and other PARPi
- ADT/ARPI/Lu-PSMA
 - Positive phase III data
- ADT/ARPI/PI3Ki (in pts with PTEN deficient tumors)
 - Positive phase III data with capivasertib

Major Questions:

- Long term outcome
- Up front vs sequential therapy
- Short & long term toxicity



What's Emerging

- Bispecific antibodies
- Antibody drug and radiotherapy conjugates
- CAR-T and other cellular therapies
- Targets
 - o STEAP
 - o Kallikrein
 - o B7H3
 - o Others

Long Term Toxicity of Other Agents

- **Taxanes - Neuropathy**

- Gait difficulties
- Balance difficulties
- Other functional impacts

- **PARPi**

- Myelosuppression
- MDS/Leukemia

- **Lu-PSMA**

- Anemia
- Myelosuppression
- MDS/Leukemia???

- **Bispecific Antibodies**

- Cytokine release syndrome
- Depends on target
- Immune effects

- **Antibody-Drug conjugates**

- ???
- Depends on target, linker and toxin
- E.g Monomethyl auristatin E: neuropathy

Conclusions

- We finally have better imaging to diagnose and monitor disease
 - Be careful of what you wish for
 - Better technology does not mean better treatment or easier decision making
- The androgen receptor is the most important therapeutic target
 - Toxicities are well understood, but underappreciated & are critically life long
 - When is “total AR targeting” not appropriate?
- **Chronic disease management is the mantra**
- Additional therapeutic targets have and are being identified
 - Efficacy is prime, but survival is not always key
 - Short and long term functional toxicities must be evaluated
- Studies & care focusing on functional endpoints are critical
- Studies & care focusing on therapy discontinuation or minimization are critical

Thank You

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