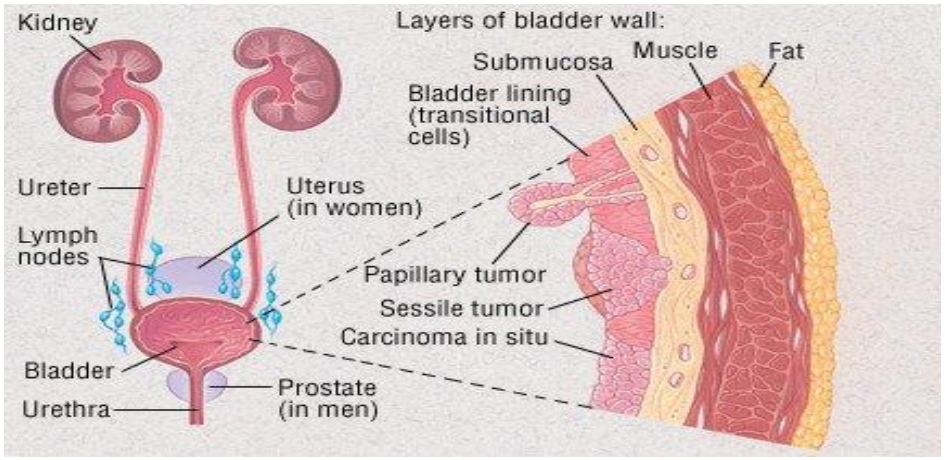
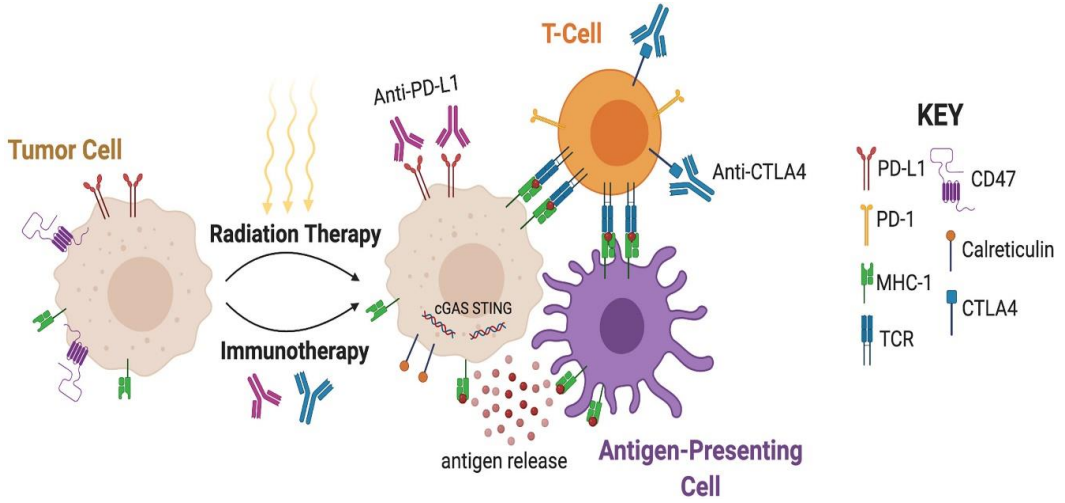
IMMUNOTHERAPY COMBINED WITH RADIATION FOR GENITO-URINARY MALIGNANCIES





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Associate Professor, Dr RMLIMS, Lucknow

EFFECT OF RT ON IMMUNE SYSTEM

Immune-stimulating effects of radiotherapy	Immune-suppressing effects of radiotherapy
Induces immunogenic cell death: Release of tumor antigens and DAMPs (calreticulin, HSP70, HMGB1) Increased MHCI expression and APCs maturation Increased CD8+T-cell infiltration and tumor cell death	Radiation-induced lymphopenia (RIL): Preferential depletion of CD4+T cells and B cells after RT
Increases: Pro-inflammatory cytokines: interferon gamma, tumor necrosis factor-α, type I interferons Cos-stimulatory molecules Adhesion molecules	Effects on infiltrating immune cells: ↑ CD4+T-reg cells ↑ MDSCs
Activates the innate immune system: Upregulation of NKG2D type II NK-cell activation	Effects on immune cell surface markers: ↑ PDL1 expression ↑ CTLA4 expression on T-reg cells
Abscopal effect: ↑ tumor antigens → ↑APCs → ↑ pro-inflammatory cytokines → ↑ CD8+T cells	

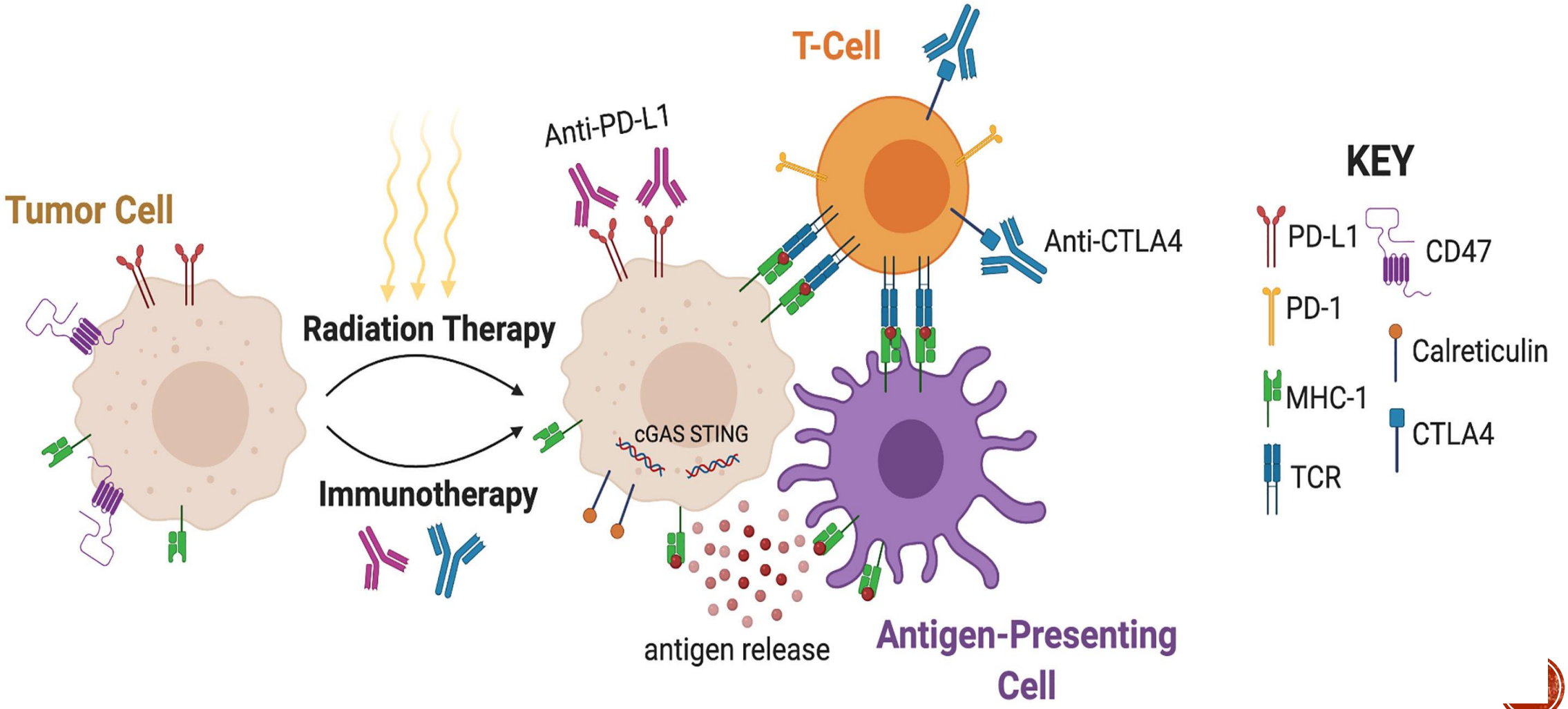
Radiotherapy and Immune System

- Immunogenic cell death and modulation of the tumour microenvironment.
- Priming of T Cell in the TME and lymph nodes.
- Radiation Induced Abscopal effect Well documented in metastatic RCC, Melanoma and HCC
- Formenti et al. showed an objective abscopal response in 9/34 patients (27%) with solid metastatic cancers that received GM-CSF and irradiation to one metastatic lesion.
- In a randomized phase 1 trial, Sundahl et al. compared Pembrolizumab with sequential versus concomitant stereotactic body radiotherapy (SBRT) to the largest metastatic lesion in MIBC patients. There was a 44% ORR in non-irradiated metastatic sites when SBRT was given concomitantly vs. 0% when given sequentially.
- Radioresistant tumor cells can still be recognized and destroyed by retargeting of T cells

Radiation Induced Lymphopenia

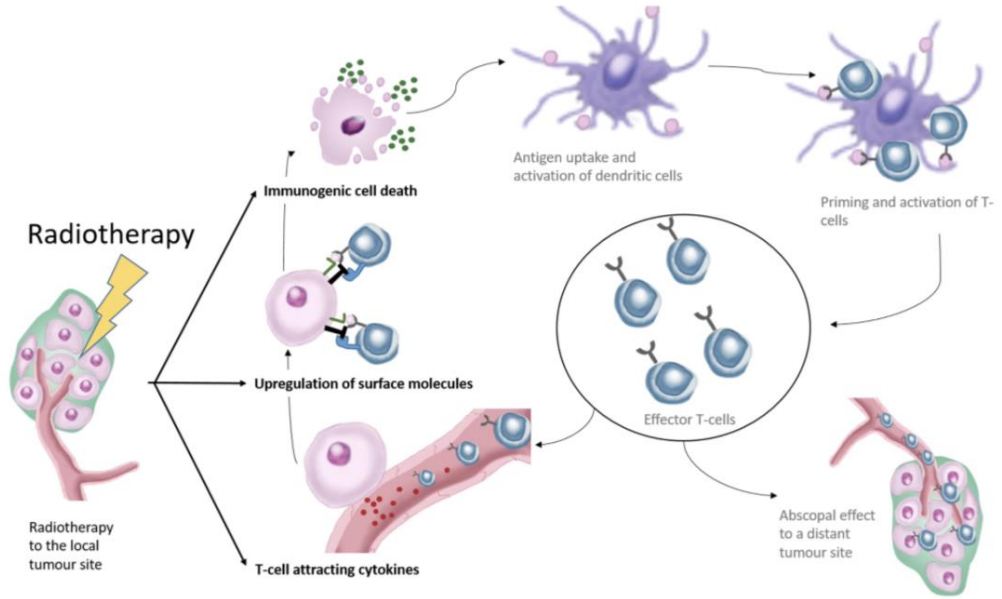
- RIL is characterized by acute preferential depletion of CD4 + T-cells and B-cells
- In a retrospective study of 167 patients treated with Nivolumab or Pembrolizumab, baseline and 3-month lymphopenia were associated with shorter PFS.
- Rudra et al. compared standard RTOG fields with more limited fields in patients with glioblastoma undergoing concurrent temozolomide and RT, and found that the standard field had a greater decline in total lymphocyte counts at 3 mo.
- In pancreatic cancer, a series compared patients undergoing SBRT to smaller target volumes with patients undergoing concurrent chemoradiotherapy to larger target volumes and found a lower incidence of radiation-induced lymphopenia in the SBRT group, albeit the concurrent chemotherapy may have been a confounder in this study.

IMMUNOTHERAPY COMBINED WITH RADIOTHERAPY



- Radiation induces an immunogenic cell death and causes modifications of the tumor microenvironment leading to enhanced antigenicity
- On the other hand, radiation can also induce upregulation of PD-L1 axis, leading to T-Cell inhibition and reduced anti-tumor activity.
- This inhibition can be overcome by checkpoint-inhibitors, which may be one of the reasons for a synergistic mode of action

Figure 1. This figure shows the effects of radiotherapy in relation to the cancer immune cycle. Radiotherapy affects the immune response by induction of immunogenic cell death releasing new antigens to the components of the immune system. This subsequently leads to improved priming and activation of effector T cells. Radiotherapy further leads to increased expression of surface molecules on the irradiated cancer cells making them more vulnerable to cytotoxic T-cell-mediated cell killing. Finally, radiotherapy leads to the release of cytokines attracting T cells towards the irradiated tumour. Improved influx of effector T cells and improved T-cell killing of cancer cells could result in new antigen presented to the components of the immune system.



ROLE OF RADIOTHERAPY FOR GENITOURINARY MALIGNANCIES

- Prostate cancers: Definitive for almost all non-metastatic stages, Adjuvant/Salvage RT, Ablative for oligometastatic sites and palliative RT
- Bladder Cancers: Definitive as part of tri-modality treatment, palliative RT, Post-operative (?)
- Renal Cancers: Mostly palliative RT, Ablative SBRT for localized RCC
- Penile Cancers: Definitive RT (Brachytherapy), Post-op RT, Palliative RT

IMMUNOTHERAPY IN UROLOGIC MALIGNANCIES: HISTORY

THE JOURNAL OF UROLOGY
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Vol. 116, August
Printed in U.S.A.

INTRACAVITARY BACILLUS CALMETTE-GUERIN IN THE TREATMENT OF SUPERFICIAL BLADDER TUMORS

A. MORALES,* D. EIDINGER AND A. W. BRUCE

From the Departments of Urology, and Microbiology and Immunology, Queen's University, Kingston, Ontario, Canada

TABLE 1. *Effect of BCG on the rate of tumor recurrence*

Pt.*	Calendar of Cystoscopic Examinations				
	Pre-BCG			Post-BCG	
1	May 74	Aug. 74	Jan. 75	May 75	Aug. 75
	Pos.† (2)‡	Pos. (2)	Pos. (1)	Neg.§	Neg.
2	Jan. 73	June 73	Oct. 73	Jan. 74	Mar. 74
	Pos. (1)	Pos. (1)	Pos. (1)	Pos. (1)	Died
3	Sept. 73	Feb. 74	Sept. 74	Jan. 75	Apr. 75
	Pos. (2)	Pos. (1)	Pos. (2)	Neg.	Neg.
4	July 74	Sept. 74	Jan. 75	Apr. 75	June 75
	Pos. (1)	Pos. (1)	Pos. (1)	Neg.	Neg.
5	July 74	Nov. 74	Jan. 75	May 75	July 75
	Pos. (1)	Neg.	Pos. (4)	Neg.	Neg.
6	Sept. 73	Feb. 74	Aug. 74	June 75	Aug. 75
	Pos. (1)	Neg.	Pos. (3)	Neg.	Neg.
7	Feb. 73	June 73	Sept. 73	Nov. 74	May 75
	Pos. (3)	Pos. (2)	Pos. (1)	Neg.	Neg.

Results of Treatment of 255 Patients With Metastatic Renal Cell Carcinoma Who Received High-Dose Recombinant Interleukin-2 Therapy

By Gwendolyn Fyfe, Richard I. Fisher, Steven A. Rosenberg, Mario Sznol, David R. Parkinson, and Arthur C. Louie

Purpose: **To determine the efficacy and toxicity of a high-dose interleukin-2 (IL-2) regimen in patients with metastatic renal cell carcinoma.**

Patients and Methods: **Two hundred fifty-five assessable patients were entered onto seven phase II clinical trials. Proleukin (aldesleukin; Chiron Corp, Emeryville, CA) 600,000 or 720,000 IU/kg was administered by 15-minute intravenous (IV) infusion every 8 hours for up to 14 consecutive doses over 5 days as clinically tolerated with maximum support, including pressors. A second identical cycle of treatment was scheduled following 5 to 9 days of rest, and courses could be repeated every 6 to 12 weeks in stable or responding patients.**

Results: **The overall objective response rate was 14% (90% confidence interval [CI], 10% to 19%), with 12 (5%) complete responses (CRs) and 24 (9%) partial responses (PRs). Responses occurred in all sites of disease, including bone, intact primary tumors, and visceral metastases, and in patients with large tumor burdens or bulky individual lesions. The median response duration for patients who achieved a CR has not been reached, but was 19.0 months for those who achieved a PR. Baseline Eastern Cooperative Oncology Group (ECOG) performance status (PS) was the only predictive prognostic factor for response to IL-2. While treatment was associated with severe acute toxicities, these generally reversed rapidly after therapy was completed. However, 4% of patients died of adverse events judged to be possibly or probably treatment-related.**

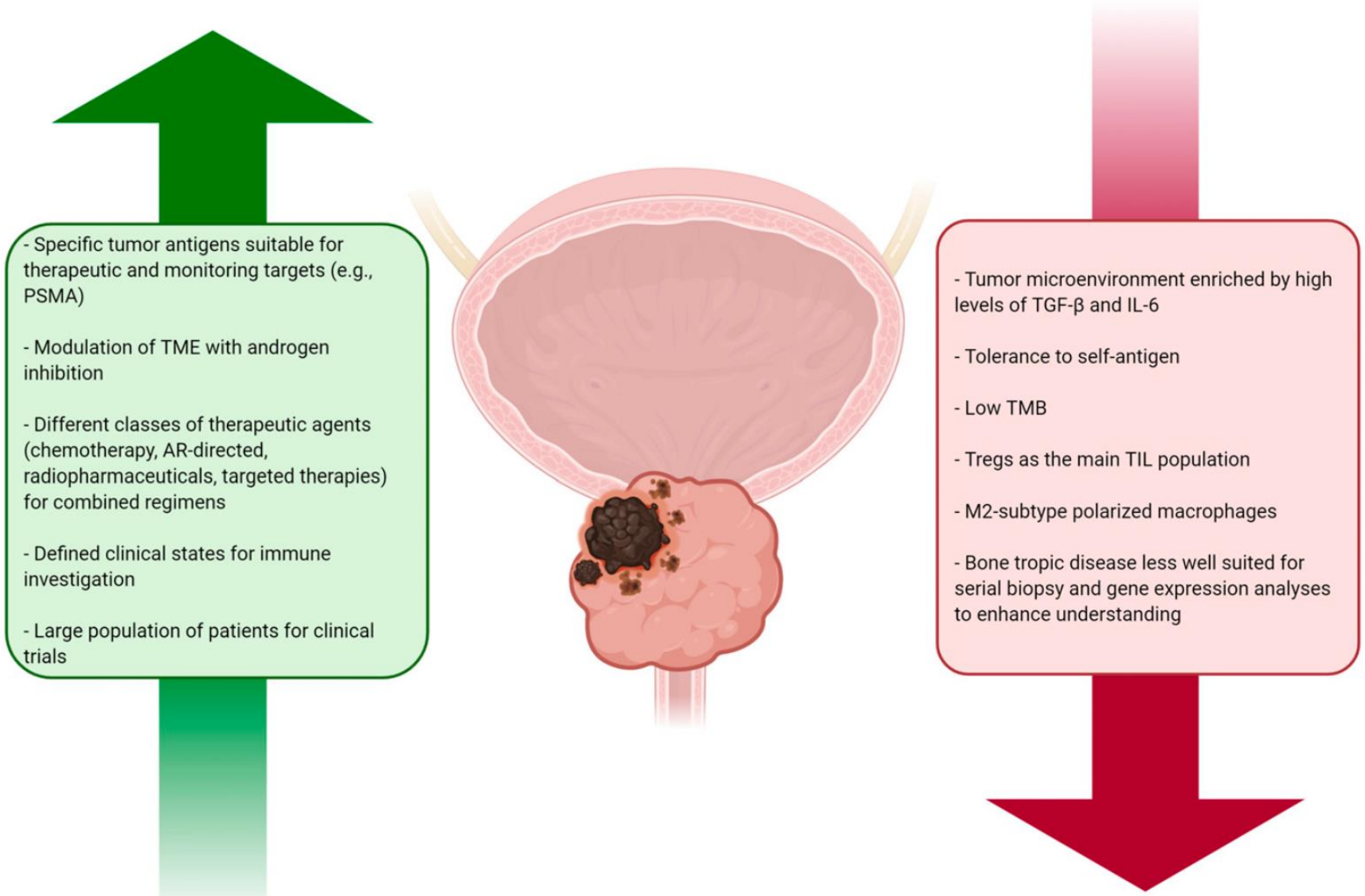
Conclusion: **High-dose IL-2 appears to benefit some patients with metastatic renal cell carcinoma by producing durable CRs or PRs. Despite severe acute treatment-associated toxicities, IL-2 should be considered for initial therapy of patients with appropriately selected metastatic renal cell carcinoma.**

J Clin Oncol 13:688-696.

Challenges with Immunotherapy in Genitourinary malignancies

- Only a subset of patients benefit from IO
- The quantum of benefit is very small except in renal cell carcinoma
- Cost effectiveness and patient selection based on biomarkers are impediments
- Rationale for combining IO with synergistic or additive therapy to improve outcome

IMMUNE-CHECKPOINT BLOCKADE FOR PROSTATE CANCERS: NICHE ROLE OR BREAKTHROUGH



IMMUNOTHERAPY IN PROSTATE CANCER

- Limited role in management of prostate cancer
- Sipuleucel-T was the first autologous vaccine to prolong survival
- Unselected immunotherapy strategies have been largely unsuccessful.
- The only current indication for immune checkpoint inhibitors is with high tumor mutational burden or microsatellite instability.

PD-1 INHIBITION IN MMR-DEFICIENT CANCER

The NEW ENGLAND JOURNAL of MEDICINE

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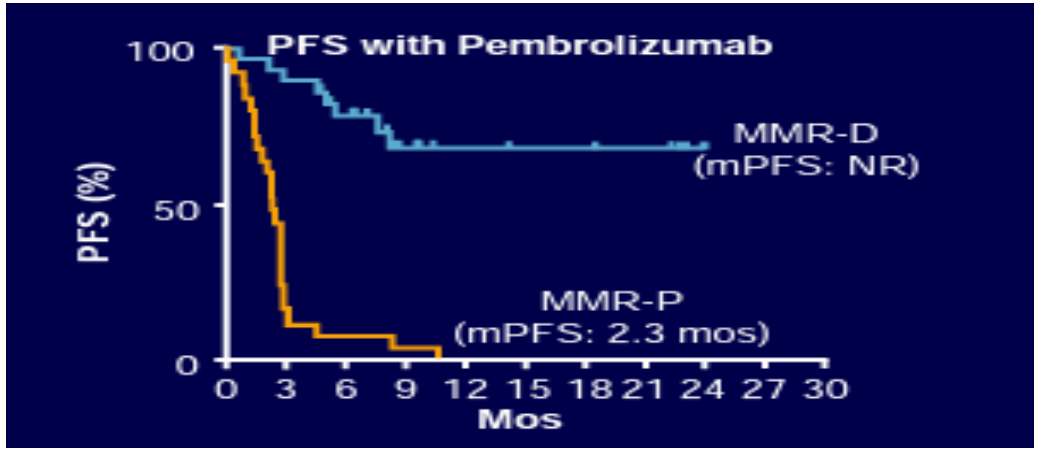
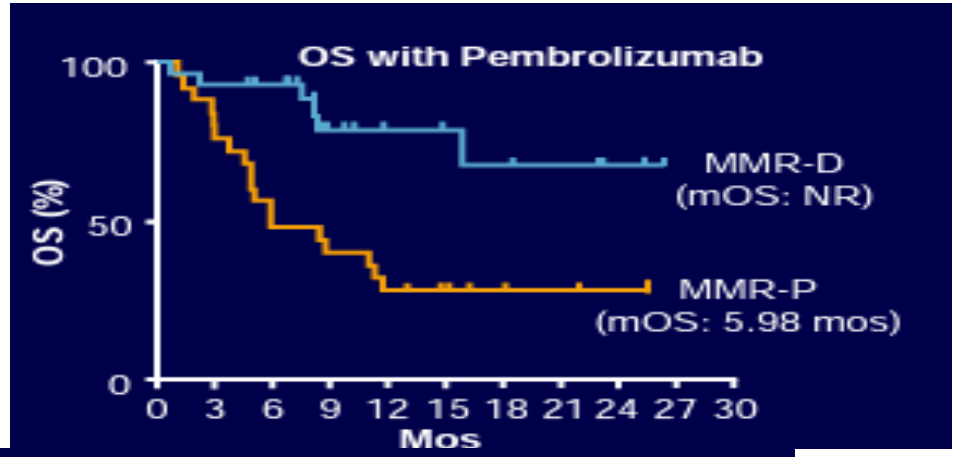
ORIGINAL ARTICLE

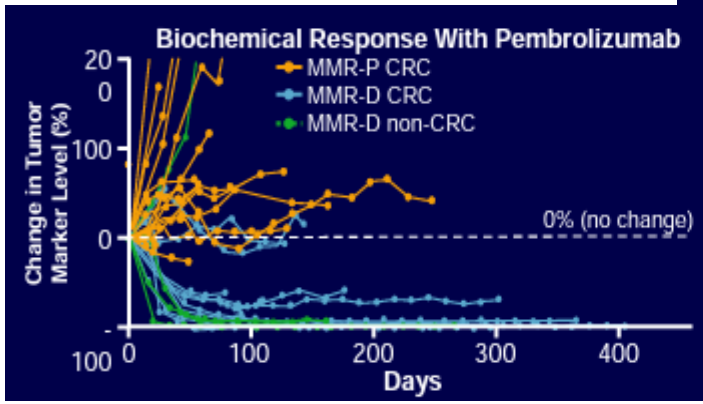
PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

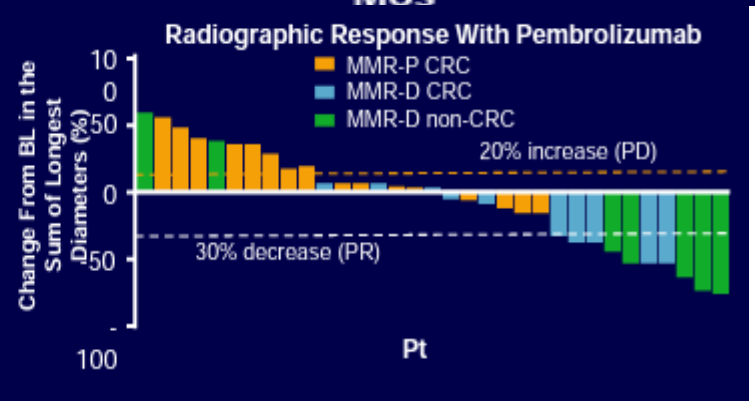
Dung T. Le, M.D., Jennifer N. Uram, Ph.D., Hao Wang, Ph.D., Bjarne R. Bartlett, B.S., Holly Kemberling, R.N., Aleksandra D. Eyring, M.Pharm., Andrew D. Skora, Ph.D., Brandon S. Luber, Sc.M., Nilofer S. Azad, M.D., Dan Laheru, M.D., Barbara Biedrzycki, Ph.D., C.N.R.P., Ross C. Donehower, M.D., Atif Zaheer, M.D., George A. Fisher, M.D., Ph.D., Todd S. Crocenzi, M.D., James J. Lee, M.D., Ph.D., Steven M. Duffy, M.D., Richard M. Goldberg, M.D., Albert de la Chapelle, M.D., Ph.D., Minori Koshiji, M.D., Ph.D., Feryal Bhaijee, M.D., Thomas Huebner, M.D., Ralph H. Hruban, M.D., Laura D. Wood, M.D., Ph.D., Nathan Cuka, M.D., Drew M. Pardoll, M.D., Ph.D., Nickolas Papadopoulos, Ph.D., Kenneth W. Kinzler, Ph.D., Shibin Zhou, M.D., Ph.D., Toby C. Cornish, M.D., Ph.D., Janis M. Taube, M.D., Robert A. Anders, M.D., Ph.D., James R. Eshleman, M.D., Ph.D., Bert Vogelstein, M.D., and Luis A. Diaz, Jr., M.D.

May 30, 2015 | DOI: 10.1056/NEJMoa1500596

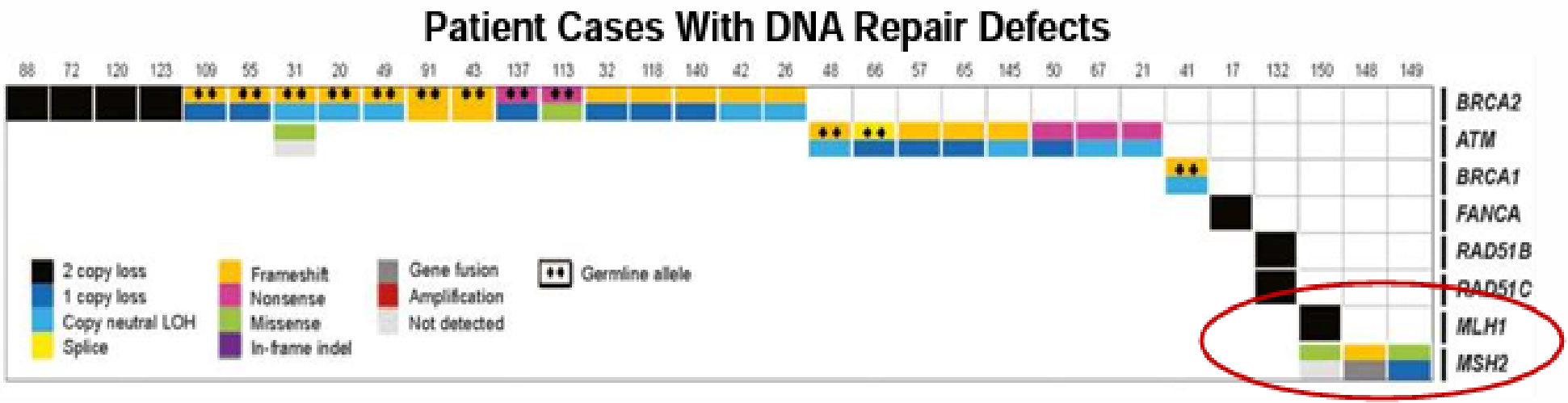








MMR MUTATIONS IN M-CRPC

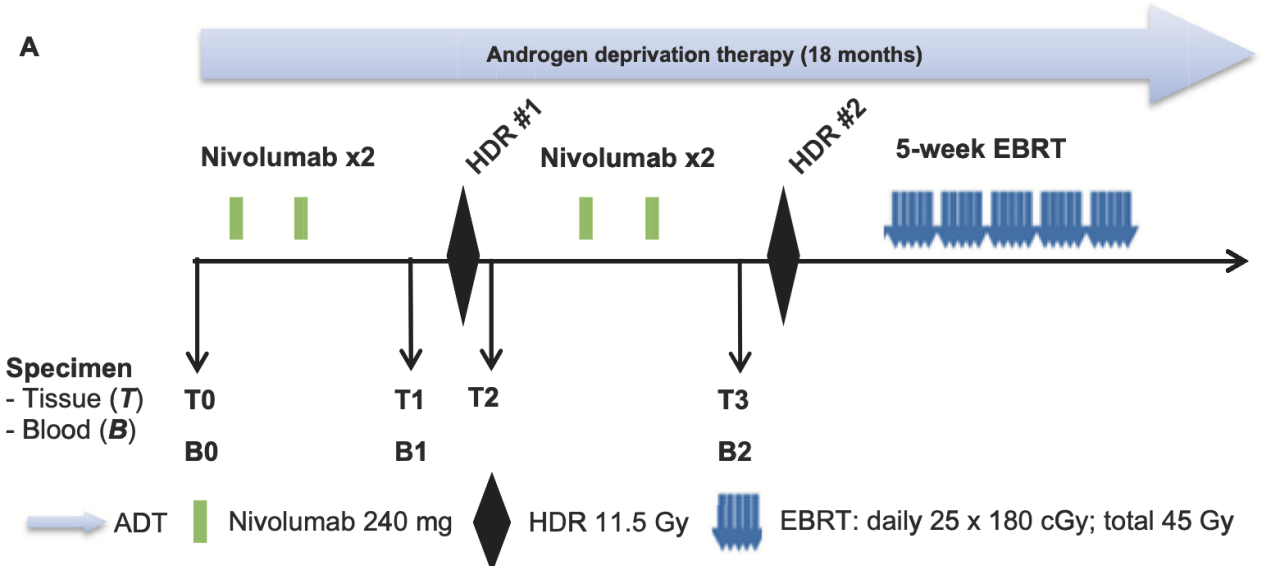


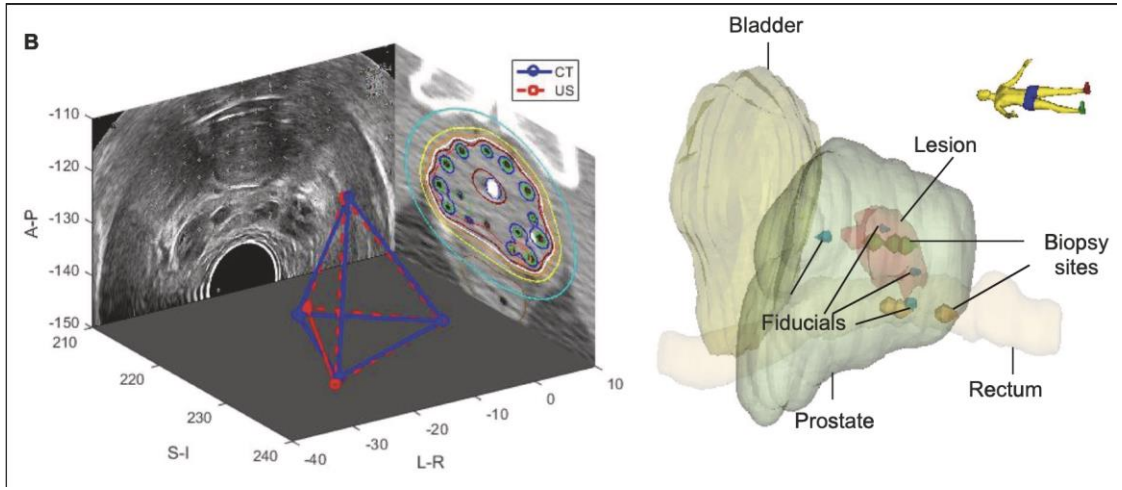
- 3/150 (2%) had MMR mutations
- 4/150 (2.7%) were MSI-high

Proof-of-principle Phase I results of combining nivolumab with brachytherapy and external beam radiation therapy for Grade Group 5 prostate cancer: safety, feasibility, and exploratory analysis

Prostate Cancer and Prostatic Diseases
https://doi.org/10.1038/s41391-020-0254-y

Zhigang Yuan[1] · Daniel Fernandez[1] · Jasreman Dhillon[2] · Julieta Abraham-Miranda[3] · Shivanshu Awasthi[3] ·





Phase I study on 6 patients. Overall, nivolumab was well tolerated in combination with ADT and HDR treatment.
One patient experienced a grade 3 dose-limiting toxicity (elevated Alanine aminotransferase and Aspartate aminotransferase) after the second cycle of nivolumab.
Three patients (50%) demonstrated early response with no residual tumor detected in ≥4 of 6 cores on biopsy post-nivolumab (4 cycles) and 1-month post–HDR.
Increase in CD8+ and FOXP3+/CD4+ T cells in tissues, and CD4+ effector T cells in peripheral blood were observed in early responders.

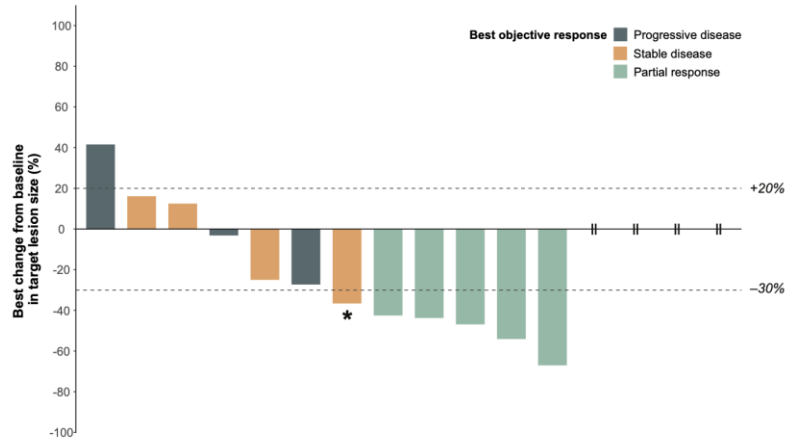
Avelumab Combined with Stereotactic Ablative Body Radiotherapy in Metastatic Castration-resistant Prostate Cancer: The Phase 2 ICE-PAC Clinical Trial

https://doi.org/10.1016/j.eururo.2021.08.011

Edmond M. Kwan [a,b], *Lavinia Spain* [c,d,e], *Angelyn Anton* [d,e,f], *Chun L. Gan* [b], *Linda Garrett* [b],

Design, setting, and participants: From November 2017 to July 2019, this prospective phase 2 study enrolled 31 men with progressive mCRPC after at least one prior androgen receptor–directed therapy. Median follow-up was 18.0 mo.
Intervention: Avelumab 10 mg/kg intravenously every 2 wk for 24 wk (12 cycles). A single fraction of SABR (20 Gy) was administered to one or two disease sites within 5 d before the first and second avelumab treatments.
Outcomes measurements and statistical analysis: The primary endpoint was the disease control rate (DCR), defined as a confirmed complete or partial response of any duration, or stable disease/non–complete response/non–progressive disease for ≥6 mo (Prostate Cancer Clinical Trials Working Group 3–modified Response Evaluation Criteria in Solid Tumours version 1.1). Secondary endpoints were the objective response rate (ORR), radiographic progression-free survival (rPFS), overall survival (OS), and safety. DCR and ORR were calculated using the Clopper-Pearson exact binomial method.
Results and limitations: Thirty-one evaluable men were enrolled (median age 71 yr, 71% with ≥2 prior mCRPC therapy lines, 81% with >5 total metastases). The DCR was 48% (15/31; 95% confidence interval [CI] 30–67%) and ORR was 31% (five of 16; 95% CI 11–59%). The ORR in nonirradiated lesions was 33% (four of 12; 95% CI 10–65%). Median rPFS was 8.4 mo (95% CI 4.5–not reached [NR]) and median OS was 14.1 mo (95% CI 8.9–NR). Grade

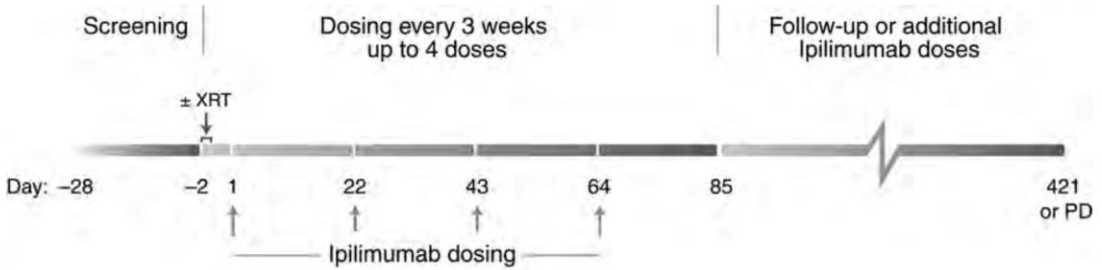
Grade 3–4 treatment-related adverse events occurred in six patients (16%), with three (10%) requiring high-dose corticosteroid therapy.



Ipilimumab alone or in combination with radiotherapy in metastatic castration-resistant prostate cancer: results from an open-label, multicenter phase I/II study

Annals of Oncology 24: 1813–1821, 2013
doi:10.1093/annonc/mdt107
Published online 27 March 2013

S. F. Slovin[1*], C. S. Higano[2], O. Hamid[3], S. Tejwani[4], A. Harzstark[5], J. J. Alumkal[6], H. I. Scher[1], K. Chin[7], P. Gagnier[7], M. B. McHenry[7] & T. M. Beer[6]



Design:
- Phase 1 – Dose escalation: 3, 5 or 10 mg/kg Ipi, then 3 or 10 mg/kg Ipi ± XRT (single dose of 8 Gy/lesion, up to 3 lesions per patient)
- Phase 2 – Cohort expansion: 10 mg/kg ± XRT cohorts

Endpoints:
- Safety
- PSA response at Day 85, overall PSA response, and tumor response by RECIST

Response assessments:
- PSA: Days 22, 43, 64, 85, then monthly
- Tumor: Day 85, then every 3 months

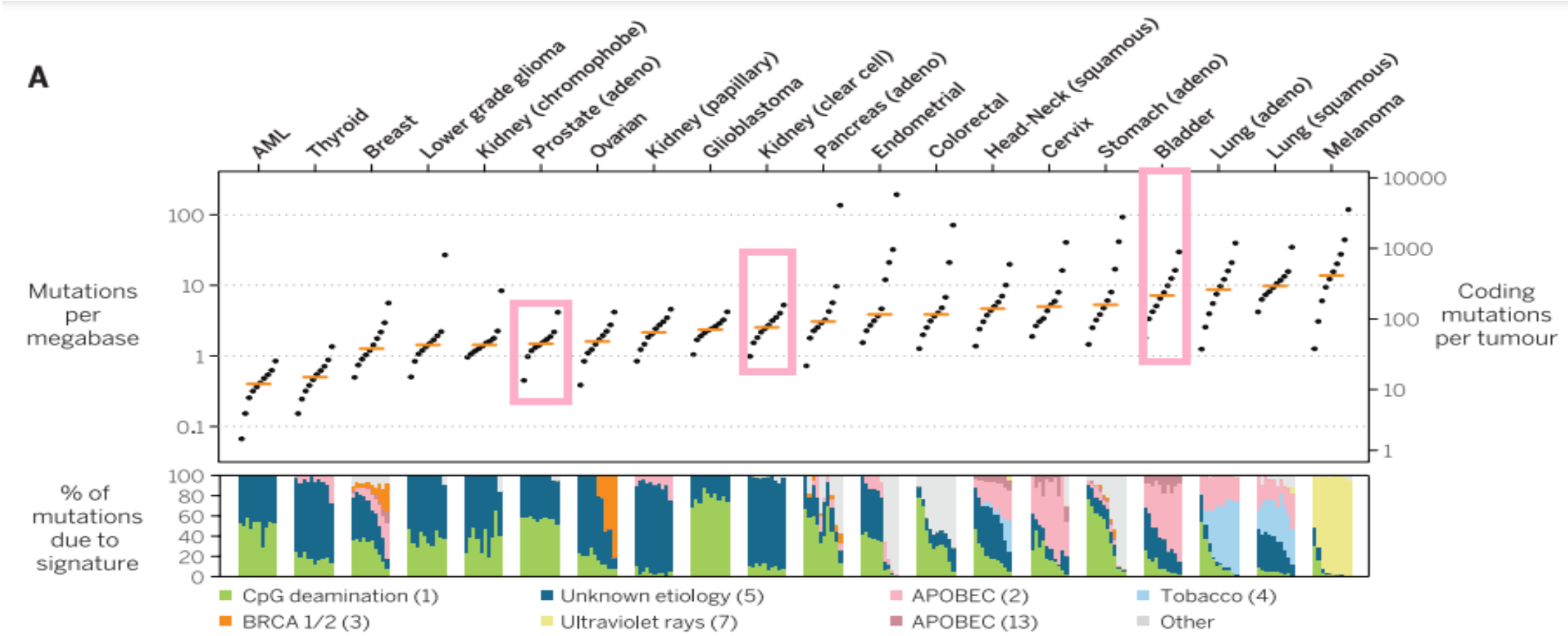
- Modest clinical response with high toxicities!!

Characteristic	Ipilimumab dose					
	3 mg/kg		5 mg/kg	10 mg/kg		
	−XRT ($n = 8$)	+XRT ($n = 7$)	−XRT ($n = 6$)	−XRT ($n = 16$; %)	+XRT ($n = 34$; %)	±XRT ($n = 50$; %)
Discontinued	8	7	6	13 (91)	32 (94)	45 (90)
Progressive disease	6	5	4	10 (63)	22 (65)	32 (64)
AE	2	1	1	1 (6)	3 (9)	4 (8)
irAE	1	1	1	1 (6)	1 (3)	2 (4)
Death	0	0	1	1 (6)	5 (15)	6 (12)
Treatment-related	0	0	1[b]	0	0	0
Unrelated to treatment	0	0	0	1 (6)[c]	5 (15)[d]	6 (12)
Other	0	1[e]	0	0	1 (3)	1 (2)
Lost to follow-up	0	0	0	1 (6)	1 (3)	2 (4)
Completed scheduled follow-up[f]	0	0	0	3 (19)	2 (6)	5 (10)

Clinical Trials of Immunotherapy and Radiotherapy in Prostate Cancer

Study	Phase	Intervention	Patient Population	Status
NCT01436968 [PrTK03]	III	Aglatimagene besadenovec + valacyclovir + standard RT	Intermediate or high risk (1 high risk feature), M0	Active, not recruiting
NCT02107430	II	Dendritic cells DCVAC/PCa + standard RT	High or very high risk	Completed
NCT03543189	I/II	Nivolumab + brachytherapy + EBRT	Grade group 5, any PSA or T stage	Recruiting
NCT01807065	II	Sipuleucel-T + EBRT	mCRPC	Completed
NCT03795207 [POSTCARD]	II	Durvalumab + SBRT	Biochemical recurrence (BCR), M0	Recruiting
NCT05361798	II	Immunocytokine M9241 + SBRT	BCR, ≤5 bone or LN metastases	Recruiting
NCT01818986	II	Sipuleucel-T + SBRT	mCRPC	Completed
NCT04071236	I/II	Avelumab + radium Ra 223 dichloride	mCRPC	Recruiting
NCT02232230	Retrospective observational	Provenge + RT	mCRPC	Completed
NCT03007732	II	Pembrolizumab + SBRT +/- intratumoral SD-101	mCSPC	Recruiting
NCT00005916	II	PSA-Based Vaccine + RT	Treatment naïve local disease	Completed
NCT04946370	I/II	225Ac-J591 (a drug that can deliver radiation to prostate cancer cells) + pembrolizumab	mCRPC	Recruiting
NCT03217747	I/II	Avelumab + utomilumab + RT	mCRPC	Active, not recruiting
NCT02463799	II	Radium-223 + sipuleucel-T	mCRPC	Completed

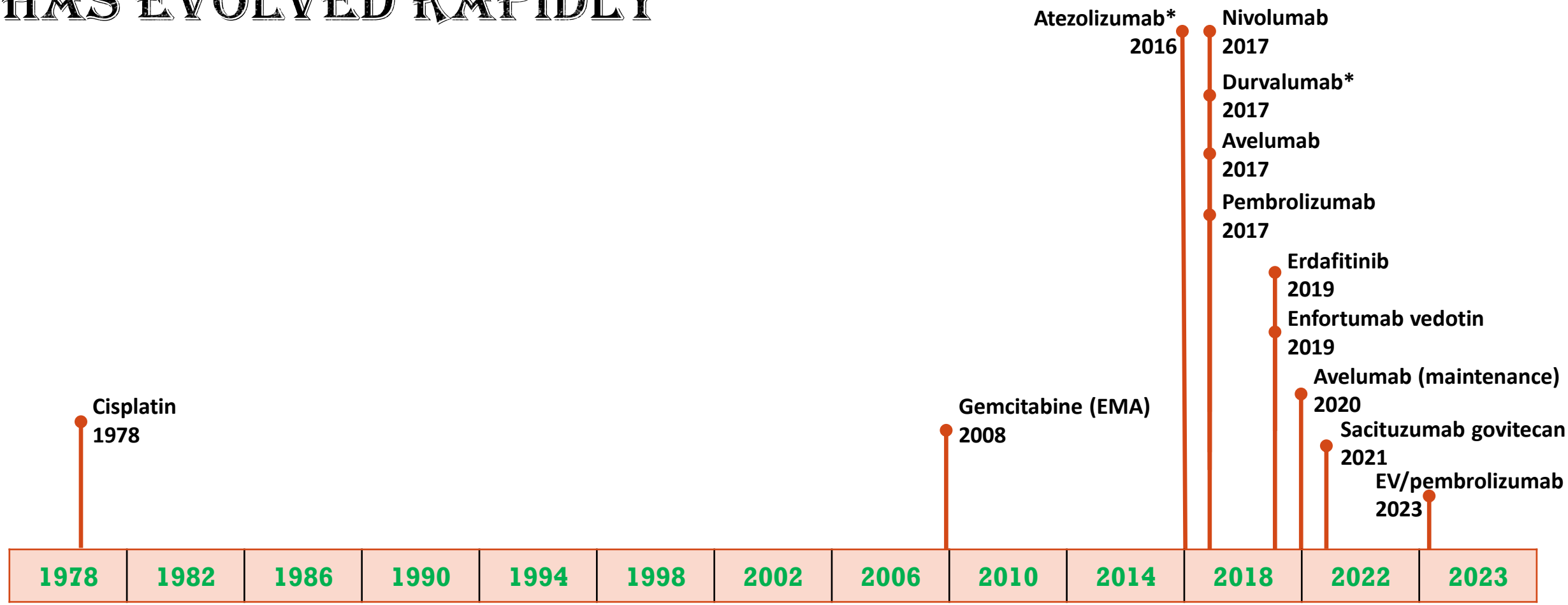
ROLE OF IMMUNE SYSTEM IN ADVANCED BLADDER CANCER



High mutational load may match up with immunogenicity and presents valuable prognostic information

Martincorena, I., & Campbell, P. J. (2015). Somatic mutation in cancer and normal cells. *Science (New York, N.Y.)*, *349*(6255), 1483–1489. https://doi.org/10.1126/science.aab4082

The treatment landscape for locally advanced/ metastatic urothelial carcinoma has evolved rapidly



*Not FDA approved; indication withdrawn.

Cisplatin PI. ema.europa.eu/en/medicines/human/referrals/gemzar. Rhea. Clin Med Insights Oncol. 2021;15:11795549211044963.
Nivolumab PI. Avelumab PI. Pembrolizumab PI. Erdafitinib PI. Enfortumab vedotin PI. Avelumab PI. Sacituzumab govitecan PI.

FRONTLINE MANAGEMENT OF METASTATIC UROTHELIAL CARCINOMA

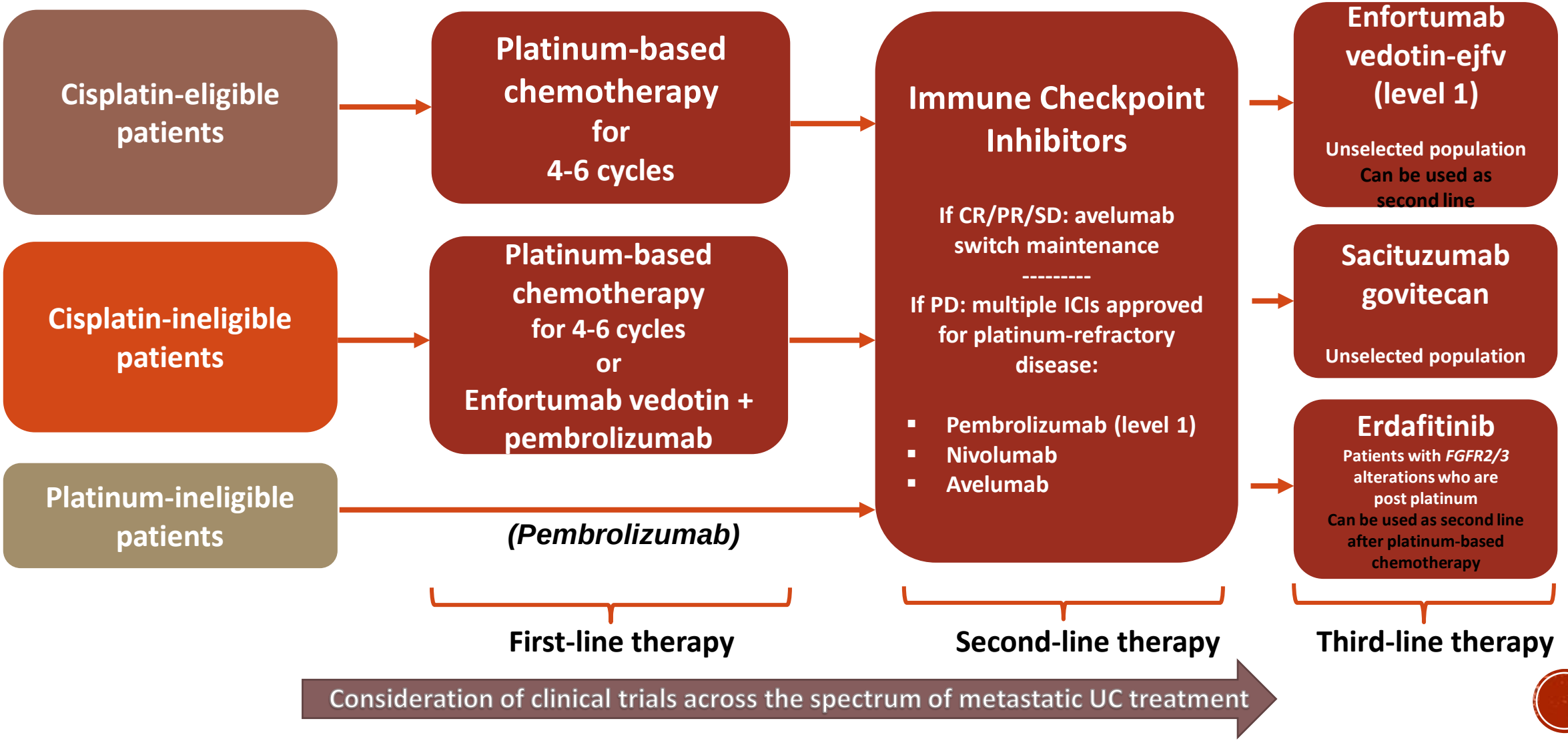
PRINCIPLES OF SYSTEMIC THERAPY

First-Line Systemic Therapy for Locally Advanced or Metastatic Disease (Stage IV)	
Cisplatin eligible	**Preferred regimens** • Gemcitabine and cisplatin[4] (category 1) followed by avelumab maintenance therapy (category 1)[a,11] • DDMVAC with growth factor support (category 1)[2,8] followed by avelumab maintenance therapy (category 1)[a,11]
Cisplatin ineligible	**Preferred regimens** • Gemcitabine and carboplatin[12] followed by avelumab maintenance therapy (category 1)[a,11] • Pembrolizumab[14] (for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for any platinum-containing chemotherapy) **Other recommended regimens** • Gemcitabine[15] • Gemcitabine and paclitaxel[16] • Atezolizumab[13] (only for patients whose tumors express PD-L1[b]) (category 2B) **Useful under certain circumstances** • Ifosfamide, doxorubicin, and gemcitabine[17] (for patients with good kidney function and good performance status) • Atezolizumab[13] (only for patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 expression) (category 3)

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Bladder Cancer V1.2023. © National Comprehensive Cancer Network, Inc 2023.

How do we sequence these agents?

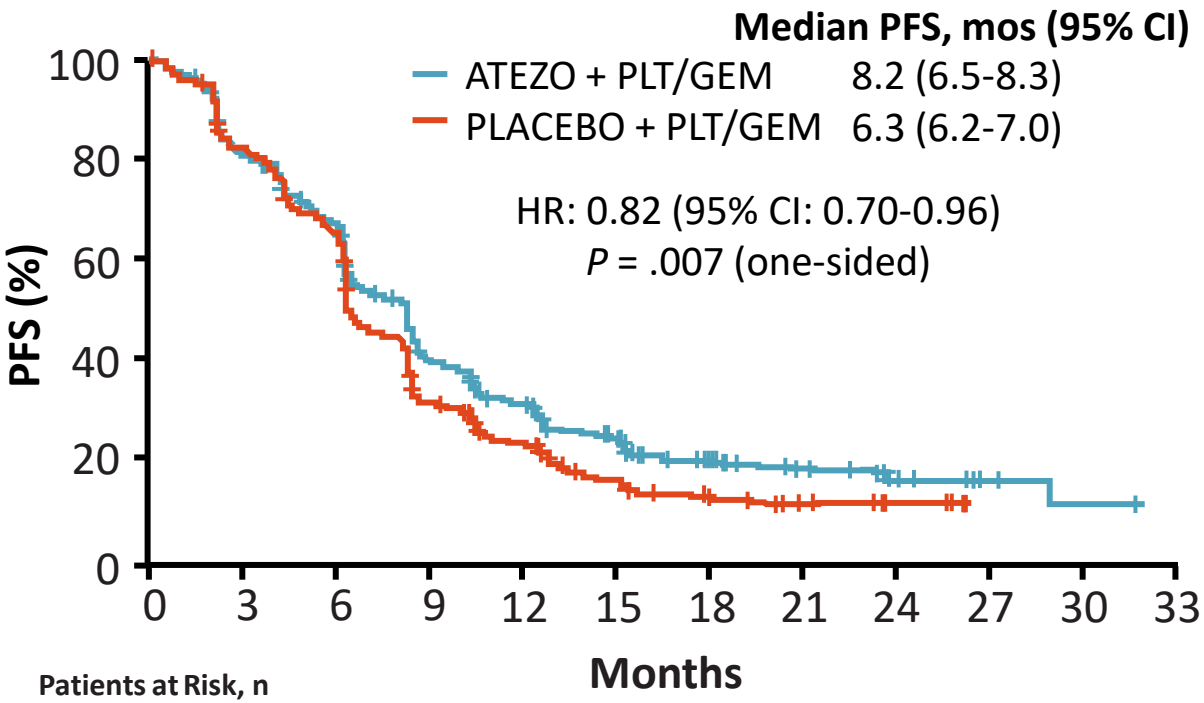
Current Treatment Landscape in Metastatic Urothelial Carcinoma



ROLE OF CHEMO + ANTI-PD-1/PD-L1

LEADS TO MINOR IMPROVEMENTS IN PFS IN ITT

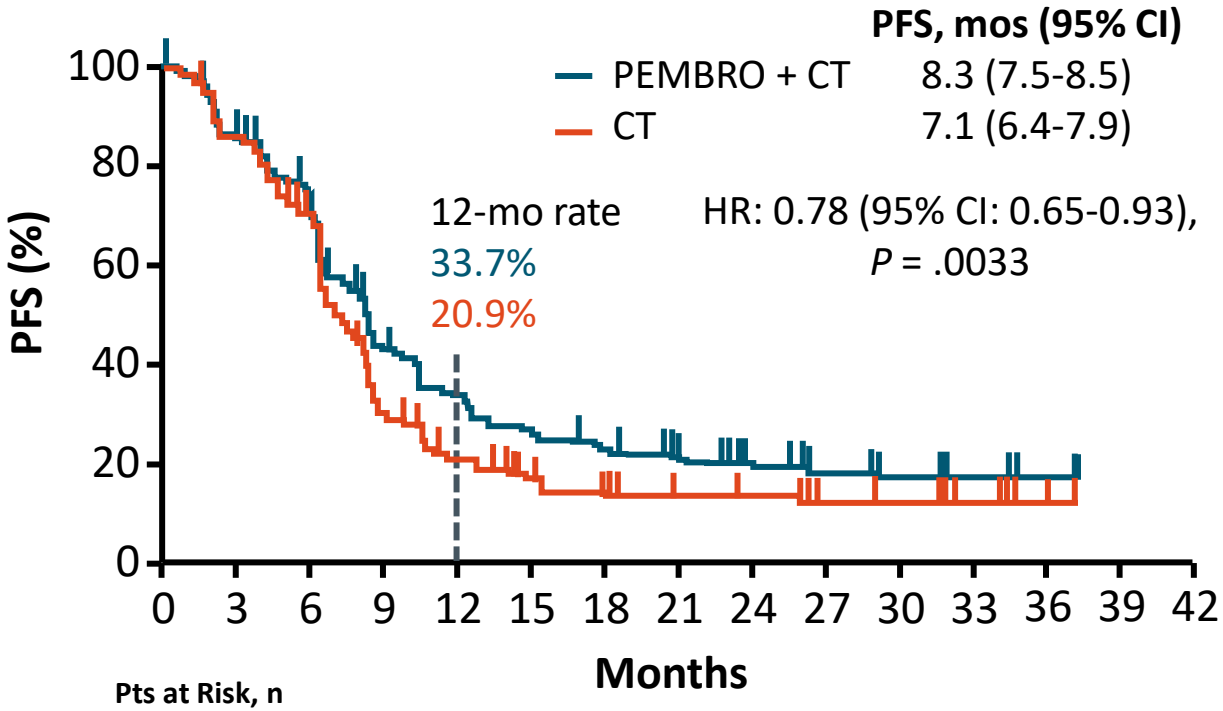
IMvigor130: PFS (ITT)



Patients at Risk, n

Atezo + plt/gem	451	345	282	160	111	74	42	22	10	4	2	NE
Placebo + plt/gem	400	317	246	116	73	40	18	11	4	NE	NE	NE

Keynote 361: PFS (ITT)



Pts at Risk, n

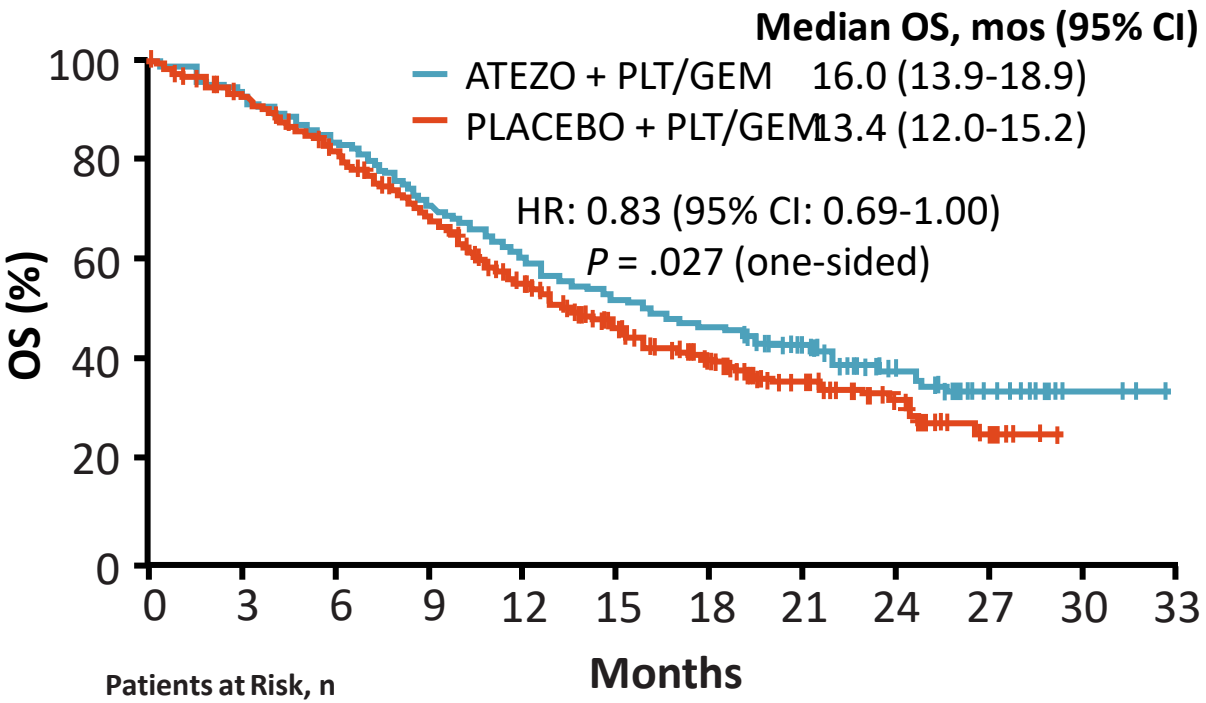
Pembro + CT	351	2882	243	135	102	79	67	55	36	27	18	9	3	0	0
CT	352	74	191	75	44	31	22	17	15	11	8	5	2	0	0

Galsky. Lancet. 2020;395:1547. Alva. ESMO 2020. Abstr LBA23.

CHEMO + ANTI-PD-1/PD-L1

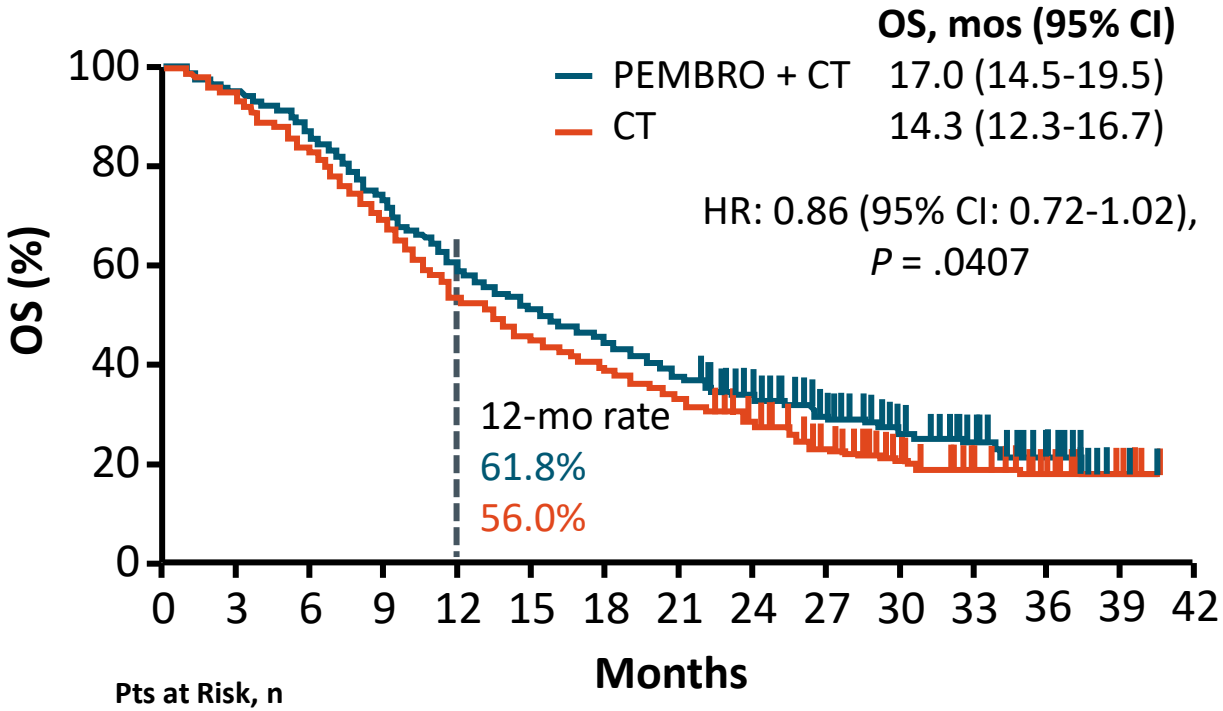
Non-Significant Improvements in OS in ITT

IMvigor130: OS (ITT)



Patients at Risk, n												
Atezo + plt/gem	451	408	360	301	229	163	117	72	36	16	3	NE
Placebo + plt/gem	400	359	308	255	182	123	79	49	25	8	NE	NE

Keynote 361: OS (ITT)

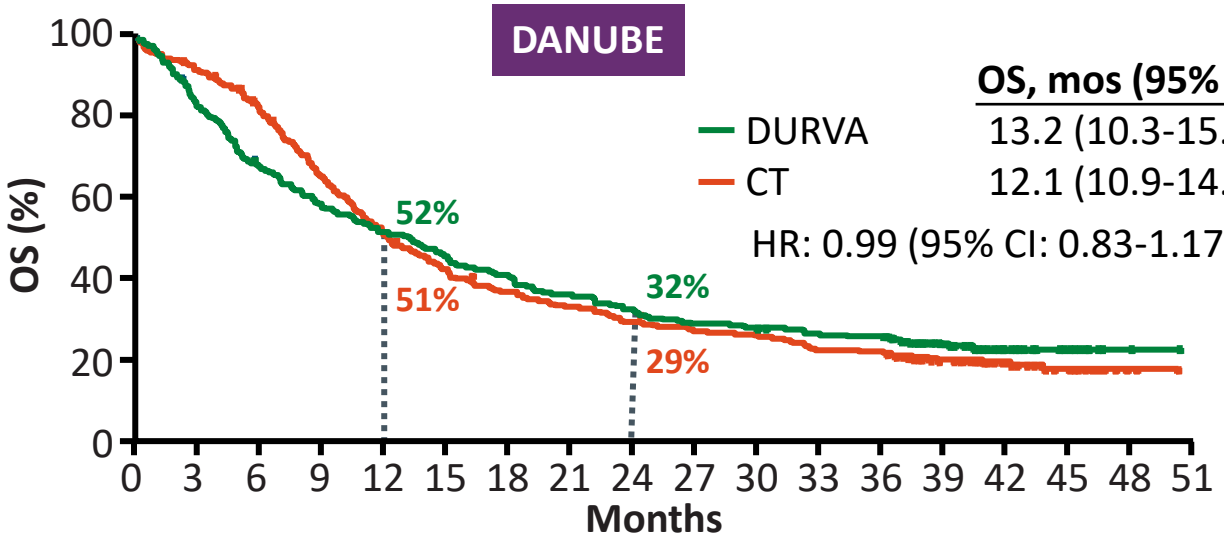


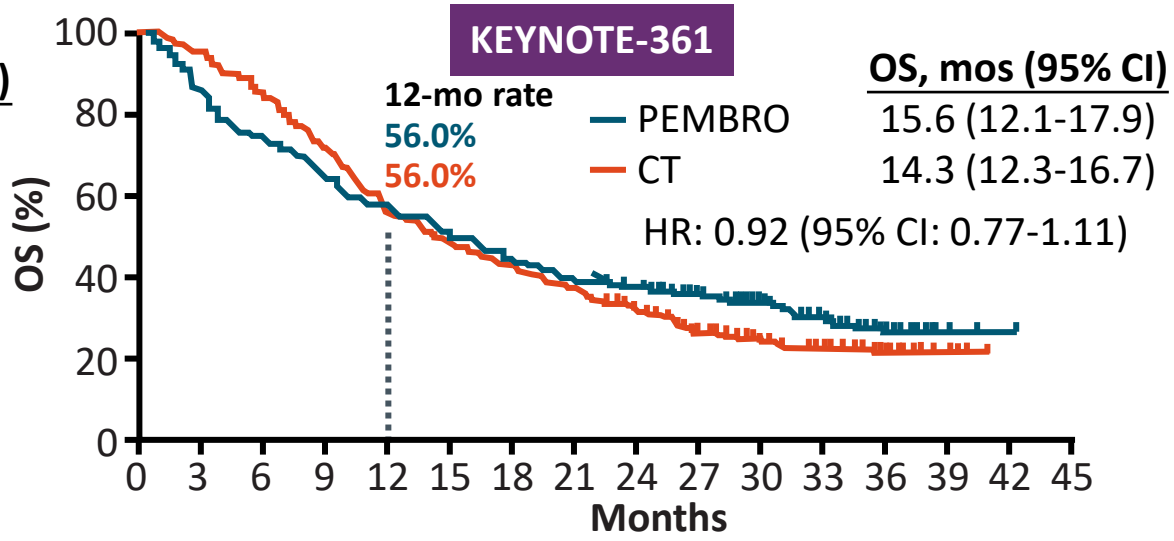
Pts at Risk, n															
Pembro + CT	351	335	306	263	217	189	168	146	118	84	56	36	17	3	0
CT	352	335	297	250	197	169	150	129	104	71	46	33	20	7	0

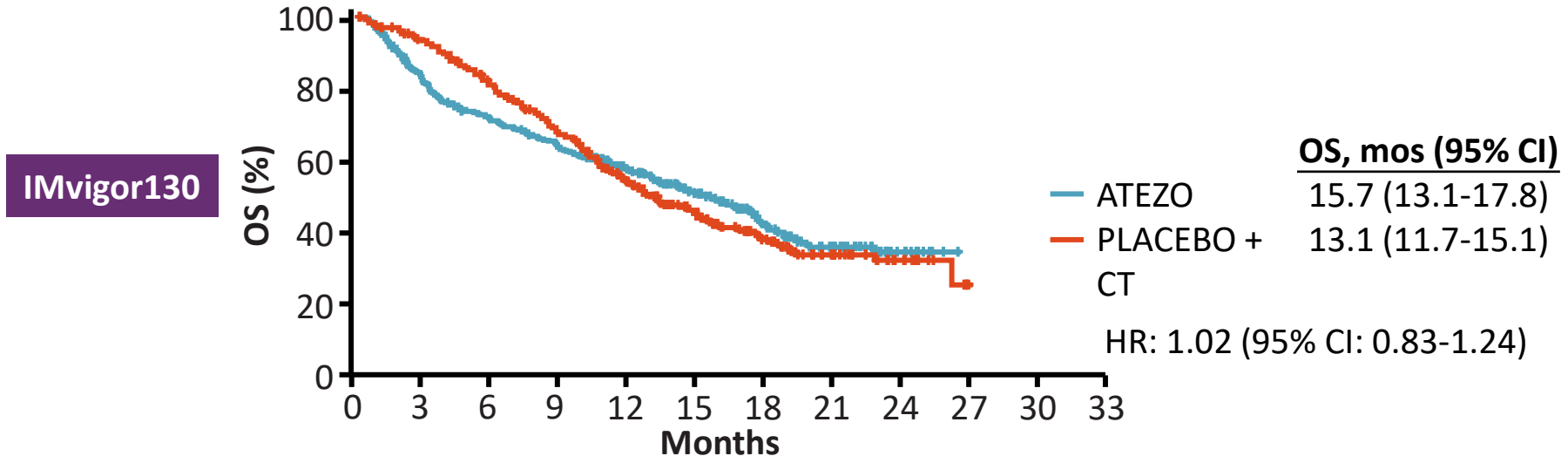
Galsky. Lancet. 2020;395:1547. Alva. ESMO 2020. Abstr LBA23.

ROLE OF ANTI-PD-1/PD-L1 UPFRONT

OS With Platinum-Based Chemo vs Anti-PD-1/PD-L1 in ITT Populations





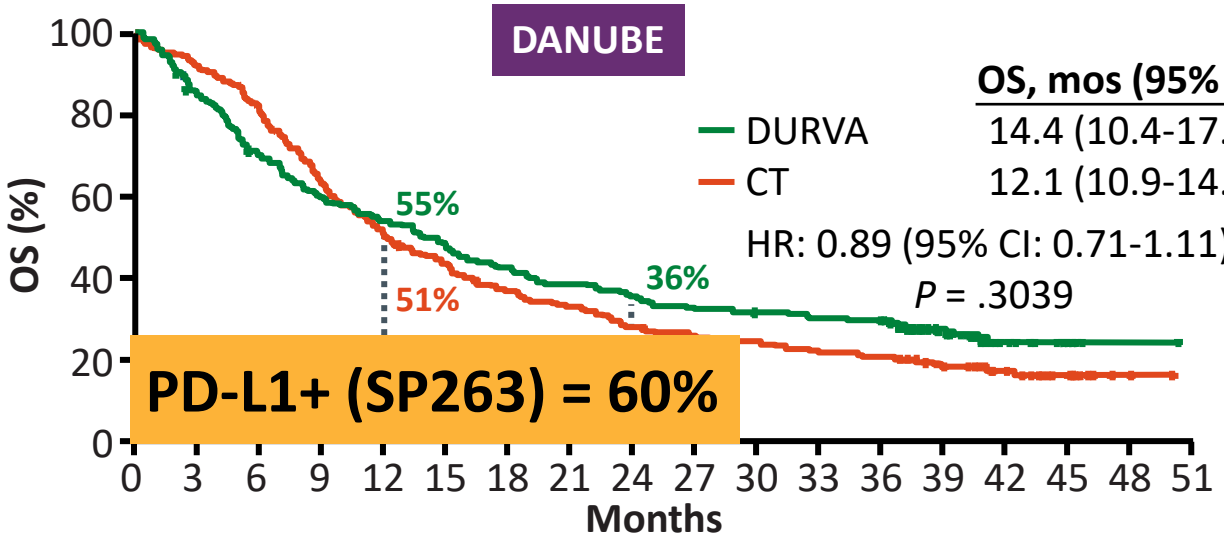


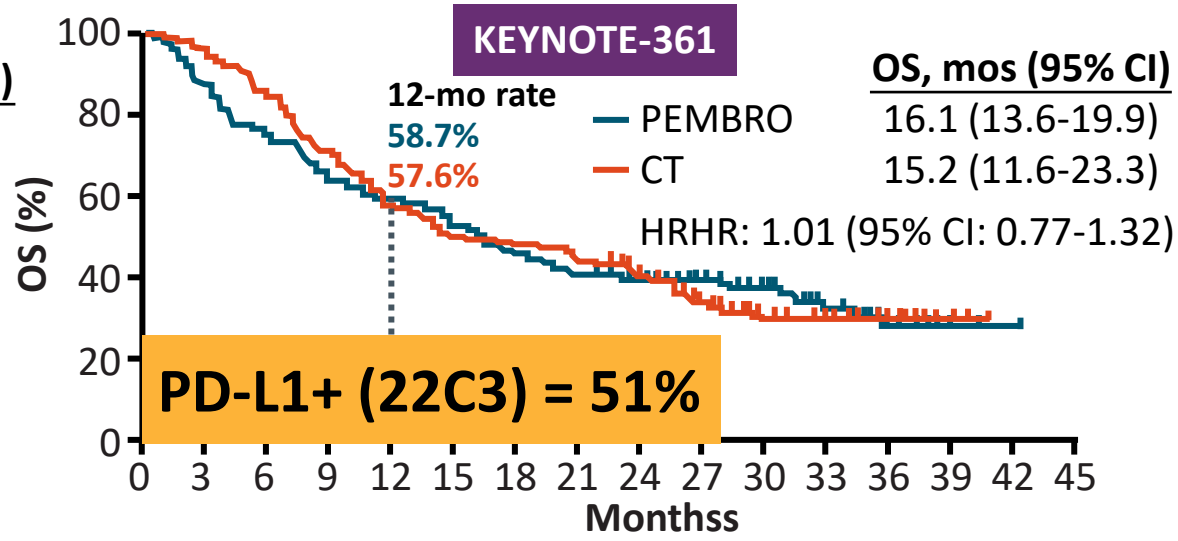
Galsky. Lancet. 2020;395:1547. Alva. ESMO 2020. Abstr LBA23. Powles. Lancet Oncol. 2020;21:1574

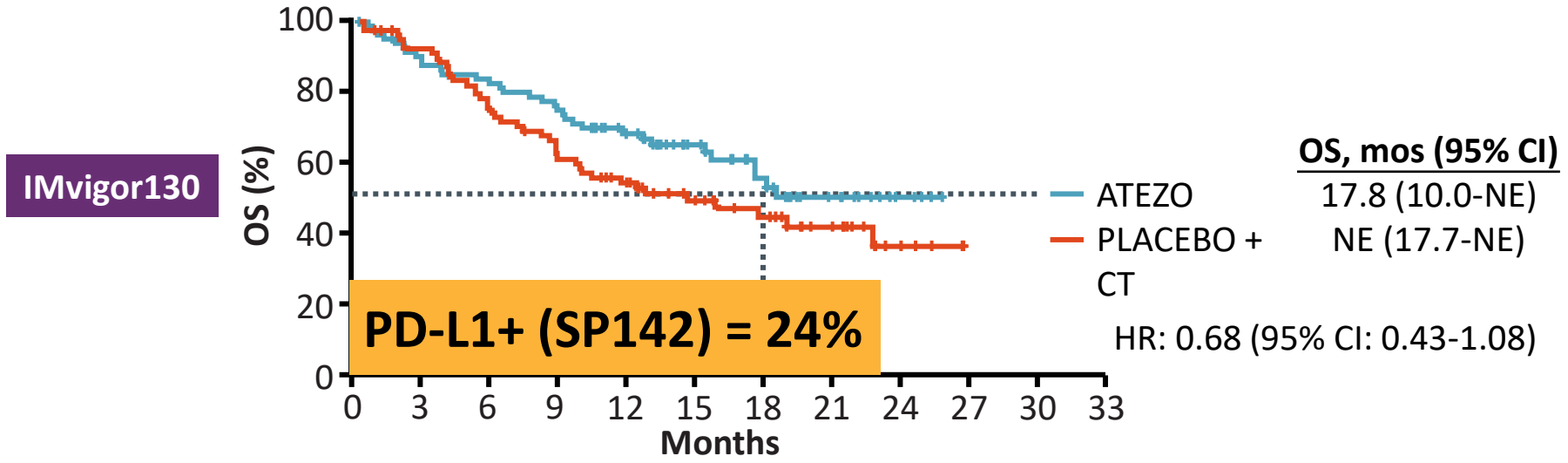
ROLE FOR BIOMARKER SELECTION FOR IMMUNOTHERAPY

Drug	Biomarker	Scoring
Pembrolizumab	22C3	TC + IC
Atezolizumab	SP142	IC
Nivolumab	28-8	TC
Durvalumab	SP263	TC + IC
Avelumab	73-10	TC + IC

OS FOR PLATINUM-BASED CHEMO VS ANTI-PD-1/PD-L1 IN PD-L1+ POPULATIONS



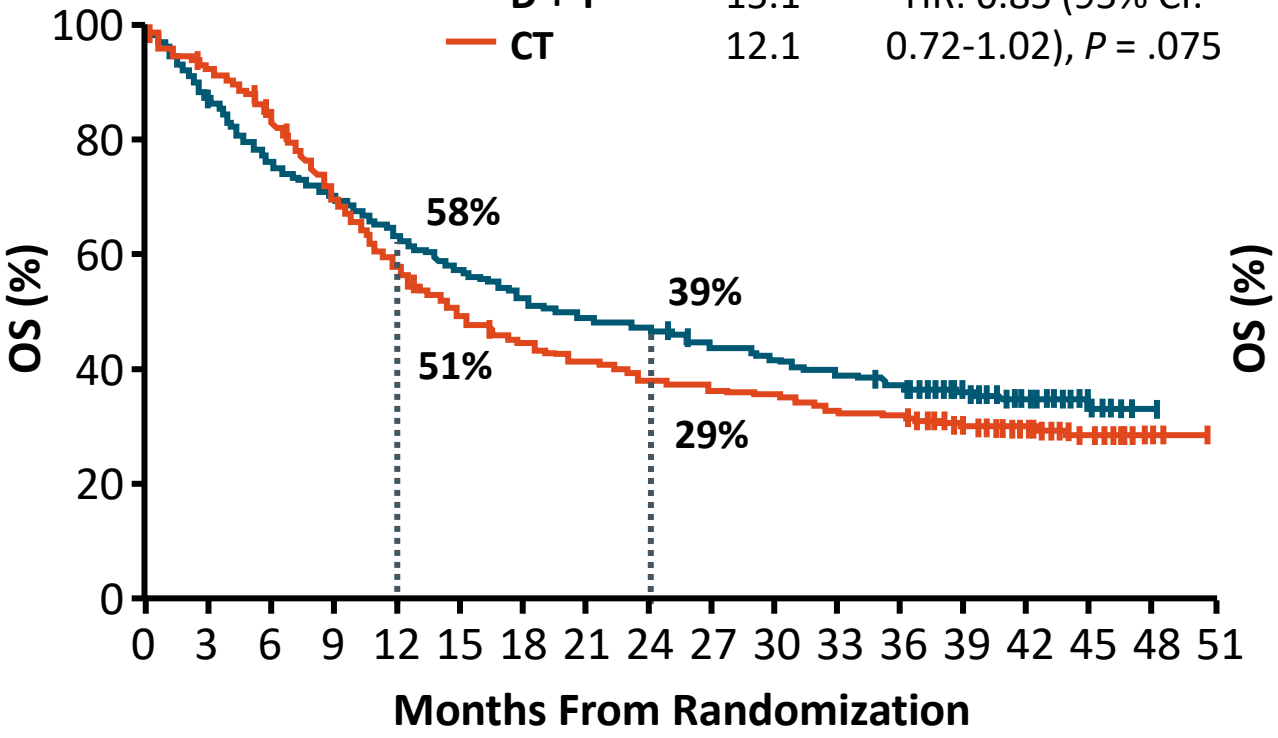




Galsky. Lancet. 2020, 395:1547. Alva. ESMO 2020. Abstr LBA23. Powles. Lancet Oncol. 2020;21:1574

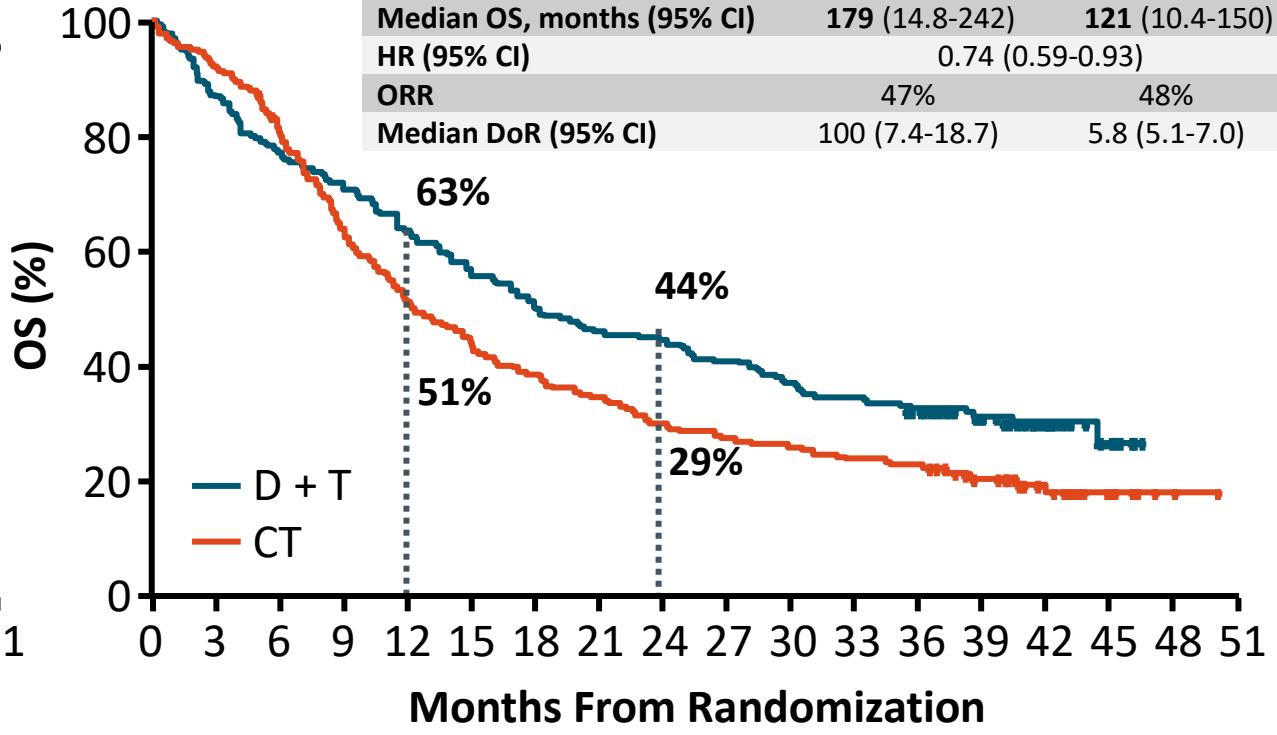
CAN ANTI-CTLA4 + PD-L1 ↑ ORR ENOUGH TO COMPETE WITH CHEMO?

DANUBE (ITT)



DANUBE (PDL1+)

	Duvalumab + Tremelimumab (n = 205)	Chemotherapy (n = 207)
Median OS, months (95% CI)	**179** (14.8-242)	**121** (10.4-150)
HR (95% CI)	0.74 (0.59-0.93)	
ORR	47%	48%
Median DoR (95% CI)	100 (7.4-18.7)	5.8 (5.1-7.0)

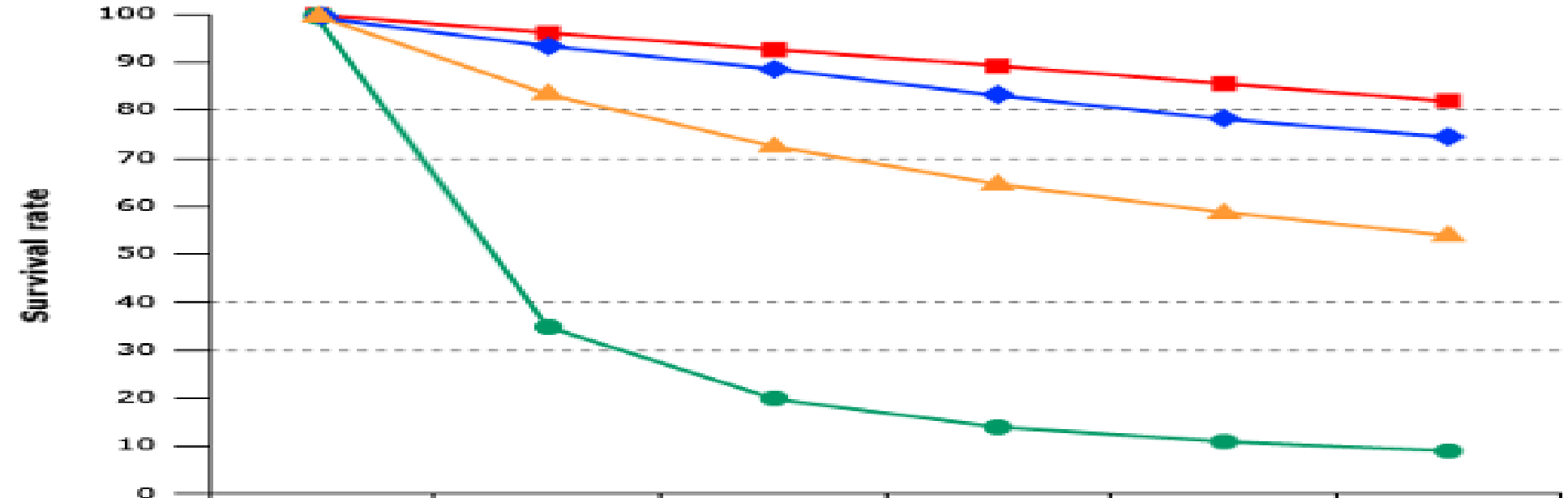


Powles. Lancet Oncol. 2020;21:1574.

Clinical Trials of Immunotherapy and Radiotherapy in Bladder Cancer

Study	Phase	Intervention	Patient Stage	Status
NCT03529890 [RACE-IT]	II	Nivolumab + RT + radical cystectomy with pelvic lymphadenectomy	cT3 –T4 cN0/N + cM0	Active, not recruiting
NCT05445648 [CBPTMI]	II	Tislelizumab + TURBT + RT	cT2 –T4a N0M0	Not yet recruiting
NCT04543110 [RADIANT]	II	Durvalumab + RT	cT2 –T4a N0M0	Recruiting
NCT03702179 [IMMUNOPRESERVE]	II	NCT04216290 + tremelimumab + RT	cT2 –T4a N0M0	Active, not recruiting
NCT03747419	II	Avelumab + RT	≥pT2, cN0M0	Recruiting
NCT04216290 [INSPIRE]	II	durvalumab + RT + chemotherapy	Any T, any N, M0	Recruiting
NCT04902040	I/II	Plinabulin + RT+ atezolizumab or Avelumab or durvalumab or Nivolumab or Pembrolizumab	Any T, any N, M+	Recruiting
NCT04936230	II	Atezolizumab + SBRT	Any T, any N, pM+	Recruiting
NCT03617913	II	Avelumab + RT + cisplatin chemotherapy	pT2 –T4a N0M0	Completed
NCT03697850 [BladderSpar]	II	Atezolizumab + chemo-radiotherapy	pT2 –T3 cM0	Recruiting
NCT02621151	II	Pembrolizumab + EBRT + gemcitabine + TURBT	T2 –T4a, N0M0	Active, not recruiting
NCT03693014	II	SBRT + ipilimumab + nivolumab + pembrolizumab + atezolizumab	Any T, any N, M+	Recruiting
NCT03775265	III	Atezolizumab + chemoradiotherapy	T2 –T4a N0M0	Recruiting
NCT05241340 [RAD-VACCINE]	II	Sasanlimab + SBRT + radical cystectomy	cT2 –4a N0M0	Recruiting
NCT03915678 [AGADIR]	II	Atezolizumab + BDB001 (toll-like receptor agonist) + RT	cM+	Recruiting
NCT04977453	I/II	GI-101 + RT	“Advanced and/or metastatic”	Recruiting
NCT04241185 [KEYNOTE-992]	III	Pembrolizumab + RT + ciplatin + 5-FU + Mytomycin C + gemcitabine vs. Placebo to pembrolizumab	cT2 –T4, N0M0	Recruiting
NCT03768570	II	Trimodality therapy +/- durvalumab	cT2 –T4 N0M0	Recruiting

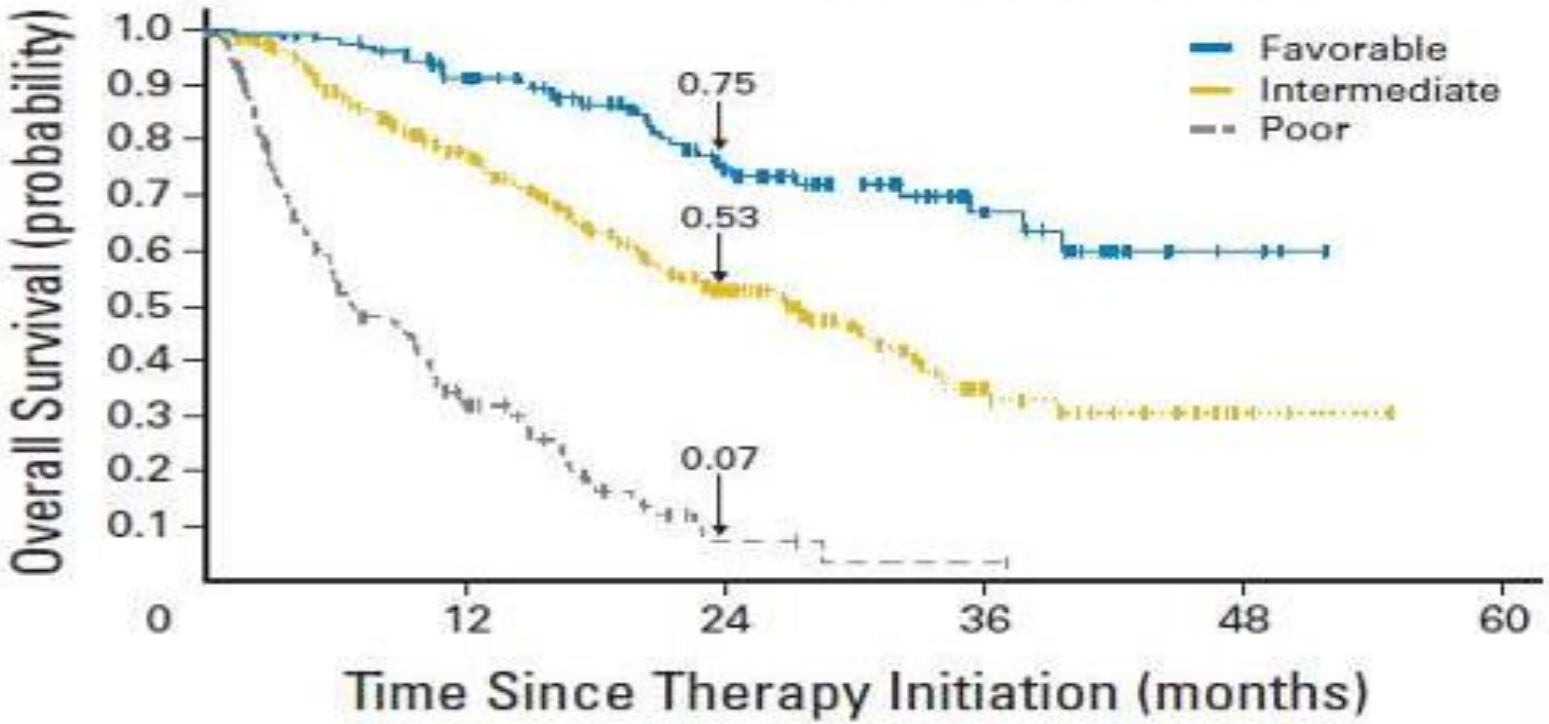
SURVIVAL IN RENAL CANCERS



	0	1	2	3	4	5
I	100.0	95.4	92.2	88.7	85.1	80.9
II	100.0	93.9	88.8	83.1	78.3	73.7
III	100.0	83.6	72.3	64.9	58.2	53.3
IV	100.0	34.2	19.4	13.4	10.0	8.2

Years from diagnosis

IMDC PROGNOSTIC SCORE



No. of events/No. at risk					
Favorable	11/133	16/110	4/62	2/22	0/3
Intermediate	61/301	50/182	17/82	2/18	0/3
Poor	94/152	19/36	1/3	0/1	0/0

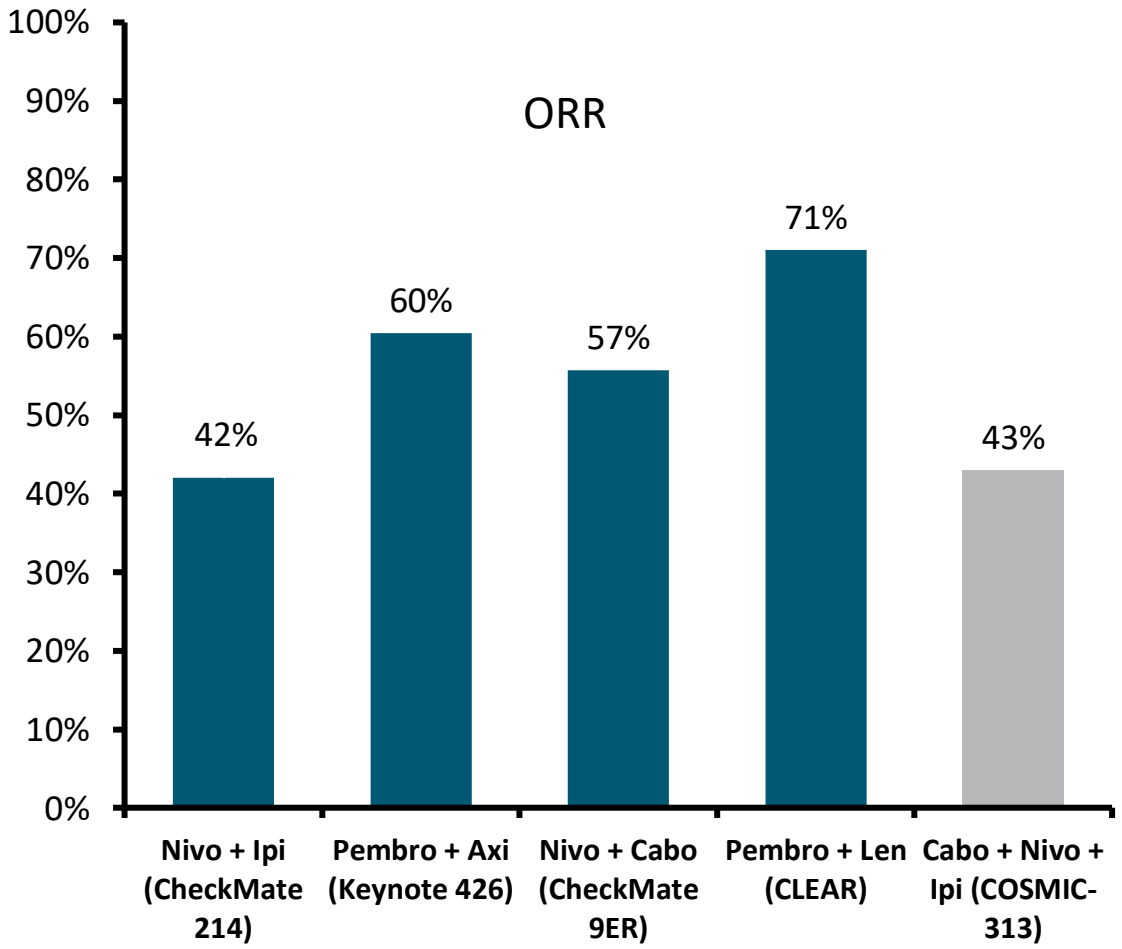
FIRST LINE IMMUNOTHERAPY TRIALS IN M-RCC

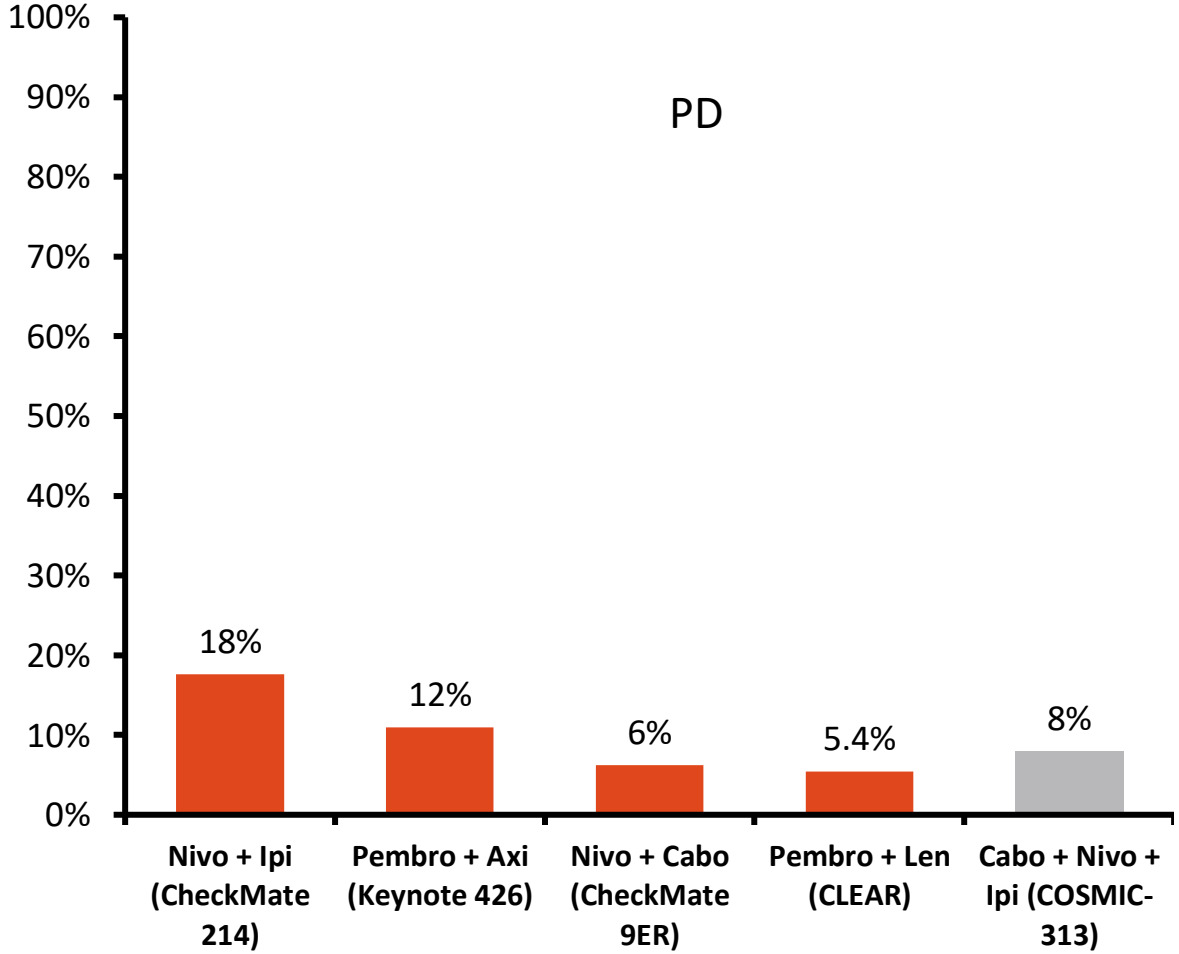
Efficacy Endpoints	CheckMate 214*[1] Ipi/Nivo (N = 1096)	KEYNOTE-426[2,3] Axi/Pembro (N = 861)	CheckMate 9ER[4] Cabo/Nivo (N = 651)	CLEAR[5,6] Len/Pembro (N = 1069)	COSMIC-313[7] Cabo/Nivo/Ipi (N = 855)
Median PFS, mo HR (95% CI)	12.3 0.86 (0.73-1.01)	15.7 0.69 (0.59-0.81)	16.6 0.58 (0.48-0.71)	23.9 0.47 (0.38-0.57)	NR 0.73 (0.57-0.94))
Median OS, mo HR (95% CI)	55.7 0.72 (0.62-0.85)	47.2 0.84 (0.71-0.99)	49.5 0.70 (0.56-0.87)	53.7 0.79 (0.63-0.99)	- -
ORR/CR, %	42/12	61/12	56/12	71/18	43/3
Sarcomatoid Features, %	13	12	11.5	7.9	NA
AEs leading to d/c	23	10.7	7	37.2	45
IMDC or MKSCC Risk F/I/P, %	23/61/17	32/55/13	23/58/20	31/59/9	0/75/25
Median follow-up, (months)	67.7	67	44.0	48	14.9

*Intermediate/poor risk group only

1. Motzer. Cancer. 2022;128:2085. 2. Rini. ASCO 2021. Abstr 4500. 3. Rini. ASCO 2023. Abstr LBA4501. 4. Burotto. ASCO GU 2023. Abstr 603. 5. Choueiri. Lancet Oncol. 2023;24:228. 6. Motzer. ASCO 2023; Abstr 4502. 7. Choueiri. NEJM. 2023;388:1767.

CROSS-TRIAL COMPARISON OF RESPONSE IN ITT POPULATION





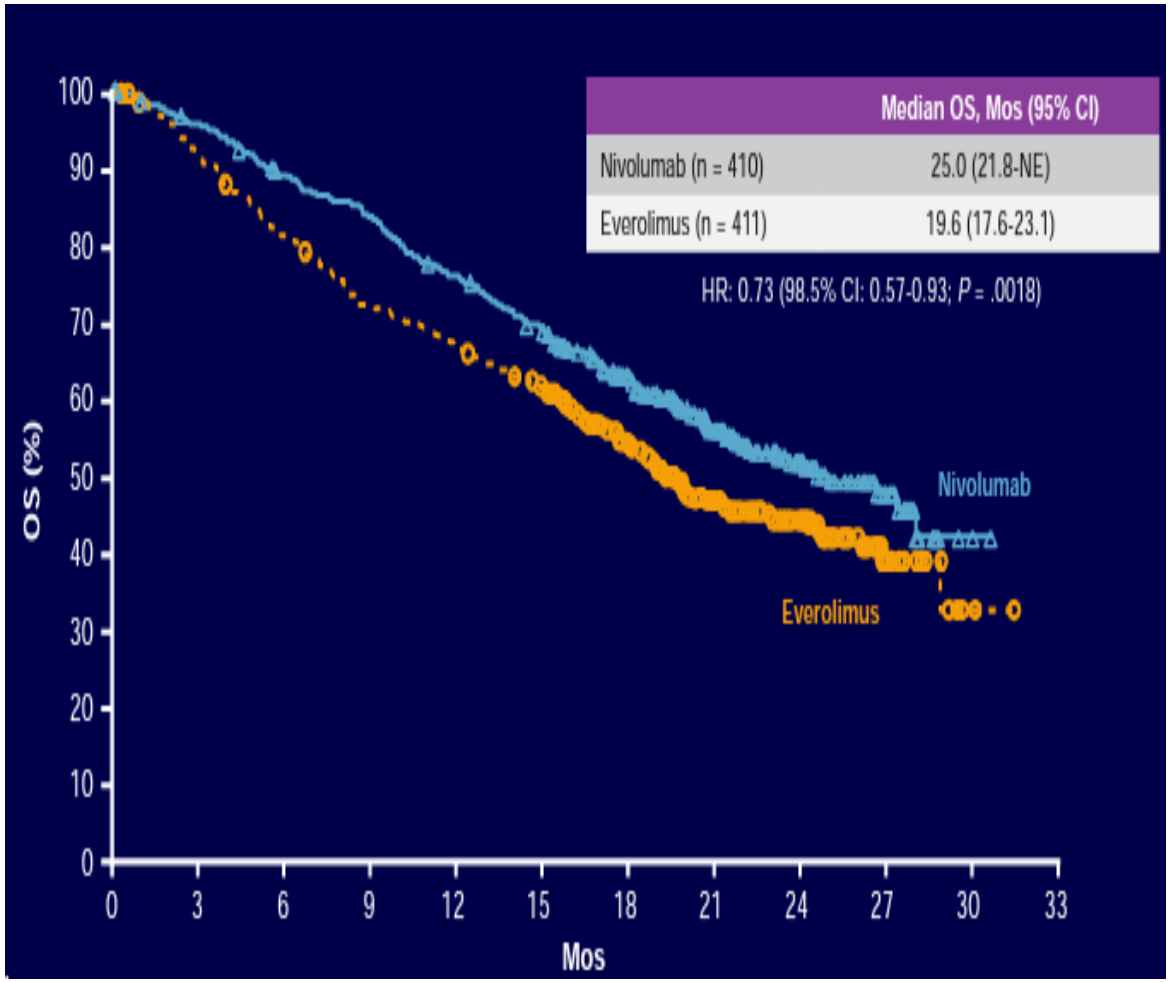
CHECKMATE-025: NIVOLUMAB IN PREVIOUSLY TREATED METASTATIC RCC NIVOLUMAB METASTATIC RCC WITH ≤ 2 PRIOR ANTIANGIOGENIC THERAPIES AND ≤ 3 TOTAL PRIOR SYSTEMIC REGIMENS (N = 821)

Metastatic RCC with ≤ 2 prior antiangiogenic therapies and ≤ 3 total prior systemic regimens (N = 821)

Nivolumab
3 mg/kg IV every 2 wks

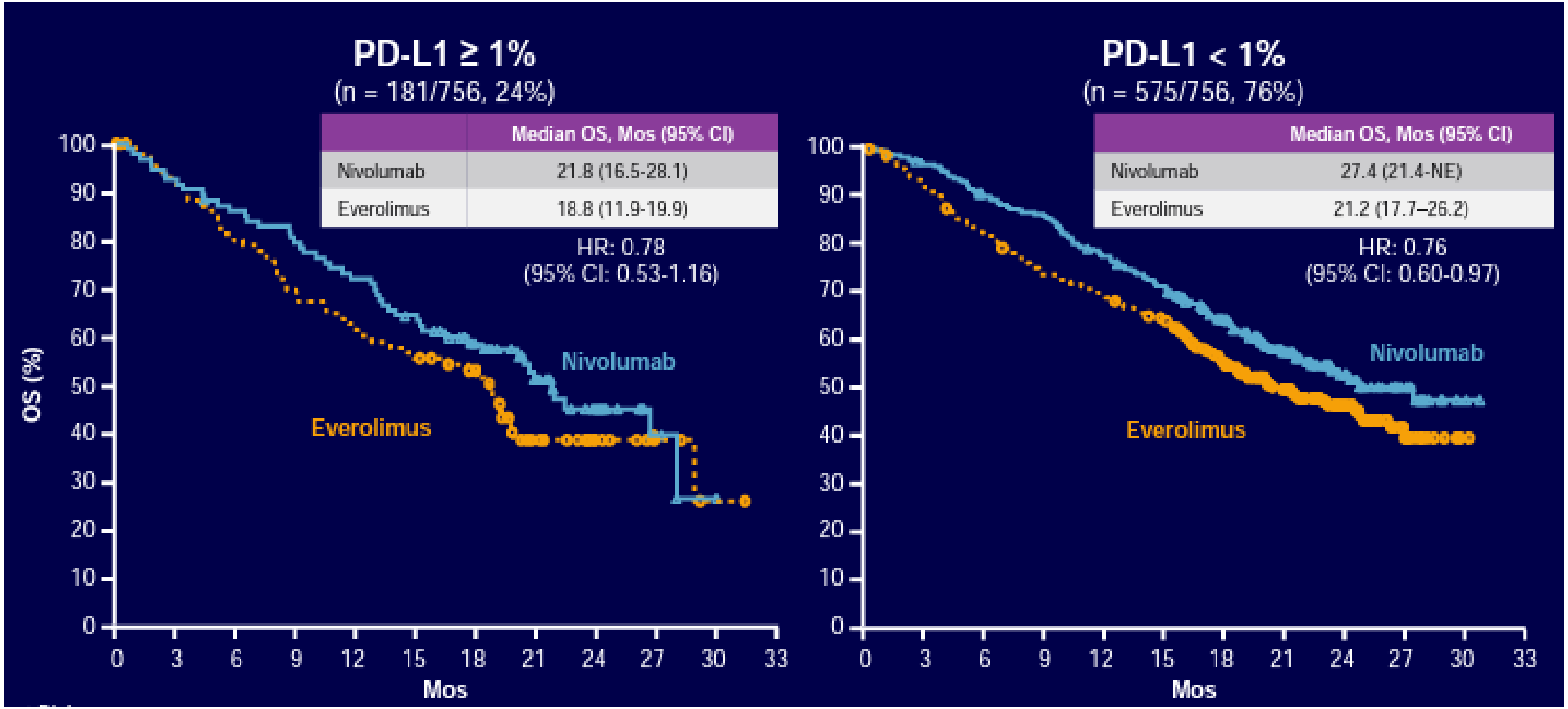
Everolimus
10 mg PO daily

- Primary endpoint: OS
- Secondary endpoints: PFS, ORR, OR duration, Safety



Motzer R, et al. N Engl J Med. 2015;373:1803-1813

CHECKMATE-025: OS BY PD-L1 EXPRESSION PD-L1 < 1%



- IO has an established role in the treatment of mRCC (Nivolumab)
- New standard established with recent IO data in first line mRCC (int/ poor risk)
- A number of ongoing studies in the first line setting with IO combination studies show promise
- Cost and access present a major challenge which needs to be overcome

Clinical Trials of Immunotherapy and Radiotherapy in Renal Cancer

Study	Eligibility	Design	Intervention	Planned Enrollment
NCT01896271	Metastatic ccRCC	Phase II	SBRT + HD IL-2	26
NCT03065179	Metastatic ccRCC	Phase II	SBRT + Nivolumab + Ipilimumab	29
NCT02306954	Metastatic RCC	Phase II	HD IL-2 ± SBRT	84
NCT02781506	Metastatic ccRCC	Phase II	SBRT + Nivolumab	7
NCT01884961	Metastatic ccRCC	Phase II	SBRT + HD IL-2	35
NCT03050060	Metastatic ccRCC	Phase II	hypofractionated RT + Nelfinavir + (Pembrolizumab or Nivolumab or Atezolizumab)	120
NCT02599779	Metastatic RCC	Phase II	SBRT + Pembrolizumab	35
NCT03115801	Metastatic RCC	Phase II	Nivolumab ± RT	112
NCT03469713	Metastatic RCC	Phase II	SBRT + Nivolumab	69
NCT03511391	RCC	Phase II	Nivolumab ± SBRT	99
NCT02992912	Metastatic RCC	Phase II	SBRT + Atezolizumab	187
NCT04090710	Metastatic RCC	Phase II	Ipilimumab/Nivolumab± SBRT	78

Practical considerations of combining RT with immunotherapy: Sequencing /dose fractionation

- Pre-clinical studies have shown that dose per fraction greater than 6–8 Gy are required to produce an effective immunogenic response.
- A multi-fractionated regimen was superior to single dose regimens in decreasing tumor growth at non-irradiated sites.
- In bladder cancer mouse models, ICIs were more effective when combined with a 10 Gy ×2 or 6.25 Gy×2 RT regimens than with a 10 Gy×1 regimen.
- Optimal sequencing of immunotherapy and RT, the optimal immunotherapy agent and its duration, and the role of chemotherapy need to be elucidated.
- Additionally, details regarding the RT, such as the optimal dose/fractionation, target volume, and site to irradiate are not known.

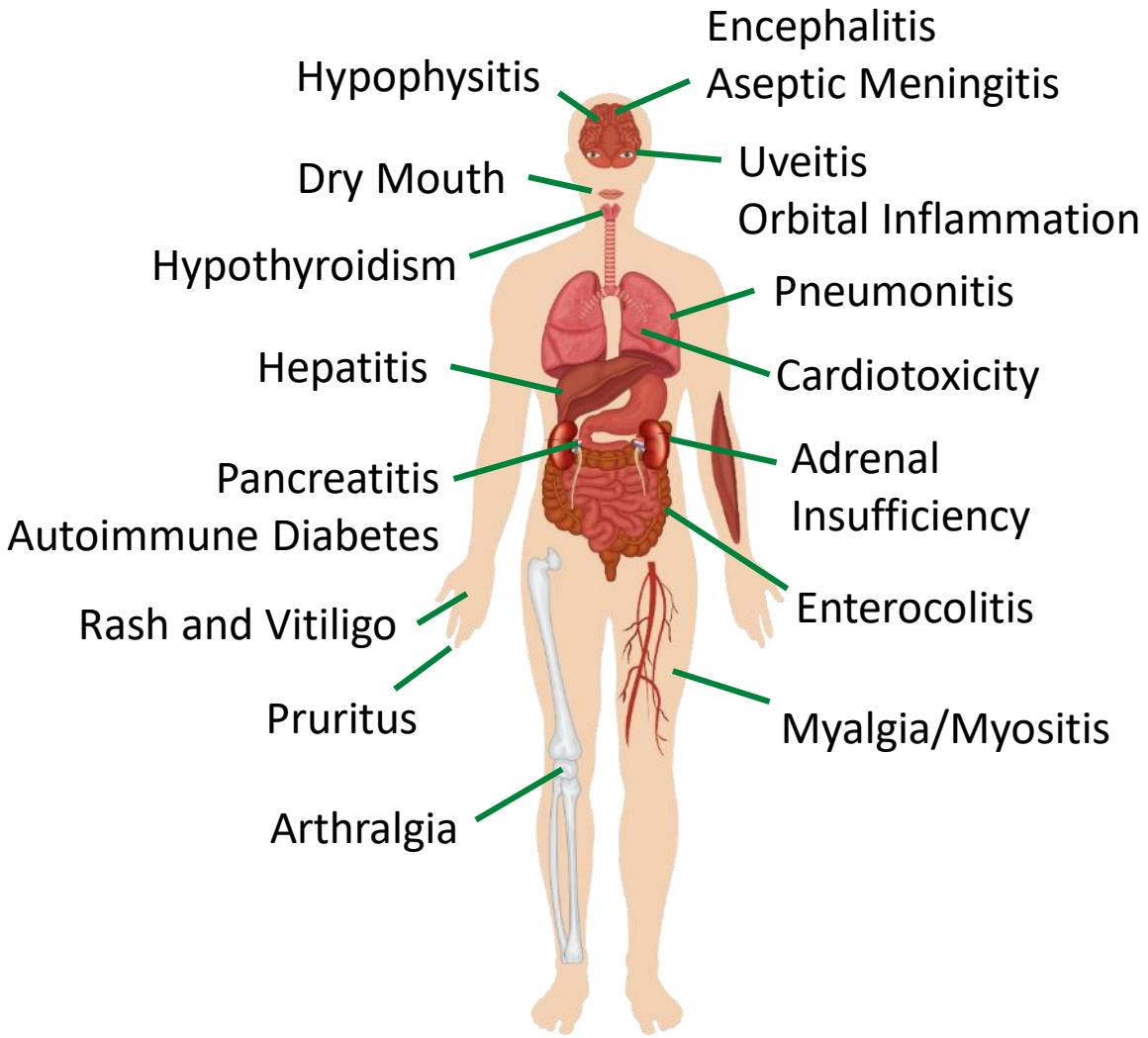
- Dovedi et al. found that 10 Gy directed to tumors in mice with colon cancer induced tumor cell PD-L1 expression, which peaked at 72 h and declined significantly in the 1st week. In this study, concurrent administration of anti- PD-L1 antibody, rather than after RT, led to improved survival.
- A similar increase in PD-L1 expression after RT was seen in an in vivo study of mice injected with murine bladder cancer, with improved survival with anti-PD-L1 antibody delivered concurrently.
- Young et al. compared the efficacy of anti-OX40 and anti-CTLA4 with 20Gy in a single fraction in a CT26 murine colorectal cancer model in mice. The investigators found that survival with RT and anti-OX40 was best if immunotherapy was delivered 1 day after RT, while survival with RT and anti-CTLA4 was best if immunotherapy was delivered 7 d prior to the start of RT.

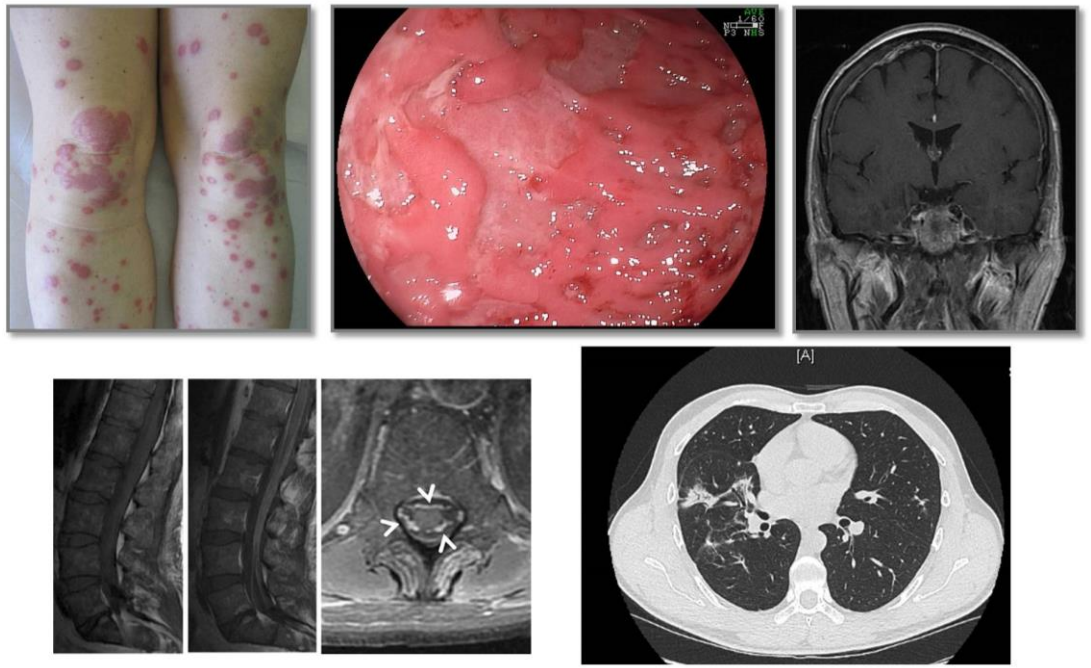
RT Volume and Sites of Disease

- Whether pelvic elective nodal irradiation (ENI) could directly or indirectly affect the immune response.
- ENI also adversely affected survival when combined with ICIs.
- Other studies have shown a strong correlation between the RT volume and RT-induced lymphopenia.
- Which metastatic site to irradiate if several are present. Most reported cases of the abscopal effect involved RT to visceral metastases. Visceral sites may be more immunogenic than osseous sites.
- In the phase I trial by Tang et al. combining ipilimumab with SBRT for metastatic cancers, irradiation to the liver led to a greater immunologic response than treatment to lung tumours.

- Irradiating multiple sites of disease reduces tumor burden while also increasing the likelihood of exposure and priming to the desired tumor-associated antigens. This would circumvent the inhibitory effects of the TME within each individual tissue bed, thus increasing the probability of activation of the anti-tumor immune process
- Inconsistency between the gene mutation of the primary lesion and the metastasis might cause the antigen released by radiotherapy of a single lesion not suitable for other lesions, which makes it unable to entirely exert the immune effect induced by radiotherapy.
- Lemons et al. reported on patients treated in an institutional trial of pembrolizumab and SBRT for metastatic disease, and found that large tumors that underwent partial irradiation had similar local control to smaller tumors that were entirely encompassed by SBRT doses

Adverse Events With Immunotherapy





Michot. Eur J Cancer. 2016;54:139. Steven. Rheumatology (Oxford). 2019;58(Suppl 7):vii29. Robert. ASCO 2017. Education session: Checkpoint inhibitor immunotherapy. Clinical images reproduced with permission of Dr. Caroline Robert, MD, PhD.

THANK YOU