Immunotherapy of Bladder Cancer and Novel Agents

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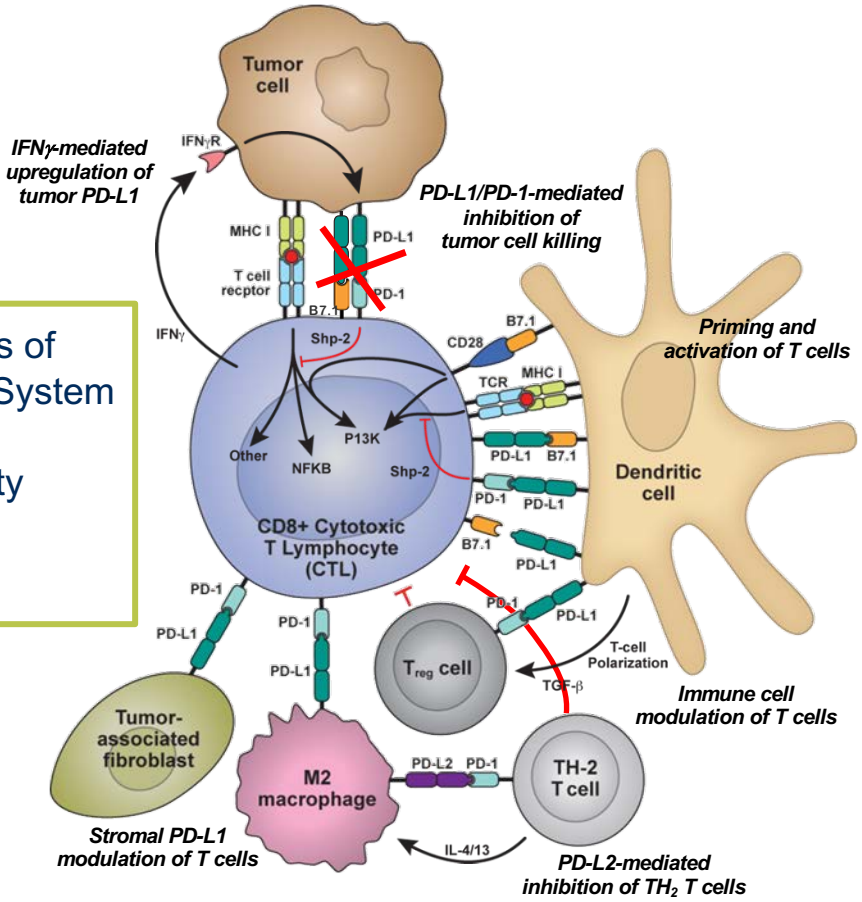
Mechanism of Immune Checkpoint Inhibitors

Key Attributes of the Immune System

- Specificity
- Memory
- Adaptive



- Cancer cells develop many mutations that can make them appear foreign to the immune system
- T cells can recognize, attack and kill these “foreign” cancer cells
- Cancer cells can evade immune attack by expressing PD-L1
- Adaptive tumor expression of PD-L1 turns the immune system OFF
- Clinically, we want to block PD-1 or PD-L1 to <u>reactivate</u> the immune system
- PD-L1 plays an important role in dampening the anti-tumor immune response

Herbst RS et al. *J Clin Oncol* . 2013;31(suppl; abstr 3000)

Checkpoint Inhibitors Approved for Use in Urothelial Carcinoma

7 US FDA Approvals May 2016-May 2017

Setting	Antibody	Approval Status
First-line (cisplatin-ineligible)	Atezolizumab	• Accelerated approval granted in April 2017.
	Pembrolizumab	• Accelerated approval granted in May 2017.
Platinum-pretreated	Atezolizumab	• Accelerated approval granted in May 2016. • In May 2017, the subsequent phase 3 IMvigor211 trial did not meet primary endpoint of overall survival.
	Nivolumab	• Accelerated approval granted in February 2017.
	Durvalumab	• Accelerated approval granted in May 2017.
	Avelumab	• Accelerated approval granted in May 2017.
	Pembrolizumab	• Full approval granted in May 2017.

Approvals: First-line, Cisplatin-Ineligible

Apr 2017 — May 2017

Atezolizumab — Pembrolizumab

Above agents are indicated in patients with locally advanced or metastatic urothelial carcinoma not eligible for cisplatin-containing chemotherapy.

First-Line Therapy for Cisplatin-Ineligible Metastatic UC
PD-1/PD-L1 Inhibitor OR Gemcitabine-Carboplatin Based on Activity?

	Gem-Carbo (Ph III)[1]	Atezolizumab (Ph II)[2]	Pembrolizumab (Ph II)[3]
Number of patients	119	119	370
% with PS 2	44.5%	20%	42%
% CrCl <60 mL/min	55.5%[a]	70%	49%
% PS 2 + CrCl <60 mL/min	26.9%[a]	7%	9%
ORR	41.2% ✓	23%	24%
Median PFS	5.8 mo ✓	2.7 mo	2 mo; 3 mo on therapy
Median OS	9.3 mo	15.9 mo ✓	Not reported
Duration of response	Not reported	Not reached (median f/u 17.2 mo) ✓	Not reached (78% ≥6 months) ✓

[a]GFR 30-60 mL/min.

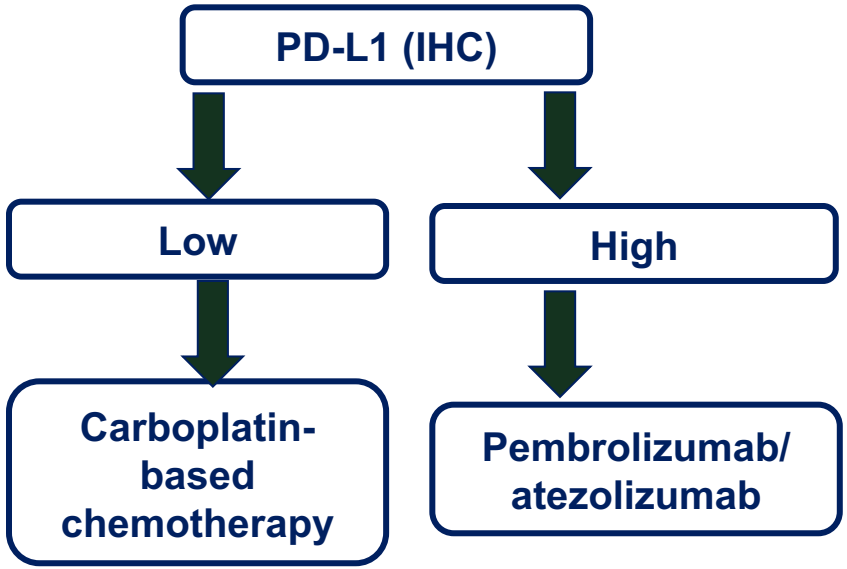
1. De Santis M, et al. J Clin Oncol. 2012;30(2):191-199; 2. Balar AV, et al. Lancet. 2017;389(10064):67-76; 3. Balar AV; et al. Lancet Oncol. 2017;18:1483-1492.

Use PD-L1 expression to select therapy for cisplatin-ineligible patients?

5/18/2018

FDA Alert

- In two ongoing clinical trials (KEYNOTE-361 and IMVIGOR-130), the Data Monitoring Committees' (DMC) found patients in the **monotherapy arms of both trials with PD-L1 low status had decreased survival compared to patients who received cisplatin- or carboplatin-based chemotherapy.**
- Both trials have stopped enrolling patients whose tumors have PD-L1 low status to the pembrolizumab or atezolizumab monotherapy arms.
- The monotherapy arms remain open only to patients whose tumors have PD-L1 high status.



First Line Chemotherapy +Checkpoint Therapy trials in Metastatic Urothelial Cancer

CT ID	Phase	Target	Experimental Arm(s)	Standard Arm
NCT02807636 IMvigor130	III	PD-L1	Atezo OR Atezo + Gem-Plat	Placebo + Gem-Plat
NCT02853305 KEYNOTE-361	III	PD-1	Pembro OR Pembro + Gem-Plat	Gem-Plat
NCT02516241 DANUBE	III	PD-L1 +/- CTLA-4	Durvalumab OR Durva + Treme	Gem-Plat
NCT03036098 CM-901	III	PD-1 + CTLA	Nivo + Ipi*	Gem-Plat

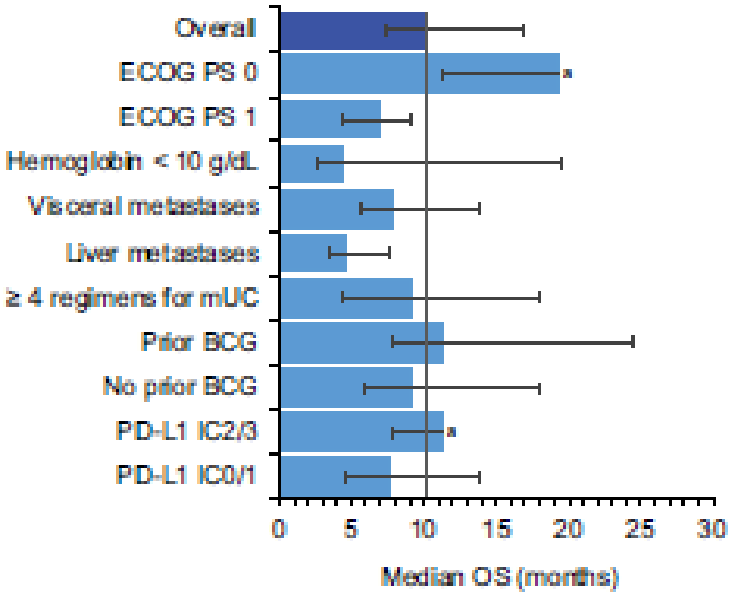
Approvals: Previously-treated Disease

May 2016 Feb 2017 May 2017

Atezolizumab Nivolumab Durvalumab Avelumab Pembrolizumab

Above agents are indicated in patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with (platinum-containing) chemotherapy.

Median Survival by Baseline Characteristics



Patterns of AE Occurrence

Time Following Initiation of Atezolizumab[a]	All Treatment-Related AEs		Serious Treatment-Related AEs	
	All Grade	Grade 3-4	All Grade	Grade 3-4
Within year 1 (N = 95)	66%	7%	5%	0%
Beyond year 1 (n = 37)	35%	5%	0%	0%
Year 2 (n = 37)	32%	5%	0%	0%
Year 3 (n = 20)	10%	0%	0%	0%

[a] Values in parentheses refer to the number of patients evaluable for safety at the beginning of each period.

- Most treatment-related AEs occurred within the first year following initiation of treatment, with the AE incidence in year 2 approximately half that in year 1
- No serious treatment-related AEs occurred beyond year 1

Adjuvant PD-1/PD-L1 Inhibitor Phase III Trials

PI	Population	Control Arm	Experimental Arm	Primary Endpoint
Industry	All-comers MIUC Prior NAC- ≥pT2 No AC ≥pT3	No therapy	Atezolizumab	PFS
Industry	All-comers MIUC Prior NAC- ≥pT2 No AC ≥pT3	Placebo	Nivolumab	PFS
Intergroup[a]	All-comers MIUC Prior NAC- ≥pT2 No AC ≥pT3	No therapy	Pembrolizumab	PFS/OS

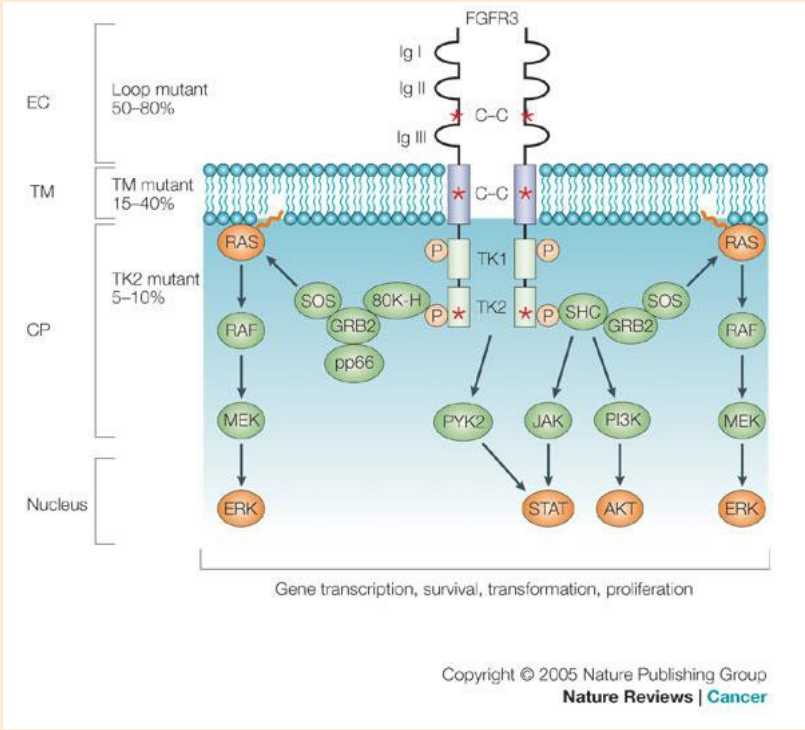
[a]PI: Apolo; SWOG PI: Sonpavde; ECOG PI: Srinivas.

Neoadjuvant Therapy With IO Agents
Selected Phase I-II Trials

	Trial ID	Phase	Regimen	Primary Endpoint
Chemo-IO	NCT03294304	II	GC-Nivolumab	pCR
	NCT02690558	II	GC-Pembrolizumab	pCR
	NCT02365766	I/II	G/GC-Pembrolizumab	Feasibility, pCR
IO	NCT02451423	II	Atezolizumab	pCR, immune response
	NCT02736266	II	Pembrolizumab	pCR
IO-IO	NCT02812420	II	Durvalumab + Tremelimumab	Feasibility
	NCT02845323	II	Nivolumab +/- Urelumab	Immune response
	Pending	I	Durvalumab +/- CD73i	Feasibility, Immune response

FGFR3—Fibroblast Growth Factor Receptor

- A membrane based TKR involved in cellular proliferation, differentiation, and steroid biosynthesis (*image, right*)[1]
- FGFR mutations and overexpression have been implicated in bladder cancer[2]
- **April 12, 2019** – FDA granted accelerated approval to the FGFR inhibitor erdafitinib for locally advanced/metastatic bladder cancer with a FGFR2 or FGFR3 alteration, that has progressed during or after platinum chemotherapy[3]
- FGFR inhibitors and anti-FGFR ADCs are in ongoing and upcoming trials in advanced UC[4]



1. Wu X-R. *Nat Rev Cancer.* 2015;5:713-725; 2. Turo R, et al. *J Urol*. 2015;193:325-330; 3. FDA. https://tinyurl.com/y2cnn9eu. April 12, 2019; 4. ClinicalTrials.gov.