
بسم الله الرحمن الرحیم

Immunotherapy for Prostate Cancer

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Introduction

- ✓ The last decade has seen a tremendous increase in the number of immunotherapy trials for various solid tumors
- ✓ Although immunotherapy appears to be promising for many solid tumors, progress made in prostate cancer is relatively moderate
- ✓ Development and progression of PCa is highly associated with chronic inflammation by prostatitis-induced cellular and genomic damage

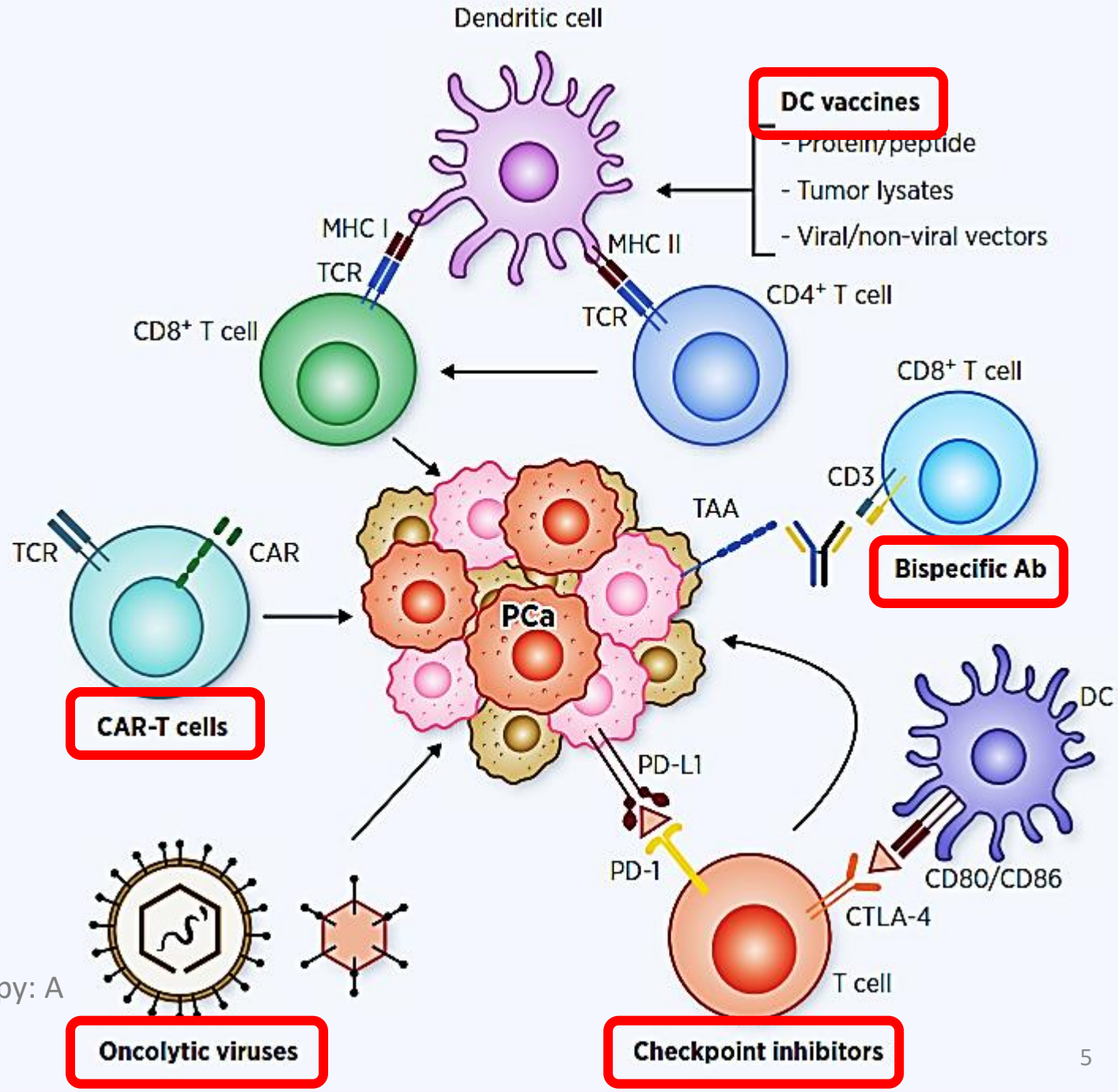
PCa: prostate cancer

Introduction

- ✓ Chronic inflammation in the prostate causes extracellular matrix remodeling and epithelial mesenchymal transition, which plays a key role in the disease development and progression

- ✓ PCa is known as a slow-growing inflammatory disease compared to other malignancies, which allows PCa to be an ideal candidate for immunotherapy

Major Immunotherapy Pathways Targeting PCa Cells



Cha H, Lee J.H, Ponnazhagan S. Revisiting Immunotherapy: A Focus on Prostate Cancer. 2020.
DOI: 10.1158/0008-5472.CAN-19-2948

Active Approaches in Cancer Immunotherapy

Sipuleucel-T (Provenge)

- An example of active immunotherapy targeting prostatic acid phosphatase (PAP), one of PSAs
- FDA-approved autologous active cellular therapy
- Designed to induce T cell-mediated immune response via ex vivo stimulation of patient's immature APCs in combination with recombinant PAP and costimulatory GM-CSF
- A completed phase III clinical trial of Immunotherapy for Prostate Adenocarcinoma Treatment (IMPACT: NCT00065442) indicated:
  - The Sipuleucel-T improved overall survival (OS) by 4.1 months and a 22% reduction of relative mortality risk in patients diagnosed with CRPC

Active Approaches in Cancer Immunotherapy

Poxvirus-Based Cancer Vaccine (PSA-TRICOM)

- **Composed of:**
  - Recombinant vaccinia virus
  - Recombinant fowlpox virus, with potential immunostimulatory and antineoplastic activities

- **Both viruses encoded modified forms of human PSA and the three co-stimulatory molecules**:
  - B7-1 (CD80)
  - ICAM-1
  - LFA-3

TRICOM : TRIad of Costimulatory Molecules

Passive Approaches in Cancer Immunotherapy

CAR-T Cell Therapy

- An example of well-established passive immunotherapy approach for targeting PCa:

1. Targeting PSMA

- CAR-T cells were generated against PSMA and embedding CD28 as a costimulator
- The CAR-T cell strategy targeting PSMA has shown improved anti-tumor effects *in vivo, compared to IgCD28TCR T cells, suggesting a translational* potential for targeting CRPC

CAR: Chimeric antigen receptor PSMA: prostate-specific membrane antigen
CRPC: castration-resistant prostate cancer

Passive Approaches in Cancer Immunotherapy

2. PSCA As an Ideal Immunotherapeutic Target

– A phase I/II clinical trial with PSCA is currently ongoing to evaluate safety and clinical activity of PSCA-Specific CAR-T cells:

to recognize PSCA-expressing PCa cells, in patients with previously treated for PSCA (NCT0274429T cells were engineered 8)

PSCA: Prostate stem cell antigen

Passive Approaches in Cancer Immunotherapy

Radiolabeled Monoclonal Antibodies Targeting PSMA

- The PSMA strategy has advantage of effective local delivery of the agent because of its high specificity and internalization into PCa cells upon PSMA binding the agent
- Besides anti-PSMA monoclonal antibody conjugates being tested as promising immunotherpeutic agent in PCa, they serve as a useful tool for CRPC diagnosis and imaging by identifying metastatic sites

Checkpoint Blockade Therapy

To Improve Effector T Cell Function

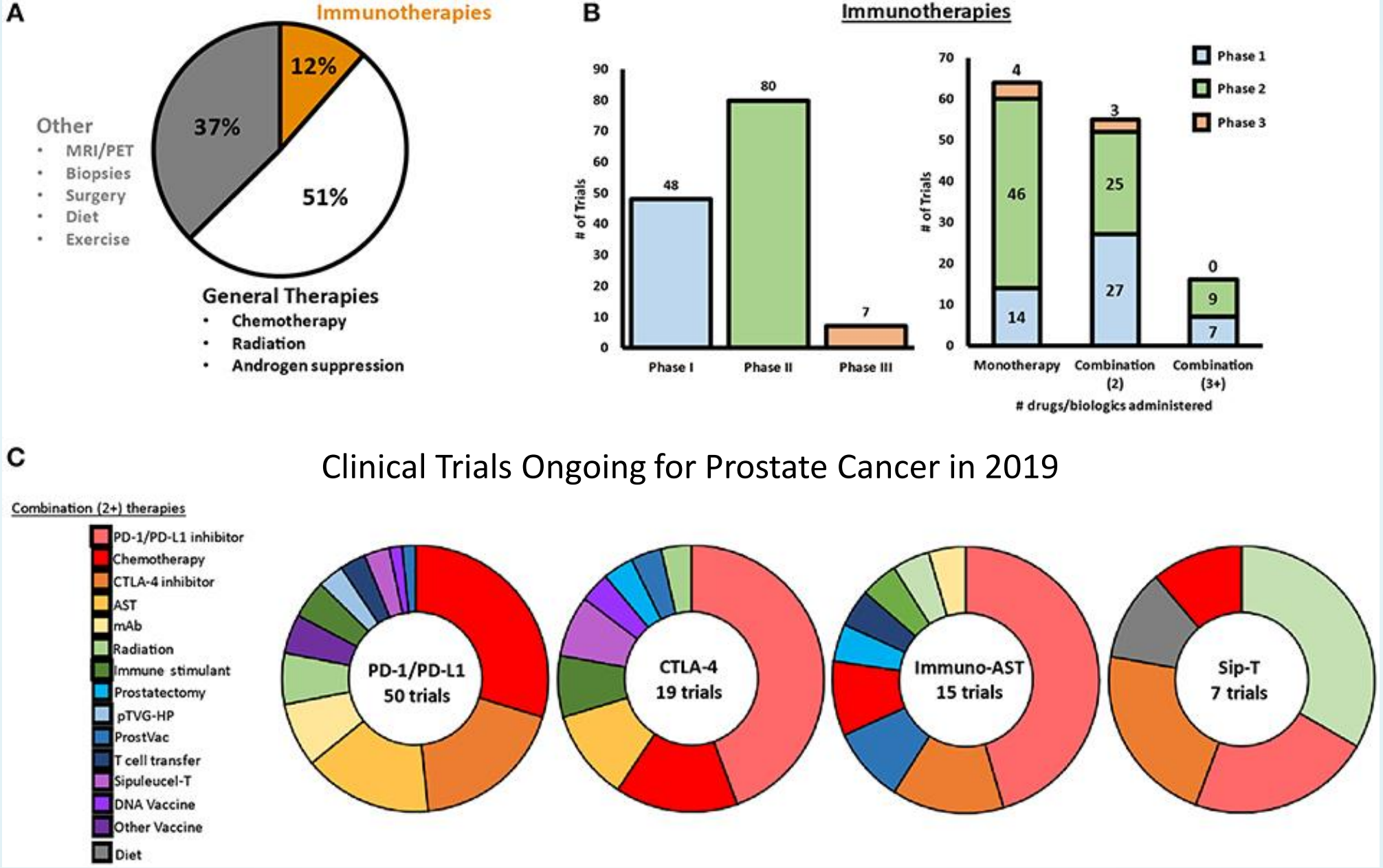
Therapy Targeting PD-1 & PD-L1

- The anti-PD-1 antibody **pembrolizumab** have received FDA approval for the treatment of advanced microsatellite instability-high (MSI-H) or DNA mismatch repair-deficient (dMMR) solid tumors
- KEYNOTE-199 findings suggest that pembrolizumab might be more effective in patients with metastatic CRPC whose tumors have DNA damage repair pathway aberrations than in molecularly unselected patients
- Inhibition with both PD-L1 and PD-L2 is more effective immunotherapeutic strategy in exerting T cell priming than targeting PDL1 alone

Checkpoint Blockade Therapy

CTLA-4 As a Potential Immune Checkpoint Inhibitor

- Ipilimumab (Yervoy) is an immune checkpoint inhibitor that blocks CTLA-4
- Recently Cancer Discovery 2019 reported that the combination of the **lipilimumab** and **nivolumab** in mCRPC patients who developed resistance to androgen receptor (AR)-targeted therapies resulted in only 25% of objective response rate



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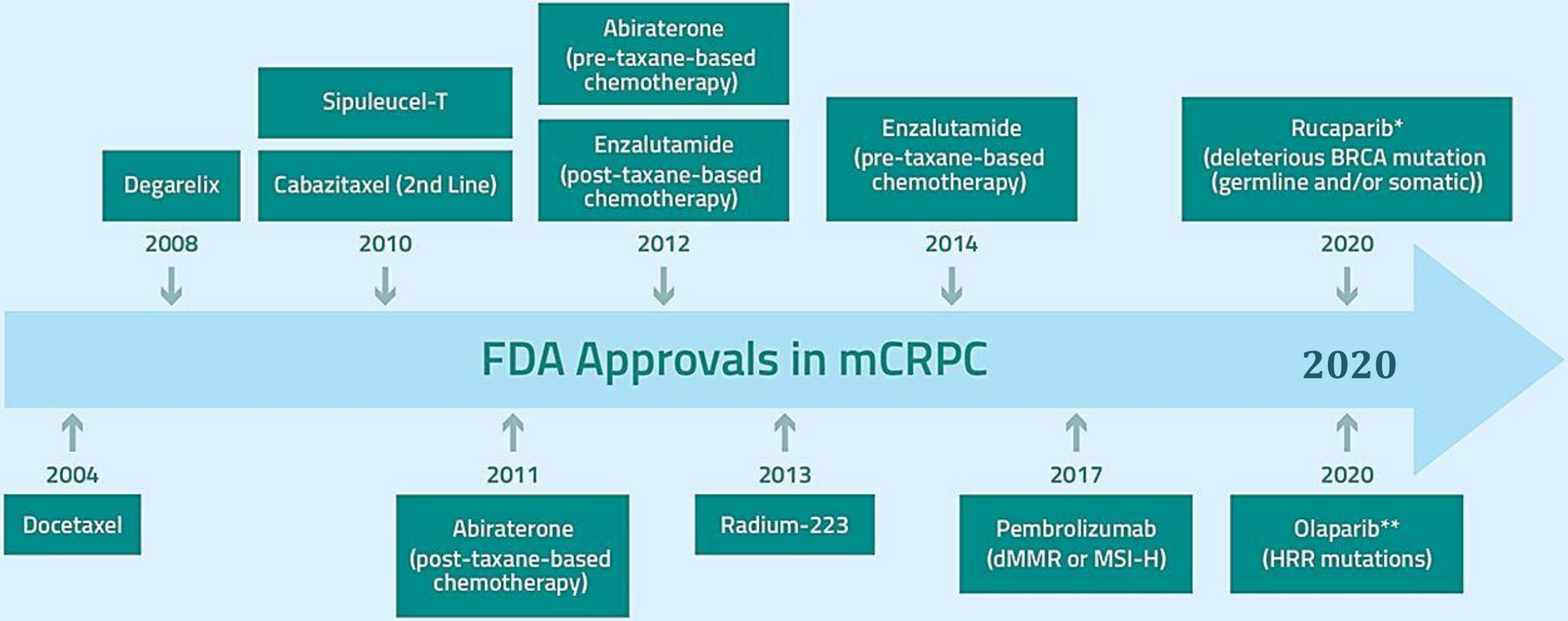


*Progressed following androgen-axis targeted treatment and taxane-based chemotherapy

**Progressed following treatment with enzalutamide or abiraterone

Targeted Therapy

Rucaparib & Olaparib

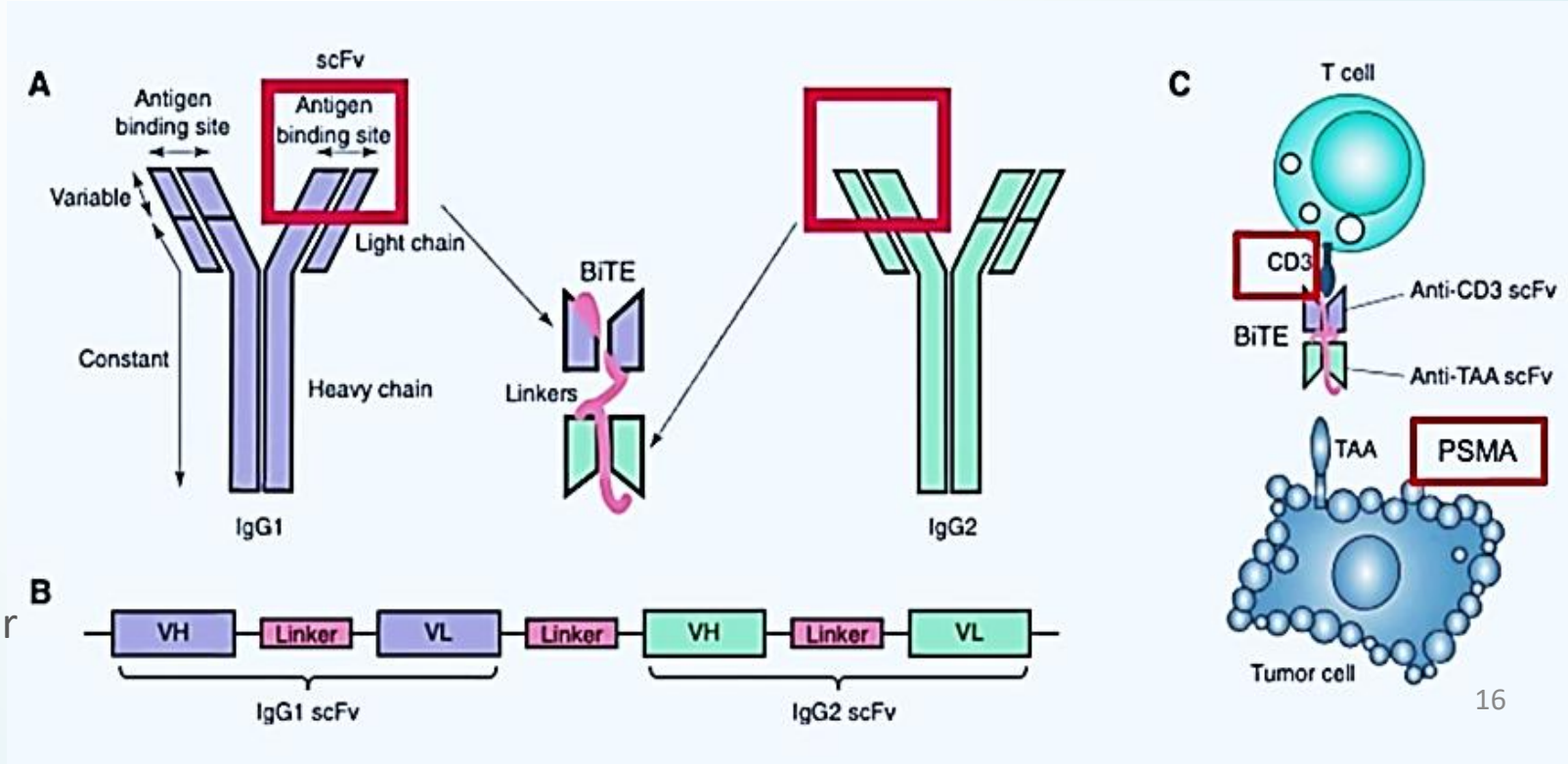
- The potent, oral PARP inhibitor (through trapping)
- For patients with advanced prostate cancer who have mutated *BRCA1/BRCA2* genes
- New treatment for BRCA-mutated metastatic prostate cancer

PARP: poly(ADP-ribose)polymerase

Bispecific Antibody Conjugates

- Conjugated to tumor antigens expressed on PCa cells and CD3 molecule on T cells
- Have emerged recently as a promising new approach to treat hormone-refractory disease

PSMA-targeted Bispecific T-cell Engager (BiTE®)



Immunotherapy Targeting Cancer Stem Cells

- Cancer stem cells:

  subpopulations of heterogeneous cancer cells with selfrenewing capability for continuous tumorigenesis

- Common cell surface markers to identify cancer stem cells in solid tumors:

  CD133 CD44 CD24 EpCaM

- Subpopulations of PCa cells with stem cell-like properties are known to coexpress cell surface markers, CD44, a2ß1 integrin, CD133, CD49f, and CD176

- Has recently been attempted in preclinical models of PCa with CAR T-cells engineered against EpCaM expressing cancer stem cell population and results indicate promising outcome with murine PCa model

EpCaM: epithelial cell adhesion molecule

Existing Limitations of Current Immunotherapy in Prostate Cancer

- ✓ Various clinical trials by active immunotherapy, passive immunotherapy, adoptive T cell therapy and immune checkpoint inhibitors in combination with chemotherapy thus far have only shown **modest clinical outcomes in mCRPC** when compared to other genitourinary cancers.
- ✓ **Unpredictable efficacy and toxicity** of the therapy often become hindrances of successful immunotherapy in many cancers
- ✓ Prostate cancer grows slowly compared to other types of malignancies, which allows it to be an **ideal candidate** where immunotherapy can be effective

Continue…

- ✓ A recent NGS analysis has identified that the PCa patients who have undergone a course of ipilimumab therapy have increased expression of **v-domain Ig suppressor of T cell activation (VISTA),** a newly discovered immune checkpoint on macrophages, suggesting a new potential immunotherapy target in prostate TME

NGS: Nextgeneration Genome Sequencing

References

- Cha H, Lee J.H, Ponnazhagan S. Revisiting Immunotherapy: A Focus on Prostate Cancer. Cancer Research, 2020 – AACR. DOI: 10.1158/0008-5472.CAN-19-2948.
- Boettcher A, Usman A, Morgans A, VanderWeele D, Sosman J, Wu J. Past, Current, and Future of Immunotherapies for Prostate Cancer. Frontiers in Oncology. 2019;9. doi: 10.3389/fonc.2019.00884.
- Fay E, Graf J. Immunotherapy in Prostate Cancer. Cancers. 2020;12(1752). doi:10.3390/cancers12071752.
- Fizazi K, Drake CG, Beer TM, et al. Final analysis of the ipilimumab versus placebo following radiotherapy phase III trial in post docetaxel metastatic castration-resistant prostate cancer identifies an excess of long-term survivors. Eur Urol. 2020;15:S0302-2838(20)30604-7.


Thanks for Your Attention