Disclosures

- Consultant for Eisai, Exelixis & Pfizer.

This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their product(s) and/or other business interests.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.

The off-label/investigational use of Actinium-225, Capivasertib & Ipatasertib 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.

This presentation is dedicated solely to research or other issues that do not contain a direct patient care component.

Learning Objectives

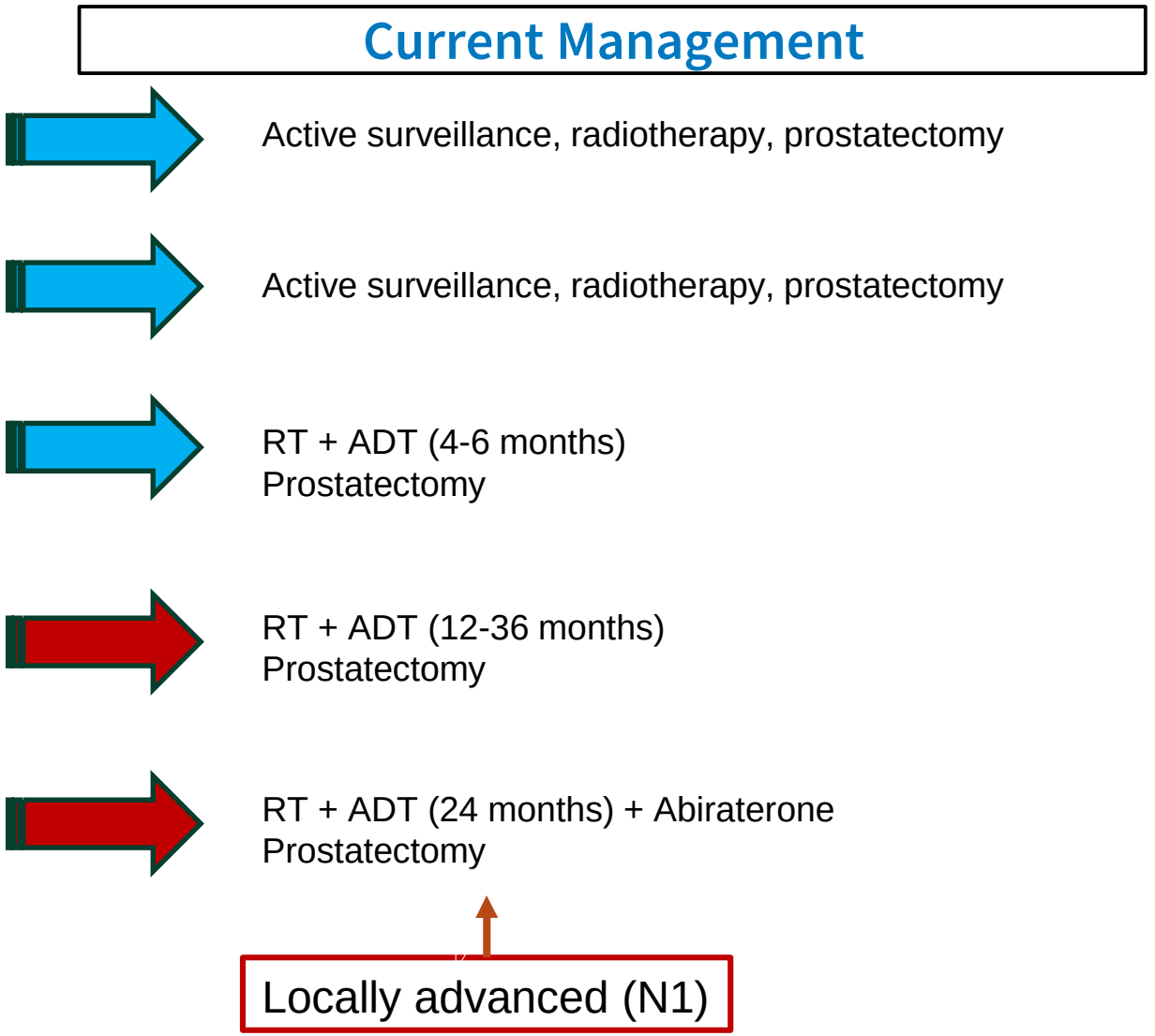
By the end of this session, participants should be able to:

- Review the systemic therapy landscape for prostate cancer
- Discuss emerging treatment modality in localized prostate cancer
- Summarize key updates in metastatic hormone-sensitive prostate cancer (mHSPC)
- Discuss advances in metastatic castration-resistant prostate cancer (mCRPC)
- Apply evidence-based sequencing strategies

Disease States in Prostate Cancer

Localized Prostate Cancer

NCCN Risk Groups



Dual Primary Endpoint

- pCR – no identifiable tumor (ypT0)
- MRD - ≤ 5 mm residual tumor (ypT2 or lower)

Baseline Characteristics

Key Secondary Endpoints

Back to The Future: 2004

Docetaxel: The first effective chemotherapy

2004

=

Evolution of Treatment Paradigm

Past

- ADT
- Chemotherapy

Present

- ARPi
- Chemohormonal
- Triple therapy
- PARPi
- Radioligands
- Immunotherapies

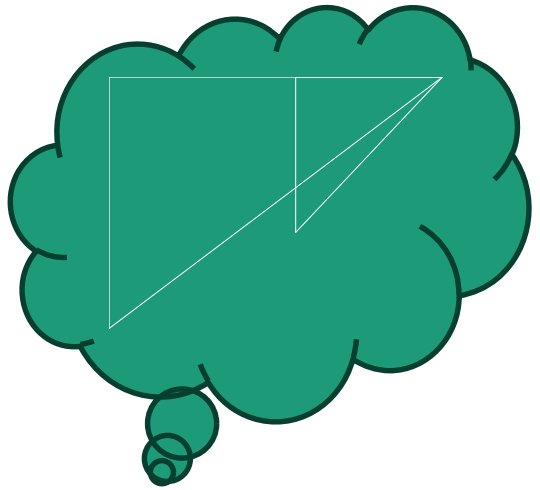
(nearest) Future

- Bispecifics
- CAR-T therapy
- AKT inhibitors
- AI-guided oncology

Early treatment intensification

Precision medicine

The (other) Future



mHSPC: Intensification is Standard

*ADT alone no longer adequate for most patients

Standard Approaches

ADT + ARPI
ADT + docetaxel
ADT + PARP inhibitor

Triple Therapy

ADT + docetaxel + abiraterone
ADT + docetaxel + darolutamide

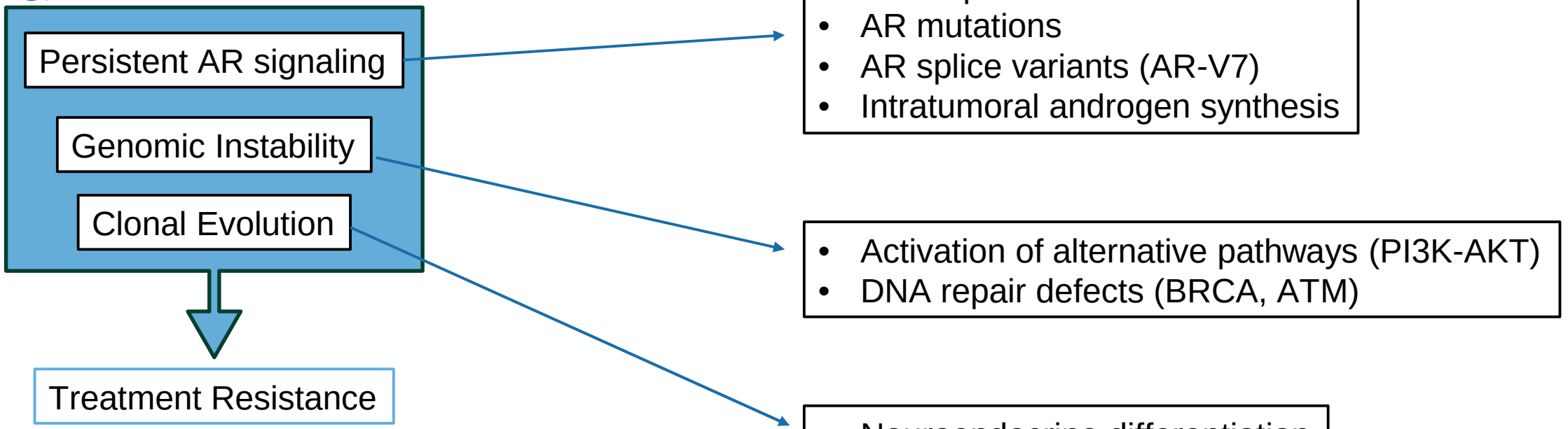
Outcomes

Improve overall survival
Delay progression
Better symptom control

Agent	Trial	Key Benefits
Docetaxel	CHAARTED	OS
Abiraterone	LATITUDE	OS
Enzalutamide	ENZAMET	OS
Apalutamide	TITAN	rPFS/OS
Darolutamide	ARANOTE	rPFS
Niraparib + Abiraterone (mBRCA)	AMPLITUDE	rPFS
TRIPLE THERAPY (HIGH-VOLUME)		
Docetaxel + abiraterone	PEACE-1	rPFS/OS
Docetaxel + darolutamide	ARASENS	OS

Metastatic CRPC

Biology of Castration Resistance



Treatment Categories

- ARPIs
- Taxanes
- PARP inhibitors
- Radioligands
- Immunotherapy

PARP Inhibition

	TALAPRO-2 (Talazoparib/enzalutamide)	PROpel (Olaparib/abiraterone)	MAGNITUDE (Niraparib/abiraterone)
Setting	HRR alteration (prospective)	HRR (unselected)	HRR alteration (prospective)
N	399 (BRCA 158)	796	423 (BRCA 225)
Randomization	1:1	1:1	1:1
Comparator	Enzalutamide	Abiraterone	Abiraterone
Primary endpoint	rPFS	rPFS	rPFS
Median rPFS, months	30.7 vs 12.3 (HR 0.47)	24.8 vs 16.6 (HR 0.66)	16.5 vs 13.7 (HR 0.73)
Median OS, months	45.1 vs 31.1 (HR 0.62)	42.1 vs 34.7 (HR 0.81)	No benefit (HR 0.94)
	Trial showed both **rPFS** and **OS** benefits	**rPFS** benefit irrespective of HRR **Numerical OS** benefit - Strong rPFS and OS in BRCA	Only **rPFS** benefit

Lancet. 2023;402:291,Lancet Oncol. 2023;24:1094, JCO. 2023;41:3339

Immunotherapies

	Sipuleucel-T	Pembrolizumab
Relevant trial	IMPACT	KEYNOTE 16/158
Biomarker	-	MSH-H/dMMR, TMB-high
	Autologous cellular immunotherapy	Anti-PD-1

Open label single arm phase II
- Pembrolizumab 200 mg IV Q3W for 2ys/progression
- Primary Endpoint - ORR

233 patients
- Advanced non-colorectal cancer
- MSI-H/dMMR by IHC or PCR
- 6 (2.6%) prostate

JCO. 2020;38:1

PSMA Radioligand Therapy

	Beta	Alpha
LET	Low (0.1-1 KeV/µm)	High (100-200 KeV/µm)
Path length	Long (0.5-2mm)	Short (50-100 µm)
DNA damage	Single stranded DNA breaks	Double stranded DNA breaks
Crossfire effect	Yes	Minimal
Distribution	Wider area	Focused, high intensity hits
Ideal tumor	Bulky/heterogenous	Micrometastasis/ uniform

NEJM. 2021;385:1091

rPFS

OS

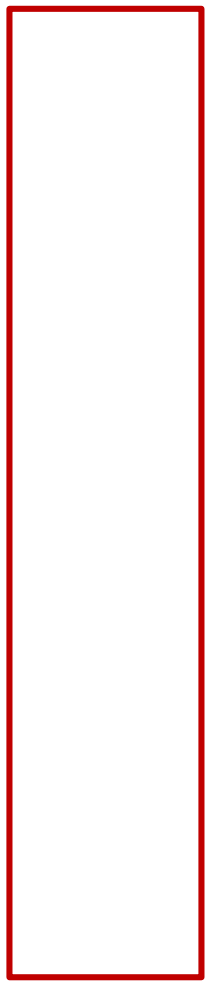
rPFS

OS

^{177}Lu-PSMA-617 pre-chemotherapy

ITT Population

Lancet. 2024;404:1227



AKT Inhibition (PTEN Loss)

Ann Oncol. 2026;37:574

Sequencing Challenges

Common Questions

- ARPI after ARPI?
- When to use chemotherapy?
- Earlier radioligand therapy?
- Best timing for PARPi combination?

Emerging Therapies

PSMA-directed
- Alpha emitters
- Combination radioligand approach

Bispecific antibodies
- PSMA x CD3

Cellular therapy
- CAR-T

Androgen receptor degraders

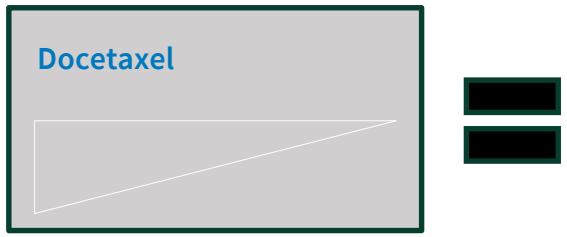
Key Take-Home Messages

ADT monotherapy is no longer standard of care for most mHSPC

Triplet therapy improves outcomes in selected patients

Genomic testing is increasingly required

2004



2026

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Thank you!