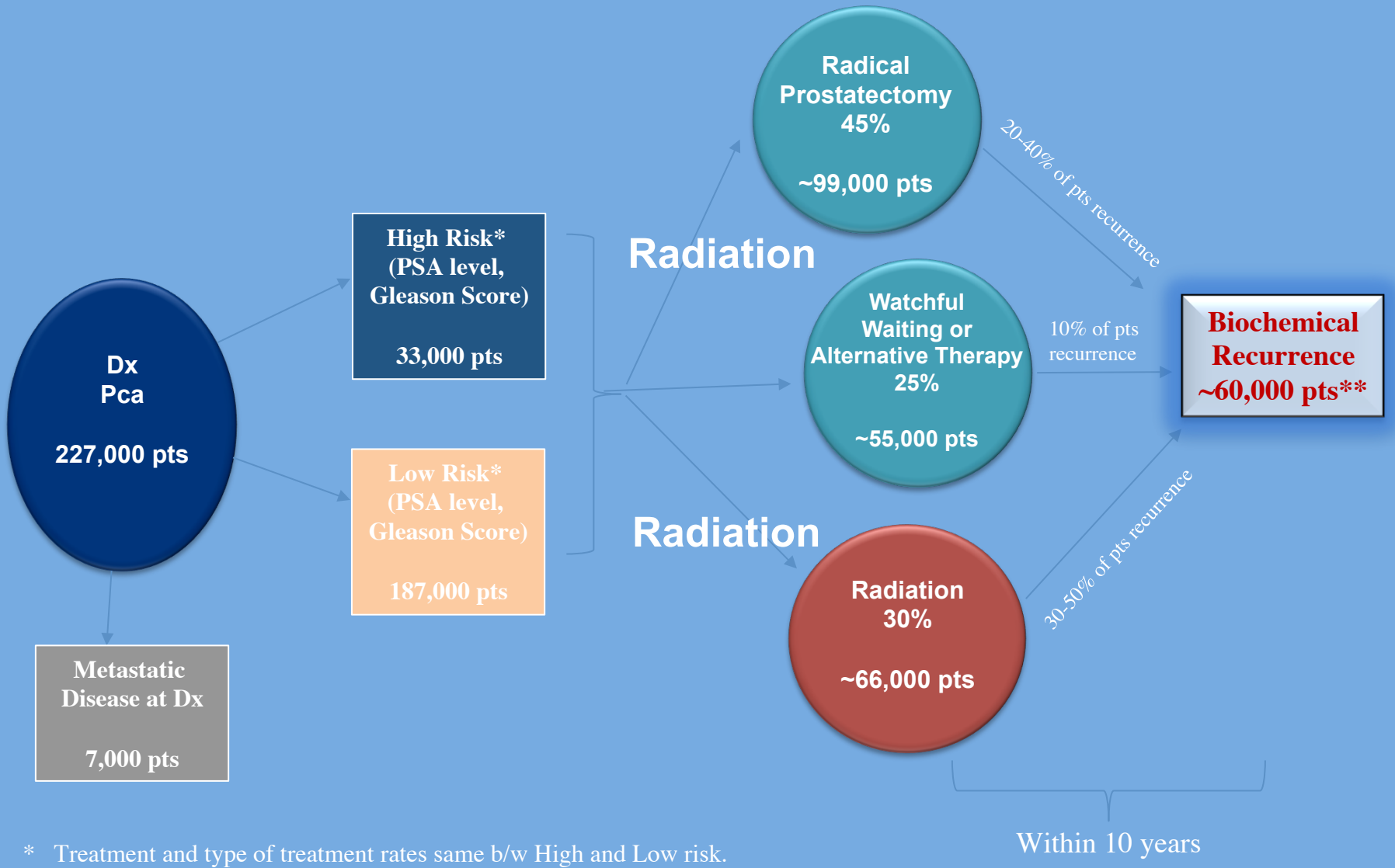
There Are Newer and More Promising Agents Than Chemotherapy

Neal D. Shore

IPCU 2016

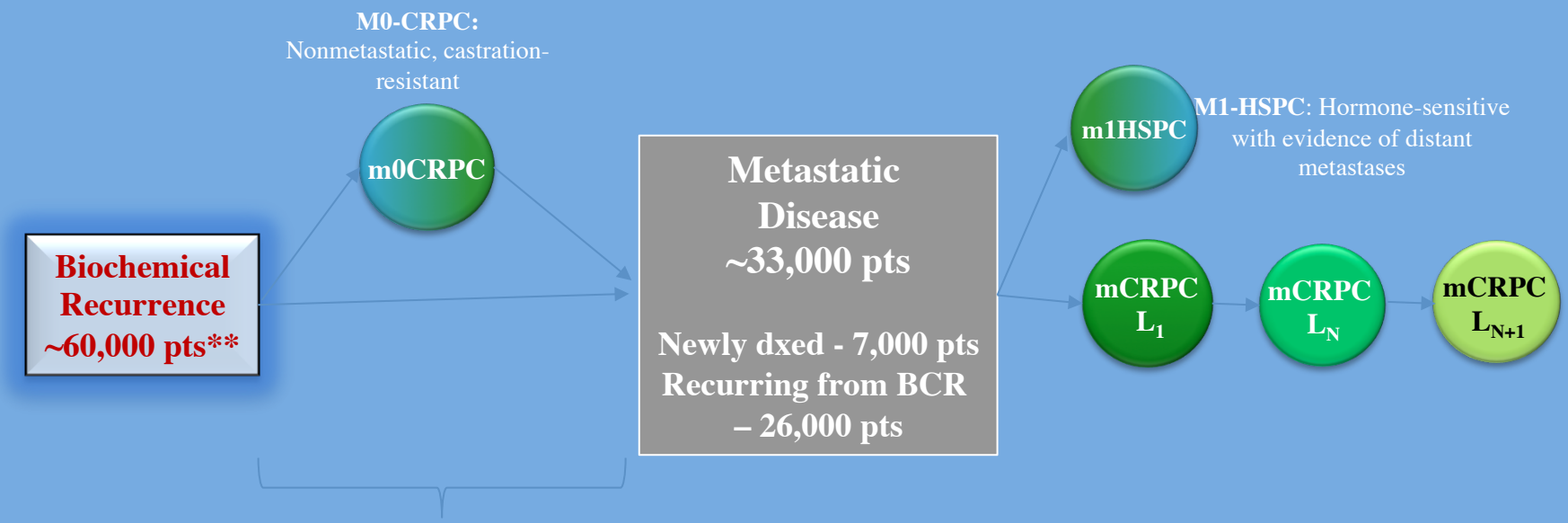
PCa Disease States - U.S. Statistics



* Treatment and type of treatment rates same b/w High and Low risk.
** Used Midpoint of the % Recurrent ranges.

Paller, C *Clinical Advanced Hematology Oncology*. 2013; 11(1):14-23.
Datamonitor

PCa Disease States - U.S. Statistics

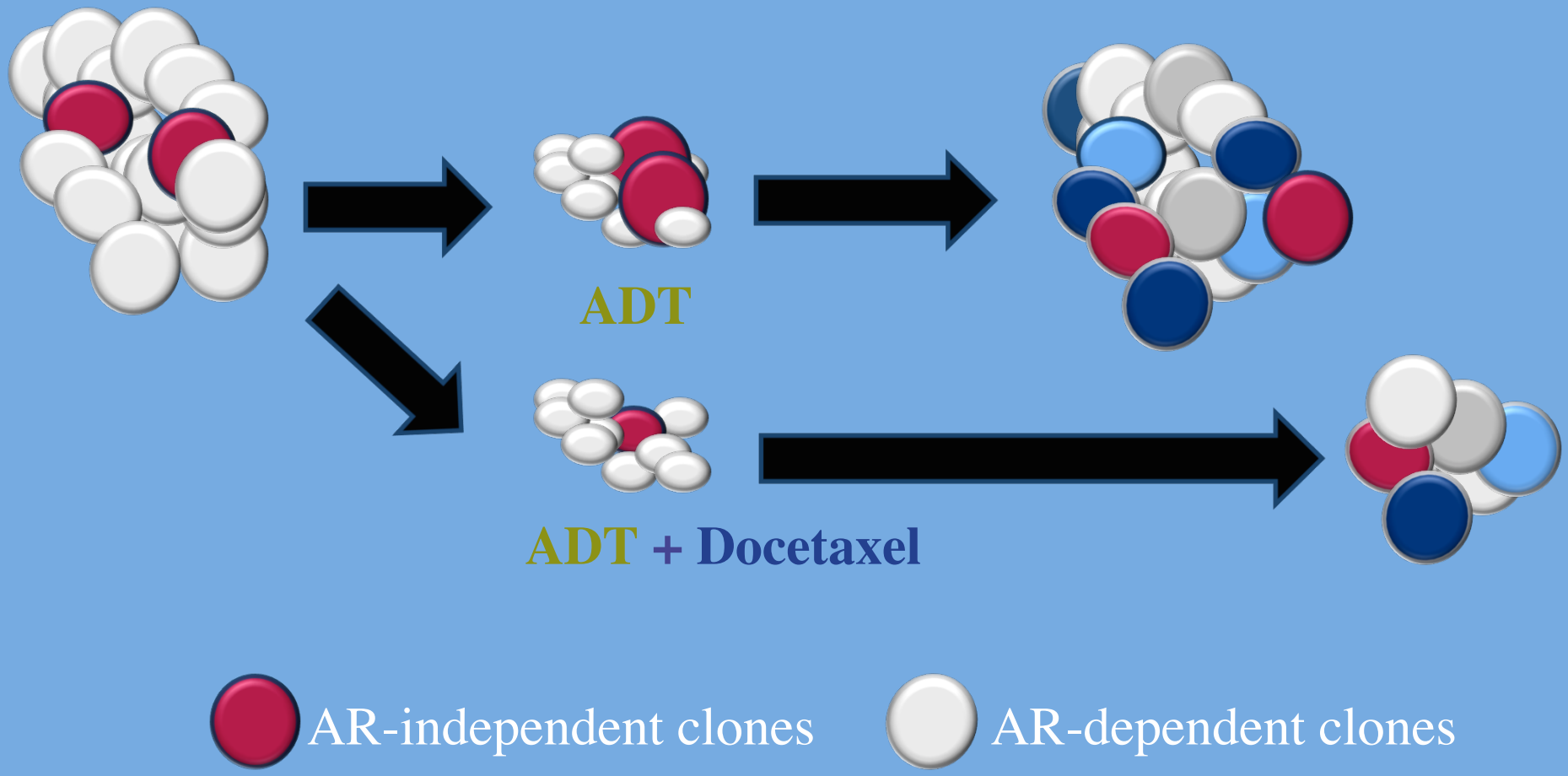


High Risk (Gleason Score, PSADT) – high % progress to metastatic disease and median time to progression is ~2 years

Low Risk – less progress to metastatic disease and time to metastatic disease is 5-7 years

Paller, C *Clinical Advanced Hematology Oncology*. 2013; 11(1):14-23.
Datamonitor

The hypothesis

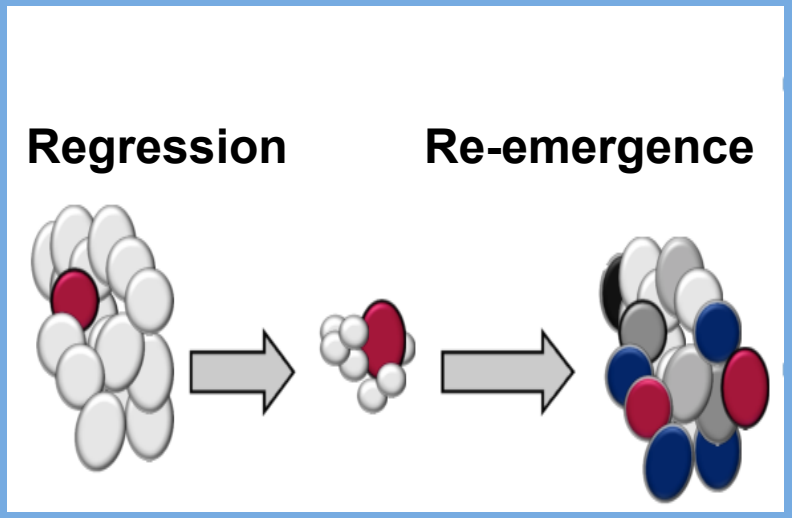


Sweeney C et al. J Clin Oncol 2014;32(June 20 suppl):abstract LBA2

ADT: Androgen Deprivation Therapy; AR: androgen receptor

Chemo + ADT: Rationale behind the combination

Androgen Deprivation Therapy



Pro

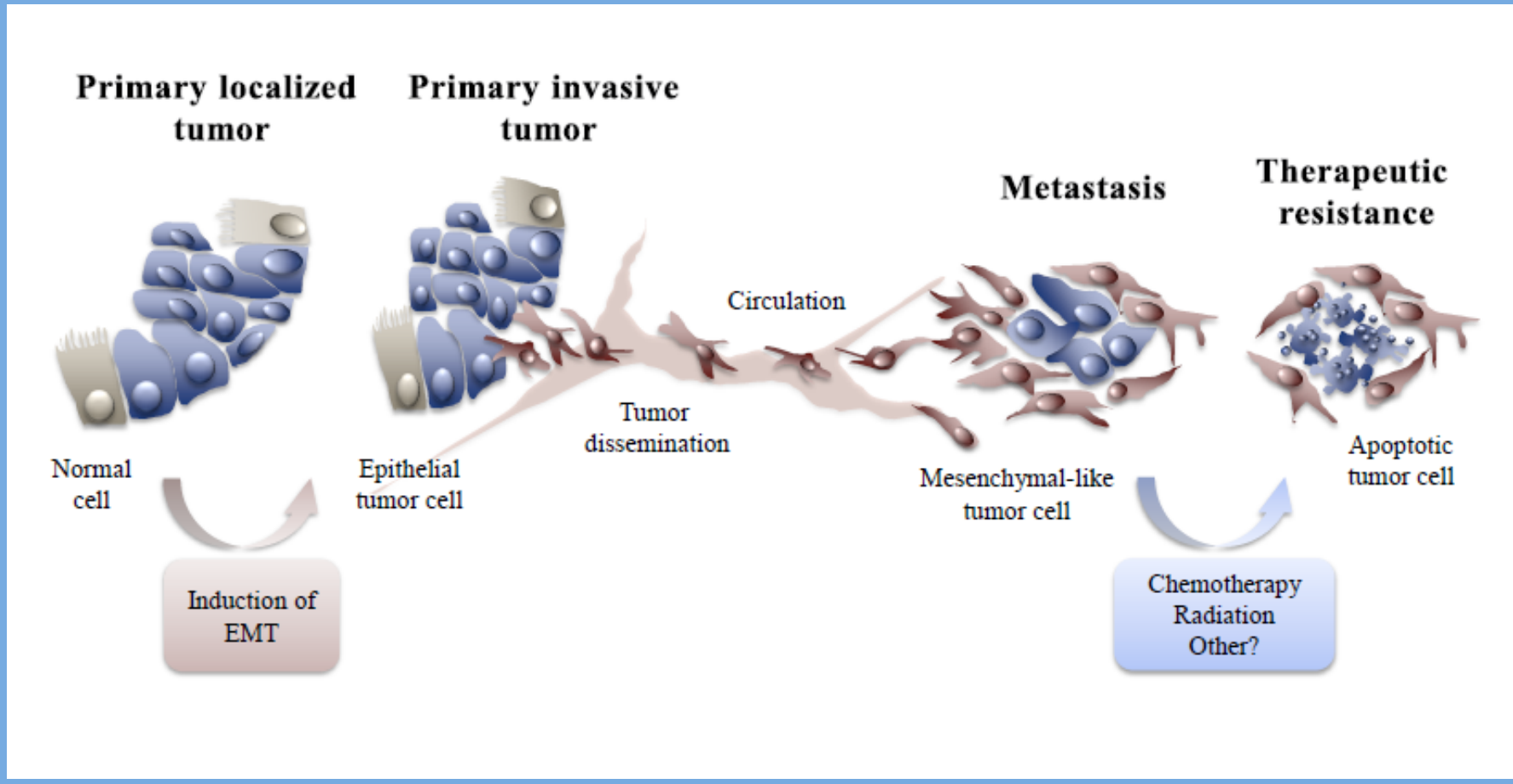
- Attack de-novo testosterone independent clones early, allowing ADT to keep PrCa in remission longer
- Docetaxel may inhibit AR nuclear expression
- Some patients may be too frail for chemotherapy at progression.

Con

- ADT will take cells out of cycle and be less responsive to cytotoxics
- Some patients respond to ADT for a long time and never need chemotherapy

Courtesy of C Sweeney

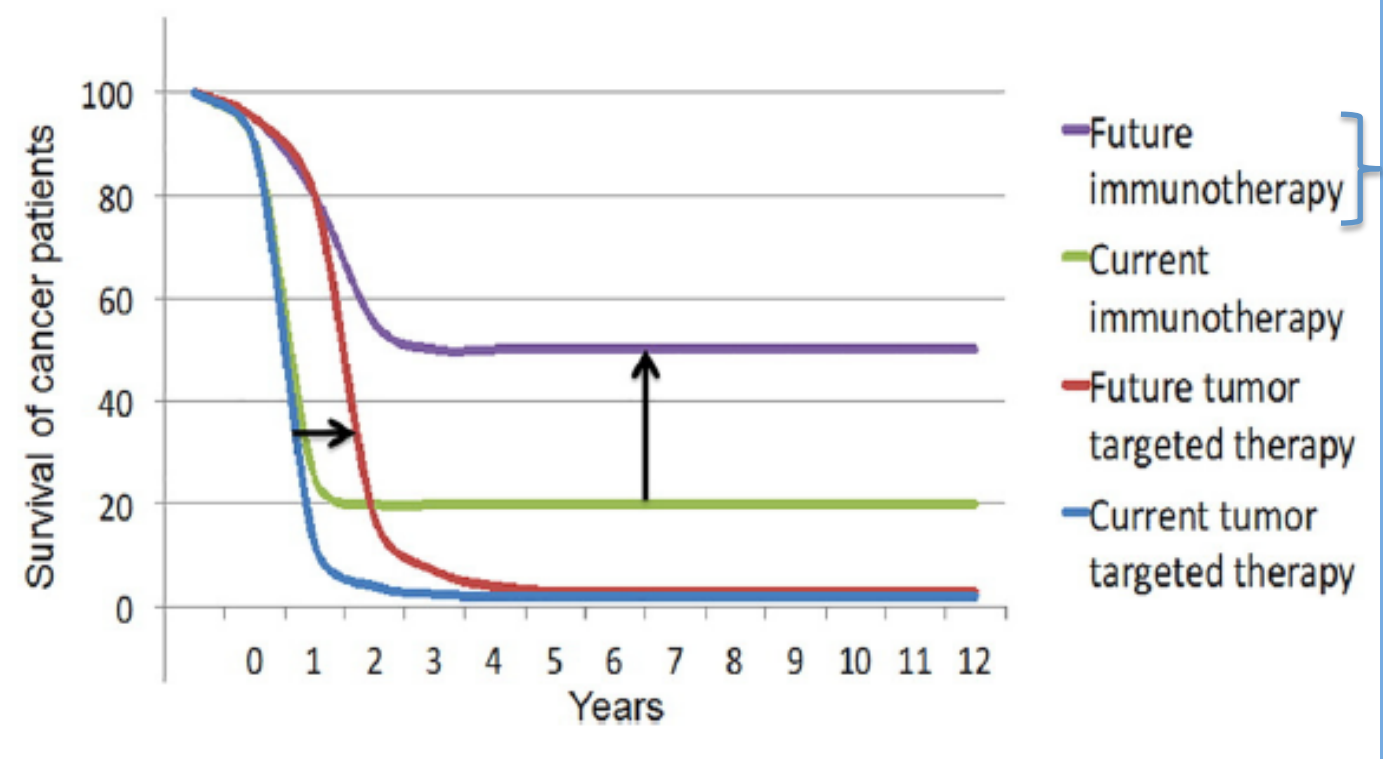
Role of Tumor EMT in Metastasis and Therapeutic Resistance



The Future

http://www.sciencemag.org/content/342/6165/1432.full

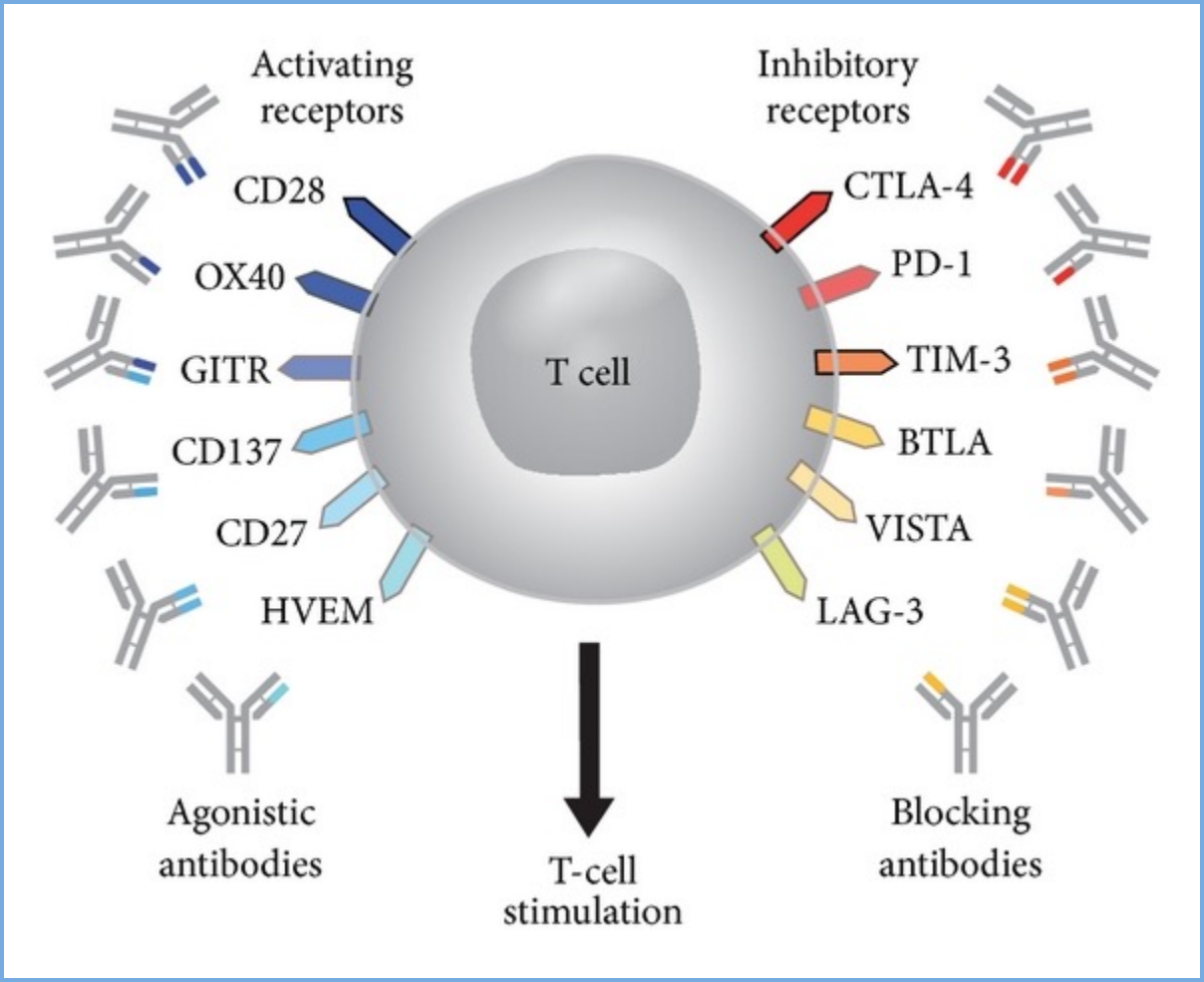
“Tail of the Curve” Sets Immunotherapy Apart from Targeted Therapy



- I-O+I-O
- I-O+Targeted/ Directed/SOC

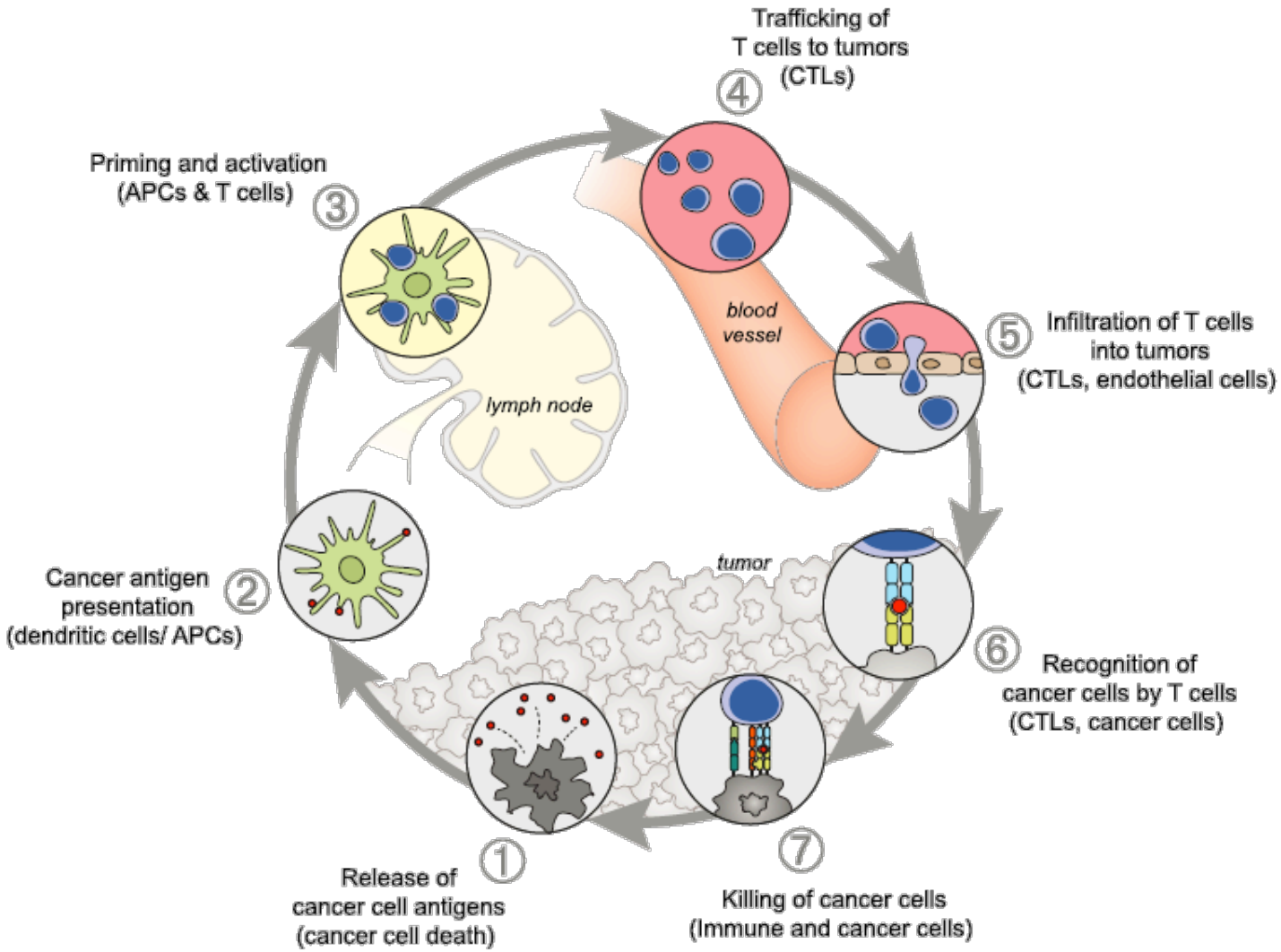
Verdeil G. et.al. 2015 Biochimica et Biophysica Acta

Targeting T cells



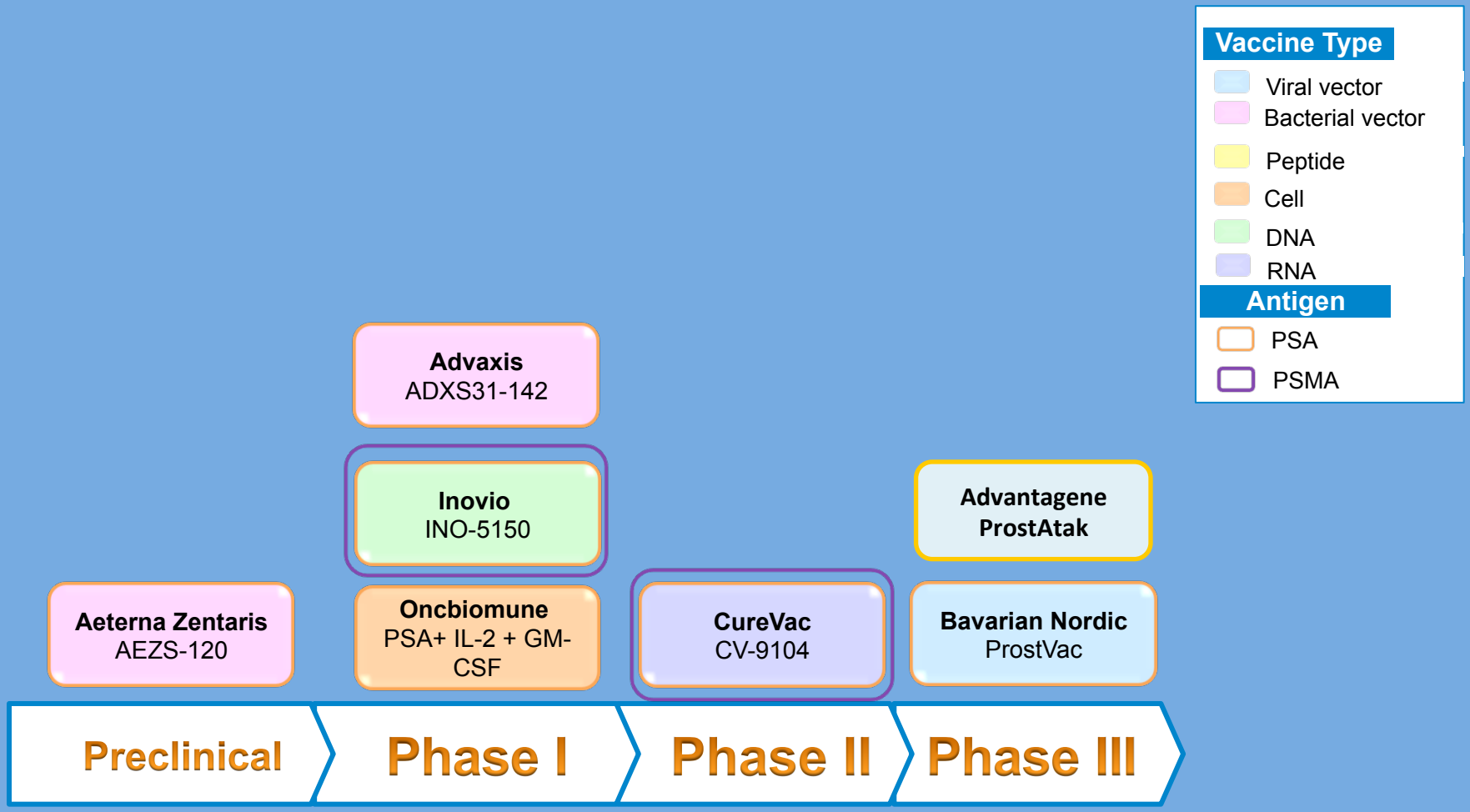
Mellman, I., et.al. 2011. Nature

The Cancer-Immunity Cycle



Chen, D.S. and I. Mellman 2013
Immunity

Numerous Oncology Vaccines Being Developed in PCa

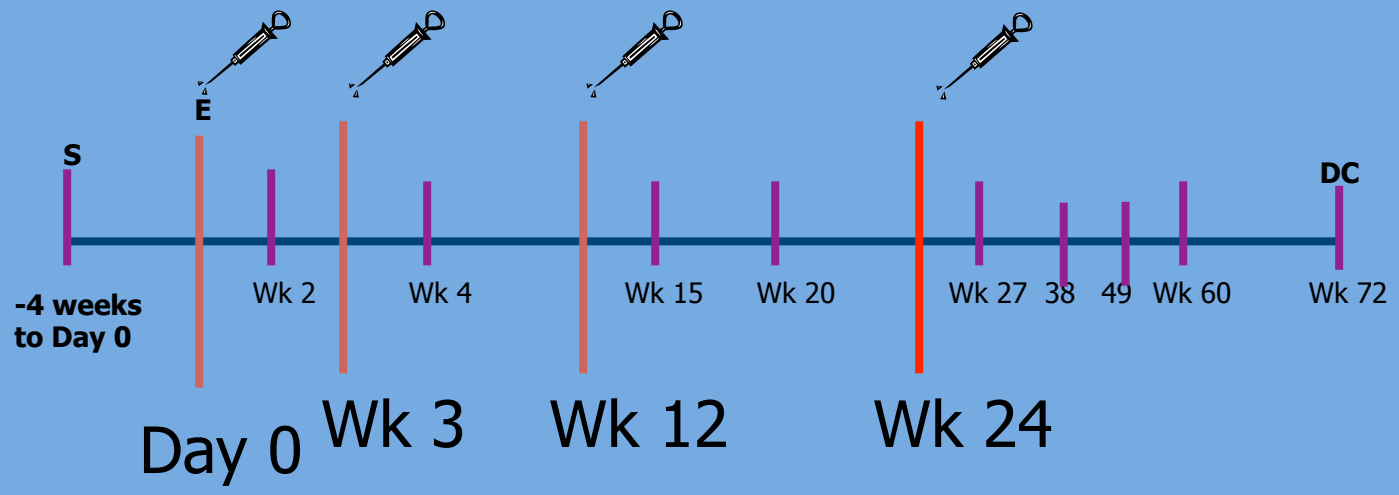


Vaccines are under investigation

Brand (molecule)	Mechanism of Action	Company	Phase	Current Study/Existing Data
Prostvac Subcutaneous inj.	PSA vaccine: Poxvirus express PSA + TRICOM (LFA-3, ICAM-1 and B7.1)	Bavarian Nordic	III	Phase III in mCRPC/ Phase II (N=125) showed successful OS as monotherapy in same population; Phase I combo with YERVOY showed long OS compared to historic controls
Prostatac(r)	PSA vaccine: transferrin transport technology	OncBio-Mune	IA/IB	BCR patients who have not started hormone therapy, N=48 / Phase I in 12 patients neo-adjuvant setting
CV9103/ CV9104	RNA Vaccine with 4 Antigens – PSA, PSCA, PSMA, STEAP1	CureVac	II	CV9104 in Phase II in mCRPC asymptomatic, N=197 patients/ Phase I in M0 CRPC, N=48, 80% of patients showed immune response and 2/3 responded to multiple antigens
ADXS31-142	PSA vaccine: Listeria monocytogenes-based vaccine	Advaxis	I/II	Phase I trial looking at safety of monotherapy and combination with pembrolizumab /Pre-clinical studies as monotherapy and combination

Source: Company websites and clinicaltrials.gov.

Inovio-On-going Phase I (PCa-001): PSA Relapse



- 6-month treatment at weeks of 0, 3, 12, 24
- 72- week follow-up
- 4 dose cohorts, total N=60

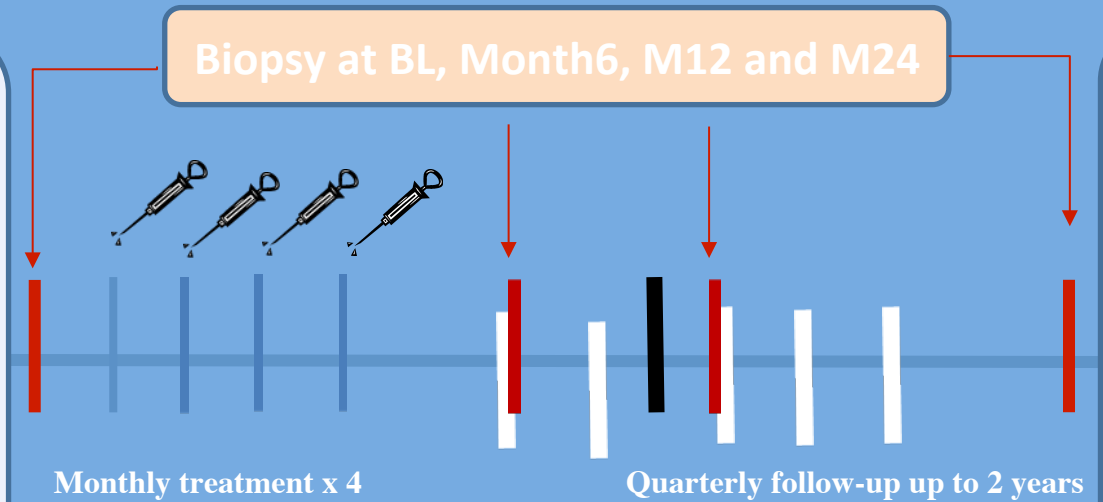
Cohort	INO-5051 (mg)	INO-9012 (mg)	N
A	2	0	15
B	8.5	0	15
C	2	1	15
D	8.5	1	15

DC = discharge; E = enrollment; S = screening; Wk = week.
The intervals between time points are not actually proportional.

Inovio-Phase I (PCa-002) Study

In patient with localized Pca under active surveillance (AS)

Subjects:
Low-intermediate risk PCa
Treatment naïve
No mets
Suitable for AS



- 4 treatments at a monthly basis
- PSA monthly x 6 months, then quarterly up to 24 months
- 2 year follow-up
- N=20-30 in single arm

Endpoints

Primary:

- **Change in TIL**

Secondary:

- **PSA control**
- **DFS**
- **Time to new treatment**

The intervals between time points are not actually proportional.

Very High Risk and Oligo-Metastatic Prostate Cancer

- Uncertain standard of care
- Multiple advances:
  - Improved disease identification (imaging)
  - Improved surgical and radiation based treatments
  - Improved systemic therapies
- Multiple questions:
  - Best local primary treatment
  - Benefit of treatment to metastatic sites
  - Benefit of early intensification of systemic therapy
- Controlled clinical trials are critical
- At a minimum, these men should be captured in prospective registries (disease/QOL outcomes, bio-specimen collection)

Large Urology Group Practice Association-- LUGPA

- The LUGPA represents 121 large urology group practices
  - >2,000 physicians
  - >20% of the nation's practicing urologists
- Committed to best practices, research, data collection and benchmarking to promote quality clinical outcomes

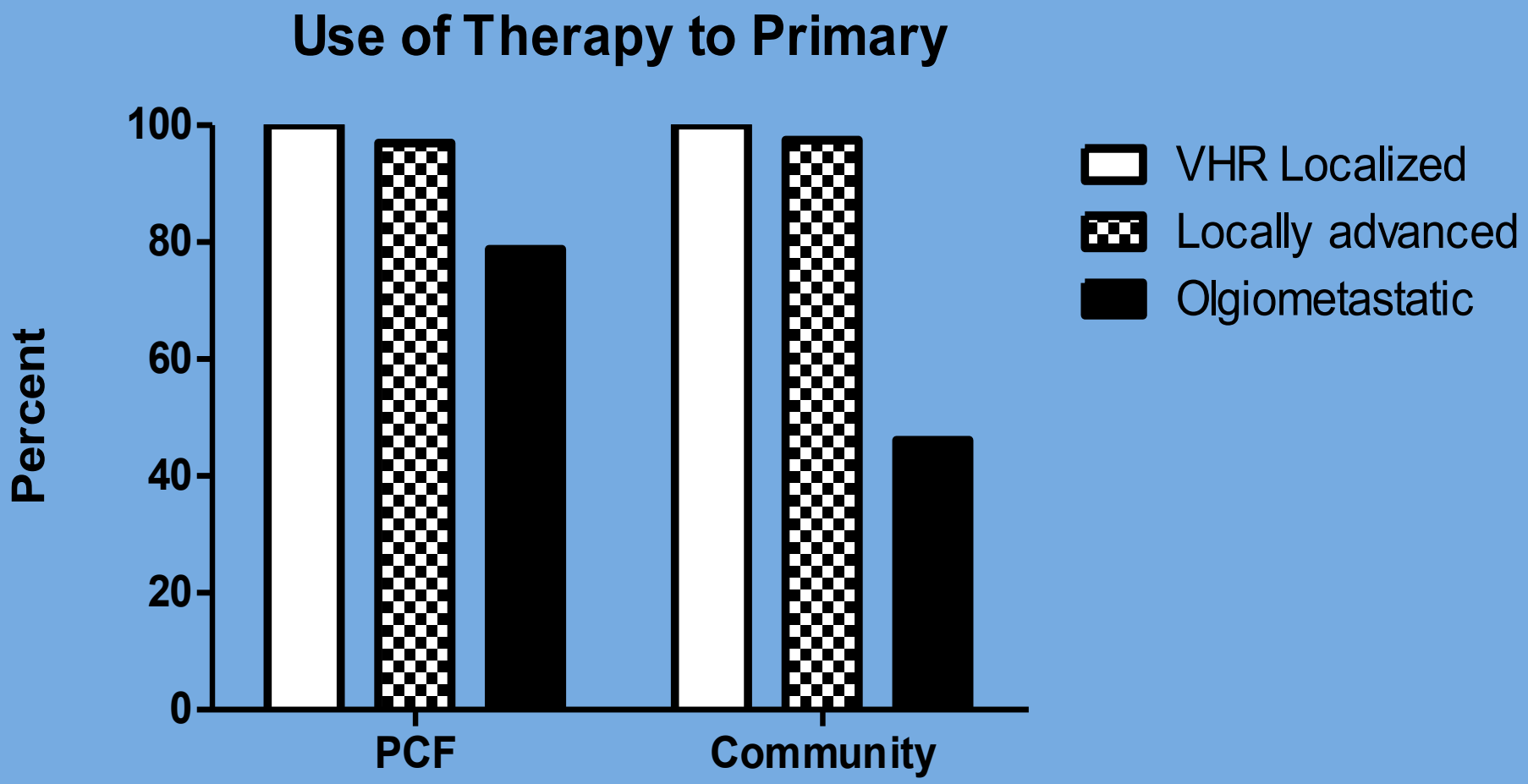
Objectives

- Review perspectives of PCF members and practitioners from large urology practice groups regarding management of contemporary very high risk localized, locally advanced, and oligo-metastatic prostate cancer
  - Gauge community practice trends towards the management of these men
  - Increase interaction between academics and community practices
  - Encourage LUGPA registries and clinical trials for these men

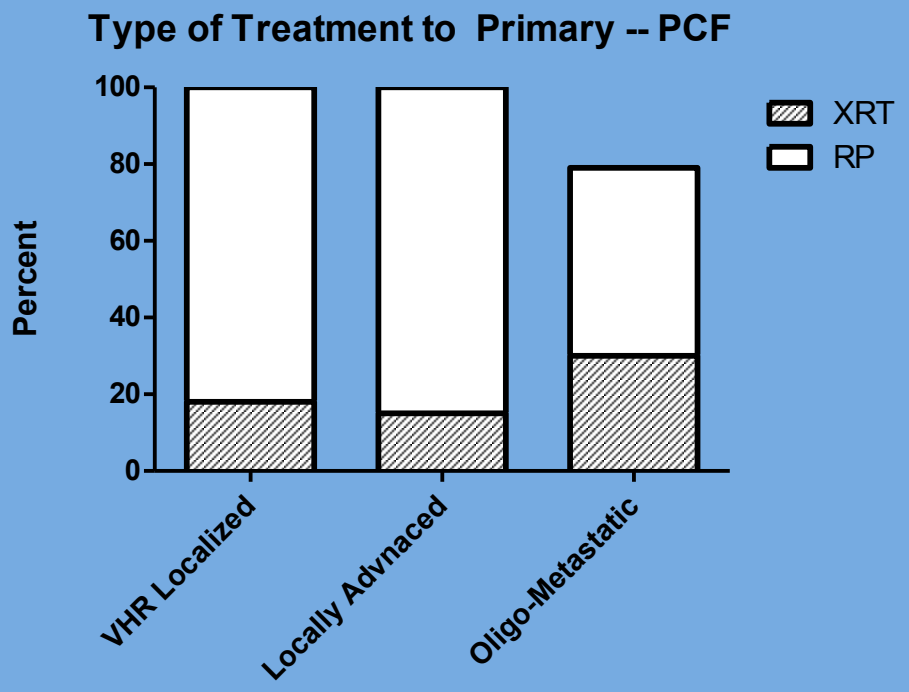
Design

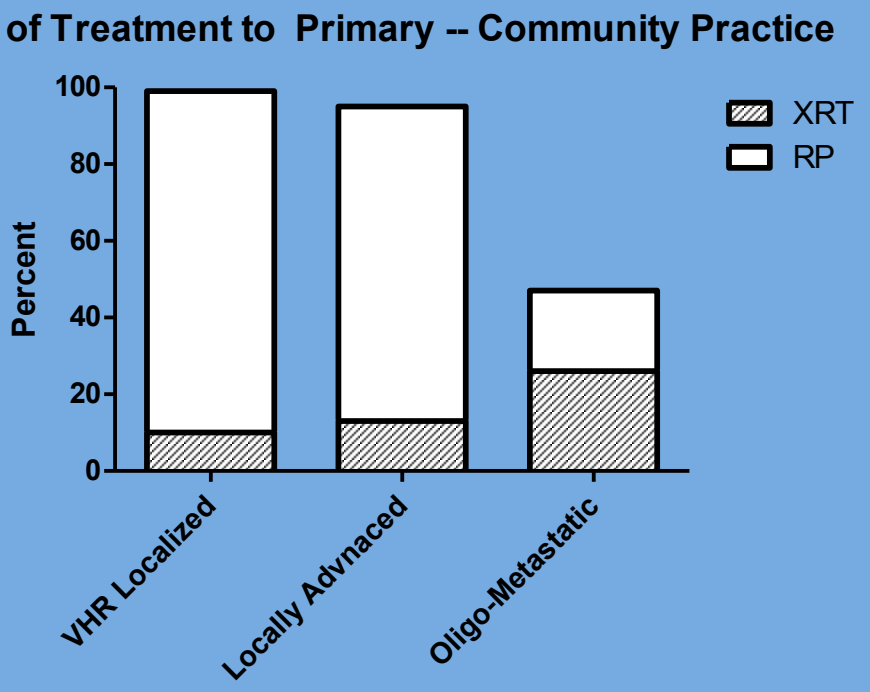
- Data acquisition based on survey completed by 33 PCF meeting attendees and 39 members of large urology practice groups
  - Based on contemporary patients
  - Assessment of perspectives on
    - Local control
    - Use of systemic chemotherapy
    - Metastasis directed therapy
    - Perspectives on what we should focus on as a field
- Tremendous caveats – all acknowledged

Local Control

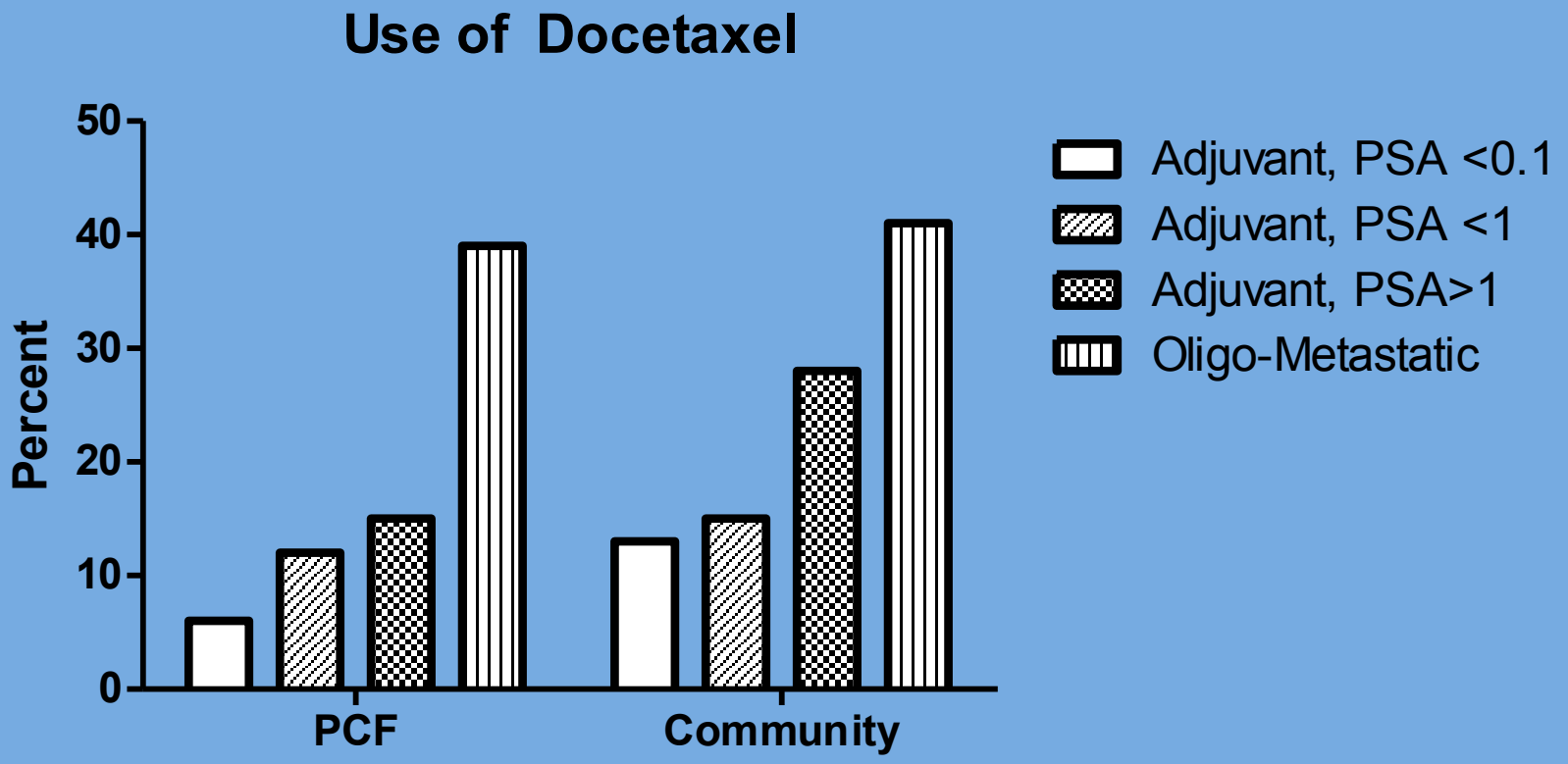


Local Control

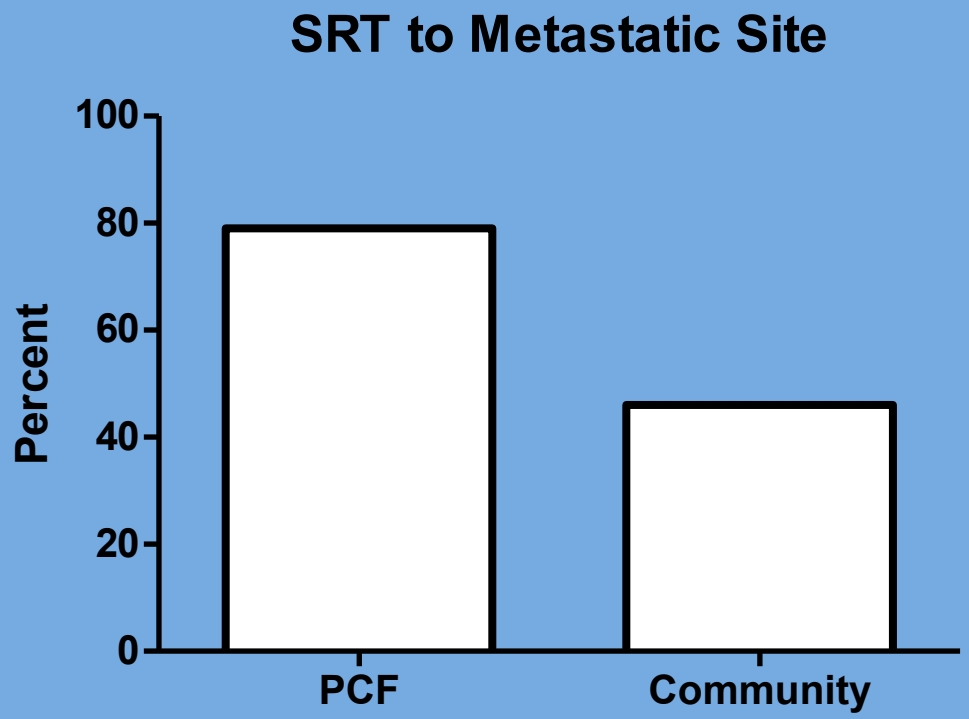




Use of Systemic Chemotherapy



Use of Local Treatment To Metastatic Sites



Future Areas of Focus

PCF

- Determine best local therapy (24%)
- Better imaging (24%)
- SRT to mets (24%)
- Immunotherapy (15%)
- Better ADT (12%)

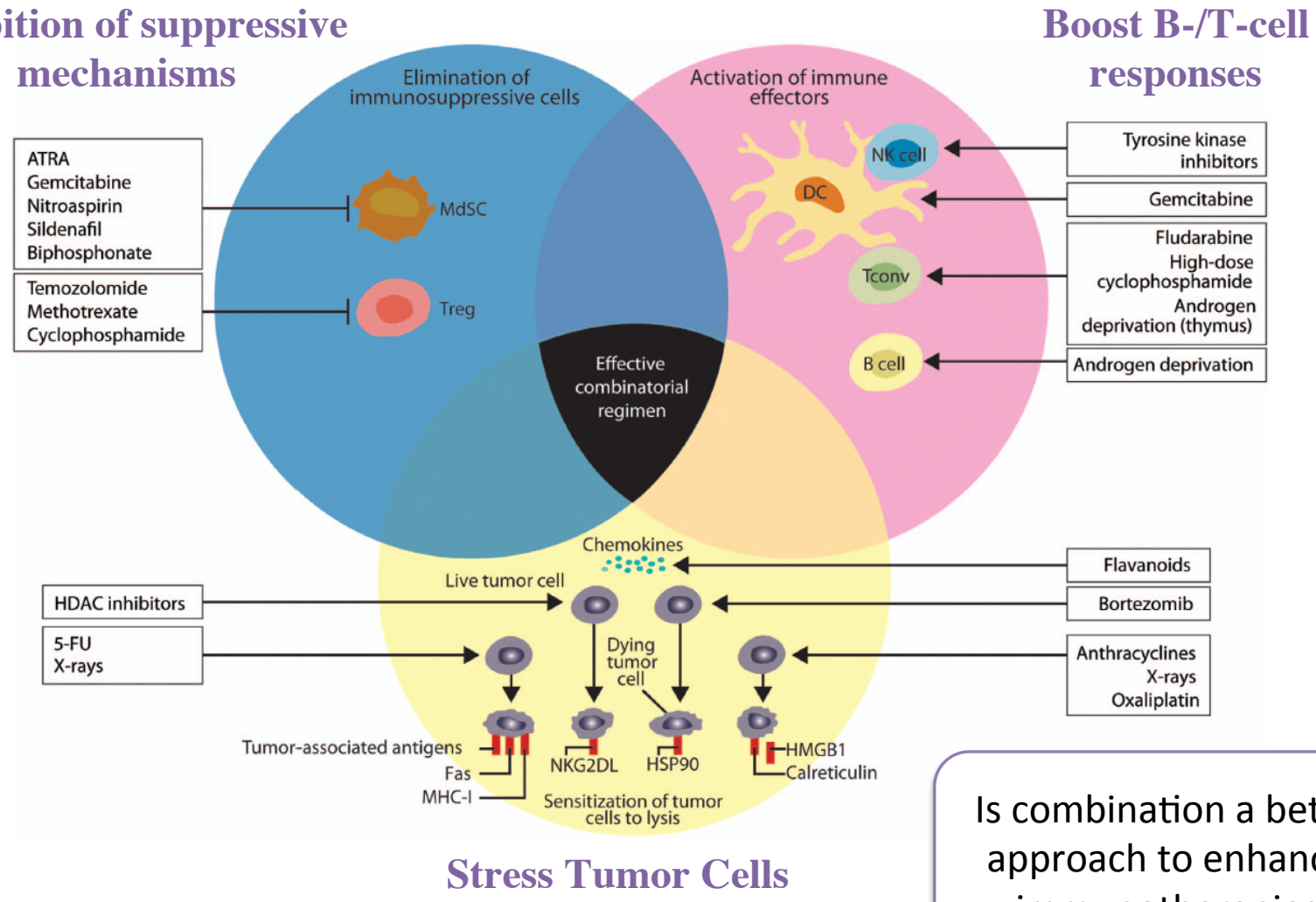
Community Practice

- Determine best local therapy (26%)
- Immunotherapy (21%)
- SRT to mets (18%)
- Small molecule inhibitors (non-androgen) (15%)
- Better ADT (10%)
- Better imaging (10%)

Conclusions

- In these men where disease progression is highly likely, there is enthusiasm for aggressive disease control using local and systemic therapies
- Benefit of aggressive approaches is unclear
- With increased organizational structure to large community based practices comes opportunity for increased research and understanding

Combination Therapy Might Enhance Immunotherapy



Is combination a better approach to enhance immunotherapies?

Drake CG. Oncogene, 2013

Spectrum of Cancer Immunotherapies

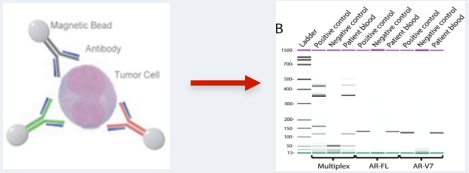
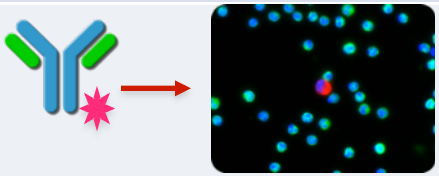
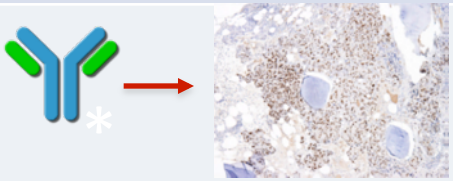
- Recombinant Vaccines
- Cytokines / Immunocytokines
- Immune Checkpoint Inhibitors

Immuno-Oncology Platform: Combination Therapies

- Chemotherapy
- Radiation Therapy
- Small Molecule Targeted Therapies
  - Hormonal Therapy

Three Different Approaches Assessing Truncated AR

- Truncated AR have been linked to lack of response when treated with abiraterone or enzalutamide in the C-terminal loss of CRPC patients

	Circulating Tumor Cells		Bone Marrow Biopsies
	Johns Hopkins/AdnaGen	Memorial Sloan/Epic Sciences	MD Anderson
Assay Methodology			
AR and AR-V7 Detection	• Immunomagnetic isolation of CTCs - AR determination (AdnaTest ProstateCancerDetect kit (AdnaGen) • AR-V7 determination, proprietary qRT-PCR assay (Johns Hopkins)	• Immunofluorescence using N/C-terminal CTC Assay (IHC) to measure the existence of AR and C-terminal truncated AR splice variants	• IHC on formalin-fixed, paraffin-embedded sections of bone marrow specimens utilizing anti-AR N-terminal and anti-AR-V7 antibodies
Assay Selective for AR-V7	YES	IN PROGRESS	YES
Pt/Physician Experience	Blood Draw	Blood Draw	Biopsy

Preferred Approaches

Hopkins Study: Current Oral Therapies Lack Activity in AR-V7+ Disease (cont'd)

- Only 1 AR-V7 positive patient showed any PSA reduction
- AR-V7 prevalence increased post additional treatments

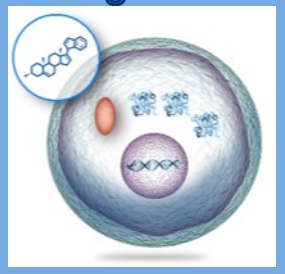
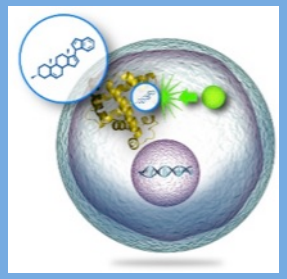
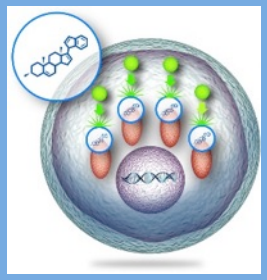
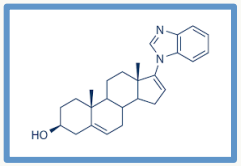
Treatment	Baseline AR-V7+	Response						
		AR-V7 status	PSA50	*P* value	rPFS	*P* value	OS (95% CI)	*P* value
Abiraterone (N=31)	19% (6/31)	+	0% (0/6)	0.004	2.3 mos	<0.001	11.1 mos (8.5–NR)	<0.001
		–	68% (17/25)		>6.3 mos		NR (>18 mos)	
Enzalutamide (N=31)	39% (12/31)	+	0% (0/12)	0.004	2.1 mos	<0.001	7.4 mos (3.9–NR)	<0.001
		–	53% (10/19)		6.1 mos		16.0 mos (14.2–NR)	

CI, confidence interval; rPFS, radiographic progression-free survival.

Antonarakis E et al. AR-V7 and resistance to abiraterone and enzalutamide in prostate cancer. *New Engl J Med*; 2014

Galeterone: Combination of 3 Distinct Mechanisms of Action

First in Class Potential

	Androgen Receptor (AR) Degrader	CYP17 Inhibitor	AR Antagonist
			
	Decreases AR Levels Differentiated Mechanism	Inhibits Androgen Synthesis Validated Mechanism	Blocks Androgen Binding Validated Mechanism
 GALETERONE	Active in CRPC patients and supporting data in patients with C-terminal Loss	No Steroids required	No Seizures to date Not a $GABA_A$ antagonist

Taplin et al. *Activity of Galeterone in Castrate-Resistant Prostate Cancer;* EORTC-NCI-AACR *Symposium Molecular Targets and Cancer Therapeutics*, 2014

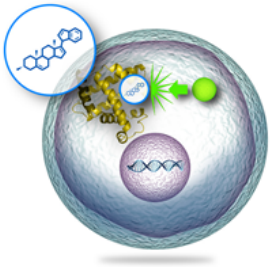
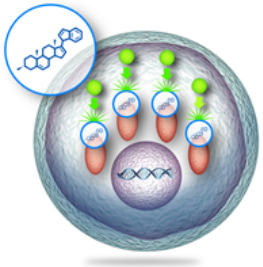
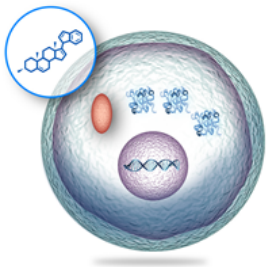
Kwegyir-Afful AK et al. *Oncotarget* [published online July 14, 2015].

Tokai Research Reports (TK-001, TK-002).

Bruno RD et al. *Steroids*. 2011;76(12):1268-1279.

Purushottamachar P et al. *J Med Chem*. 2013;56(12):4880-4898.

Galeterone: Selective, Multi-targeted, Small Molecule for Treatment of CRPC

	CYP17 Lyase Inhibitor	AR Antagonist	AR Degrader
	 Inhibits androgen synthesis	 Blocks androgen binding	 Decreases AR levels
Abiraterone	✓		
Enzalutamide		✓	
Galeterone	✓	✓	✓
	• No mandatory steroids • Fasting not required • Preclinical activity in mutation T878A	• Not a $GABA_A$ antagonist • No seizures • Preclinical activity in mutation F876L	• Active in C-terminal loss AR splice variants

ARMOR3-SV: First Precision Medicine Prostate Cancer Pivotal Trial

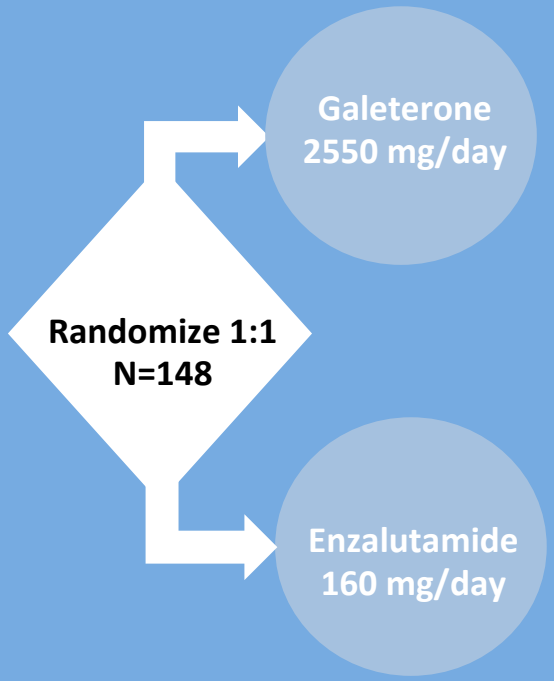
Unique trial design finalized in consultation with FDA and EMA

Key Inclusion:

- Progressive metastatic (M1) disease on androgen deprivation therapy based on PCWG2
- Detectable AR-V7 from CTCs
- ECOG 0 or 1

Key Exclusion:

- Prior treatment with second generation antiandrogens (eg, abiraterone, enzalutamide)
- Prior treatment with chemotherapy for CRPC



Primary Endpoint:

- Radiographic progression free survival (rPFS)

Secondary Endpoints:

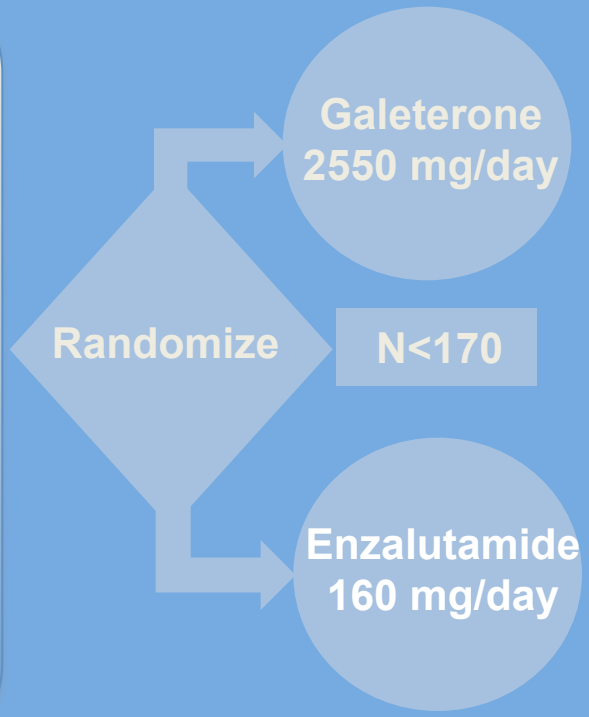
- Time to cytotoxic therapy
- OS

Taplin et al. *Androgen Receptor Modulation Optimized for Response: Splice Variant (ARMOR3-SV)*; ASCO 2015

ARMOR3-SV Trial Schematic: Open Label Phase 3 Pivotal Trial for Registration

Key Inclusion Criteria
- M1 disease
- Progressive disease on androgen deprivation therapy based on PCWG2
- Detectable AR-V7 from CTCs
- ECOG 0 or 1

Key Exclusion Criteria
- Prior treatment with second generation antiandrogens (abiraterone, enzalutamide)
- Prior treatment with chemotherapy for CRPC

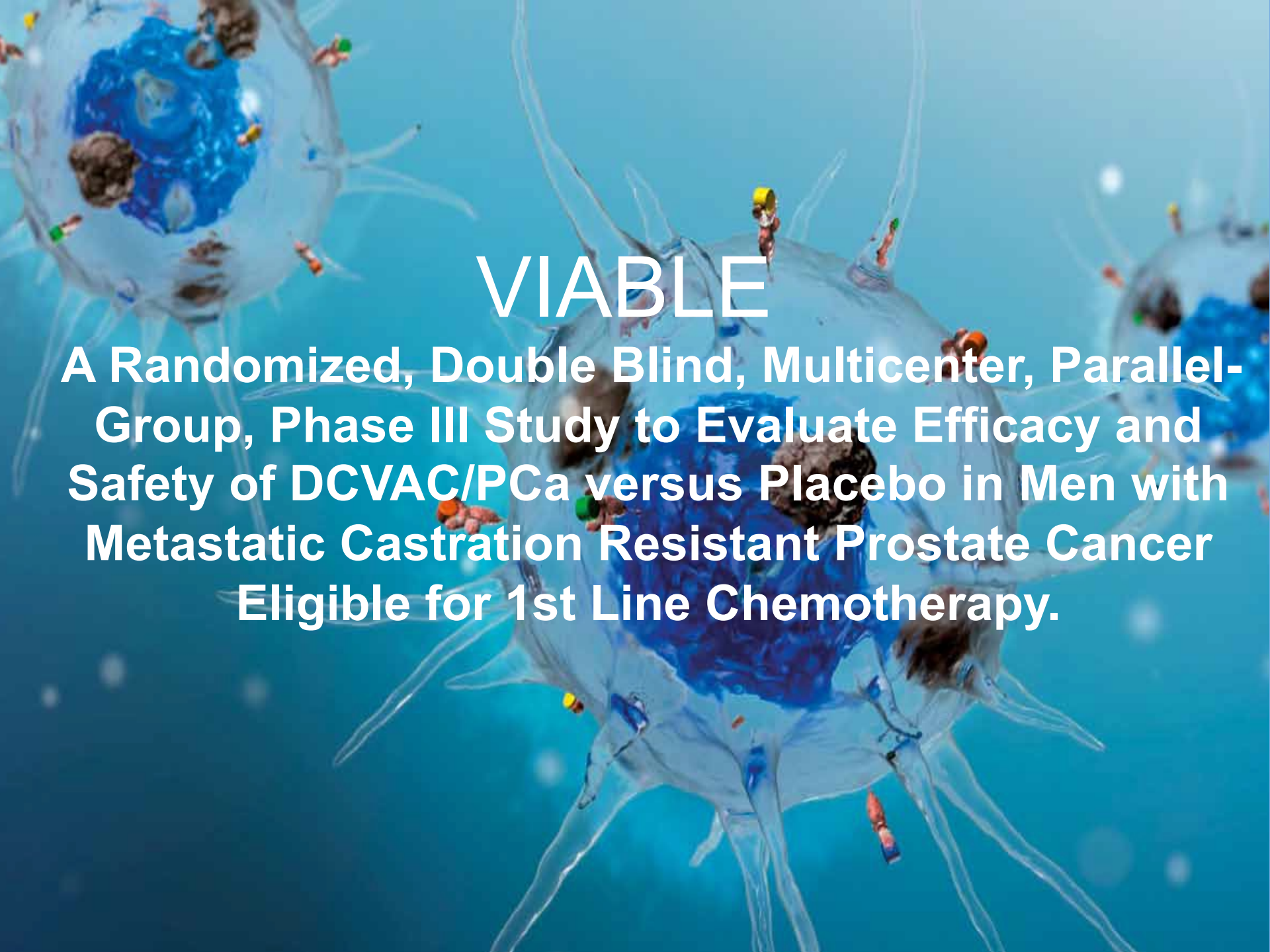


Primary Endpoint
- Radiographic progression free survival

Secondary Endpoints
- Overall Survival
- Skeletal related events
- Time to cytotoxic therapy

Other Endpoints
- Safety
- PSA50
- Time to progression and ECOG deterioration
- Best overall response by RECIST 1.1
- CTC characterization
- Pharmacokinetics
- Quality of life

- Independent Data Monitoring Committee planned



VIABLE

A Randomized, Double Blind, Multicenter, Parallel-Group, Phase III Study to Evaluate Efficacy and Safety of DCVAC/PCa versus Placebo in Men with Metastatic Castration Resistant Prostate Cancer Eligible for 1st Line Chemotherapy.

Introduction of DCVAC/PCa

SOTIO's lead product is Active Cellular Immunotherapy for patients with prostate cancer, entitled DCVAC/PCa

About the product

- SOTIO's prostate cancer immunotherapy treatment DCVAC/PCa is an autologous immunotherapy manufactured from the patient's own white blood cells collected during leukapheresis procedure (1) at the apheresis center.

Manufacturing

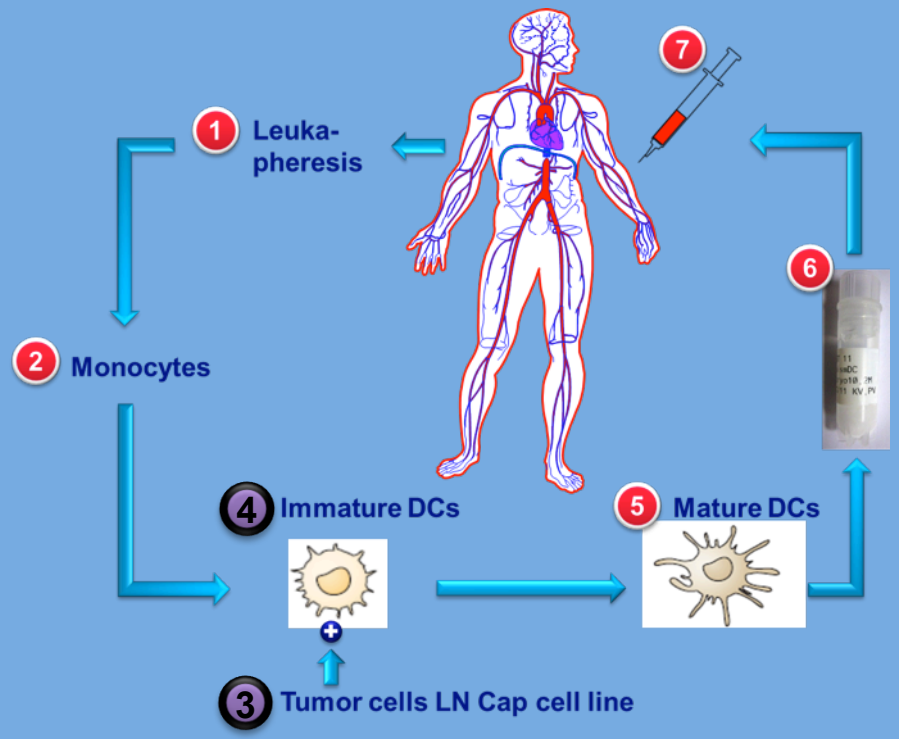
- After leukapheresis, the harvested cells are sent to SOTIO`s GMP certified laboratories where they are processed into the DCVAC immunotherapy.
- Monocytes separated from the entire leukapheresis product (2) are cultivated *ex vivo* into immature dendritic cells (3). These immature dendritic cells are then pulsed with tumor cells killed by immunogenic cell death (4) using proprietary high hydrostatic pressure (HHP) technology. Subsequently, pulsed dendritic cells are matured (5) and the resulting product is frozen, stored in liquid nitrogen and shipped to the treatment site (6).

Treatment

- The first dose of the treatment is available for administration to the patient approximately four weeks after leukapheresis. A single leukapheresis session yields multiple doses (up to 15 doses) of DCVAC, which is sufficient to treat the patient for up to a year or more.
- After being thawed and diluted, the ACI is administered subcutaneously at regular treatment intervals (every 2-6 weeks) depending on the trial design.
- Following subcutaneous administration, dendritic cells migrate into lymph nodes. There they meet and activate naïve T-lymphocytes which allows them to recognize tumor antigens.
- Naïve lymphocytes become effector lymphocytes which rapidly proliferate. Anti-tumor specific T cells migrate via bloodstream through the entire body, searching for and destroying tumor cells.

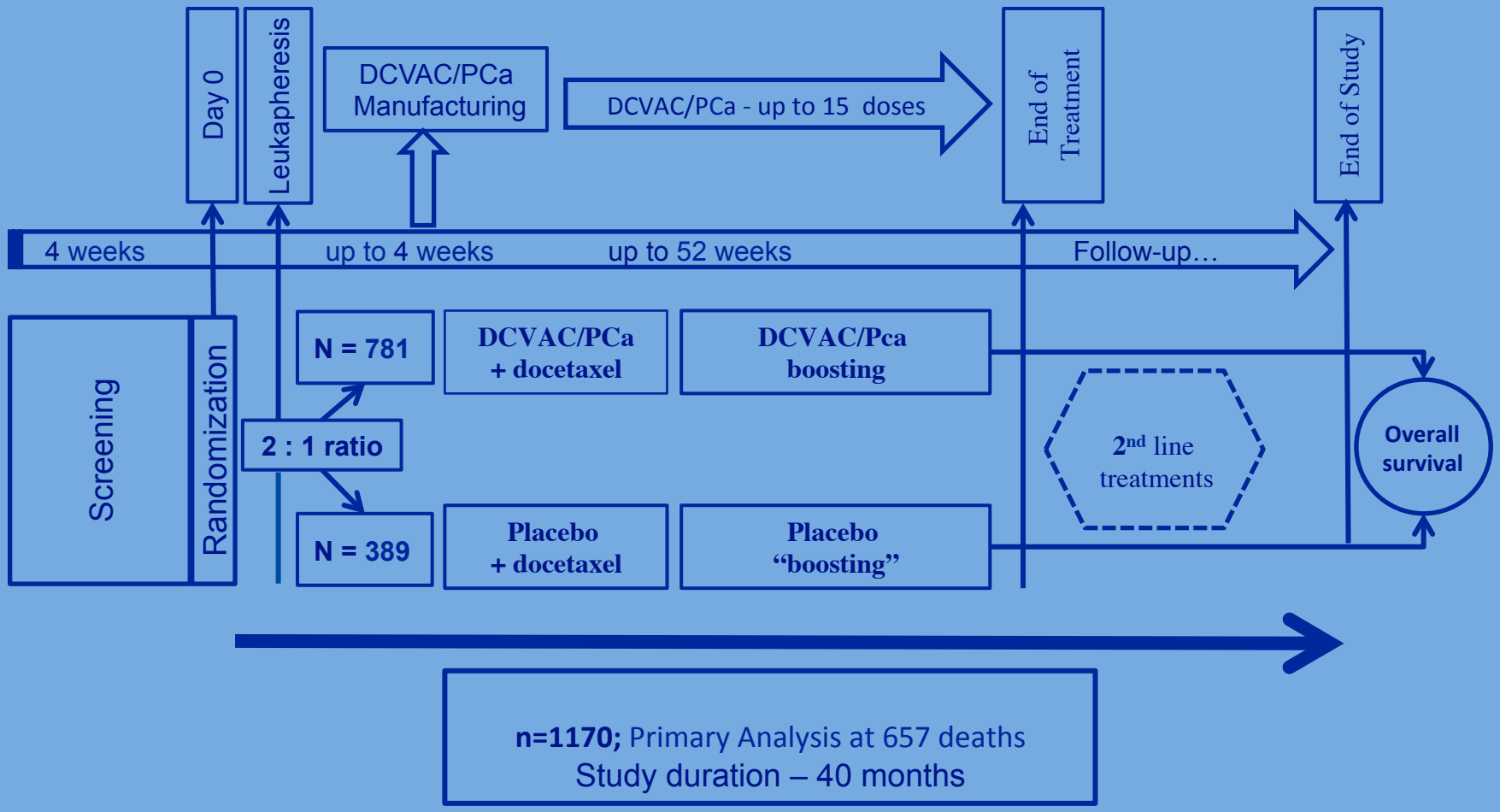
Clinical trials

- Since 2012 SOTIO has launched five Phase II clinical trials with DCVAC/PCa. SOTIO`s global Phase III VIABLE study, was launched in May 2014 and is recruiting ~ 1200 patients in over 20 countries in Europe and USA.



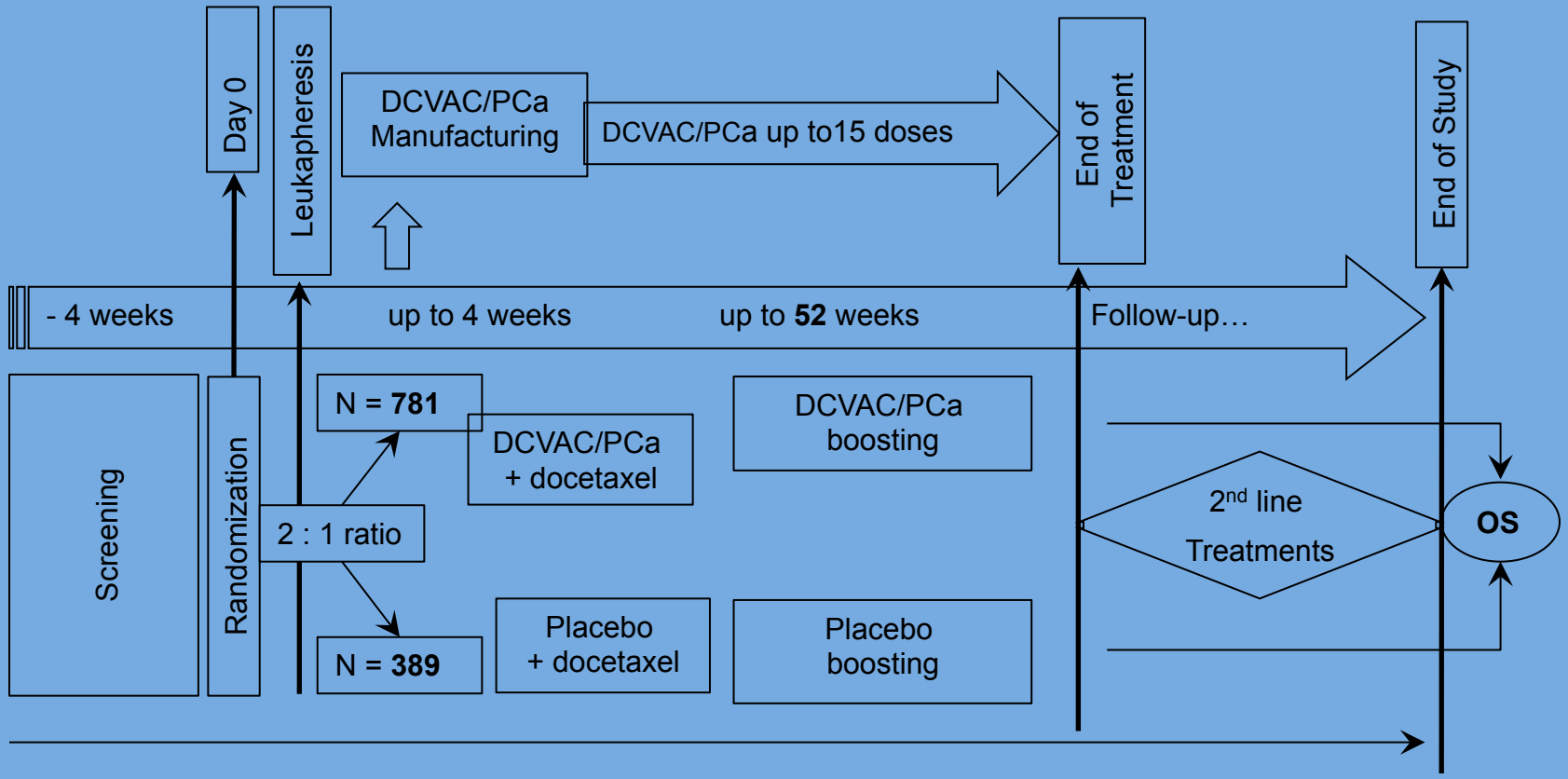
DCVAC/PCa – Prostate cancer

Design of the global Phase III trial



Source: SOTIO

Design of SP005



P = 80 %,
5% significance
HR: 0.792

Enrollment: 18 months
Study Duration: 40 months

n=1170
657 deaths (trial stops)

New Stratification factors:

- Region
- Prior therapy
- ECOG score

VIABLE: Study Phases

1)PRE-TREATMENT PERIOD

- Screening (up to 28 days)
- Randomization (IVRS or IWRS) 2:1 randomization ratio
- Leukapheresis: within 14 days from randomization

2)CONCURRENT TREATMENT PERIOD

- Standard of Care chemotherapy (docetaxel 75mg/m2+prednisone 5mg/m^2 bid, D1) q3w
- The chemotherapy starts within 7 days after Leukapheresis and the 1st dose of the vaccine starts in Cycle 2
- DCVAC/PCa q3w

3)MAINTENANCE BOOSTING PERIOD

– After completion of 1st line standard of care for any reason, patient will continue on DCVAC or placebo until completion, refusal, intolerance or introduction of second line.

4)FOLLOW-UP PERIOD

- After completing DCVAC doses, all patients will be followed until refusal, death or study closure upon reaching targeted number of events
- Second line anti-tumor therapies under investigator´s discretion (based on the list of allowed therapies per protocol)

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STAMPEDE: Patient eligibility

High-risk, newly diagnosed, non-metastatic, node-negative

OR

Newly diagnosed metastatic or node-positive disease

OR

Previously treated with radical surgery and/or RT, now relapsing

STAMPEDE (UK): Trial design

Patients eligible for STAMPEDE >6500 recruited

Newly diagnosed M1 patients[1]

Randomization

A	ADT
B	Arm A + ZA
C	Arm A + DOC
F	Arm A + ZA + DOC
G	Arm A + ABI
H	Arm A + RT to prostate

All other patients[2]

Randomization

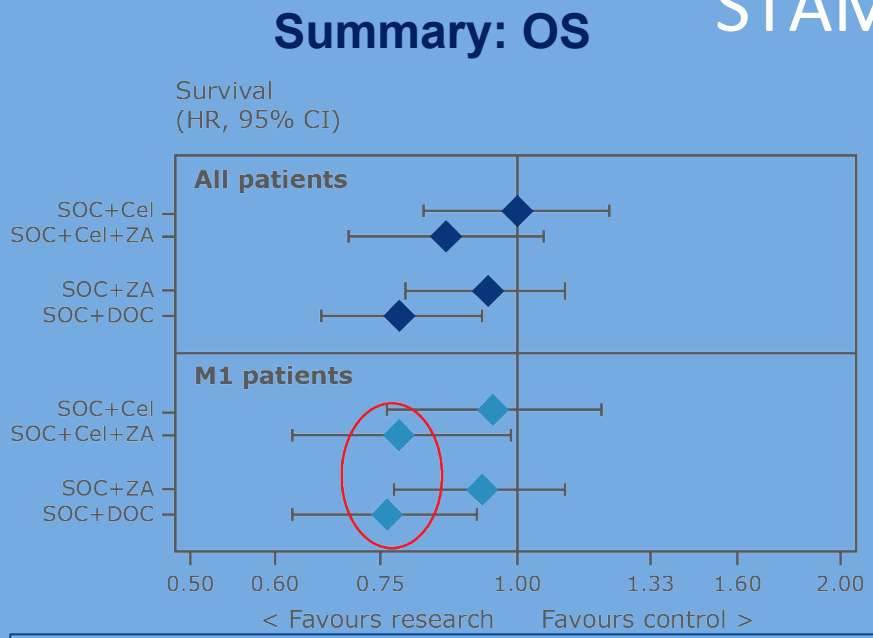
A	ADT (+RT if N0 M0)
B	Arm A + ZA
C	Arm A + DOC
F	Arm A + ZA + DOC
G	Arm A + ABI

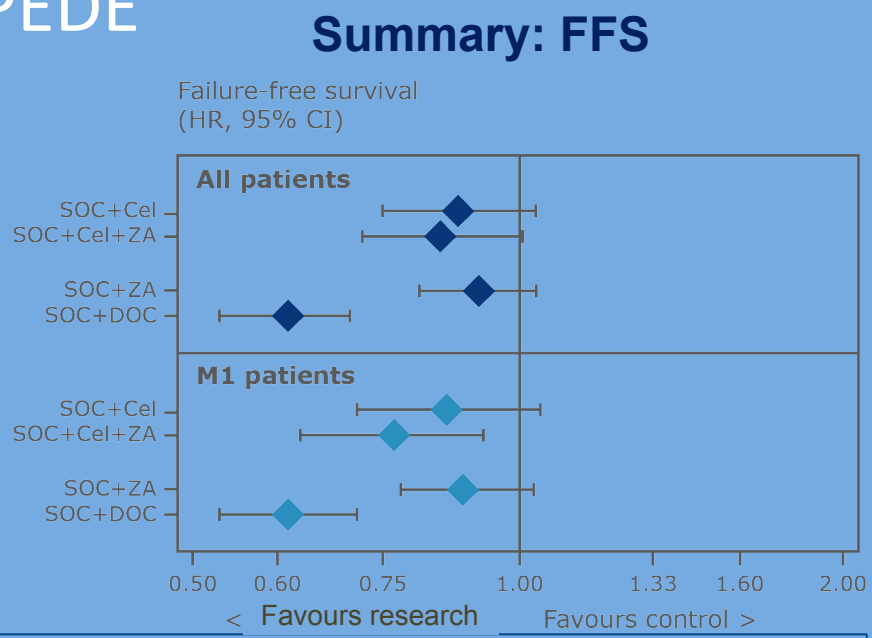
[1]Except patients with contraindication to RT
[2]Locally advanced (either node positive, or with 2 of 3 risk factors: stage T3/4, PSA ≥40ng/ml or Gleason sum score 8–10)

Parker CC et al. BJU Int 2013;111:697–9 (NCT00268476)

ADT: Androgen Deprivation Therapy; ZA: Zoledronic acid; DOC: docetaxel; RT: radiotherapy

Celecoxib with or without zoledronic acid for hormone-naïve prostate cancer: Results from STAMPEDE





Conclusions:

- Adding ZA does not improve FFS or OS
- Adding Cel does not improve FFS or OS
- Adding Cel+ZA does not improve FFS or OS in whole trial population
- However, adding Cel+ZA improves FFS and OS in M1
- Point estimate in M1 disease similar to adding docetaxel

James et al. J Clin Oncol 2016;34(suppl 2S): abstract 162

Newer Therapeutic Possibilities

- High risk localized(A)- BCR(B)-ASMC(C)-CRPC(D)

- (A)Androgen Annihilation/Intervention
- (B)Immunotherapy +/- ADT
- (C &D)Advanced Disease: Chemhormonal-Chemoimmunologic-Targeted/Selected Combinations

Thank You