Novel Immunotherapies in Bladder Cancer

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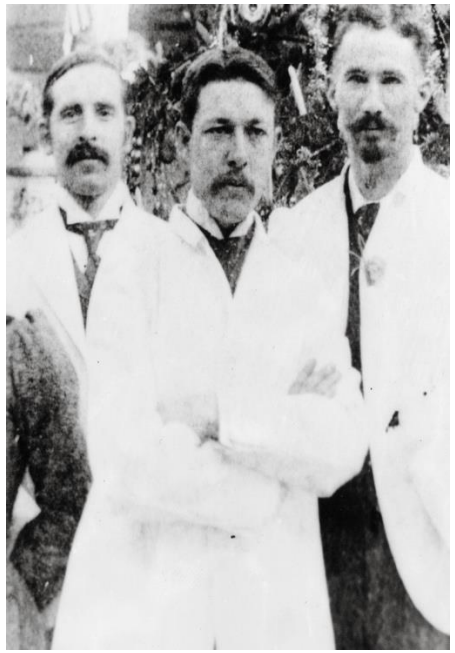
SCRI Sarah Cannon Research Institute

Objectives

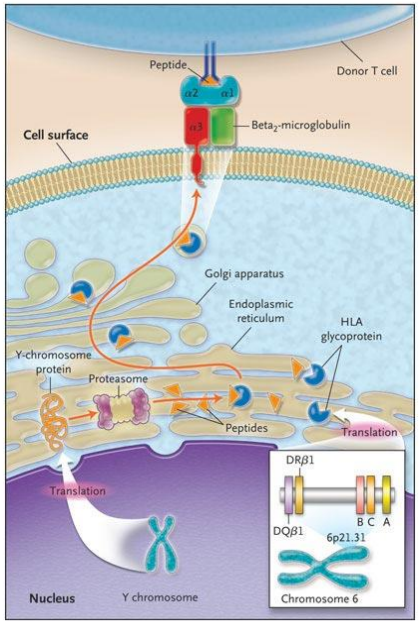
- Historical Perspective
- Scientific basis of systemic therapy
- Novel Trials/Therapies in BCG Naïve NMIBC

The History…

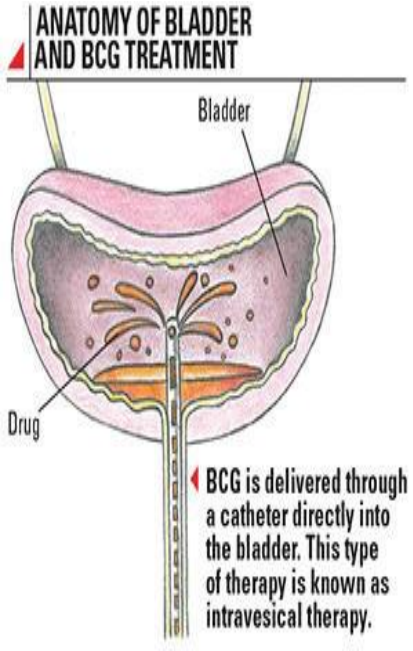
1893 | 1960s | 1980s | 2000s | Now



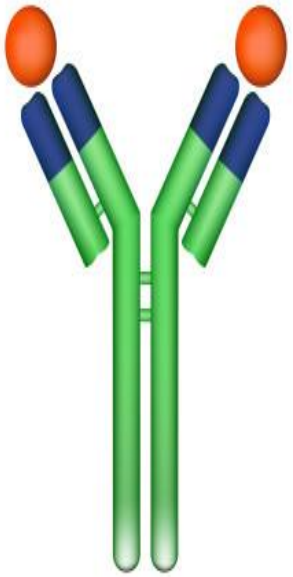
Coley's toxin



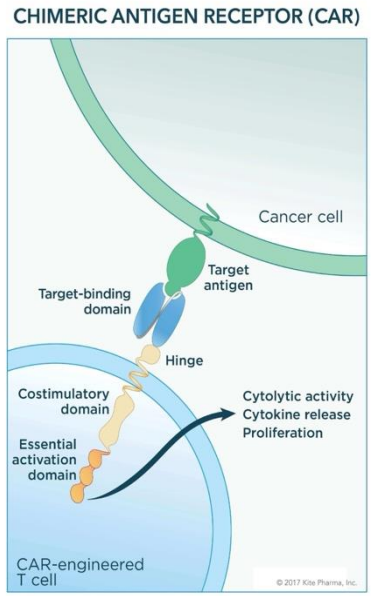
Graft-versus-Leukemia Effect



BCG in bladder cancer

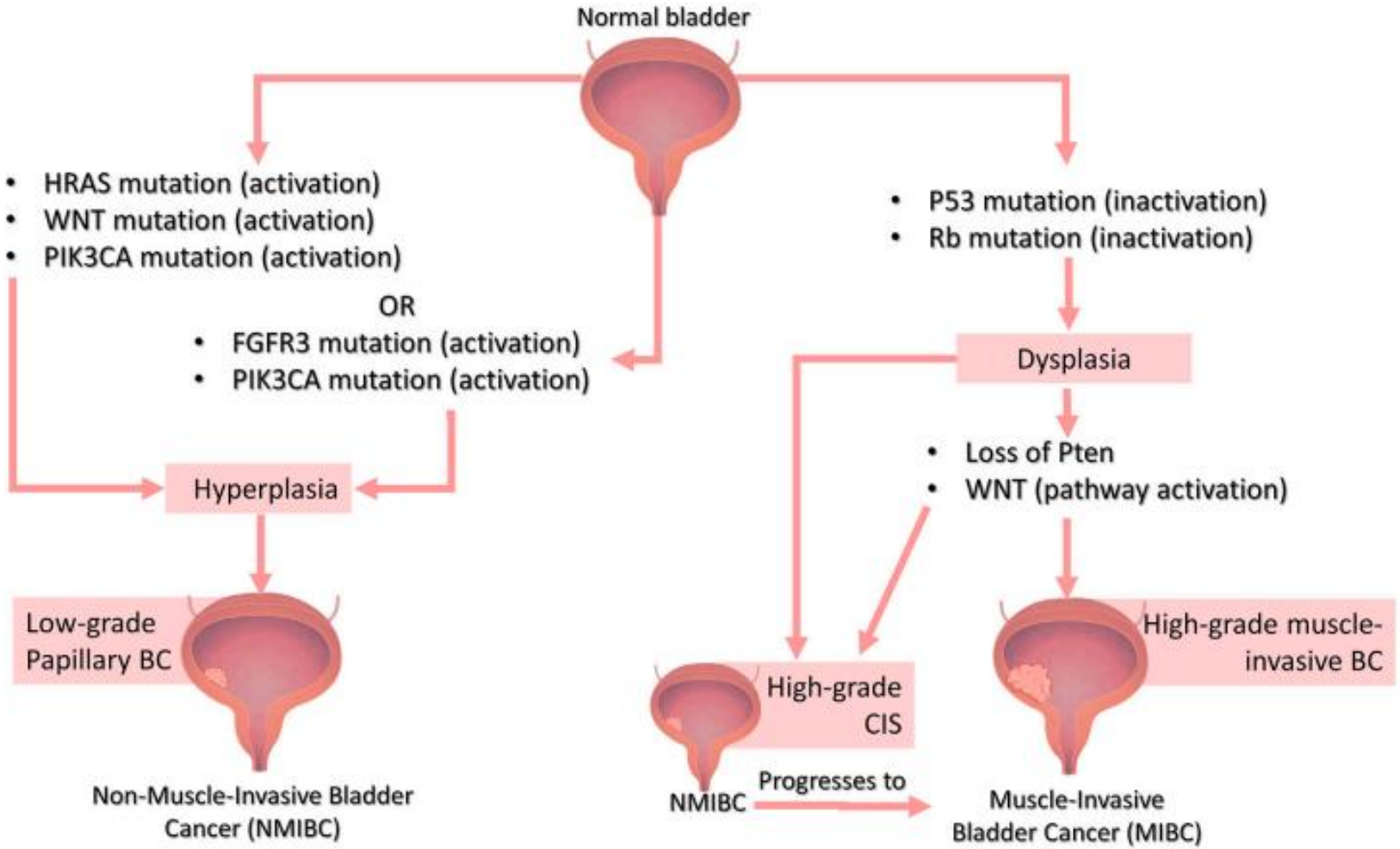


Monoclonal antibodies and Checkpoint Inhibitors



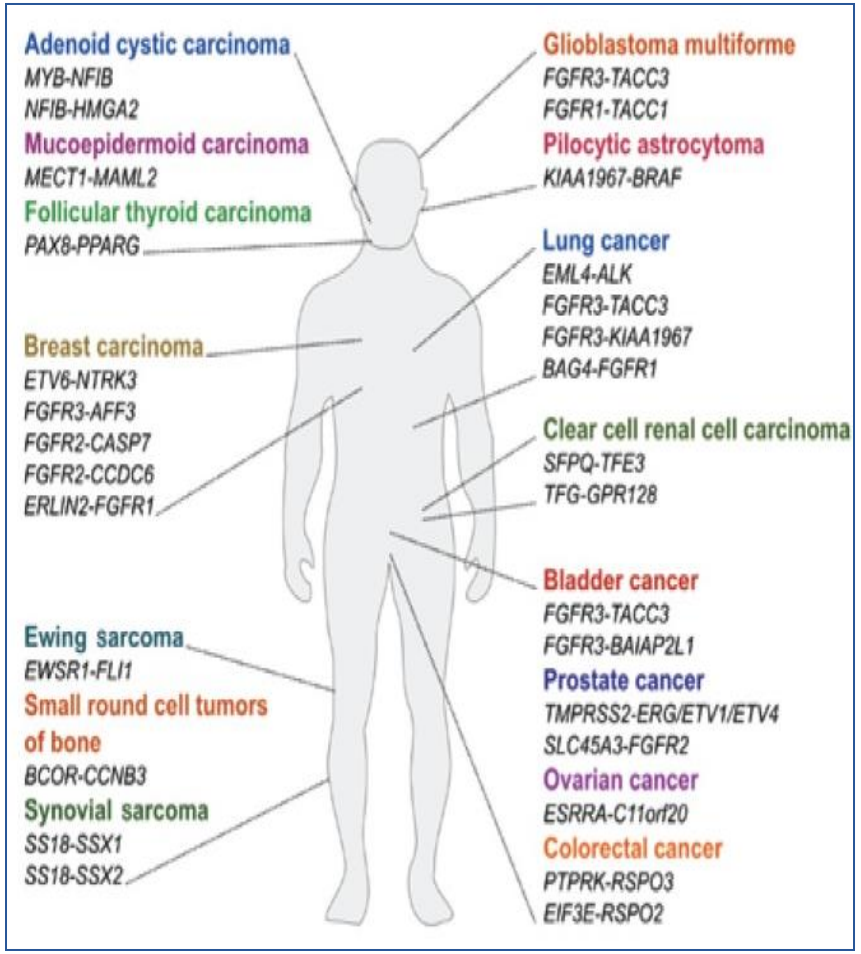
ADC Combinations and Cellular Therapies

The Genetic Basis of Bladder Cancer



Segatto, N. et al., Frontiers in Molecular Biosciences 2021.

FGFR Gene Alterations Present in Multiple Tumor Histologies



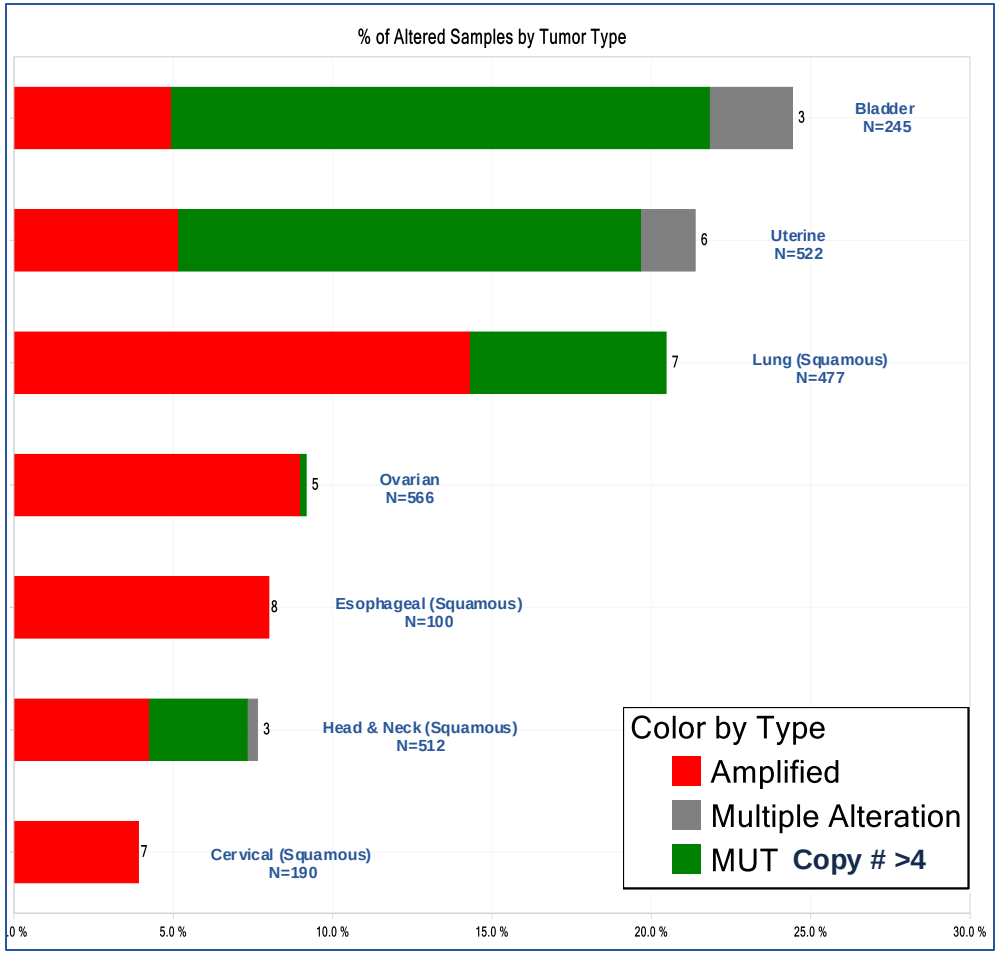
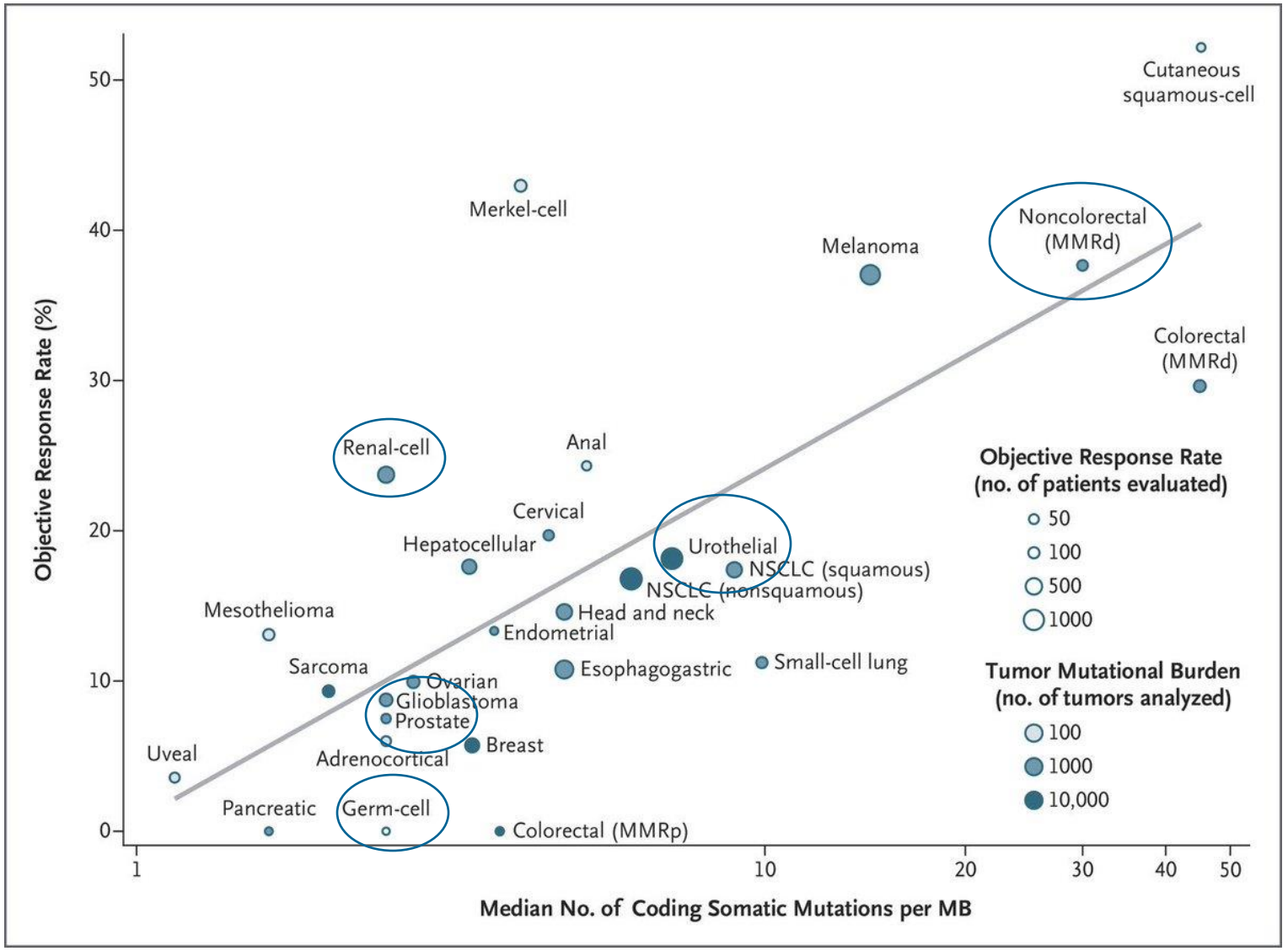


Figure at left, Parker BC and Wang W. *Chin J Cancer*. 2013;32(11):594-603.

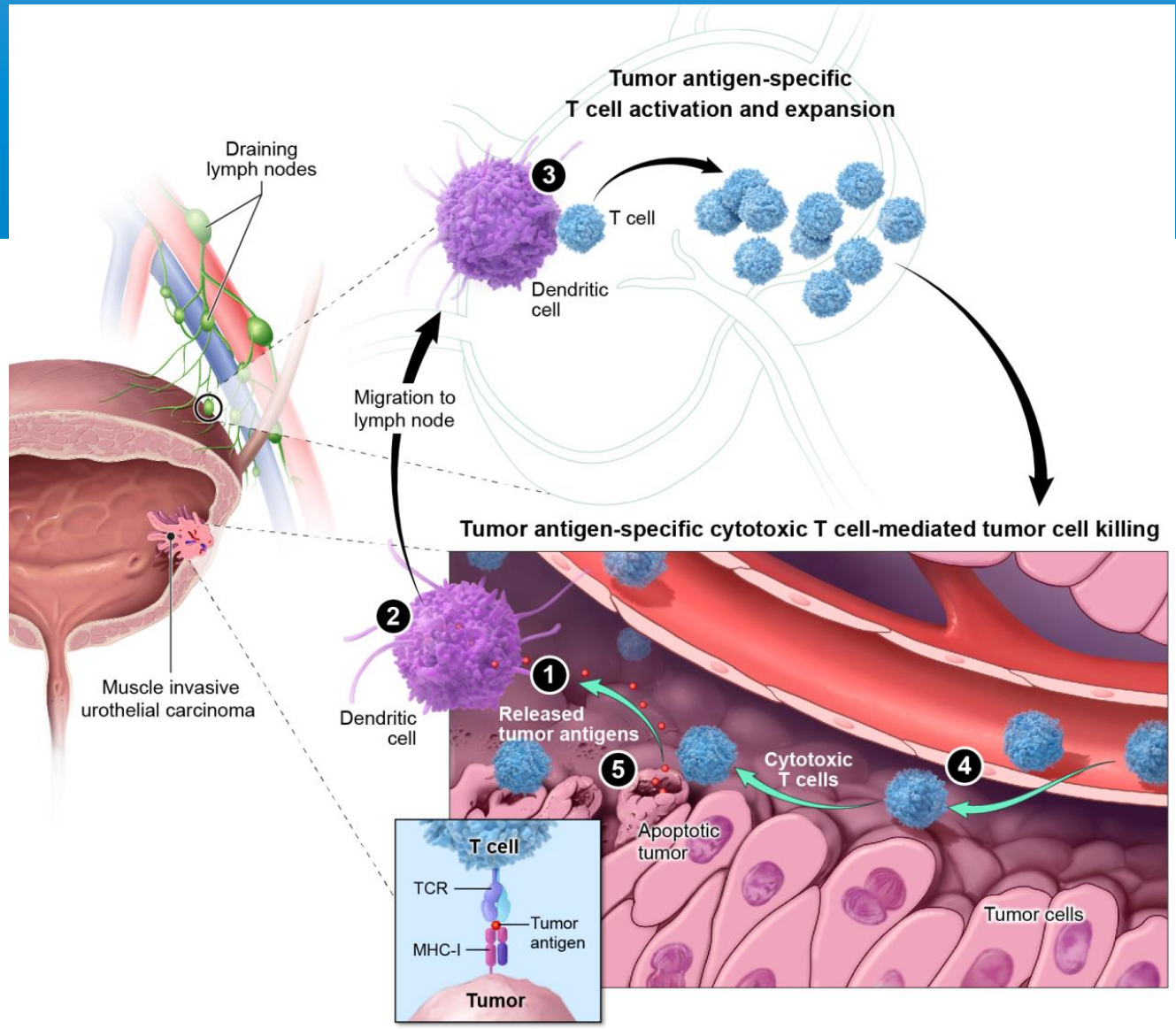
Tumor Mutational Burden and Response Rate to PD-1 Inhibition



Yarchoan et al. NEJM 2017

Urothelial carcinoma-specific antitumor T-cell immunity cycle

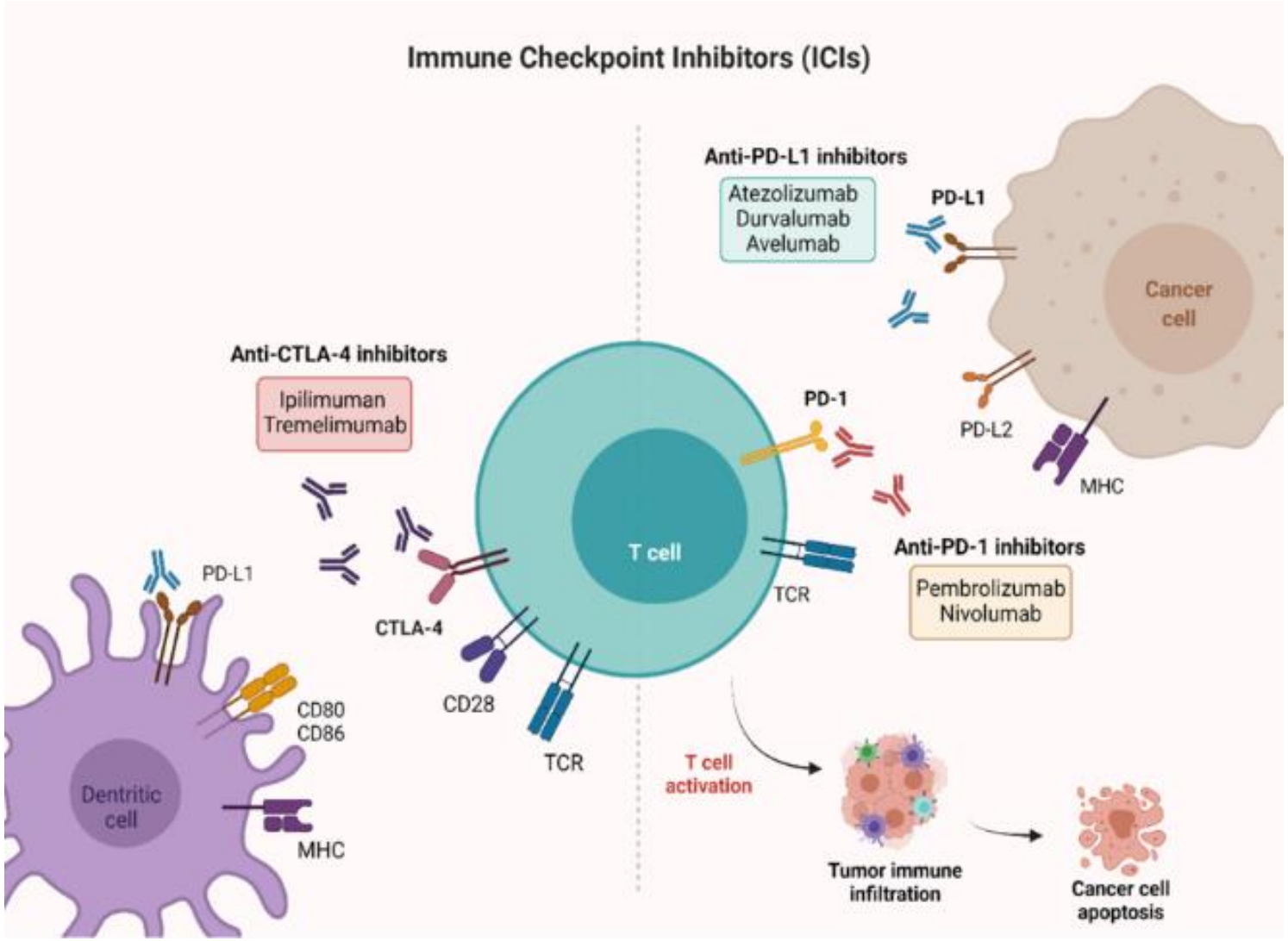
- Tumors maintain an immunosuppressive
- via **PD-L1/PD-1** binding
- Inhibiting:
- T-cell migration, proliferation and secretion of cytotoxic mediators



Kim JW, Tomita Y, Trepel J and Apolo AB Current Opinion in Oncology 2015

Mechanism of Action of Immune Checkpoint Inhibitors

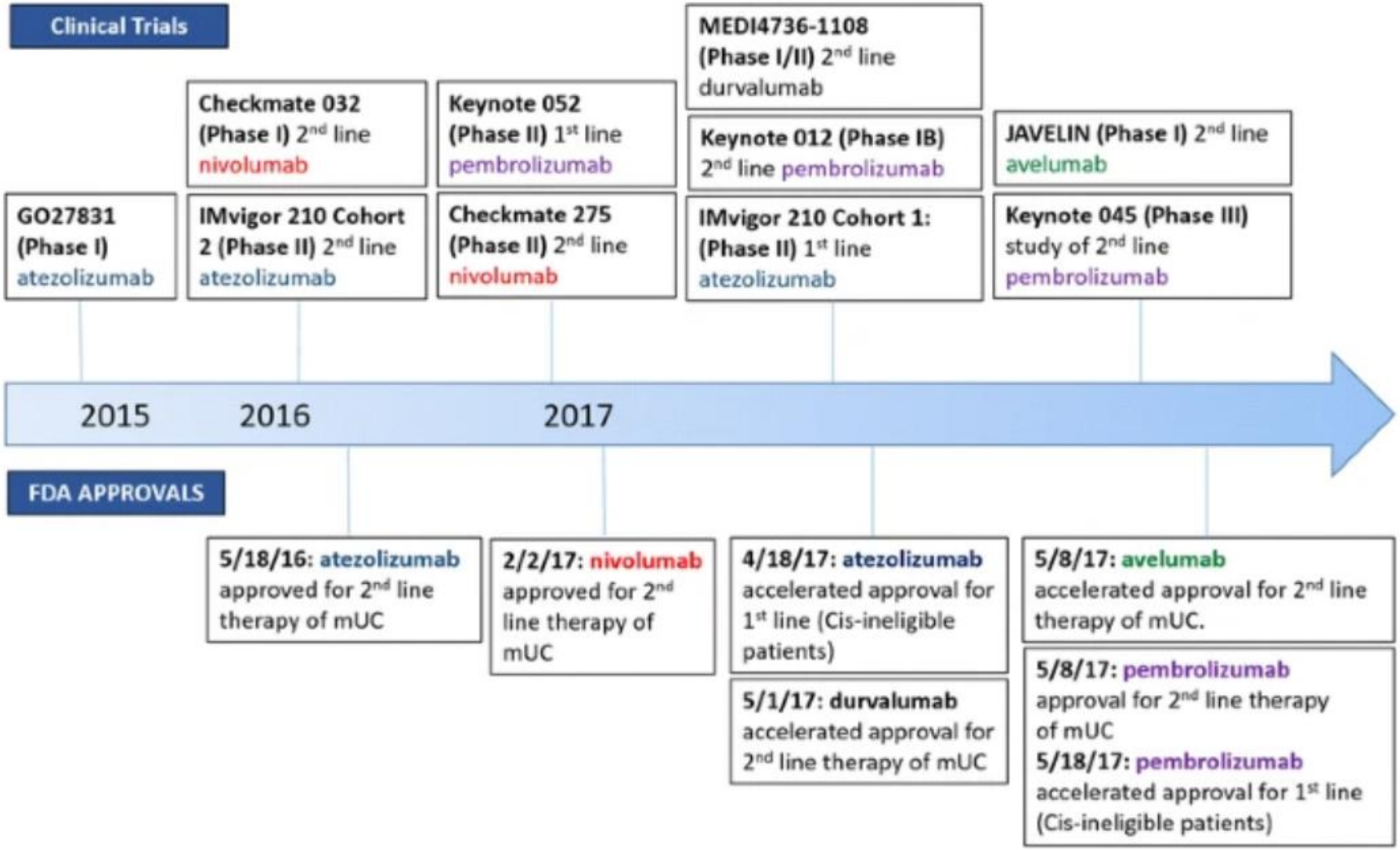
The immune checkpoint blockade ensures the activation of T cells and favors antitumor activity.



Roviello, G. et al. Cancers 2021.

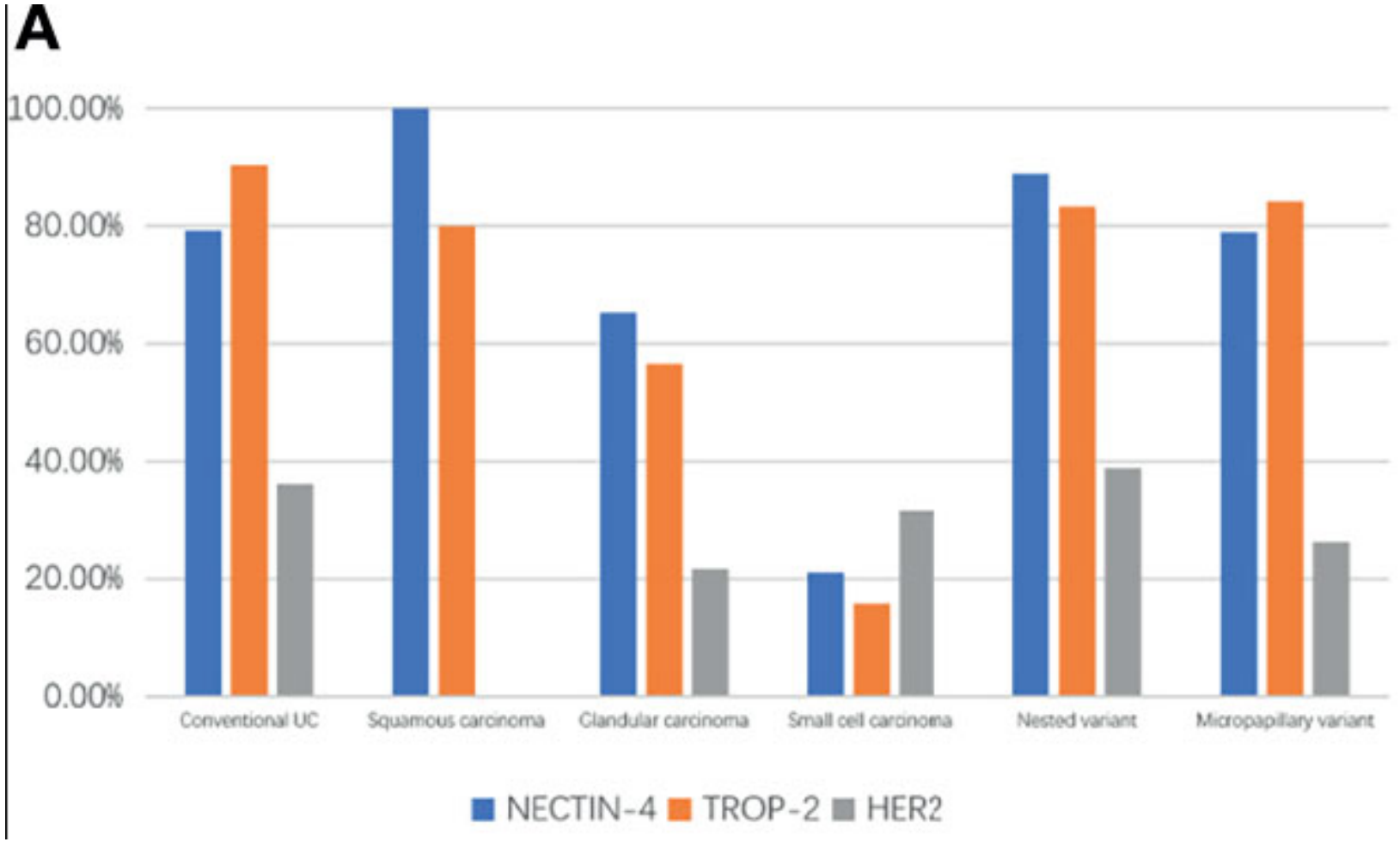
Metastatic Urothelial Carcinoma

Clinical Studies of PD-1/PD-L1 Inhibitors in UC



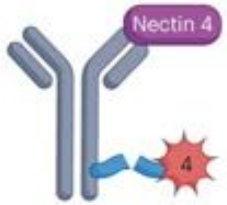
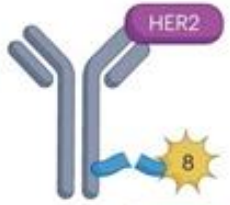
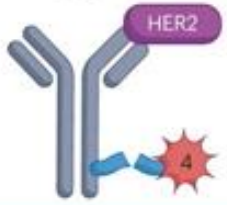
Aggen, D.H., et al. J for ImmunoTherapy of Cancer 2017.

“Established” Targets in Urothelial Carcinoma



Fan et al. Front Oncol 2022.

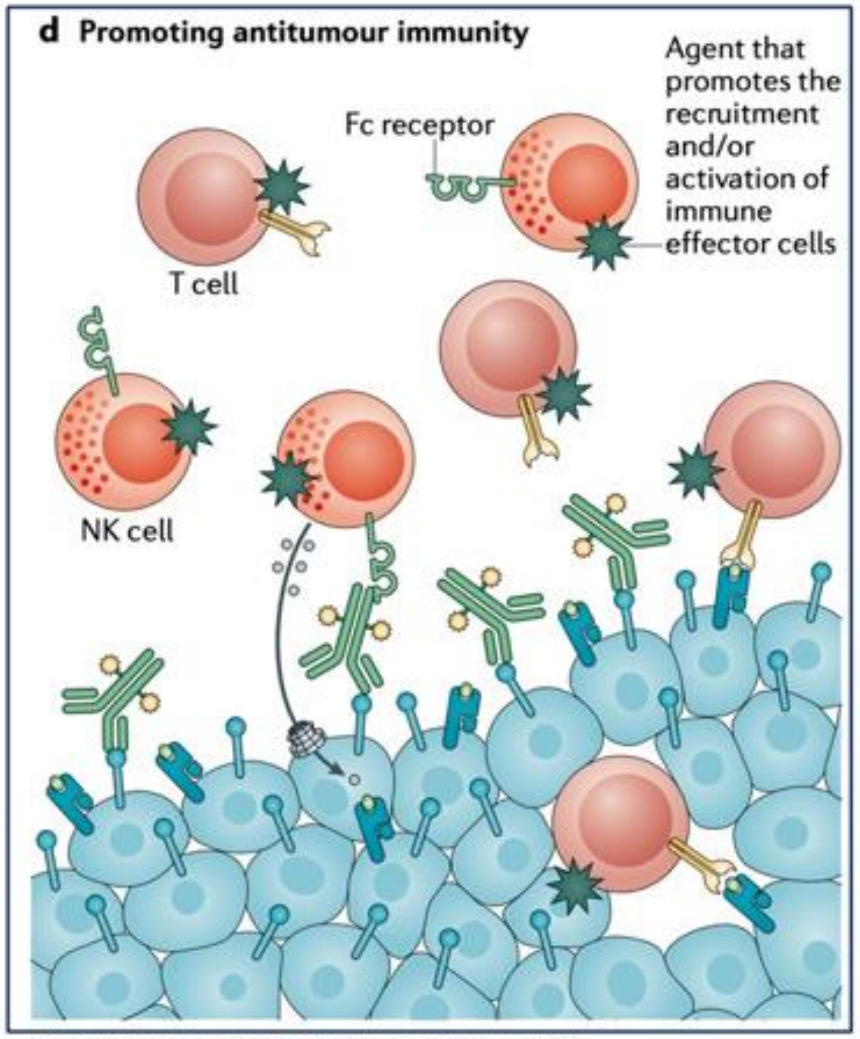
Key ADCs in Metastatic Urothelial Cancer

ADC	Biomarker	Antibody	Linker	Payload	Regulatory Approval
Enfortumab vedotin 	No selection required, >90%	Humanized IgG1, anti-Nectin 4	Protease cleavable linker	MMAE (microtubule inhibitor)	FDA approval - EV 2019, EV + Pembro 2023; also EMA, Health Canada
Sacituzumab govitecan 	No selection required, >90%	Humanized IgG1, anti-Trop2	pH-sensitive cleavable linker	SN38 (topoisomerase I inhibitor)	Withdrawn from FDA 2024
Trastuzumab deruxtecan 	HER2 3+, 15%	Humanized IgG1, anti-HER2	Tetrapeptide-based cleavable linker	Deruxtecan (topoisomerase I inhibitor)	FDA approval - tumor agnostic HER2 IHC 3+ (gastric ca scoring) 2024
Disitamab vedotin 	HER2 2-3+, 50%	Humanized IgG1, anti-HER2	Protease cleavable linker	MMAE (microtubule inhibitor)	FDA breakthrough designation 2020; approved in China for HER2 2+/3+ platinum refractory mUC

HER2, human epidermal growth factor receptor 2; IgG1, immunoglobulin G1; MMAE, monomethyl auristatin E; Trop2, trophoblast cell surface antigen 2

Rosenberg, J Clin Oncol. 2020; Loriot, Clin Cancer Res. 2024; Aggen, ASCO 2024; Nally Eur Urol Focus. 2024; Dumontet, Nat Rev Drug Discov. 2023; Grant, Bladder Cancer 2024; Scherrer, Front Oncol. 2022; Koshkin, 2023 GU ASCO

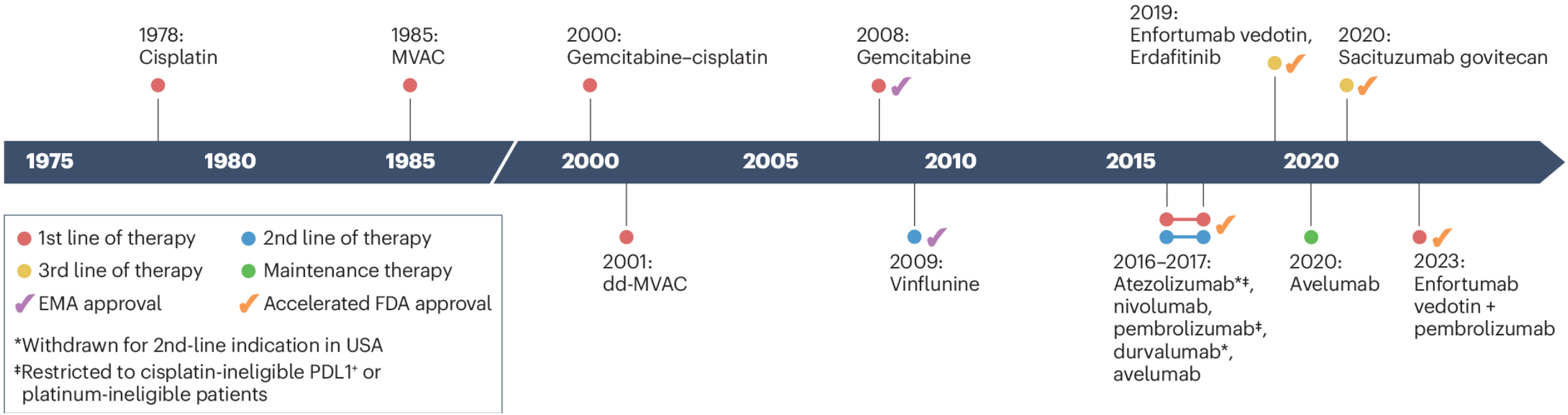
Rationale for Combining ADC with ICI



Drago, Nat Rev Clin Oncol. 2021, Nicolo, Cancer Treat Rev. 2022

- Pre-clinical evidence suggests ADCs have immunomodulatory activity.
  - Induce immunogenic cell death
  - Recruit T cells to the tumor microenvironment
  - Activate dendritic cells
- This provides a strong rationale for testing ADC combination strategies with immune checkpoint inhibitors.

The Evolving Treatment Landscape of Metastatic Urothelial Cancer



Roviello, G., et al. Nature Reviews Urology 2024.

What is the Future of Bladder Cancer Trials?

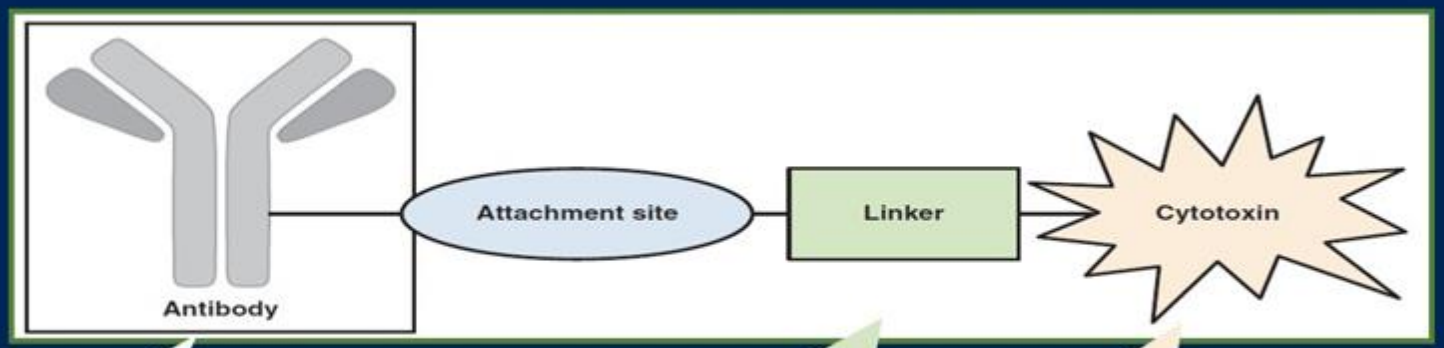
On the Horizon:

- Novel ADCs (TROP2, HER2, NECTIN4, etc)
- Novel Immunotherapy post Pembrolizumab
- ADCs moving earlier into the perioperative and NMIBC space
- Trials dedicated to Variant Bladder Histology
- Subcutaneous Administration IO

Further Away:

- Bispecifics and CART/NK cells
- Radioligands
- Trial collaboration incorporating real world “community” Bladder Cancer patients

Disitamab Vedotin (RC48): HER2 MMAE ADC



Antibody

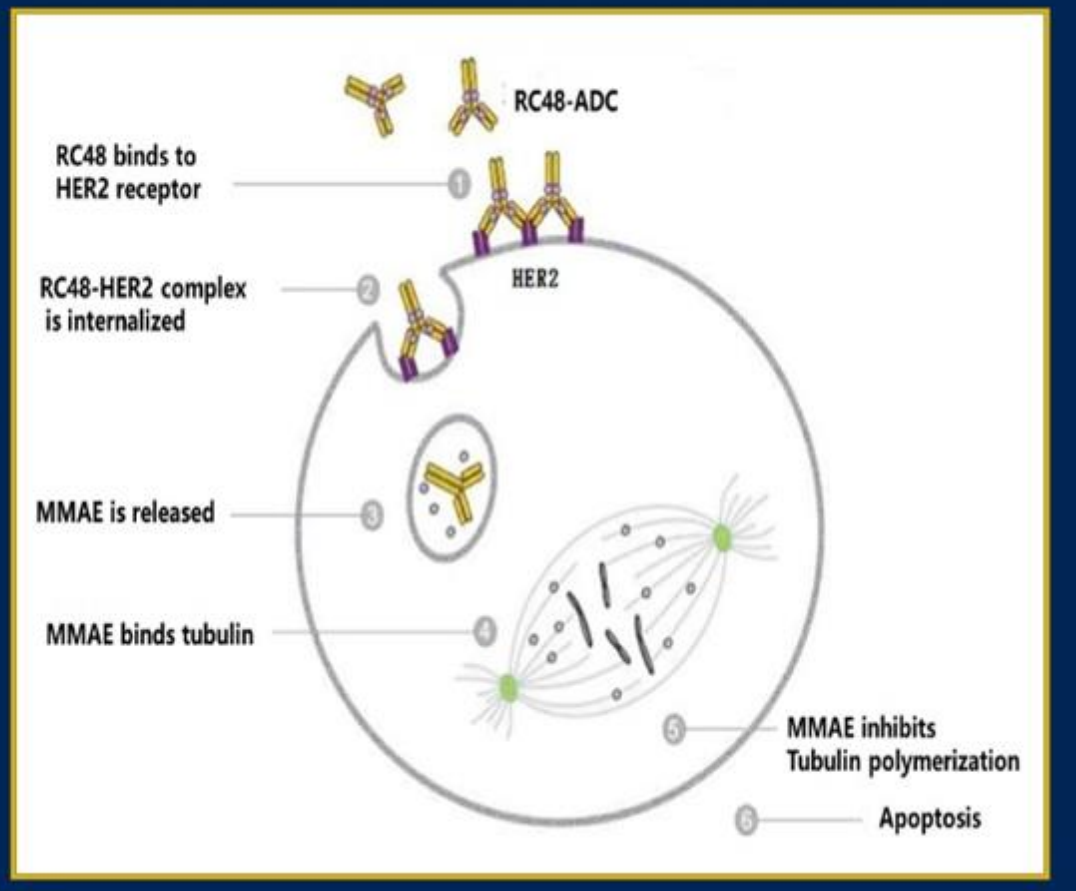
- Newly screened HER2 monoclonal antibody
- Different antigen recognition regions, and preferable affinity compared with trastuzumab

Linker

- Cleavable: A cathepsin cleavable valine–citrulline (VC) linker enables an easier release of payload post to the endocytosis
- Bystander Effect: Payload promotes potent cell killing upon initial release of the ADC and has the ability to kill surrounding tumor cells

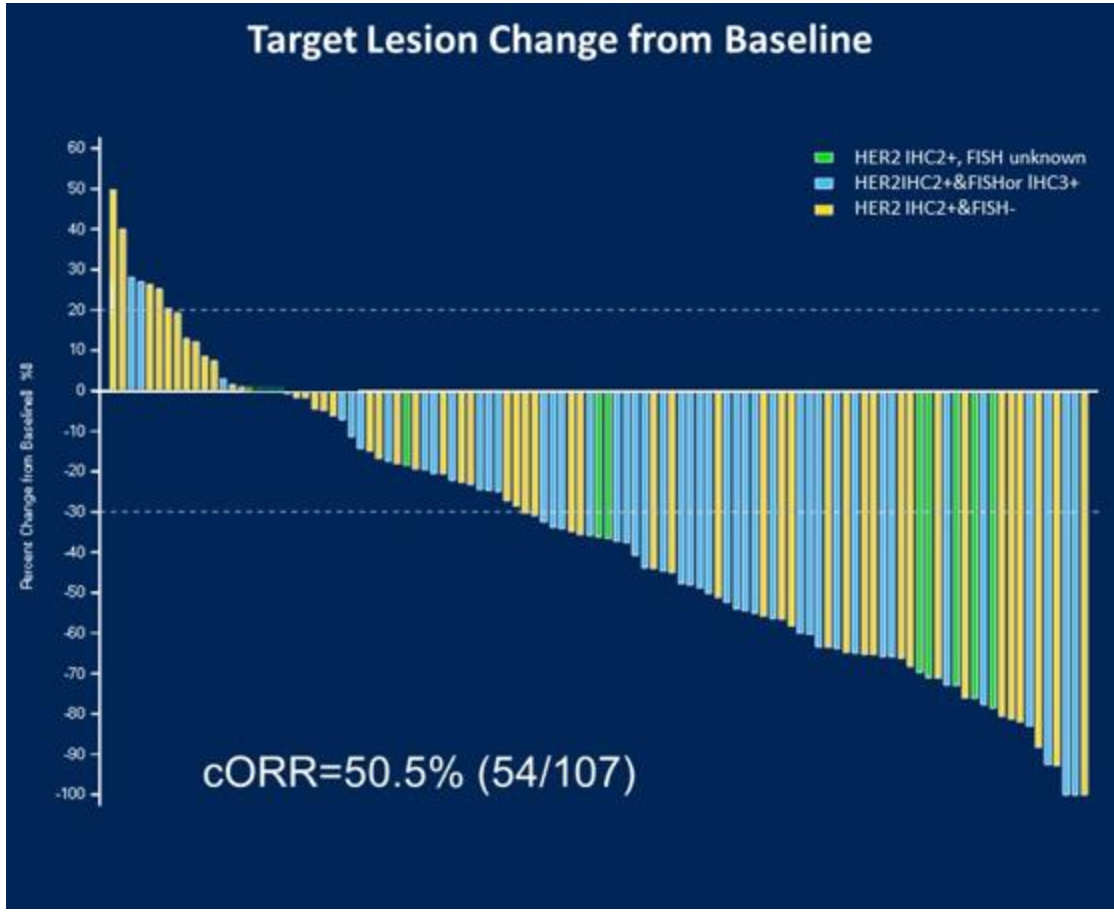
Payload

- MMAE: A potent antimitotic drug derived from peptides occurring in marine shell-less mollusc dolabella auricularia called dolastatins
- Inhibits cell division by blocking the polymerisation of tubulin



Sheng et al, ASCO 2022.

Disitamab Vedotin (RC48): HER2 MMAE ADC



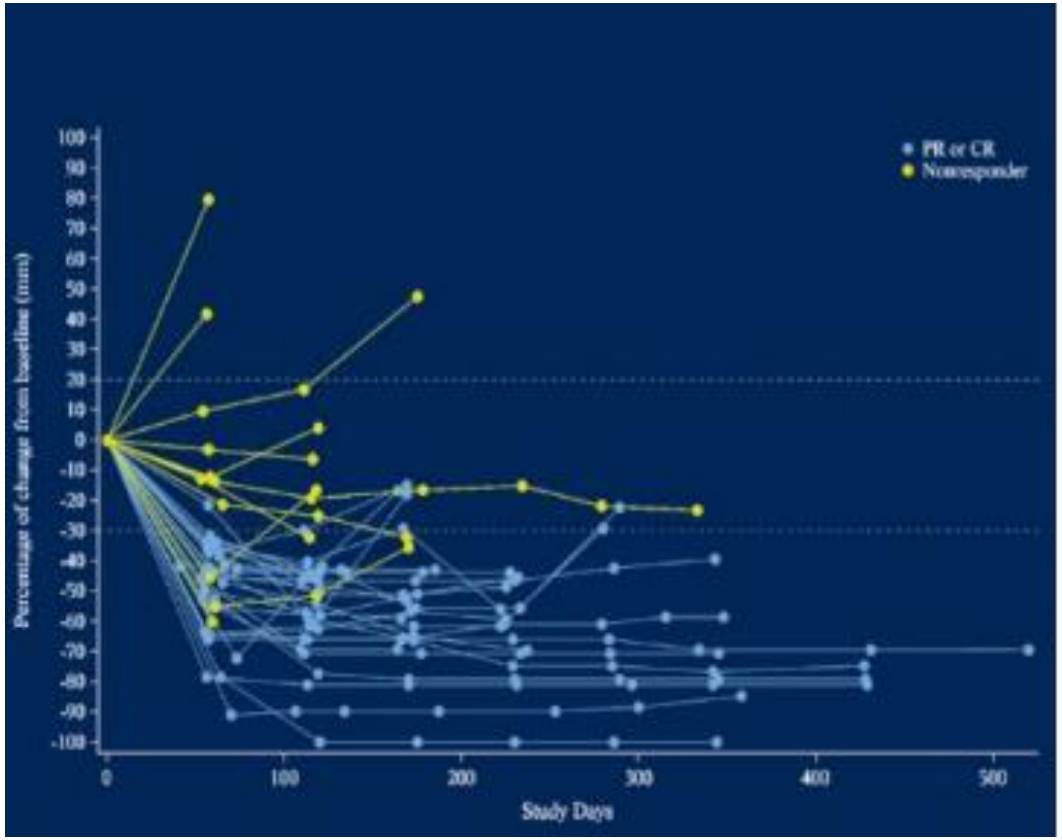
Subgroup Analysis for cORR

Subgroups	cORR (%, 95% CI)
HER2 status	
IHC2+FISH+ or IHC3+ (n=45)	62.2% (46.5%, 76.2%)
IHC2+FISH- (n=53)	39.6% (26.5%, 54.0%)
metastasis site	
Visceral Metastasis (n=97)	51.5% (41.2%, 61.8%)
Metastasis to Liver (n=48)	52.1% (37.2%, 66.7%)
Prior therapies	
Post PD1/PDL1 Treatments (n=27)	55.6% (35.3%, 74.5%)
Post 1 line of Chemotherapy (n=38)	50.0% (33.4%, 66.6%)
Post ≥2 Lines of Chemotherapy (n=69)	50.7% (38.4%, 63.0%)

mPFS 5.9m; mOS 14.2m

Sheng et al, ASCO 2022.

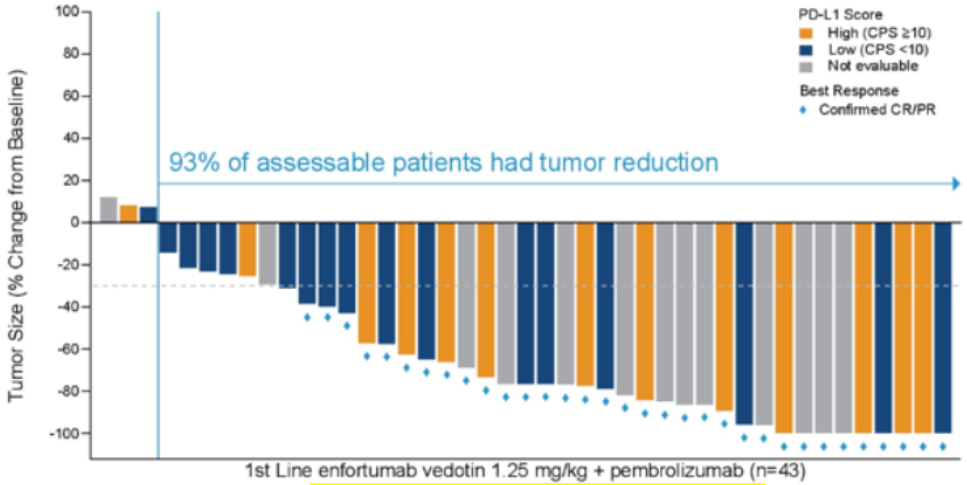
Disitamab Vedotin + Torpalimab (anti-PD1)



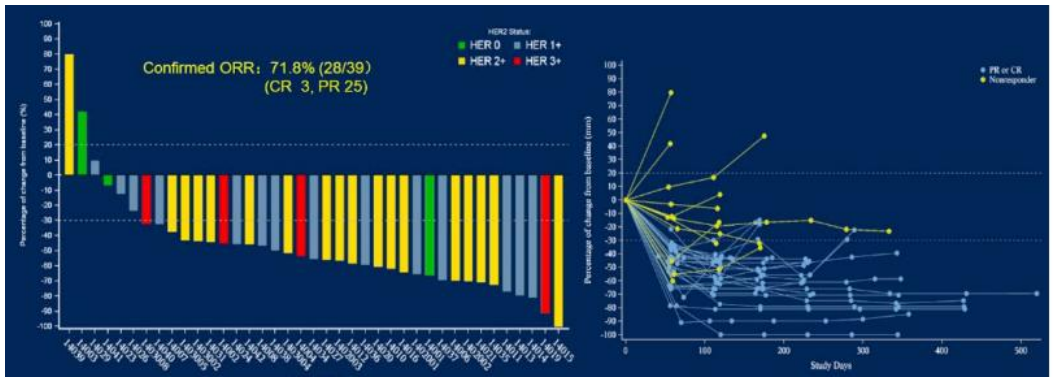
61% had not received prior systemic therapy

Sheng et al, ASCO 2022.

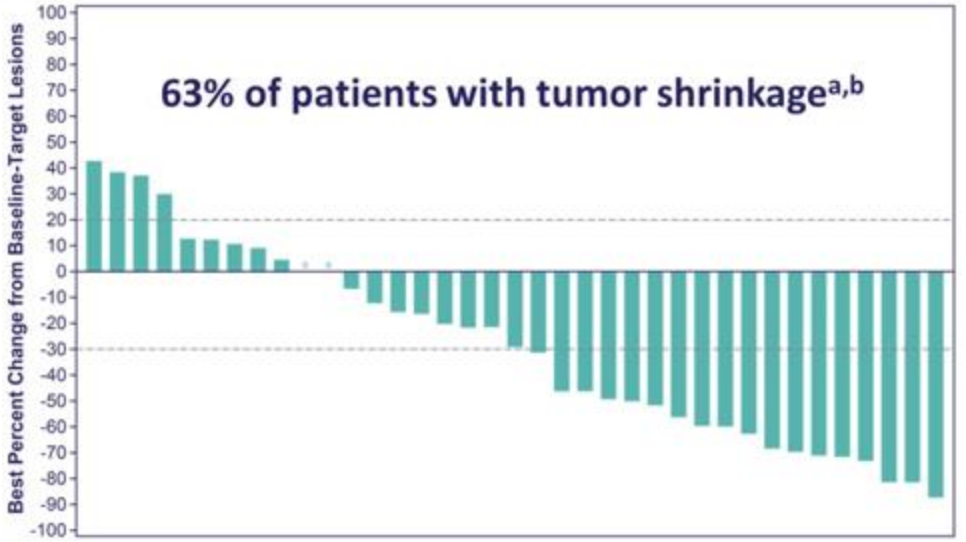
IO Combos: Is MMAE Special?



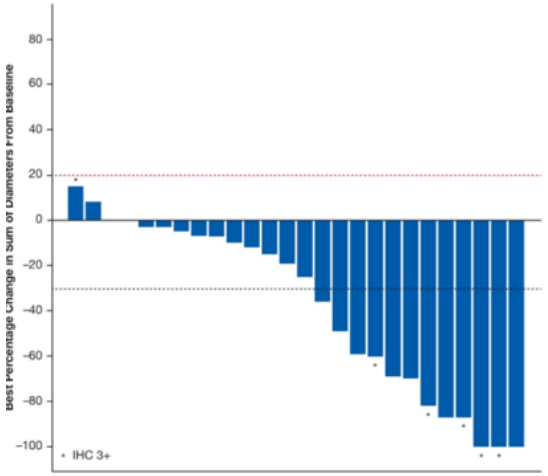
EV + PD1: ORR 67%



DV + PD1: ORR 72%



SG + PD1: ORR 34%



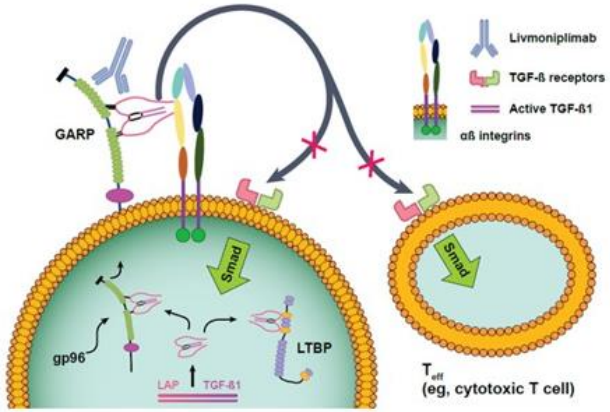
T-Dxd + PD1: ORR 37%

Grivas et al. GU ASCO 2022.
Petrylak et al. ASCO Annual Meeting 2019.
Galsky et al. GU ASCO 2022.
Sheng X et al. ASCO Annual Meeting 2022.

LIVIGNO-3: Livmoniplimab (anti-GARP-TGF-β) in Combination with Budigalimab (anti-PD-1) versus Chemotherapy in Patients with mUC

Livmo Mechanism of Action

Livmo is a first-in-class antibody to target the GARP–TGF-β1 complex; binding of livmo locks TGF-β1 to GARP, preventing the release of TGF-β1 to effector T cells



Key Eligibility Criteria

Inclusion

- Subjects with histologically or cytologically confirmed urothelial cancer
- Progressed on a previous PD(L)1 in metastatic setting
- Received platinum-based chemotherapy OR platinum ineligible
- ECOG 0-1

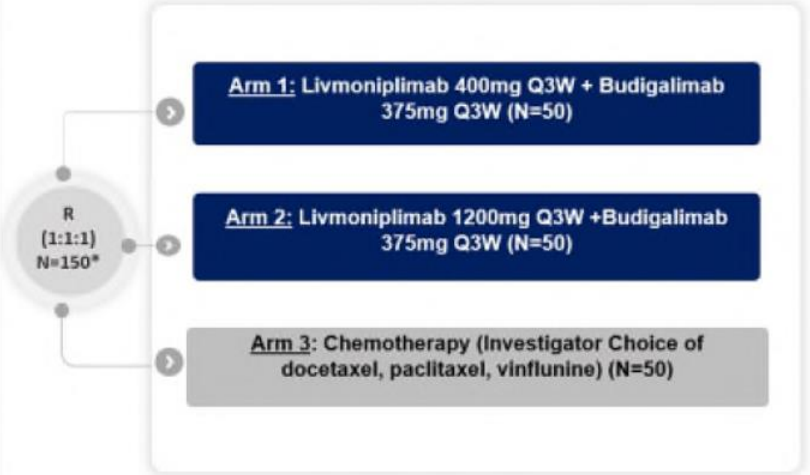
Exclusion

- More than 1 prior chemotherapy regimen (platinum administered in neo/adjuvant will count as prior CT regimen if progression within 6 months)
- >1 antibody-drug conjugate (ADC) in metastatic setting

Stratification Factors

- ECOG (0 vs 1)
- 1L Therapy (Pembrolizumab +EV vs platinum-based CT)

We are participating in the SCRI network!



Endpoints

Primary
- OS

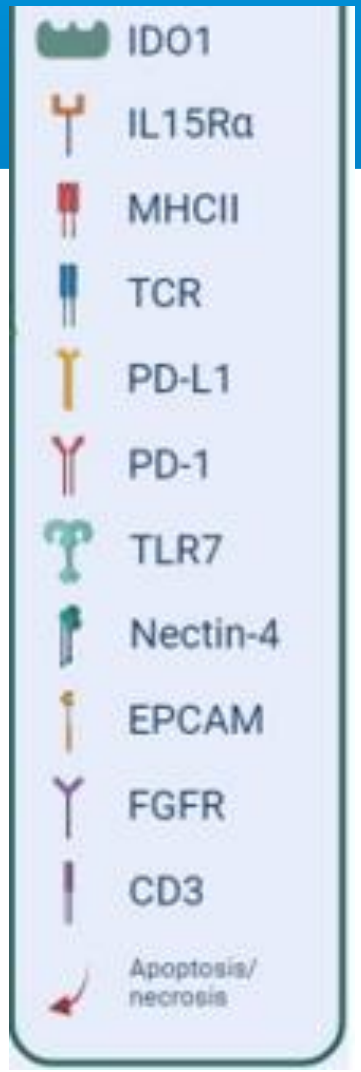
Secondary
- PFS, ORR, DOR RECIST 1.1 per Investigator
- PK and Safety

Exploratory
- PRO
- Biomarker

Dandamudi, D.B. et al., ASCO 2024.

clinicaltrials.gov NCT06632951

Scientific Targets in NMIBC



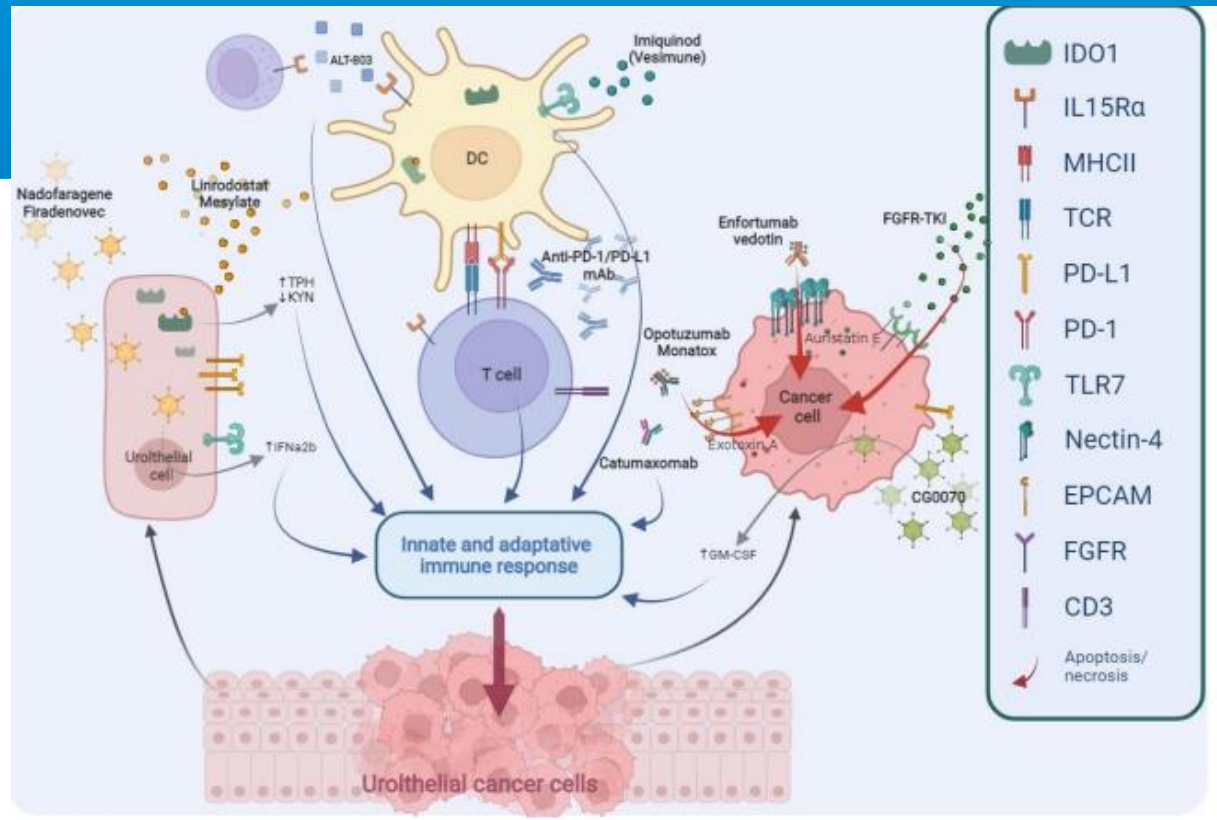


Figure 2. Main targets of novel drugs being investigated in BCG-unresponsive NMIBC. TPH, Tryptophan; KYN, Kynurenine; IFNα2b, Interferon α2b; DC, Dendritic Cell; PD1, Programmed cell Death protein 1; PD-L1, Programmed Death-Ligand 1; mAb, monoclonal Antibody; GM-CSF, Granulocyte-Macrophage Colony-Stimulating Factor; FGFR, Fibroblast Growth Factor Receptor; TKI, Tyrosine Kinase Inhibitors; IDO1, Indoleamine 2,3-Dioxygenase 1; IL-15Rα, Interleukin-15 receptor α; MHCII, Major Histocompatibility Complex Class II; TCR, T Cell Receptor; TLR7, Toll-like Receptor 7; EpCAM, Epithelial Cell Adhesion Molecule; CD3, Cluster of Differentiation 3.

Audisio, A; Buttigliero, C;Delcuratolo MD et al. Cells 2022,11, 357

Expression of Nectin-4 and PD-L1 in Variant Histology

Nectin-4 and PD-L1 staining results among BCVH subtypes.

			Nectin-4 H-score		PD-L1
Histology	No. of specimens	% of total (N = 117)	Mean	Median (range)	CPS ≥ 10 n(%)
Squamous	31	26.5	207.7	219.5 (17-300)	15/30 (50)
Adenocarcinoma	24	20.5	166.9	140.0 (45-299)	4/24 (16.7)
Sarcomatoid	24	20.5	52.3	2.5 (0-300)	17/24 (70.8)
Plasmacytoid	20	17.1	253.5	257.5 (108-300)	1/20 (5)
Small cell	10	8.5	46.8	0 (0-233)	2/10 (20)
Mixed	8	6.8	122	105 (20-265)	2/8 (25)

Case et al., ASCO 2022

Treatment Options for BCG Unresponsive NMIBC

	*Pembrolizumab[1]	*Nadofaragene firadenovec [2]	Gemcitabine/Docetaxel[4]	*N-803+BCG[3]	TAR-200 monotherapy
Mechanism	PD-1	Adenovirus mediated delivery of interferon alfa-2b gene	Direct cytotoxicity	IL-15 superagonist	Direct cytotoxicity
3 month CR CIS	41 %	53 %	-	71% (anytime)	**83.5%**
12 month CR CIS	19 %	24 %	60% (2yr 43%)	56 %	**57.4%**
Duration of CR-responders	24.1 mo	9.7 mo	13.1 mo	19.2 mo	82% at med f-up 9.2 mo
G3-5 AEs	13 %	3.8 %	3.3 % stop tx	11 % (no G5)	9.4% TRAE ≥G3

* So far, no approval in Europe

CIS, carcinoma in situ; CR, complete response; AE, adverse event;

1. Balar AV, et al. Lancet Oncol. 2021;22:919-930. 2. ADSTILADRIN® (nadofaragene firadenovec-vncg) [prescribing information]. Kastrup, Denmark: Ferring Pharmaceuticals; 2024., 3. Chamie K, et al. NEJM Evid. 2023;2(1):EVIDoa2200167. 4. Phan T. Urologic Oncology: Seminars and Original Investigations, Volume 41, Issue 3, 2023, Pages 148.e1-148.e7, ISSN 1078-1439, https://doi.org/10.1016/j.urolonc.2022.10.030.; Mathieu Roumiguié, Peter C. Black. Sequential Gemcitabine plus Docetaxel is the Standard Second-line Intravesical Therapy for BCG-unresponsive Non-muscle-invasive bladder cancer: Pro, European Urology Focus, Volume 8, Issue 4, 2022, Pages 1117-1120, ISSN 2405-4569, https://doi.org/10.1016/j.euf.2021.07.018.

BARCELONA 2024 ESMO congress

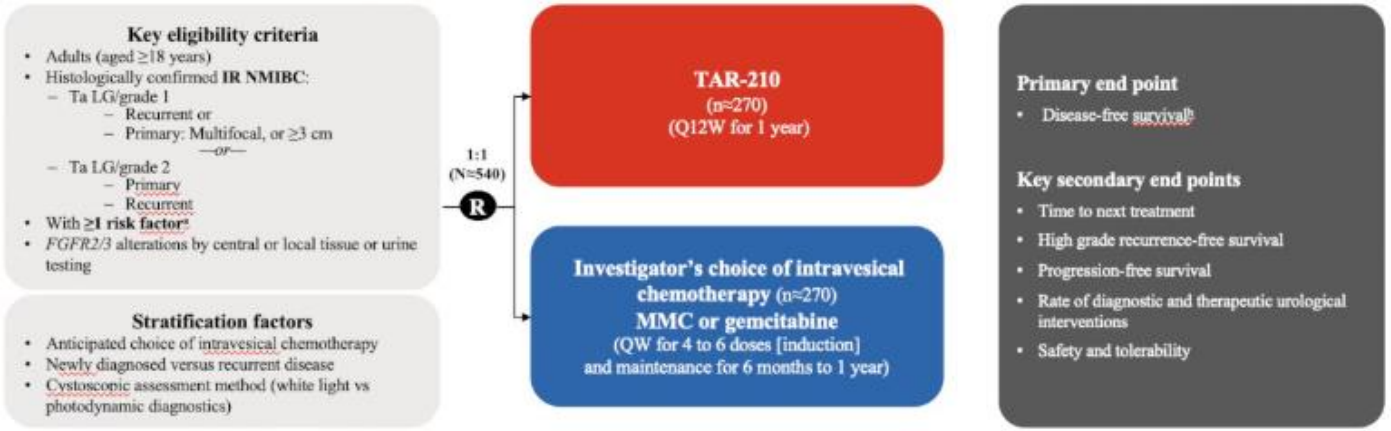
Maria De Santis

De Santis, M. et al. ESMO 2024.

Research Efforts in NMIBC

Project	Description	Status	Data so far
TAR-210	Erdafitinib intravesical drug delivery system	Ph3 Moonrise-1 vs chemo in intermediate-risk pts with FGFR alterations	Ph1 data at ESMO 2023: 87% CR rate in 15 pts in cohort 3 (BCG-naive)
Balversa	Erdafitinib, oral FGFR kinase inhibitor	Ph2 Thor-2 vs chemo in high-risk BCG-experienced pts with FGFR mutations	Data at ESMO 2023: 72% reduction in risk of recurrence/death in 73 pts in cohort 1 (post-BCG)
TAR-200	Gemcitabine intravesical drug delivery system	Ph3 Sunrise-3 +/- cetrelimab vs BCG in BCG-naive high-risk pts; ph3 Sunrise-5 vs investigator's choice chemo in high-risk BCG-experienced pts	Ph2 Sunrise-1 in high-risk BCG-unresponsive pts, data at ESMO 2023: 77% CR rate in 30 pts

Ph3 Moonrise-1 Study Design



Oncology/Pipeline & clinicaltrials.gov.

Considerations include:

- There is a lack of data with neoadjuvant chemotherapy
- How to manage Erdafitinib toxicity early on
- Collaboration with urology groups
- Requirement for research biopsy could be problematic

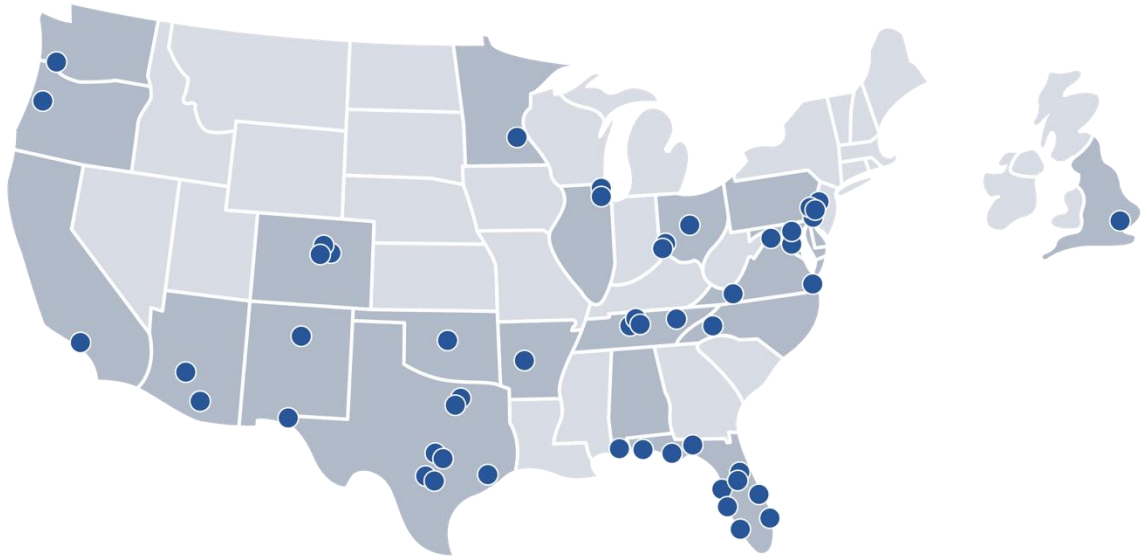
Subcutatenous Administration of IO

Although subcutatenous administration of immunotherapy gives patients more treatment options, there are concerns with patients not being seen as frequently by clinical staff during the duration of their therapy.

1. **Subcutaneous formulations of Nivolumab and Pembrolizumab are available.**
2. **Pfizer’s Subcutaneous PD-1 Blocker, Sasanlimab in the Phase 3 CREST trial in HR NMIBC achieved significant efficacy.**
3. **Much to be seen with standard of care in the use of subcutaneous IO formulations.**

SCRI: Can we Partner with You?

250+ Locations **IN** **24** States

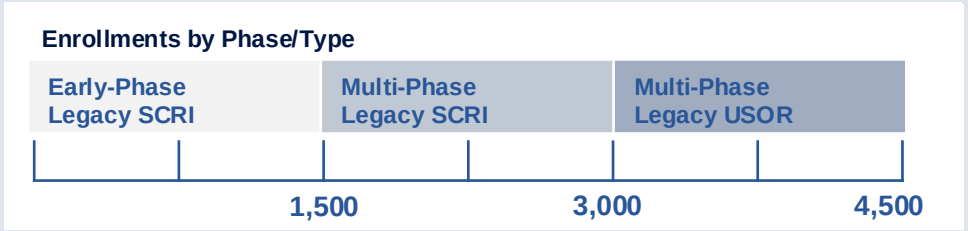


Our research network touches 1 in 5 patients with cancer through our affiliated sites

1,300+
Research Physicians

1,000+
Trials Actively Enrolling

4,500+
Registered Patients Participating in Trials Yearly*



*Based on combined annual data from 2019 to present

Thank you!

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