Immunotherapy in Genitourinary Malignancies and Exciting Developments

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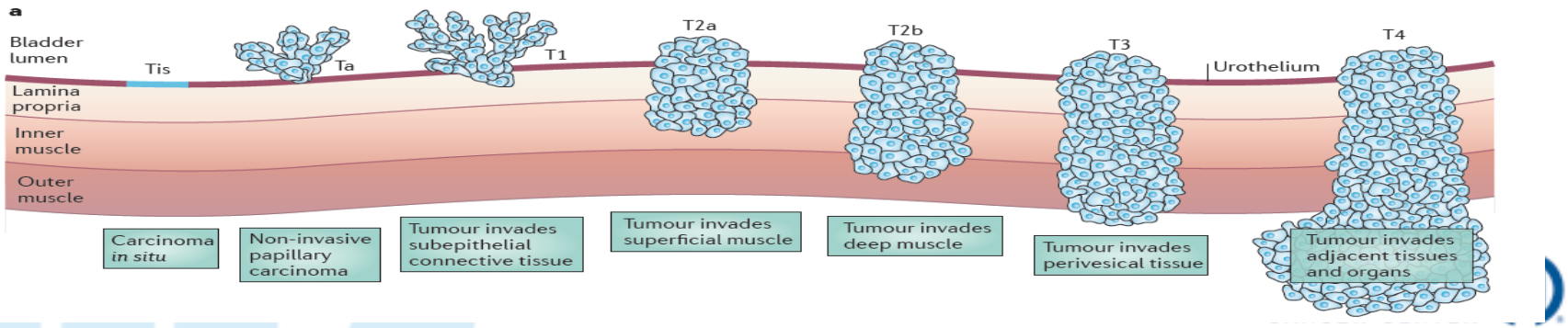
Introduction

- Urinary bladder cancer (BC) is the 9th most common cancer in the world
- In 2022 in USA: 83,730 new cases and 17,200 deaths are estimated
- Notable facts
  - Men: Women ratio 3:1
  - Median age: 73 years at diagnosis
  - Tobacco use is the most common culprit



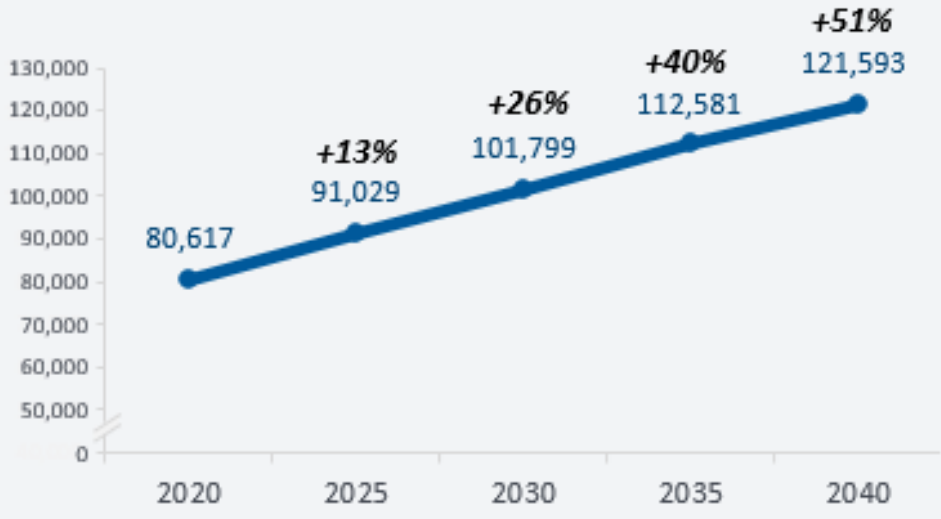
Bladder Cancer Is Projected to Be a Growing Health Problem in the US

Bladder cancer is estimated to be the 6th most common cancer in the United States[1]

		Estimated New Cases 2021	Estimated Deaths 2021
1	Breast cancer (female)	281,550	43,600
2	Prostate cancer	248,530	34,130
3	Lung and bronchus cancer	235,760	131,880
4	Colorectal cancer	149,500	52,980
5	Melanoma of the skin	106,110	7,180
6	**Bladder cancer**	**83,730**	**17,200**
7	Non-Hodgkin lymphoma	81,560	20,720
8	Kidney and renal pelvis cancer	76,080	13,780
9	Uterine cancer	66,570	12,940
10	Leukemia	61,090	23,660

In the United States, the incidence of bladder cancer is projected to increase[2]

Estimated incidence and increase compared with 2020[2,a]



[a]As with all estimates, cancer predictions for future years should be interpreted with due caution. The key assumptions are that national rates, as estimated in 2020, do not change in the prediction period 2020-2040 and that the national population projections are correct for these years.

1. National Cancer Institute. Cancer stat facts: bladder cancer. https://seer.cancer.gov/statfacts/html/urinb.html. Accessed 06-08-2021.2. International Agency for Research on Cancer. Cancer tomorrow: bladder. http://gco.iarc.fr/tomorrow. Accessed 02-08-2021.

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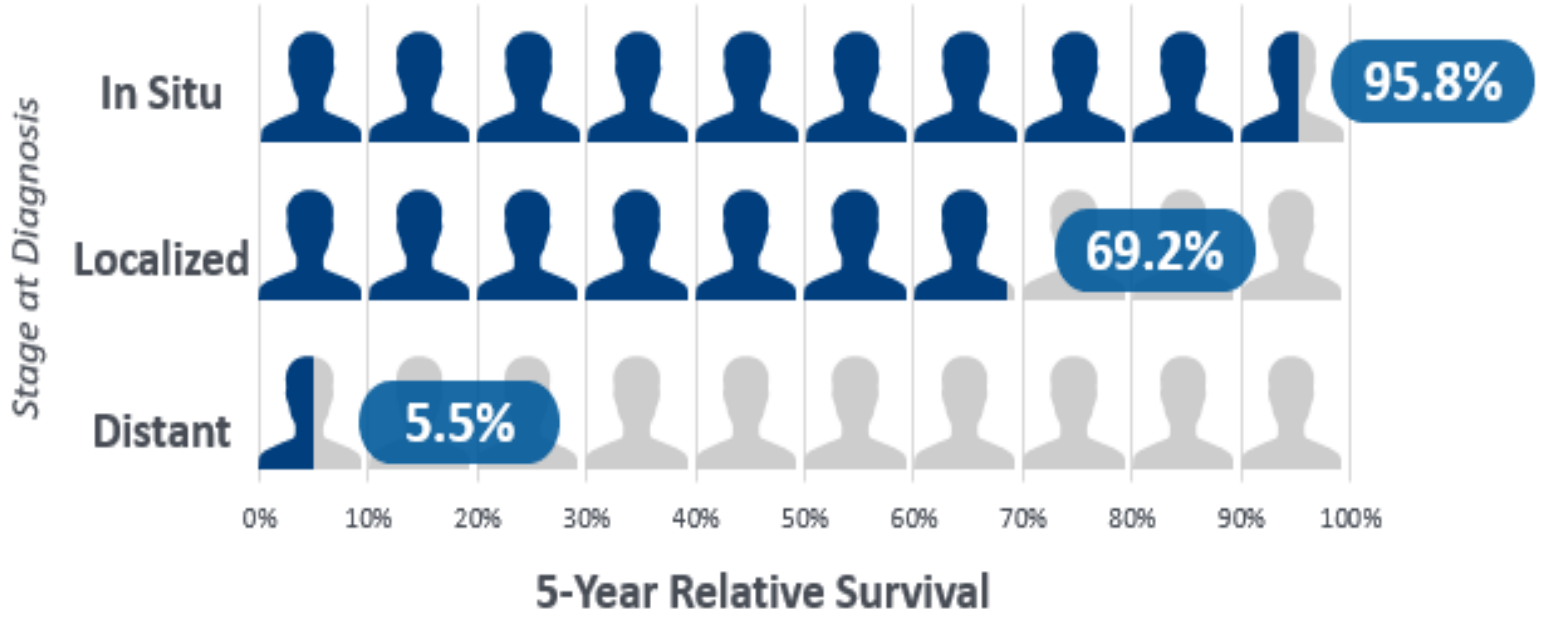
5-Year Relative Survival Rates of Urinary Bladder Cancer in the US



National Cancer Institute. SEER cancer statistics review (CSR), 1975-2017. Cancer of the urinary bladder (invasive and in situ). https://seer.cancer.gov/csr/1975_2017/. Accessed 02-01-2021.

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NMIBC

- Standard treatment for high-risk non-muscle-invasive bladder cancer is TURBT followed by intravesical BCG immunotherapy.
- However, despite high initial responses rates, up to 50% of patients have recurrence or become BCG-unresponsive.
- BCG refractory is when there is failure to achieve a disease-free state within 6 months after initial BCG, with either maintenance or re-treatment at 3 months because of either persistent or rapidly recurrent disease.

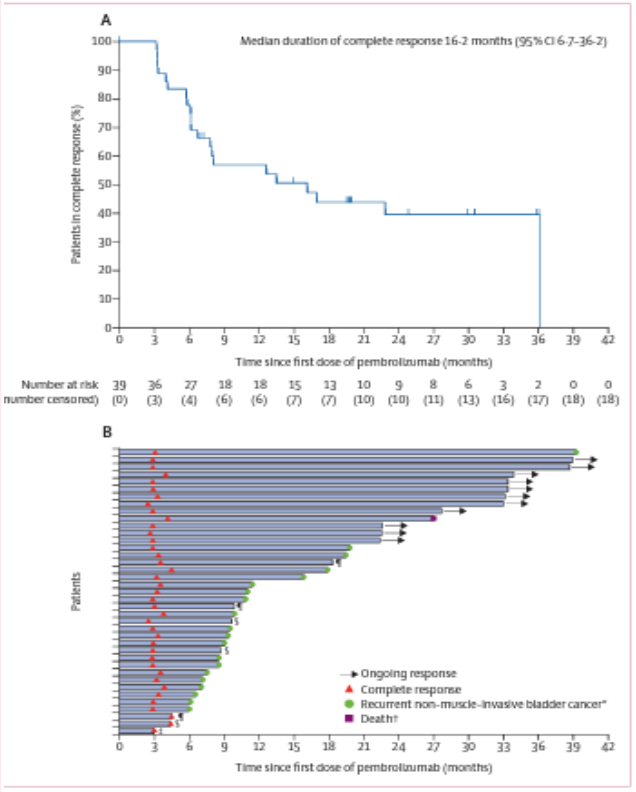
Pembrolizumab monotherapy for the treatment of high-risk non-muscle-invasive bladder cancer unresponsive to BCG (KEYNOTE-057): an open-label, single-arm, multicentre, phase 2 study

Prof Arjun V Balar, MD • Prof Ashish M Kamat, MD • Girish S Kulkarni, MD • Prof Edward M Uchio, MD • Joost L Boormans, MD • Mathieu Roumiguié, MD • et al. Show all authors

	Cohort A efficacy population (n=96)*
Complete response	39 (41%, 30·7–51·1)
Non-complete response	56 (58%, 47·8–68·3)
Persistent disease†‡	40 (42%, 31·7–52·2)
Recurrent disease	6 (6%, 2·3–13·1)
Non-muscle-invasive bladder cancer stage progression§	9 (9%, 4·4–17·1)
Non-bladder malignancy¶	1 (1%, 0·0–5·7)
Progression to muscle-invasive disease (T2)	0 (NA–NA)
Non-evaluable‖	1 (1%, 0·0–5·7)

Data are n (%, 95% CI). NA=not applicable. *Patients with high-risk non-muscle-invasive bladder cancer who received at least one dose of the study drug, had baseline evaluations, and had at least one post-baseline disease assessment. †Defined as patients with carcinoma in situ at baseline who also had carcinoma in situ with or without papillary tumour at month 3. ‡Defined as pathologically confirmed appearance of papillary tumour (high-grade Ta or T1) without carcinoma in situ at month 3. §Defined as an increase in stage from carcinoma in situ or high-grade Ta at baseline to T1 disease. ¶For this patient, new liver lesions were found on imaging; later, a second primary malignancy of pancreatic cancer was found. Subsequent review of the baseline scan showed subtle findings that, in retrospect, could be attributed to pancreatic cancer, and later scans showed metastases that were most likely from the pancreatic cancer. Clinical course and laboratory values further supported the diagnosis of metastatic pancreatic cancer. ‖Patients whose protocol-specified efficacy assessments were missing or who discontinued from the trial for reasons other than progressive disease were not evaluable for efficacy and considered non-responders.

Table 2: **Best overall response at month 3 by central review in patients with BCG-unresponsive carcinoma in situ**



Balar A et al Lancet 2021

Muscle Invasive Bladder Cancer

PRINCIPLES OF SYSTEMIC THERAPY

Neoadjuvant Chemotherapy (preferred for bladder)
<u>Preferred regimen</u> • DDMVAC (dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin) with growth factor support for 3–6 cycles[1,2] <u>Other recommended regimens</u> • Gemcitabine and cisplatin for 4 cycles[3,4]

Adjuvant Therapy	
No previous platinum-based neoadjuvant therapy (pT3, pT4a, pN+)	<u>Preferred regimen</u> • DDMVAC with growth factor support for 3–6 cycles[1,2] <u>Other recommended regimens</u> • Gemcitabine and cisplatin for 4 cycles[3,4] • Nivolumab[5]
Previous platinum-based neoadjuvant therapy (ypT2–ypT4a or ypN+)	<u>Other recommended regimen</u> • Nivolumab[5]

NCCN Guidelines 2022

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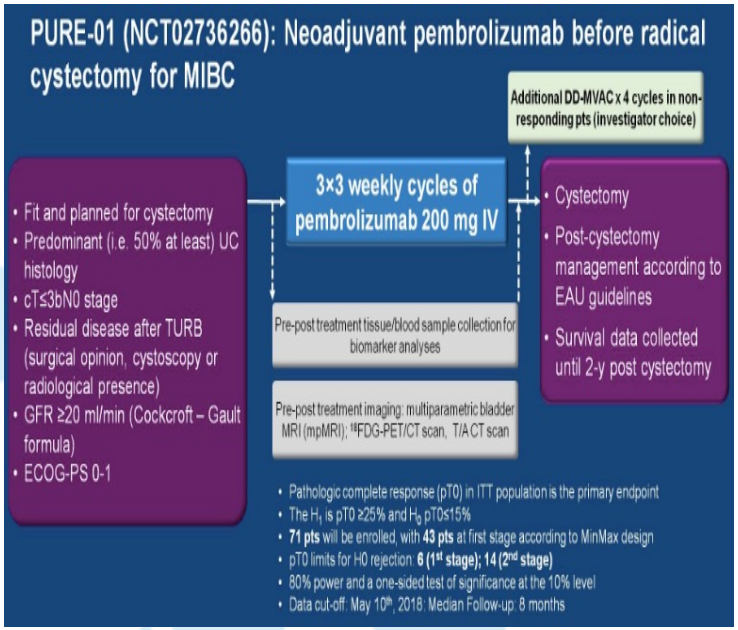
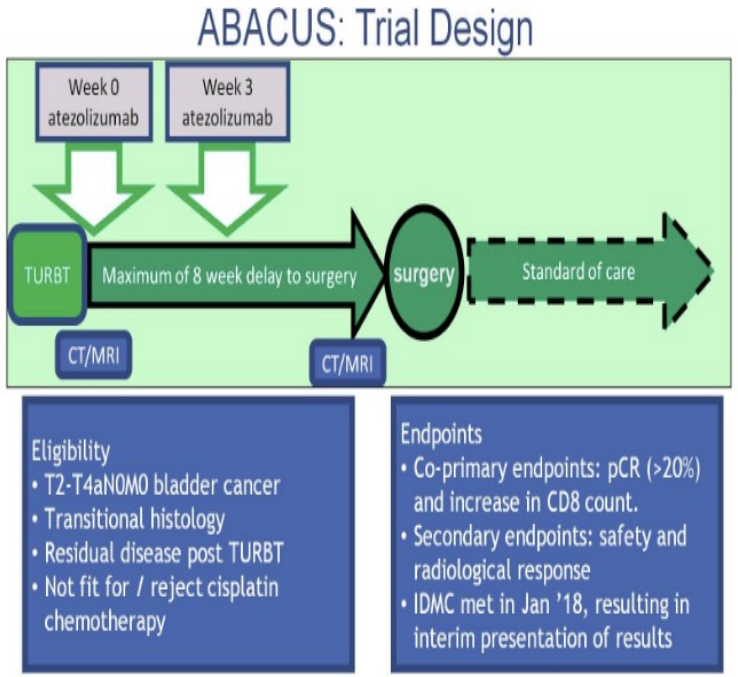
Neoadjuvant immunotherapy for MIBC





Adapted Necchi A, 2018 ASCO Annual Meeting

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Neoadjuvant Single-agent IO and enfortumab vedotin is also effective in MIBC

	PURE-01[1]	ABACUS[2]	NABUCCO[3]	AURA[4]	MDACC[5]	DUTRENEO[6]
N	114	95	24 (14)	28	28	23
Immunotherapy	Pembrolizumab	Atezolizumab	Ipi/Nivo	Avelumab	Durval/Tremi	Durva/Tremi
Cisplatin eligible	✓	✓	✗	✗	✗	✗
pCR (pT0)	37%	31%	46%	36% *(includes Tis)	37.5%	34.8%
PFS	91% (1yr)	79% (1yr)	92% (1yr)	Not reported	82.8% (1yr)	Not reported

1Necchi et al, Eur Urol 2022, 2 Powles et al, Nat Med 2019, 3Van Dijk et al, ASCO Annual Mtg 2020;abstr 5020, 4 Kaimakliotis et al, ASCO Annual Mtg 2020;abstr 5019
5Gao J et al Nature Med 2020 6. Grande E et al. J Clin Oncol Suppl 5012 7. Petrylak D et al. ASCO GU 2022

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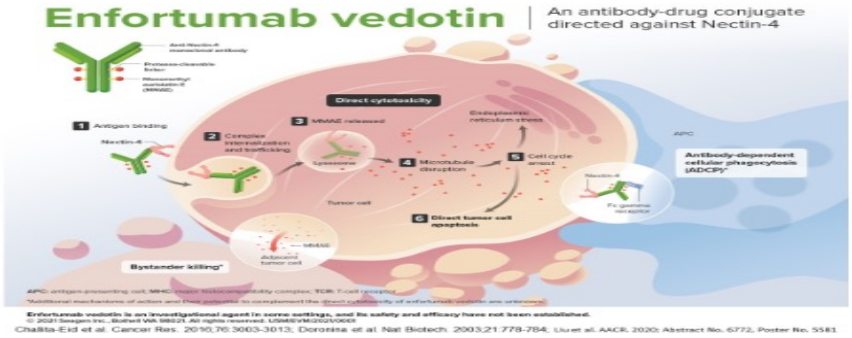
Enfortumab Vedotin Proposed Mechanism of Action



EV-103 Cohort H Study Design

Eligibility

- Cisplatin-ineligible
- Clinical stage T2-T4aN0M0
- No upper tract or urethral tumors allowed
- >50% Urothelial carcinoma histology
- ECOG 0–2
- Medically fit for RC+PLND
- TURBT ≤90 days from C1D1

Imaging ≤4 weeks

Neoadjuvant EV monotherapy x 3 cycles
1.25 mg/kg of EV on D1 and D8 of 21-day cycle

Pre-RC Imaging ≤4 weeks

Radical cystectomy and pelvic lymph node dissection
4 to 12 weeks after last dose of neoadjuvant EV

Follow-Up Imaging
Q12W for the first 2 years, then Q24W

Primary endpoint: pCR rate by central pathology review

Secondary endpoints: pDS rate (central review), EFS, DFS,OS, safety, PROs, biomarkers

Pathological Response	Central Pathology Results (N=22) n (%) [95% Confidence Interval]
Pathological Complete Response Rate (defined as absence of any viable tumor tissue: ypT0 and N0)	**8 (36.4%)** [17.2–59.3]
Pathological Downstaging Rate (defined as presence of ypT0, ypTis, ypTa, ypT1, and N0)	**11 (50.0%)** [28.2–71.8]

Petrylak D et al
GU ASCO 2022

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Neoadjuvant Chemo-IO is effective in cis-eligible MIBC

	BLASST-1[1] (N = 41)	HCRN GU14-188[2] (N = 43)	LCCC1520[3] (N = 39)	MKSCC[4] (N = 39)	SAKK 06/17[5] (N = 53)
Immunotherapy	Nivolumab	Pembrolizumab	Pembrolizumab	Atezolizumab	Durvalumab
Chemotherapy	Gem-Cis	Gem-Cis	Split dose Gem-Cis	Gem-Cis	Gem-Cis
pCR (pT0), %	49% *(includes Tis)	44	39	38	34
RFS	85.4% (1yr)	Not reported	Not reported	Not reported	83.5% (2yr)

1. Gupta S et al. ASCO GU 2020. Abstract 439. 2. Holmes CJ et al. ASCO 2020. Abstract 5047. 3. Rose TL et al. J Clin Oncol. 2021;39:3140-3148. 4. Funt SA et al. J Clin Oncol. 2022;40:1312-1322. 5. Cathomas R et al. ASCO 2022. Abstract 4515

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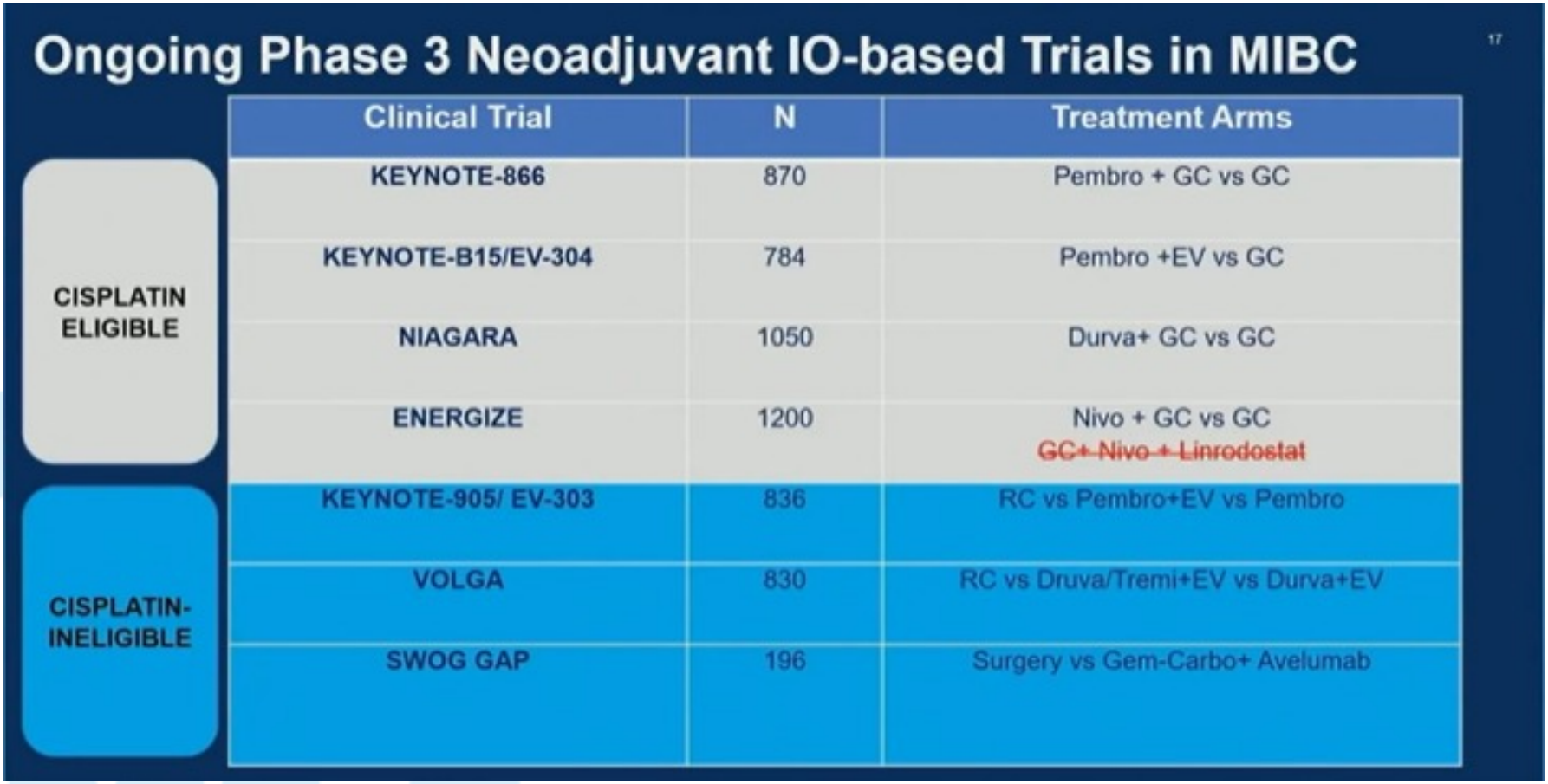
Ongoing Phase 3 trials



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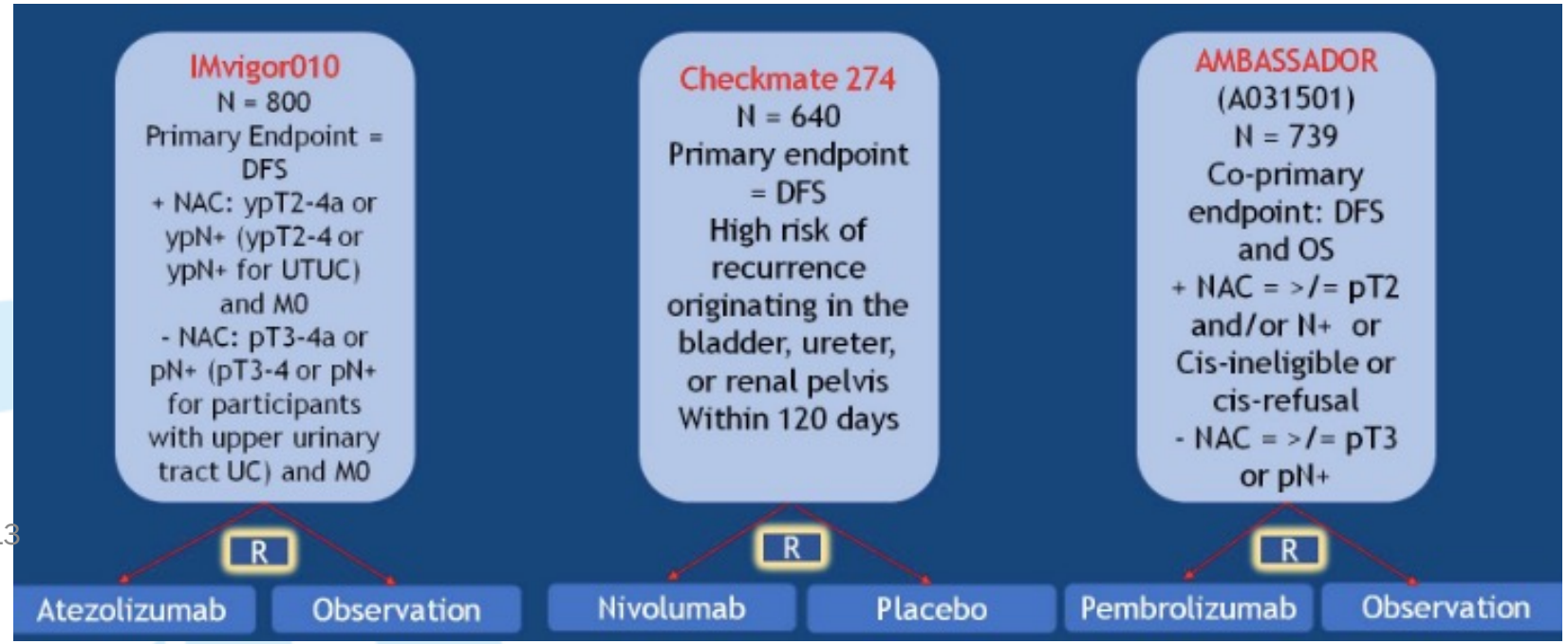
Post cystectomy ≥ pT2 or N+



Adapted Aragon-Ching JB 2018 ASCO Annual meeting

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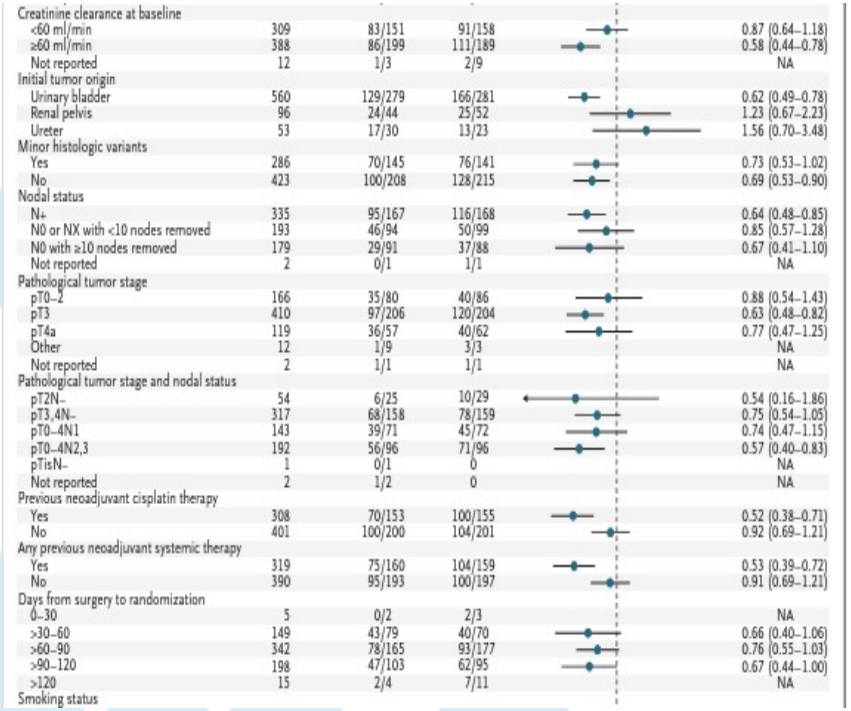
ORIGINAL ARTICLE

Adjuvant Nivolumab versus Placebo in Muscle-Invasive Urothelial Carcinoma

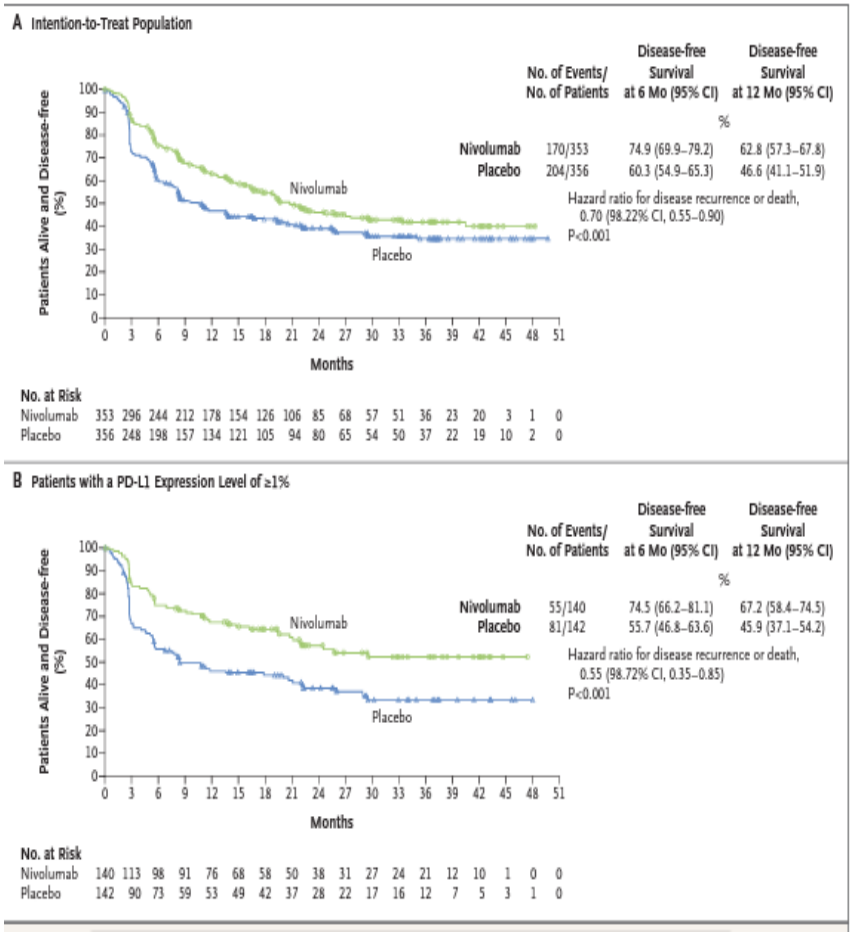
Dean F. Bajorin, M.D., J. Alfred Witjes, M.D., Jürgen E. Gschwend, M.D., Michael Schenker, M.D., Begoña P. Valderrama, M.D., Yoshihiko Tomita, M.D., Ph.D., Aristotelis Bamias, M.D., Thierry Lebret, M.D., Shahrokh F. Shariat, M.D., Se Hoon Park, M.D., Dingwei Ye, M.D., Mads Agerbaek, M.D., Deborah Enting, M.D., Ray McDermott, M.D., Pablo Gajate, M.D., Avivit Peer, M.D., Matthew I. Milowsky, M.D., Alexander Nosov, M.D., João Neif Antonio, Jr., M.D., Krzysztof Tupikowski, M.D., Laurence Toms, B.M., B.Ch., Bruce S. Fischer, M.D., Anila Qureshi, M.D., Sandra Collette, M.Sc., Keziban Unsal-Kacmaz, Ph.D., Edward Broughton, Ph.D., Dimitrios Zardavas, M.D., Henry B. Koon, M.D., and Matthew D. Galsky, M.D.

Key inclusion criteria

- Patients with ypT2-ypT4a or ypN+ MIUC who had neoadjuvant cisplatin chemotherapy
- Patients with pT3-pT4a or pN+ MIUC without prior neoadjuvant cisplatin chemotherapy and not eligible/refuse adjuvant cisplatin chemotherapy
- Radical surgery within the past 120 days
- Disease-free status within 4 weeks of dosing



Creatinine clearance at baseline				
<60 ml/min	309	83/151	91/158	0.87 (0.64–1.18)
≥60 ml/min	388	86/199	111/189	0.58 (0.44–0.78)
Not reported	12	1/3	2/9	NA
Initial tumor origin				
Urinary bladder	560	129/279	166/281	0.62 (0.49–0.78)
Renal pelvis	96	24/44	25/52	1.23 (0.67–2.23)
Ureter	53	17/30	13/23	1.56 (0.70–3.48)
Minor histologic variants				
Yes	286	70/145	76/141	0.73 (0.53–1.02)
No	423	100/208	128/215	0.69 (0.53–0.90)
Nodal status				
N+	335	95/167	116/168	0.64 (0.48–0.85)
N0 or NX with <10 nodes removed	193	46/94	50/99	0.85 (0.57–1.28)
N0 with ≥10 nodes removed	179	29/91	37/88	0.67 (0.41–1.10)
Not reported	2	0/1	1/1	NA
Pathological tumor stage				
pT0–2	166	35/80	40/86	0.88 (0.54–1.43)
pT3	410	97/206	120/204	0.63 (0.48–0.82)
pT4a	119	36/57	40/62	0.77 (0.47–1.25)
Other	12	1/9	3/3	NA
Not reported	2	1/1	1/1	NA
Pathological tumor stage and nodal status				
pT2N–	54	6/25	10/29	0.54 (0.16–1.86)
pT3,4N–	317	68/158	78/159	0.75 (0.54–1.05)
pT0–4N1	143	39/71	45/72	0.74 (0.47–1.15)
pT0–4N2,3	192	56/96	71/96	0.57 (0.40–0.83)
pTisN–	1	0/1	0	NA
Not reported	2	1/2	0	NA
Previous neoadjuvant cisplatin therapy				
Yes	308	70/153	100/155	0.52 (0.38–0.71)
No	401	100/200	104/201	0.92 (0.69–1.21)
Any previous neoadjuvant systemic therapy				
Yes	319	75/160	104/159	0.53 (0.39–0.72)
No	390	95/193	100/197	0.91 (0.69–1.21)
Days from surgery to randomization				
0–30	5	0/2	2/3	NA
>30–60	149	43/79	40/70	0.66 (0.40–1.06)
>60–90	342	78/165	93/177	0.76 (0.55–1.03)
>90–120	198	47/103	62/95	0.67 (0.44–1.00)
>120	15	2/4	7/11	NA
Smoking status				



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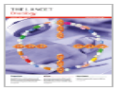
Bajorin, D NEJM 2021

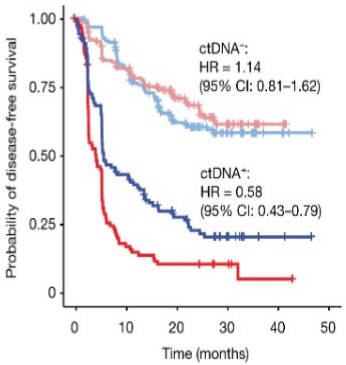
THE LANCET
Oncology
Volume 22, Issue 4, April 2021, Pages 525-537

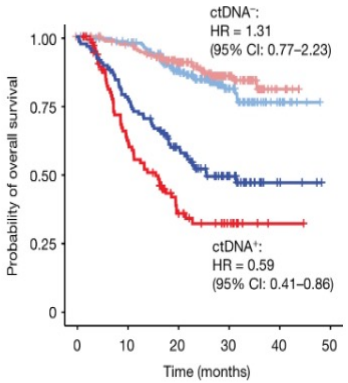


Articles

Adjuvant atezolizumab versus observation in muscle-invasive urothelial carcinoma (IMvigor010): a multicentre, open-label, randomised, phase 3 trial

Joaquim Bellmunt MD [a], Prof Maha Hussain MD [b], Prof Jürgen E Gschwend MD [c], Prof Peter Albers MD [d], Prof Stephane Oudard MD [e], Daniel Castellano MD [f], Siamak Daneshmand MD [g], Prof Hiroyuki Nishiyama MD [h], Martin Majchrowicz MPH [i], Viraj Degaonkar PharmD [i], Yi Shi PhD [i], Sanjeev Mariathasan PhD [i], Petros Grivas MD [j k l], Alexandra Drakaki MD [m], Peter H O'Donnell MD [n], Prof Jonathan E Rosenberg MD [o p], Daniel M Geynisman MD [q], Prof Daniel P Petrylak MD [r], Jean Hoffman-Censits MD [s],





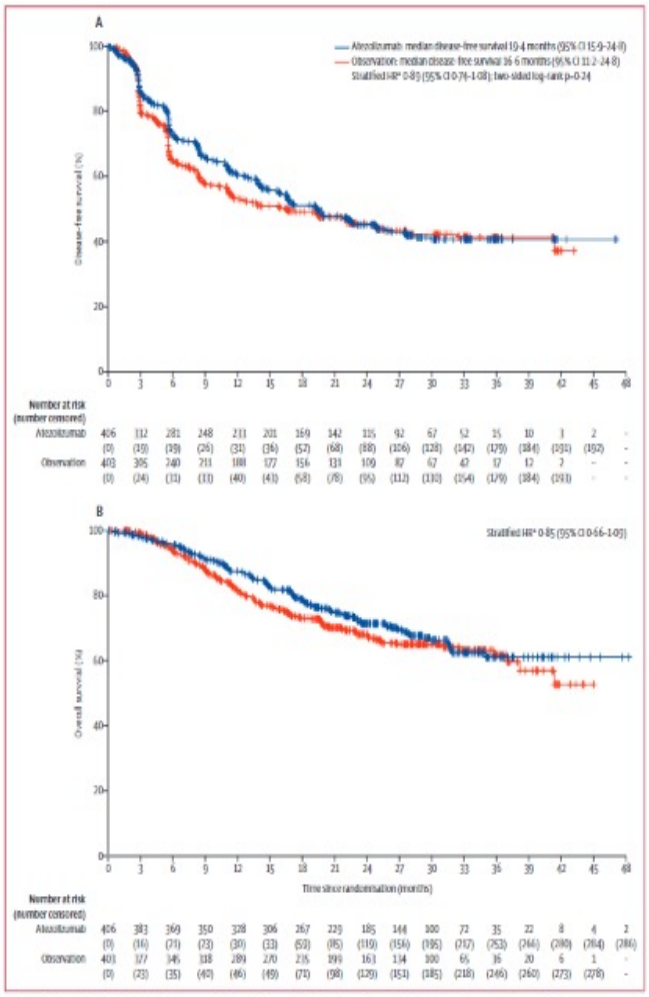


Figure 2: Kaplan-Meier plots for investigator-assessed disease-free survival (A) and overall survival (B) in the intention-to-treat population
HR=hazard ratio. *Stratified by post-resection tumour stage, nodal status, and PD-L1 status.

Bellmunt et al 2021 Lancet
Powles T et al 2021 Nature

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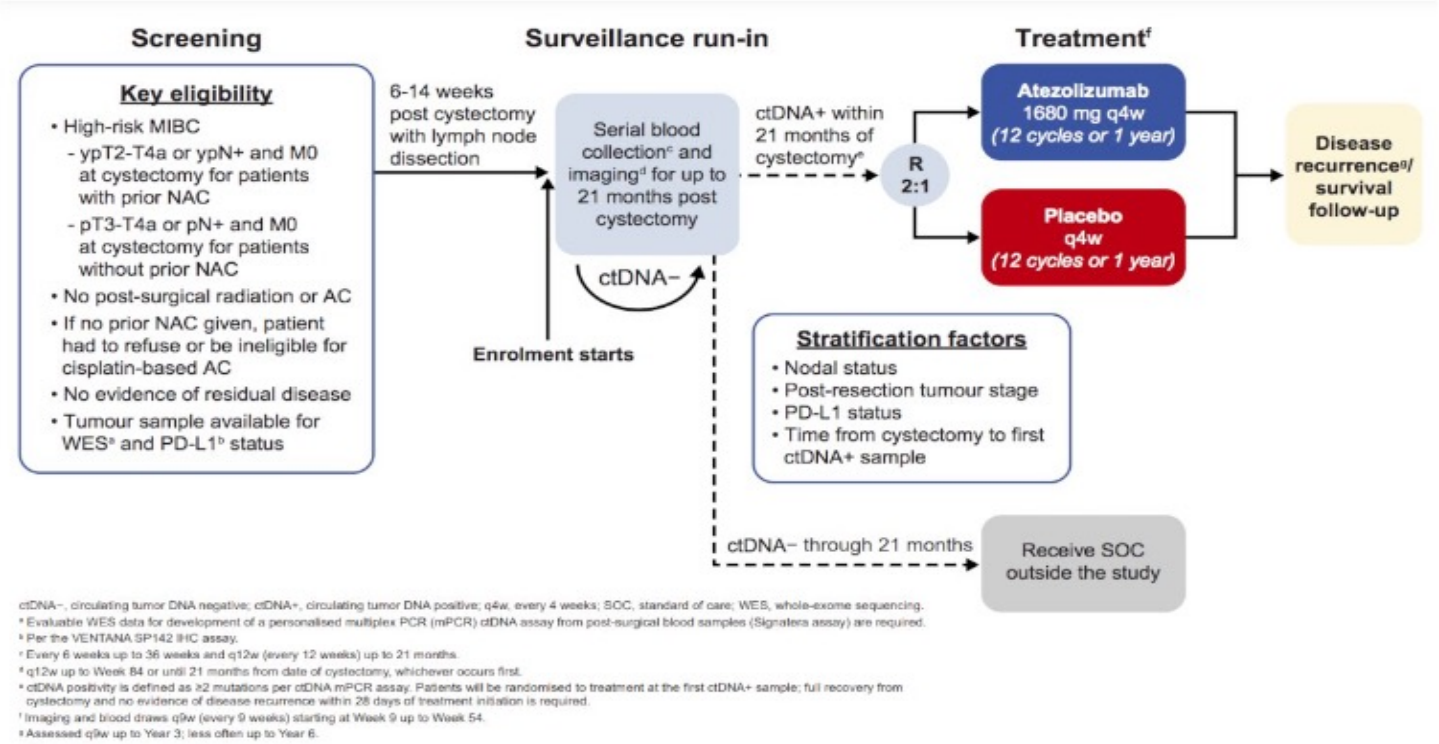
IMvigor 011



ctDNA−, circulating tumor DNA negative; ctDNA+, circulating tumor DNA positive; q4w, every 4 weeks; SOC, standard of care; WES, whole-exome sequencing.
[a] Evaluable WES data for development of a personalised multiplex PCR (mPCR) ctDNA assay from post-surgical blood samples (Signatera assay) are required.
[b] Per the VENTANA SP142 IHC assay.
[c] Every 6 weeks up to 36 weeks and q12w (every 12 weeks) up to 21 months.
[d] q12w up to Week 84 or until 21 months from date of cystectomy, whichever occurs first.
[e] ctDNA positivity is defined as ≥2 mutations per ctDNA mPCR assay. Patients will be randomised to treatment at the first ctDNA+ sample; full recovery from cystectomy and no evidence of disease recurrence within 28 days of treatment initiation is required.
[f] Imaging and blood draws q9w (every 9 weeks) starting at Week 9 up to Week 54.
[g] Assessed q9w up to Year 3; less often up to Year 6.

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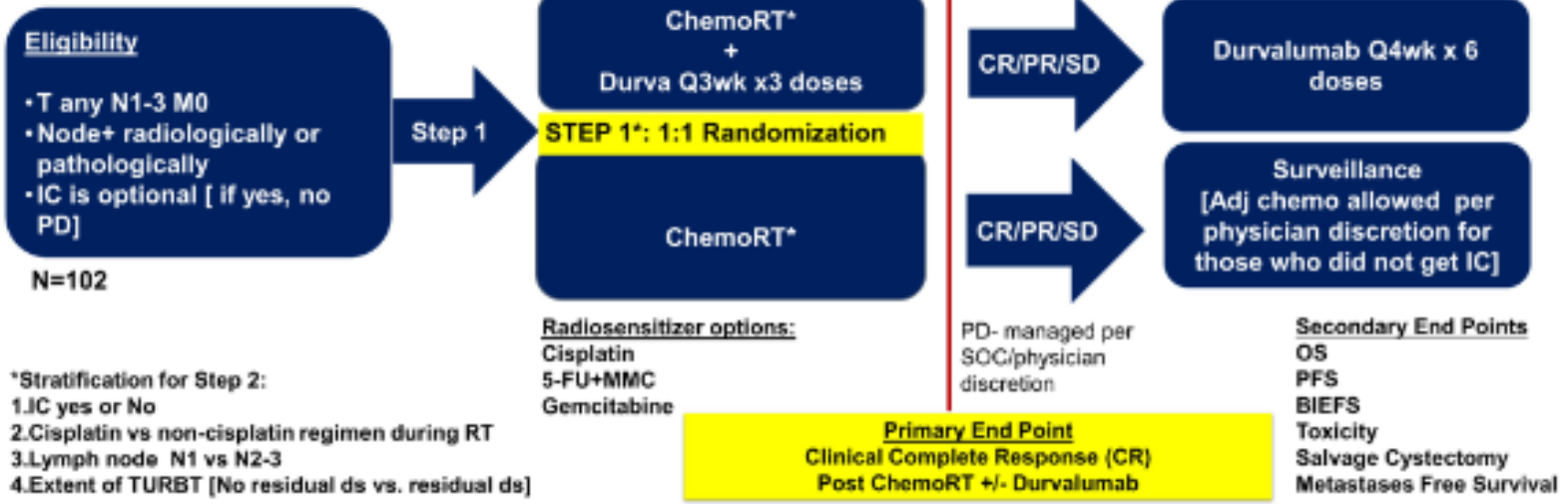
EA8185: Phase 2 study of bladder-sparing chemoradiation (chemoRT) with durvalumab in clinical stage III, node-positive urothelial carcinoma (INSPIRE), an ECOG-ACRIN/NRG collaboration.

Schema [Amendment # 4]:



Joshi M GU ASCO 2022, Shilpa Gupta GU ASCO 2023

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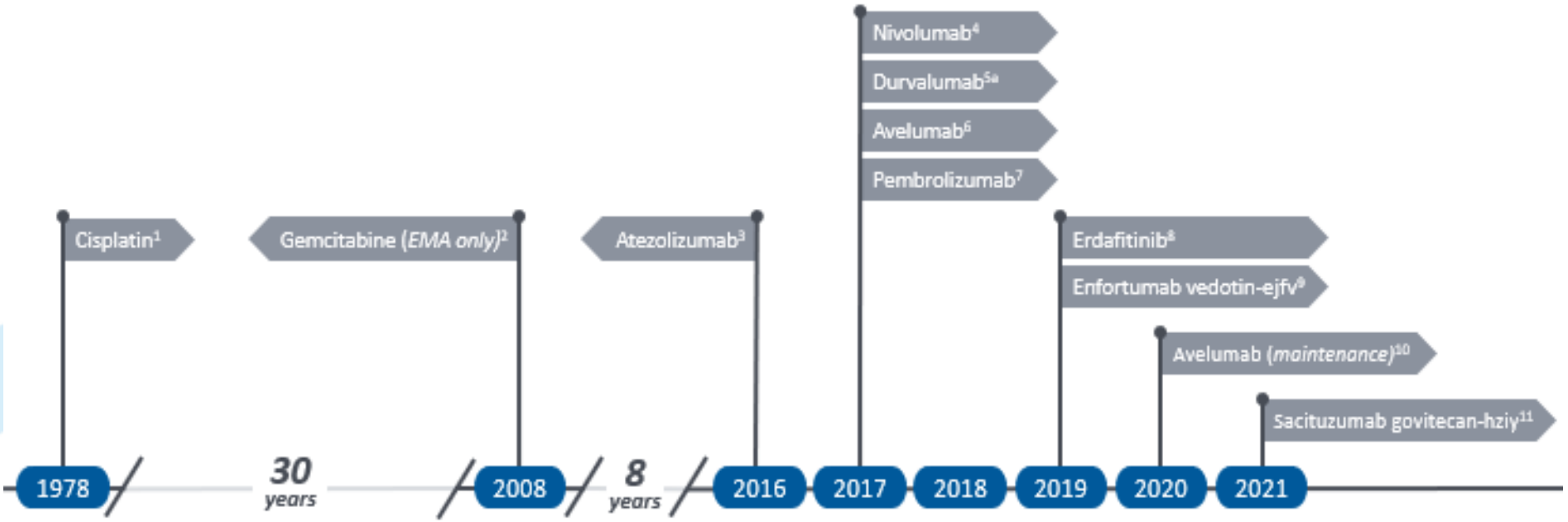
The la/mUC Treatment Landscape Has Evolved in Recent Years



EMA, European Medicines Agency; la/mUC, locally advanced/metastatic urothelial carcinoma.

[a] Indication in urothelial carcinoma withdrawn.

1. Cisplatin [package insert]. Durham, NC: Accord Healthcare, Inc. 2. European Medicines Agency. Opinion following an Article 30 referral for Gemzar: international non-proprietary name (INN): gemcitabine (09-24-2008). Accessed 02-04-2021. 3. US Food and Drug Administration. Tecentriq BLA accelerated approval letter: BLA 761034 (05-18-2016). Accessed 04-27-2021. 4. US Food and Drug Administration. Opdivo BLA 125554/S-024 accelerated approval letter (02-02-2017). Accessed 04-19-2021. 5. US Food and Drug Administration. Imfinzi BLA approval letter: BLA 761069 (05-01-2017). Accessed 04-05-2021. 6. US Food and Drug Administration. Bavencio BLA accelerated approval letter: BLA 761078 (05-09-2017). Accessed 04-27-2021. 7. US Food and Drug Administration. Keytruda supplemental approval letter: BLA 125514/S-018 (05-18-2017). Accessed 06-09-2021. 8. US Food and Drug Administration. Balversa accelerated approval letter NDA 212018 (04-12-2019). Accessed 03-19-2021. 9. U.S. Food & Drug Administration. PADCEV BLA 761137 accelerated approval letter (12-18-2019). Accessed 11-30-2020. 10. US Food and Drug Administration. Bavencio supplement approval letter: BLA 761049/S-009 (06-30-2020). Accessed 02-10-2021. 11. US Food and Drug Administration. Trodelvy BLA 761115/S-009 accelerated approval letter (04-13-2021). https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2021/761115Orig1s008ltr.pdf. Accessed 06-02-2021.

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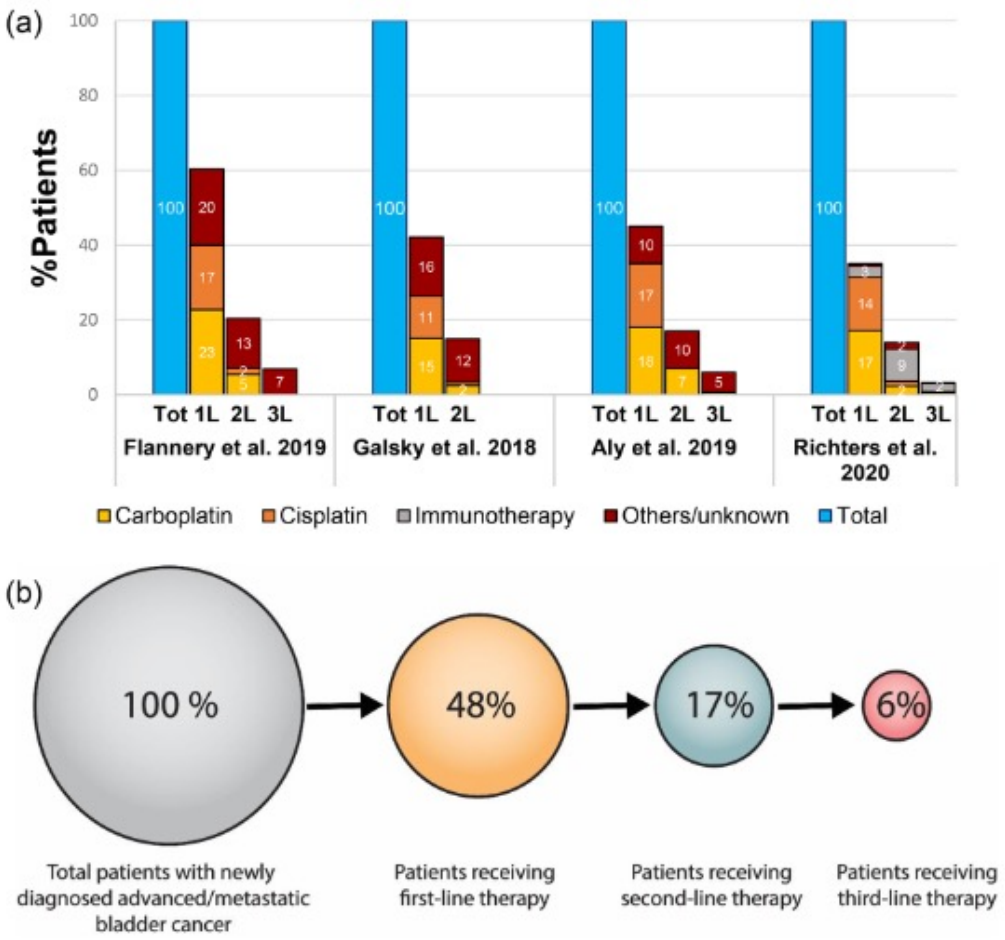
Utilization of Systemic Therapies



Swami et al Cancer Treat Research Comm 2021

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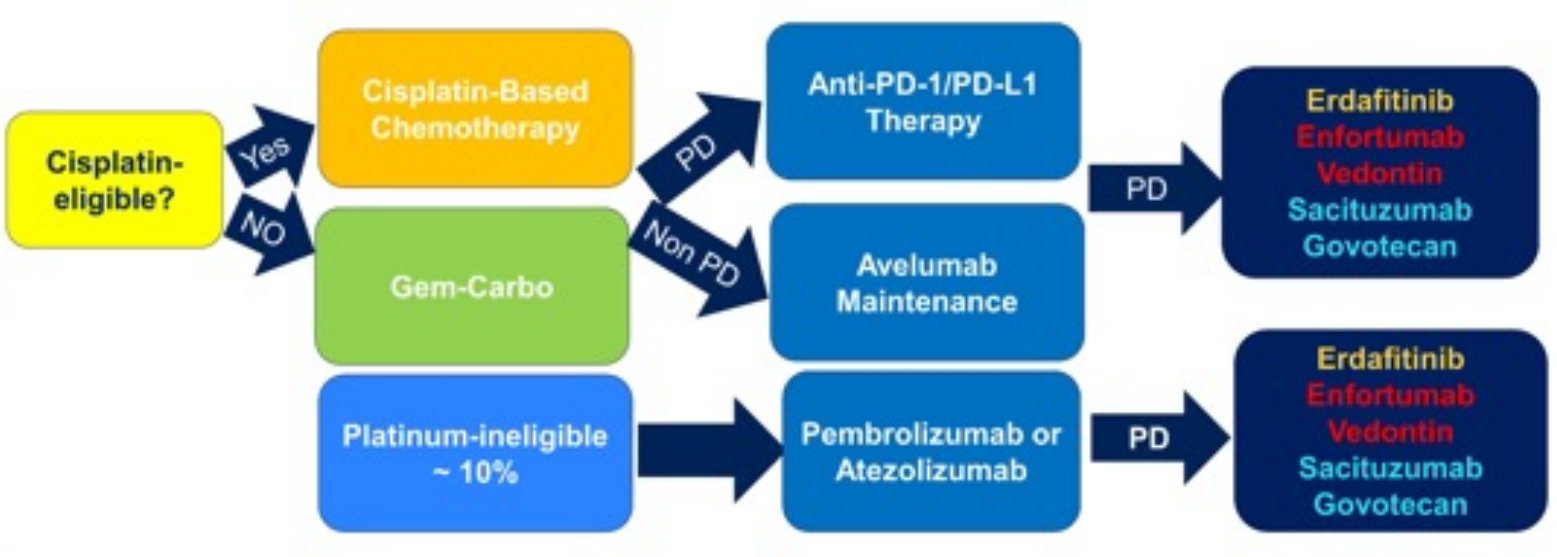
Management of Metastatic Urothelial Carcinoma



Gupta S ASCO 2021

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Systemic Therapy

PRINCIPLES OF SYSTEMIC THERAPY

First-Line Systemic Therapy for Locally Advanced or Metastatic Disease (Stage IV)	
Cisplatin eligible	<u>Preferred regimens</u> • 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	<u>Preferred regimens</u> • 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) <u>Other recommended regimens</u> • Gemcitabine[15] • Gemcitabine and paclitaxel[16] • Atezolizumab[13] (only for patients whose tumors express PD-L1[b]) (category 2B) <u>Useful under certain circumstances</u> • 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)

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Atezolizumab with or without chemotherapy in metastatic urothelial cancer (IMvigor130): a multicentre, randomised, placebo-controlled phase 3 trial

Matthew D Galsky, José Angel Arranz Arija, Aristotelis Bamias, Ian D Davis, Maria De Santis, Eiji Kikuchi*, Xavier Garcia-del-Muro, Ugo De Giorgi, Marina Mencinger, Kouji Izumi, Stefano Panni, Mahmut Gumus, Mustafa Özgüroğlu, Arash Rezazadeh Kalebasty, Se Hoon Park, Boris Alekseev, Fabio A Schutz, Jian-Bi Li, Dingwei Ye, Nicholas J Vogelzang, Sandrine Bernhard, Darren Tayama, Sanjeev Mariathasan, Almut Meda, AnnChristine Thåström, Enrique Grande, for the IMvigor130 Study Group†

- Locally advanced or mUC
- No prior systemic therapy in the metastatic setting
- ECOG PS ≤ 2
- 1L platinum-eligible
- N = 1200
- Randomised 1:1:1

→ **Arm A** Atezo + plt/gem

→ **Arm B** Atezo monotherapy

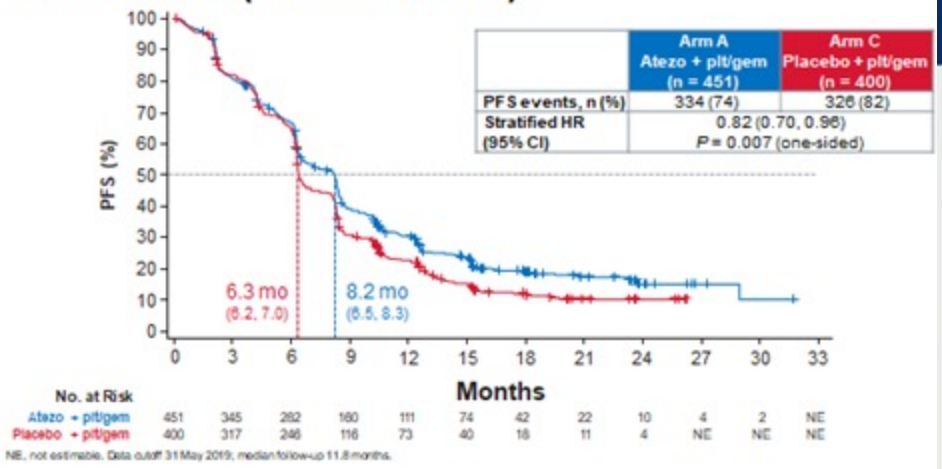
→ **Arm C** Placebo + plt/gem

Stratification factors:
- PD-L1 IC status (IC0 vs IC1 vs IC2/3)
- Bajorin risk factor score including KPS < 80% vs ≥ 80% and presence of visceral metastases (0 vs 1 vs 2 and/or patients with liver metastases)
- Investigator choice of plt/gem (cisplatin + gem or carboplatin + gem)

Co-primary endpoints:
- INV-assessed PFS[a] and OS (Arm A vs C)
- OS (Arm B vs C, hierarchical approach)

Key secondary endpoints:
- INV-ORR[a] and DOR
- PFS[a] and OS (Arm B vs C; PD-L1 IC2/3 subgroup)
- Safety

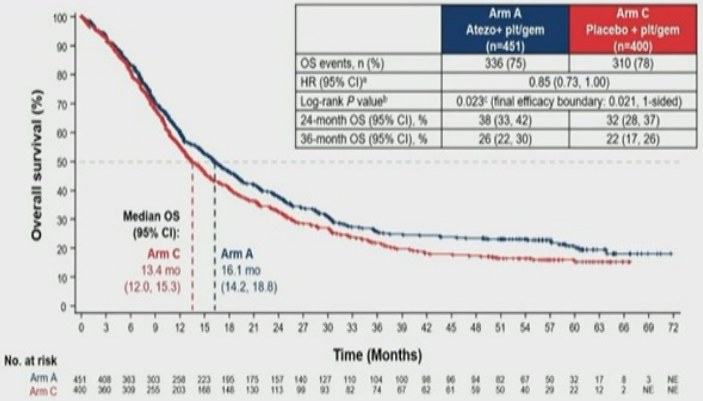
Final PFS: ITT (Arm A vs Arm C)



	Arm A Atezo + plt/gem (n = 451)	Arm C Placebo + plt/gem (n = 400)
PFS events, n (%)	334 (74)	326 (82)
Stratified HR (95% CI)	0.82 (0.70, 0.96)	
	P = 0.007 (one-sided)	

NE, not estimable. Data cutoff 31 May 2019; median follow-up 11.8 months.

Final OS analysis in the ITT population



	Arm A Atezo+ plt/gem (n=451)	Arm C Placebo + plt/gem (n=400)
OS events, n (%)	336 (75)	310 (78)
HR (95% CI)[a]	0.85 (0.73, 1.00)	
Log-rank P value[b]	0.023[c] (final efficacy boundary: 0.021, 1-sided)	
24-month OS (95% CI), %	38 (33, 42)	32 (28, 37)
36-month OS (95% CI), %	26 (22, 30)	22 (17, 26)

Grande et al GU ASCO 2023

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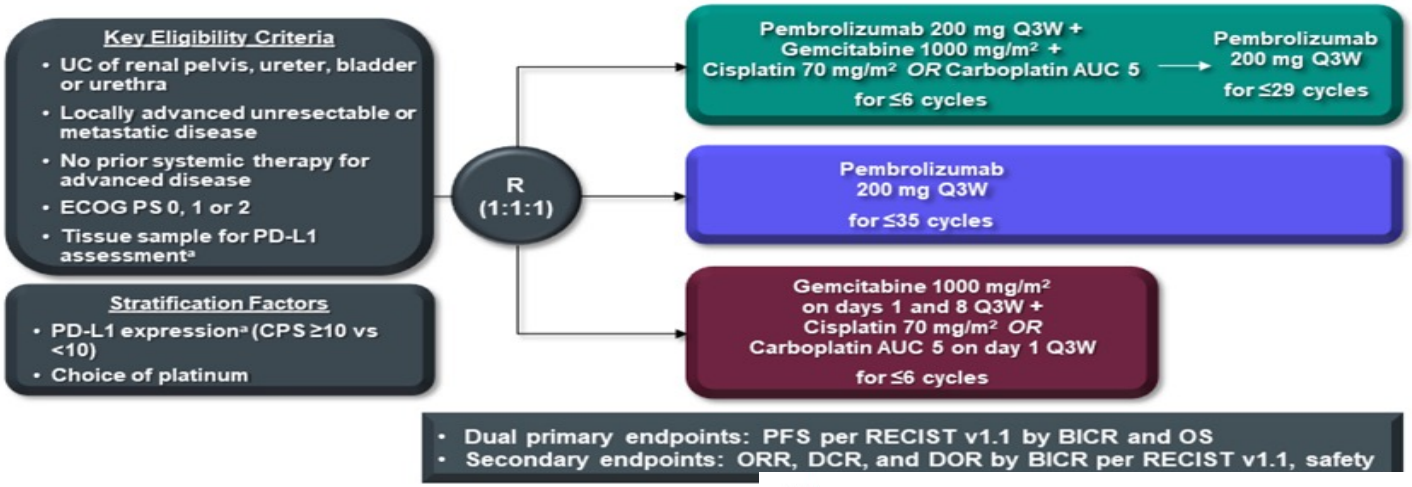
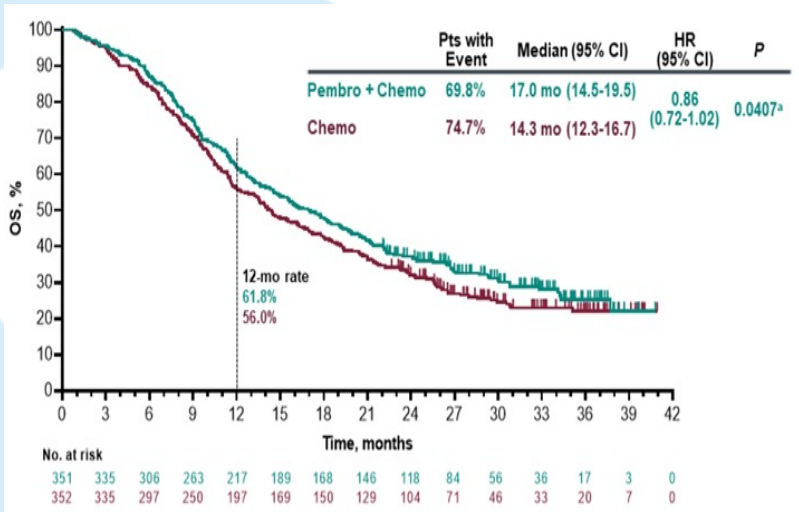
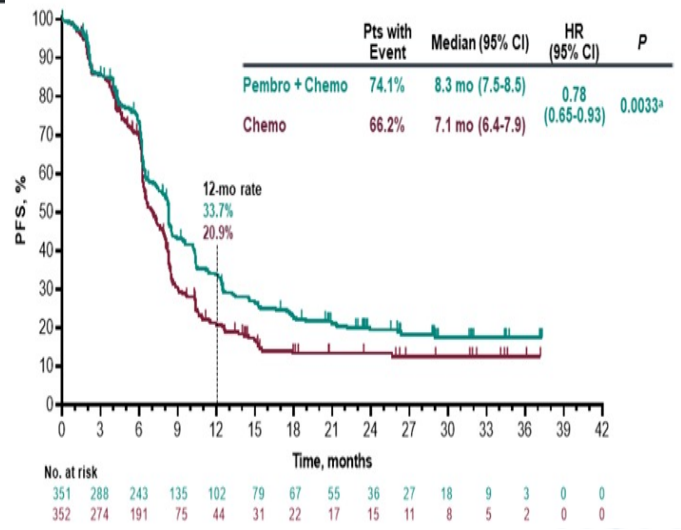
Pembrolizumab alone or combined with chemotherapy versus chemotherapy as first-line therapy for advanced urothelial carcinoma (KEYNOTE-361): a randomised, open-label, phase 3 trial

*Thomas Powles, Tibor Csőszi, Mustafa Özgüroğlu, Nobuaki Matsubara, Lajos Géczi, Susanna Y-S Cheng, Yves Fradet, Stephane Oudard, Christof Vulsteke, Rafael Morales Barrera, Aude Fléchon, Seyda Gunduz, Yohann Loriot, Alejo Rodriguez-Vida, Ronac Mamtani, Evan Y Yu, Kijoeng Nam, Kentaro Imai, Blanca Homet Moreno, Ajjai Alva, for the KEYNOTE-361 Investigators**



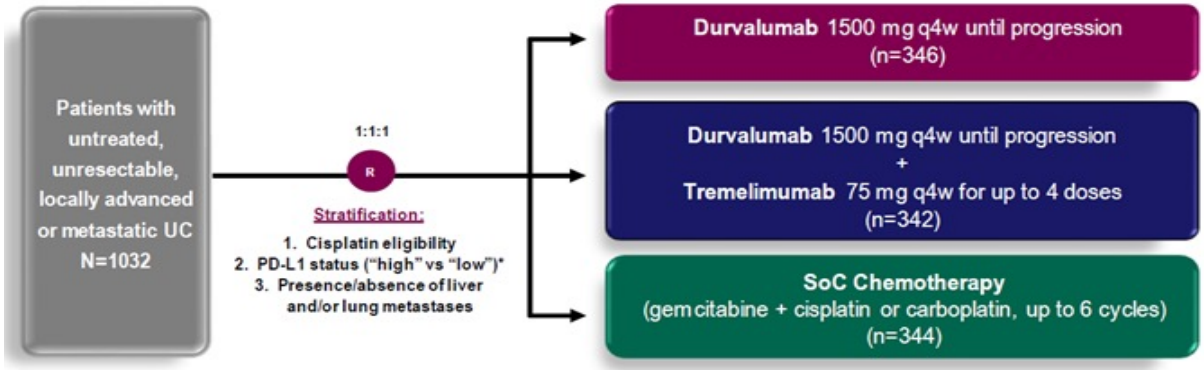




Powles et al Lancet 2022

Durvalumab alone and durvalumab plus tremelimumab versus chemotherapy in previously untreated patients with unresectable, locally advanced or metastatic urothelial carcinoma (DANUBE): a randomised, open-label, multicentre, phase 3 trial

*Thomas Powles, Michiel S van der Heijden, Daniel Castellano, Matthew D Galsky, Yohann Loriot, Daniel P Petrylak, Osamu Ogawa, Se Hoon Park, Jae-Lyun Lee, Ugo De Giorgi, Martin Bögemann, Aristotelis Bamias, Bernhard J Eigl, Howard Gurney, Som D Mukherjee, Yves Fradet, Iwona Skoneczna, Marinos Tsiatas, Andrey Novikov, Cristina Suárez, André P Fay, Ignacio Duran, Andrea Necchi, Sophie Wildsmith, Philip He, Natasha Angra, Ashok K Gupta, Wendy Levin, Joaquim Bellmunt, for the DANUBE study investigators**



CO-PRIMARY ENDPOINTS

- OS (D vs SoC in PD-L1 high)
- OS (D+T vs SoC in all comers)

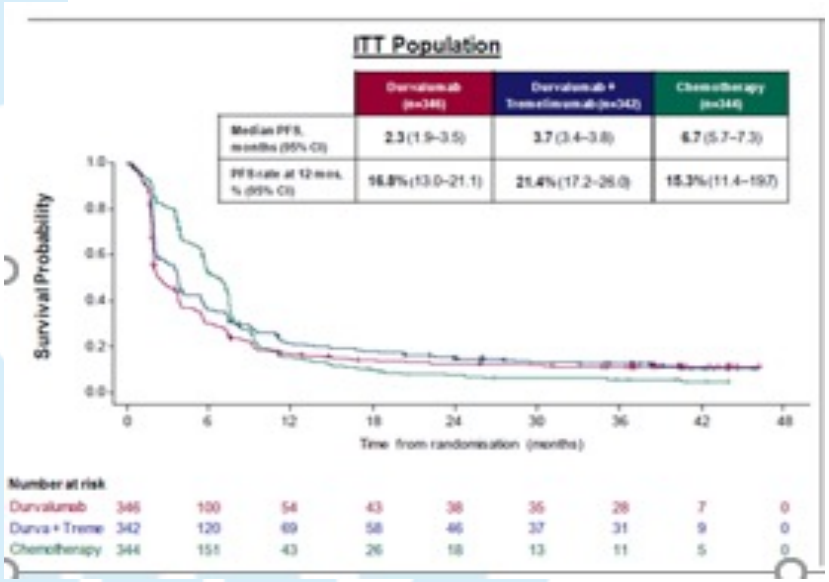
SELECT SECONDARY ENDPOINTS

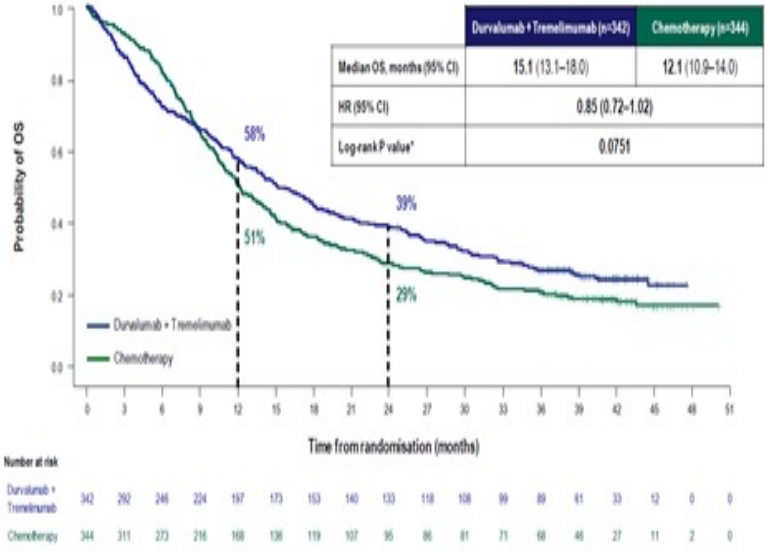
- OS (D vs SoC in all comers)
- OS (D+T vs SoC in PD-L1 high)
- PFS, ORR, and DoR

Data cutoff date (final analysis): January 27, 2020

Minimum follow-up from date last patient randomised: 34 months

Median follow-up for survival: 41.2 months for all patients

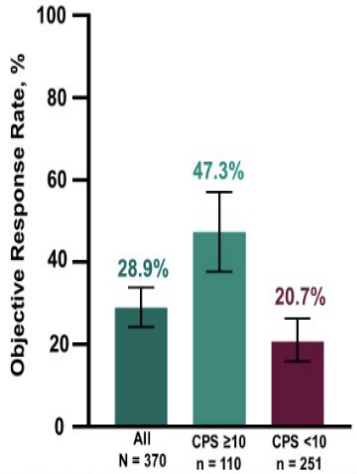




First-line pembrolizumab in cisplatin-ineligible patients with locally advanced and unresectable or metastatic urothelial cancer (KEYNOTE-052): a multicentre, single-arm, phase 2 study

Arjun V Balar, Daniel Castellano, Peter H O'Donnell, Petros Grivas, Jacqueline Vuky, Thomas Powles, Elizabeth R Plimack, Noah M Hahn, Ronald de Wit, Lei Pang, Mary J Savage, Rodolfo F Perini, Stephen M Keefe, Dean Bajorin, Joaquim Bellmunt

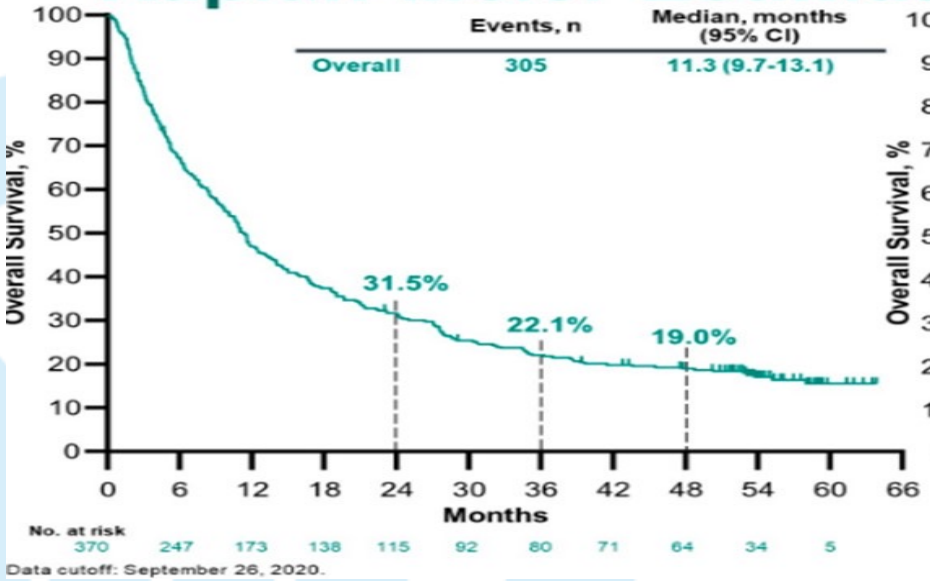
Confirmed ORR per RECIST v1.1

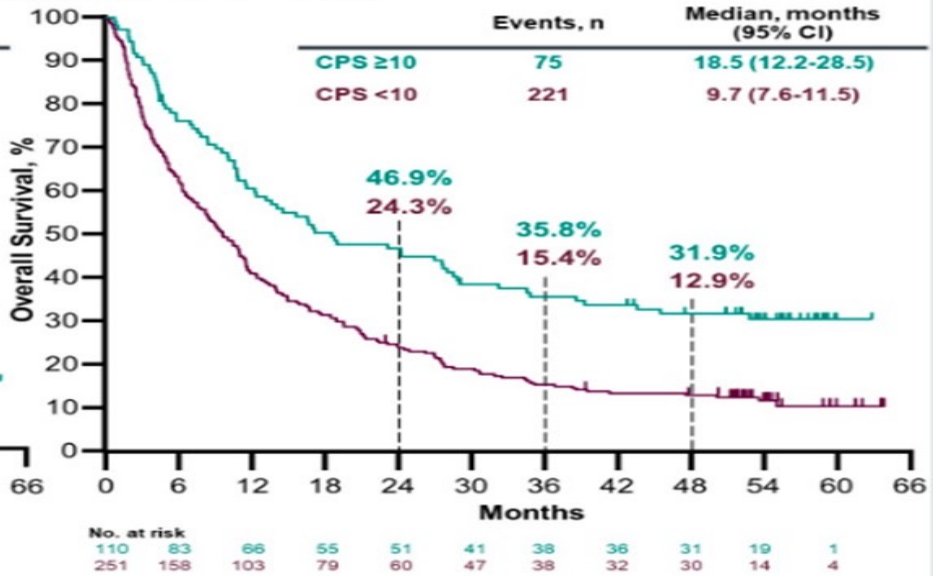


Best Response n (%)	All Patients N = 370	CPS ≥10 n = 110	CPS <10 n = 251
CR	35 (9.5)	23 (20.9)	10 (4.0)
PR	72 (19.5)	29 (26.4)	42 (16.7)
SD	67 (18.1)	22 (20.0)	44 (17.5)
PD	155 (41.9)	30 (27.3)	121 (48.2)
NA[a]	32 (8.6)	6 (5.5)	25 (10.0)
NE[b]	9 (2.4)	0 (0)	9 (3.6)

o available postbaseline imaging data. [b]Had postbaseline imaging, and best objective response was determined to be NE by RECIST v1.1. Data cutoff: September 26, 2020.

Kaplan-Meier Estimates of OS





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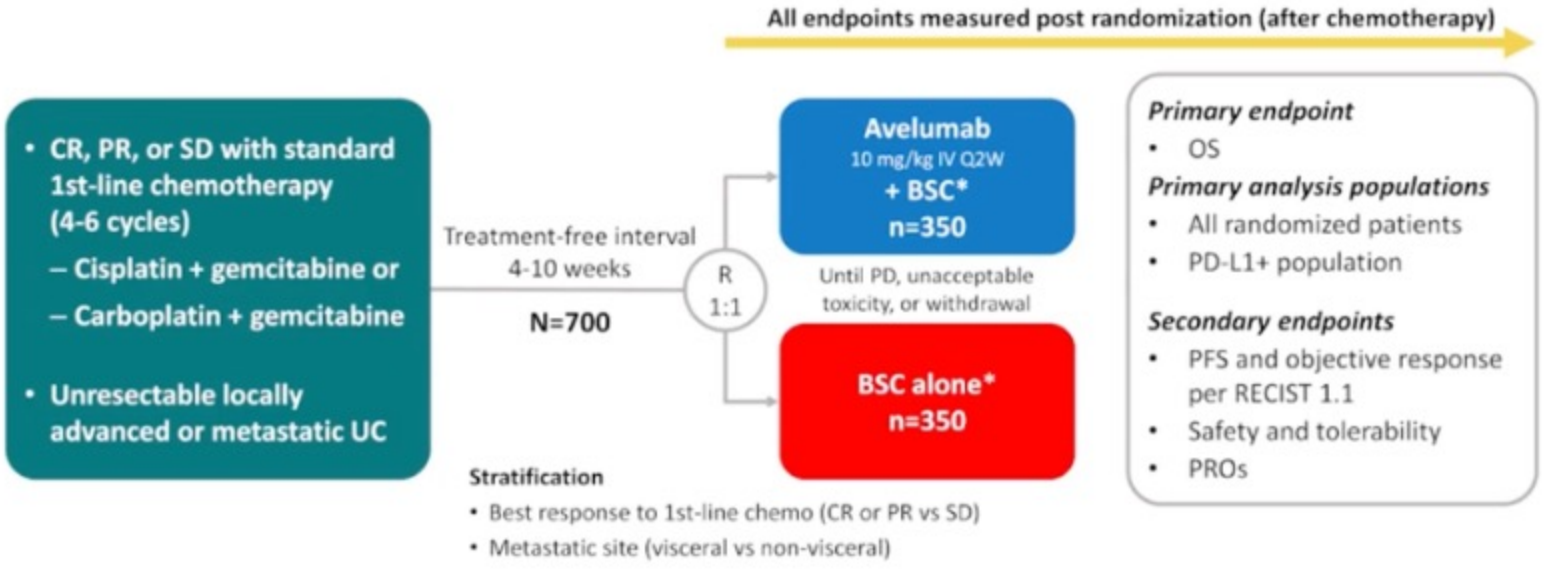
Balar et al 2017 Lancet oncology; O'Donell P. ASCO 2021

JAVELIN Bladder 100 study design (NCT02603432)



PD-L1+ status was defined as PD-L1 expression in ≥25% of tumor cells or in ≥25% or 100% of tumor-associated immune cells if the percentage of immune cells was >1% or ≤1%, respectively, using the Ventana SP263 assay; 358 patients (51%) had a PD-L1–positive tumor

BSC, best supportive care; **CR**, complete response; **IV**, intravenous; **PR**, partial response; **PRO**, patient reported outcome; **Q2W**, every 2 weeks; **R**, randomization; **RECIST 1.1**, Response Evaluation Criteria in Solid Tumors version 1.1; **SD**, stable disease

*BSC (eg, antibiotics, nutritional support, hydration, or pain management) was administered per local practice based on patient needs and clinical judgment; other systemic antitumor therapy was not permitted, but palliative local radiotherapy for isolated lesions was acceptable

Powles T, et al. J Clin Oncol 38: 2020 (suppl; abstr LBA1

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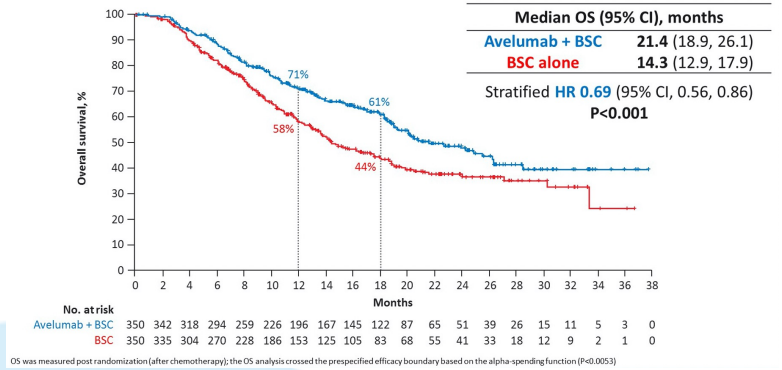
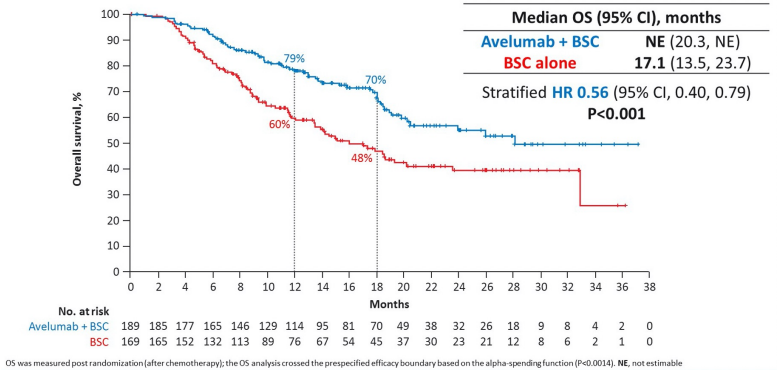
JAVELIN Bladder 100: Overall Survival

OS in the overall population



OS was measured post randomization (after chemotherapy); the OS analysis crossed the prespecified efficacy boundary based on the alpha-spending function (P<0.0053)

OS in the PD-L1+ population



OS was measured post randomization (after chemotherapy); the OS analysis crossed the prespecified efficacy boundary based on the alpha-spending function (P<0.0014). NE, not estimable

	Overall Population		PD-L1+ Population	
	Avelumab	***BSC***	***Avelumab***	***BSC***
OS (mo)	21.4	14.3	NE	17.1
PFS (mo)	3.7	2.0	5.7	2.1
ORR	9.7%	1.4%	13.8%	1.2%

*Crossover from the BSC to avelumab arm was not permitted per study protocol, though 52.9% of patients received subsequent IO therapy

Powles T, et al. J Clin Oncol 38: 2020 (suppl; abstr LBA1)

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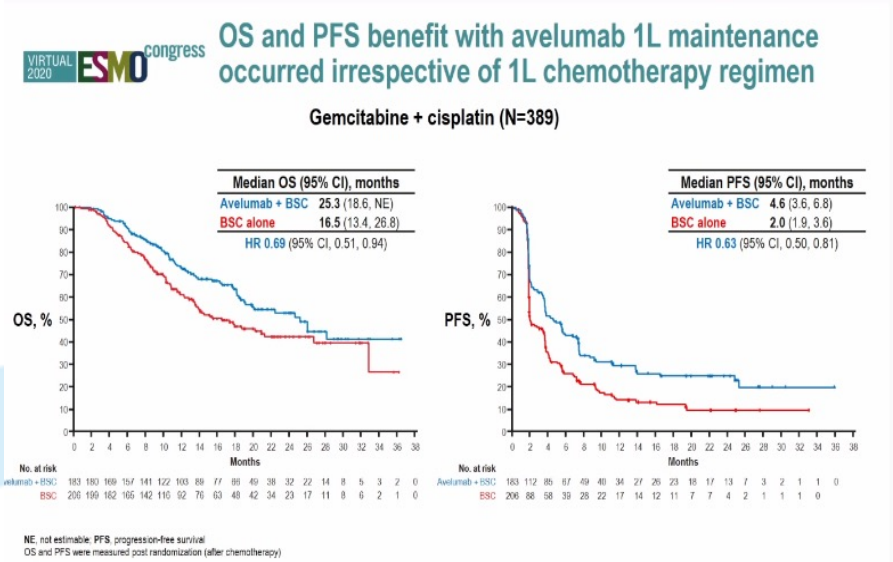
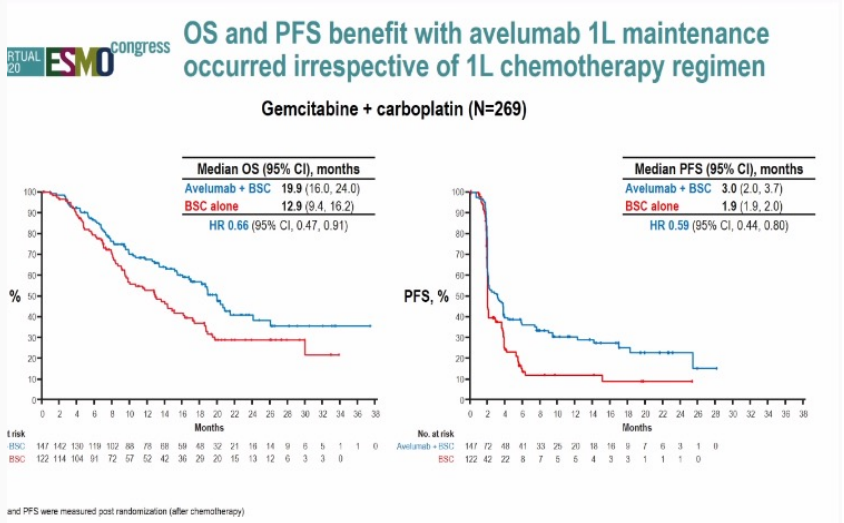
JAVELIN Bladder 100: Subgroup Analysis





Grivas et al ESMO 2020

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Second-Line Treatment Options Post-Platinum Treatment*

	KEYNOTE-045[1] Pembrolizumab Phase 3	IMvigor 210[2] Atezolizumab Phase 2	CheckMate 275[3] Nivolumab Phase 2	Study 1108[4] Durvalumab Phase 1/2	JAVELIN solid tumor [5] Avelumab Phase 1B
Patient number	542	310 (Cohort 2)	270	191	242
Study Arms	**Pembrolizumab** 200 mg (IV) q3w	**Atezolizumab** 1200 mg (IV) q3w	**Nivolumab** 3 mg/kg IV q2w	**Durvalumab** 10 mg/kg IV q2w	**Avelumab** 10 mg/kg q2w
Key Inclusion Criteria	• Metastatic or locally advanced urothelial cancer • Progression after 1 or 2 lines of platinum-based therapy • Measurable disease • ECOG PS 0-2	Cohort 2: • ≥1 Platinum-containing or ≤12 months of neoadjuvant/ adjuvant treatment • Tumor tissue for PD-L1 testing • ECOG PS 0-1	• ≥1 Platinum-containing or ≤12 months of neoadjuvant/ adjuvant treatment • Tumor tissue for PD-L1 testing • ECOG PS 0-1	• Histologically confirmed solid tumors Locally advanced or mUC cohort: • Had progressed, on were ineligible for, or refused any number of prior therapies • ECOG PS 0-1	Solid tumors mUC cohort: • Had progressed post-platinum treatment or cisplatin-ineligible • Unselected for PD-L1 • ECOG PS 0-1
ORR (%)	• 21.1	• 15	• 19.6	• 20.4	• 16.1 (after ≥6 weeks follow-up)
Median PFS (months)	• 2.1	• 2.1	• 2.0	• NA	• NA
Median OS (months)	• 10.3	• 7.9	• 8.7	• NA	• NA

*No head-to-head studies have been conducted and direct comparisons cannot be made between these studies.

1. Bellmunt et al. N Engl J Med 2017; 376:1015-1026; 2. Loriot Y et al. Poster presentation at ESMO 2016. 783P; 3. Sharma P, et al. Lancet Oncol. 2017; 4. Powles T, et al. Poster presentation at ASCO GU. 286; 5. Patel M et al. Poster presentation at ASCO GU. 330.

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Withdrawn

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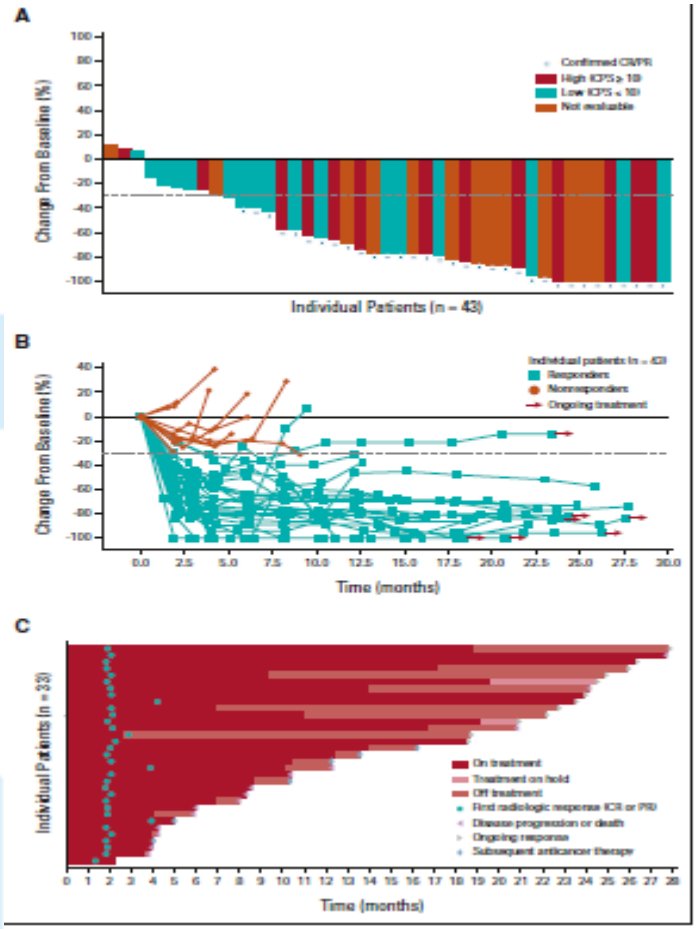
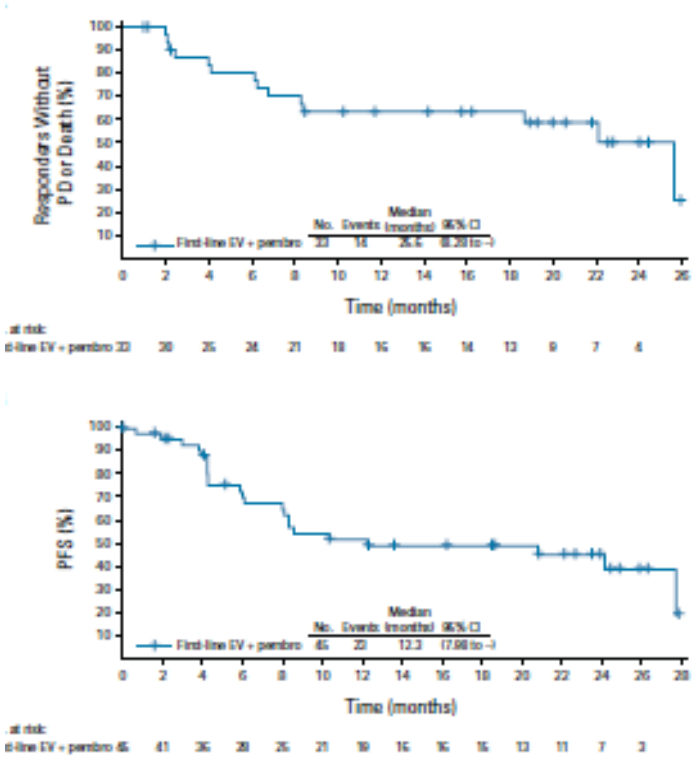
Enfortumab Vedotin Plus Pembrolizumab in Previously Untreated Advanced Urothelial Cancer

Christopher J. Hoimes, DO[1,2]; Thomas W. Flaig, MD[3]; Matthew I. Milowsky, MD[4]; Terence W. Friedlander, MD[5]; Mehmet Asim Bilen, MD[6]; Shilpa Gupta, MD[7]; Sandy Srinivas, MD[8]; Jaime R. Merchan, MD[9]; Rana R. McKay, MD[10]; Daniel P. Petrylak, MD[11]; Carolyn Sasse, BS[12]; Blanca Homet Moreno, MD, PhD[13]; Yao Yu, PhD[14]; Anne-Sophie Carret, MD[14]; and Jonathan E. Rosenberg, MD[15]





Hoimes C et al JCO 2022

MOFFITT CANCER CENTER

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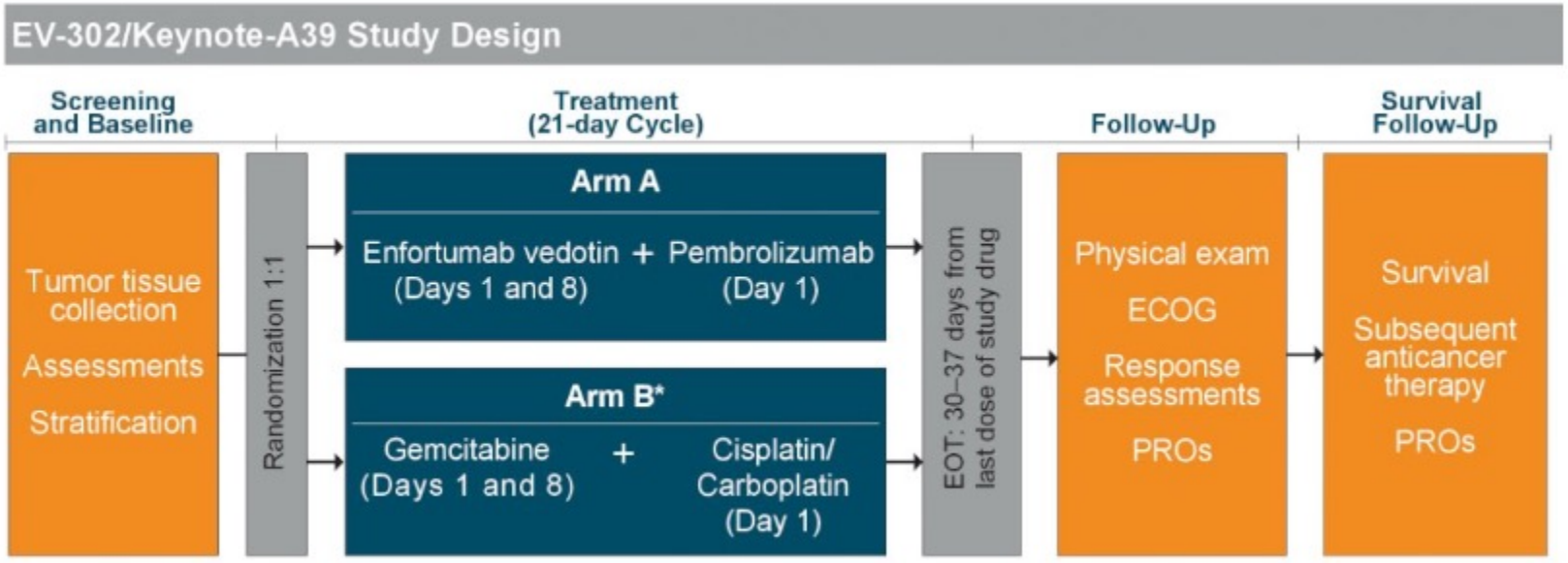

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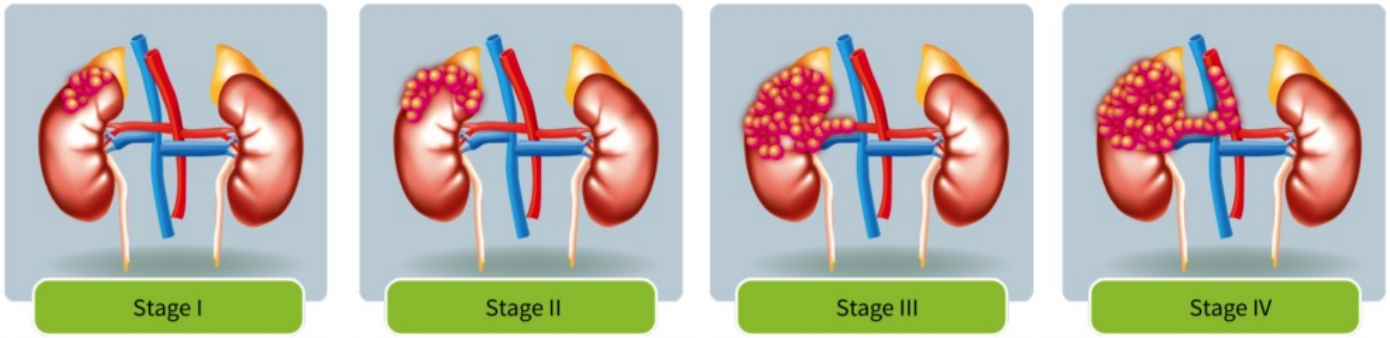
Stages of Kidney Cancer



Stage I	Stage II	Stage III	Stage IV
The cancer is only within the kidney and has not spread. The cancer is less than 7 cm in size. If the cancer can be removed it is most likely to be cured with surgery. 9 out of 10 people will be alive and free of the cancer at five years after an operation.	The cancer is larger than 7 cm but is still confined to the kidney and has not spread outside of the kidney. Surgery is a good treatment option. The five year survival rate is still very high after surgery for stage 2 kidney cancer.	The kidney cancer has moved nearby outside the kidney, but has not spread to distant organs. For example, the cancer might have spread into the fat around the kidney, into the blood vessel coming out of the kidney, or into lymph nodes near the kidney. Ask your doctor about all treatment options and clinical trials.	The kidney cancer has spread widely outside the kidney; to the abdominal cavity, to the adrenal glands, to distant lymph nodes or to other organs, such as the lungs, liver, bones, or brain. Ask your doctor about all treatment options and clinical trials.

https://ikcc.org/infohubpost/what-are-the-different-kidney-cancer-stages

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Neoadjuvant treatment

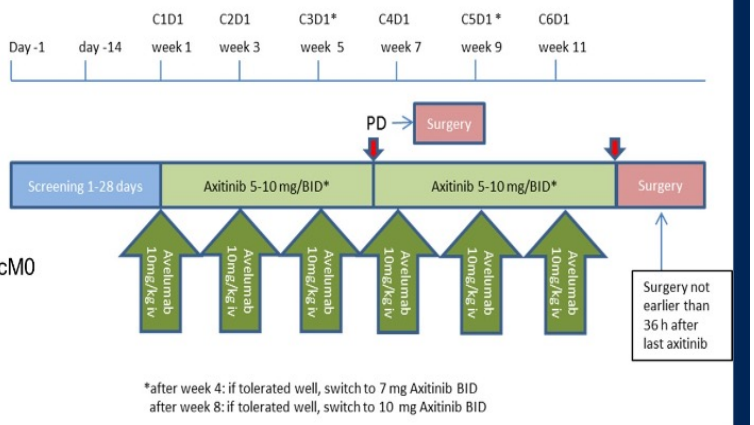
- Neoadjuvant systemic therapy is not a standard of care in localized RCC
- Early systemic therapy could also theoretically eradicate micrometastatic disease and reduce recurrence rates.
- Neoadjuvant systemic therapy allows for the correlation of treatment with pathologic response and immune response

NEOAVAX

Major eligibility criteria

Age ≧ 18 years
Clinical high-risk clear-cell RCC by cTNM/biopsy Fuhrman grade
- cT1b-T2a G_4 cN0 cM0
- cT2b-T3a G_{3-4} cN0 cM0
- cT3b-T4 G_{any} cN0 cM0
- cT_{any} cN1 (fully resectable) G_{any} cM0

WHO performance status 0-1
No comorbidities precluding systemic therapy or surgery



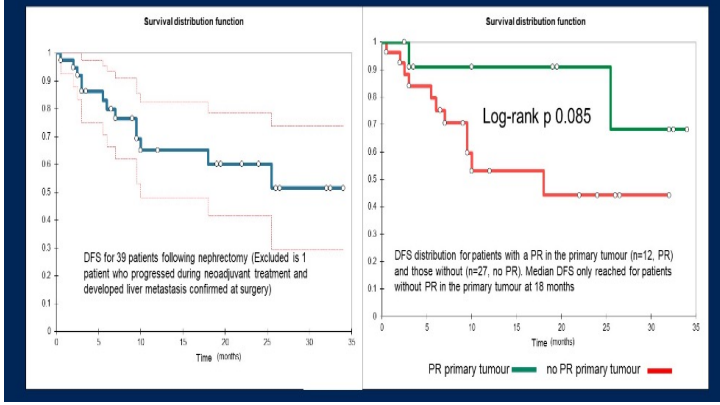
*after week 4: if tolerated well, switch to 7 mg Axitinib BID
after week 8: if tolerated well, switch to 10 mg Axitinib BID

Neoavax (NCT03341845) is an open label, single arm, phase II trial, investigating 12 weeks of neoadjuvant avelumab/axitinib prior to nephrectomy in patients with high-risk non-metastatic clear-cell RCC.

Secondary endpoint

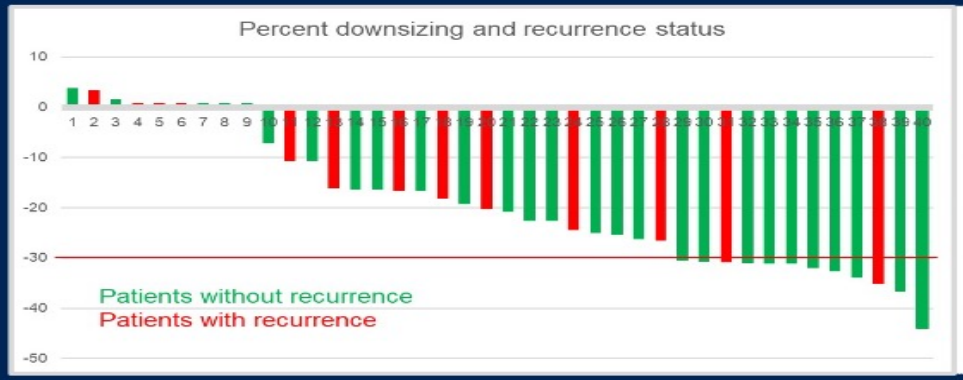
Disease-Free Survival

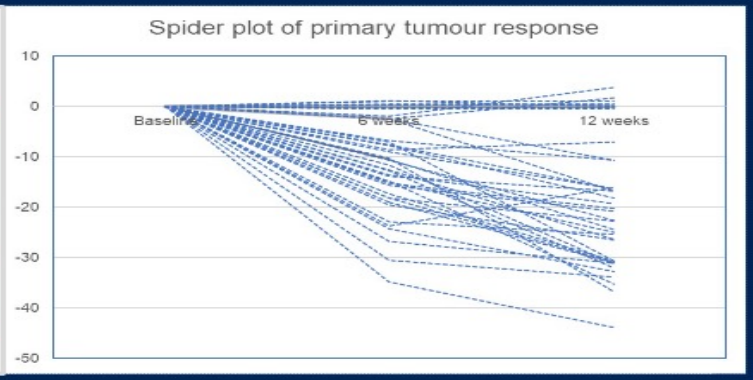
At a median follow-up of 23.5 months, recurrence occurred in 13 (32.5%) patients and 3 died of disease. Median DFS and OS were not reached.



Primary endpoint

Primary tumour response



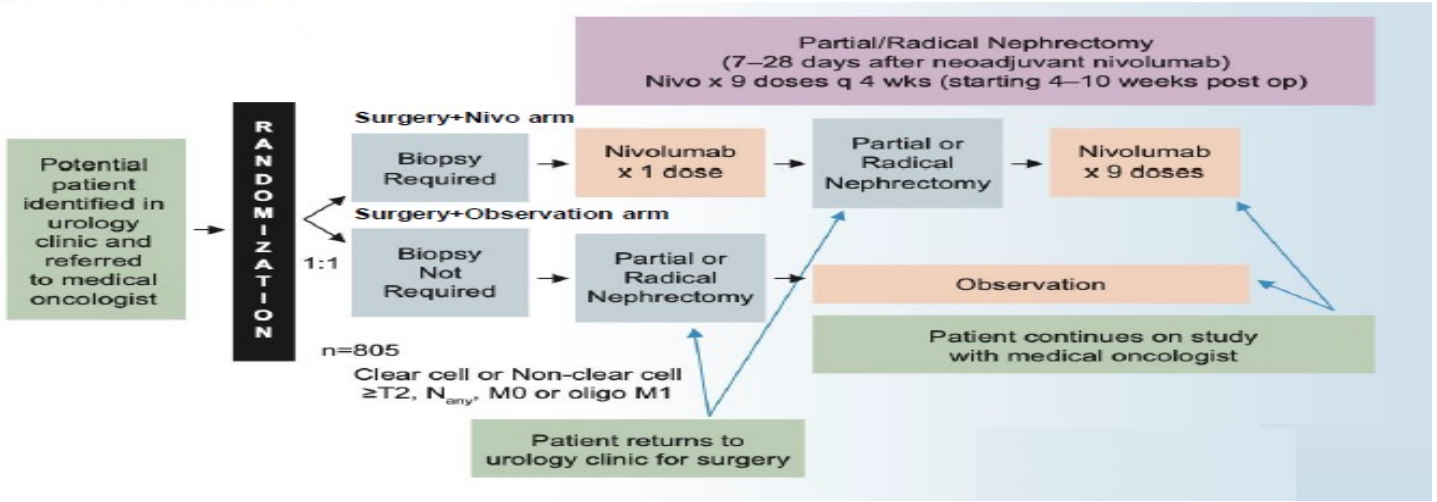


Twelve patients (30%) had a partial response (PR) of their primary tumour. Median primary tumour downsizing was 20 % (+3.8--43.5). Of the 12 patients with PR of the primary tumour, 10 (83%) are disease-free. None of the primary tumours progressed by RECIST 1.1.

Bex A et al GU ASCO 22

PROSPER (ECOG-ACRIN EA8143)

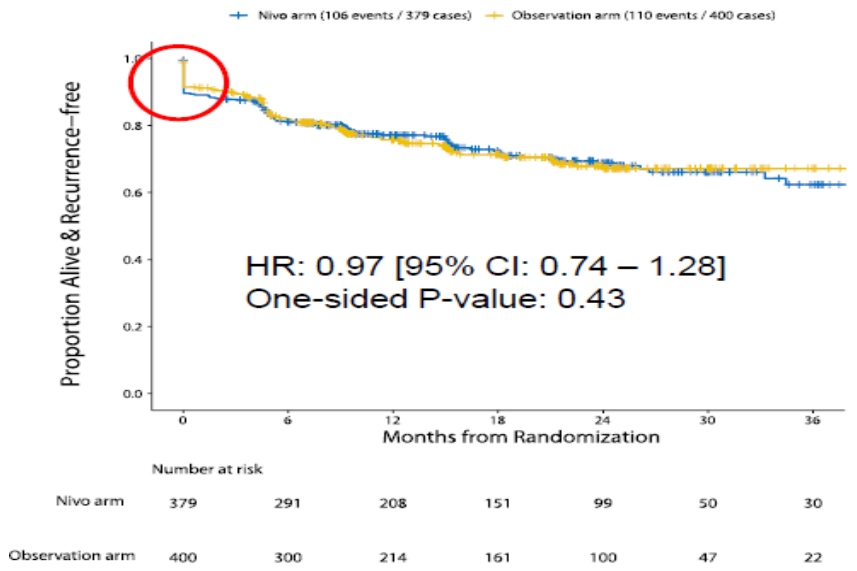
Study Schema



Event	Surgery+Nivo arm n = 356	Surgery+Observation arm n = 387
	no. of patients with event (%)	
Any-cause adverse events		
Adverse event of any grade	332 (93)	230 (59)
Adverse event of grade 3-4 as the highest grade**	118 (33)	51 (13)
Discontinuation of treatment due to any grade adverse event	51 (14)	N/A
Adverse event of grade 5	14 (4)	10 (3)
Treatment-related adverse events, as assessed by investigator		
Adverse event of any grade	276 (78)	103 (27)
Adverse event of grade 3-4 as the highest grade**	54 (15)	16 (4)
Discontinuation of treatment due to any grade adverse event	46 (13)	N/A
Adverse event of grade 5	9 (3)	4 (1)

** = Statistically different between the two arms using the Fishers exact test

Grade 5 events: Acute kidney injury, cardiac arrest, cardiac disorder, death, injury to inferior vena cava, myasthenia gravis, progressive disease, respiratory failure, stroke



Studies of Adjuvant IO in RCC

Trial	Sample Size	Inclusion Criteria	Treatment	Primary Endpoint	Expected Results
Keynote-564[1]	994	pT2G4, pT3aG3-4, pT3b-T4Gx, pTxN1, pTxNxM1 (resected to NED within 1 year); clear cell	Pembrolizumab vs placebo	DFS	**ASCO 2021** **ASCO GU 2022**
IMmotion010[2]	778	pT2G4, pT3aG3-4, pT3b-T4Gx, pTxN1, pTxNxM1 (resected to NED*); clear cell	Atezolizumab vs placebo	DFS	**ESMO 2022** **NS DFS** **HR 0.93; P=0.4950**
CheckMate-914[3]	1600	pT2aG3-4N0, pT2b-T4GxN0, pTxGxN1; clear cell	Nivolumab + ipilimumab vs. nivolumab + placebo vs placebo *(6 months)*	DFS	**ESMO 2022** ***Part A (Nivo+Ipi)*** **NS DFS** **HR, 0.92; P=0.5347**
PROSPER RCC[4]	766	cT2Nx, cTxN1, cTxNxM1 (resected to NED); any RCC histology	Nivolumab vs observation	EFS	**ESMO 2022** **NS DFS** **HR, 0.97; P=0.43** **Trial stopped for futility**
RAMPART[5]	1750	Leibovich score 3-11; any RCC histology	Durvalumab + tremelimumab vs durvalumab vs observation	DFS, OS	7/2024

*Metachronous pulmonary, lymph node, or soft tissue recurrence >12 months from nephrectomy.

DFS, disease-free survival; EFS, event-free survival; NED, no evidence of disease; RCC, renal cell carcinoma; OS, overall survival; NS, non-significant.

1. Choueiri TK et al. *N Engl J Med*. 2021;385:683-694. 2. NCT03024996. 3. NCT03138512. 4. NCT03055013. 5. NCT03288532.

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KEYNOTE 564

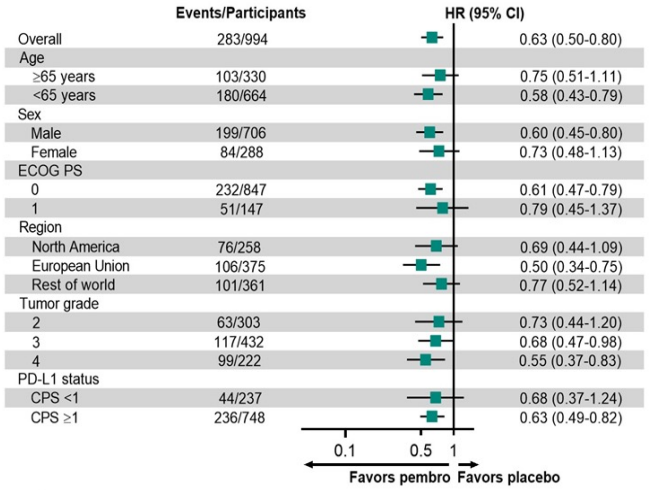
Key Eligibility Criteria
- Histologically confirmed clear cell renal cell carcinoma
- Nephrectomy ≤12 weeks prior to randomization
- No prior systemic therapy
- ECOG PS 0 or 1
- Tissue sample for PD-L1 assessment

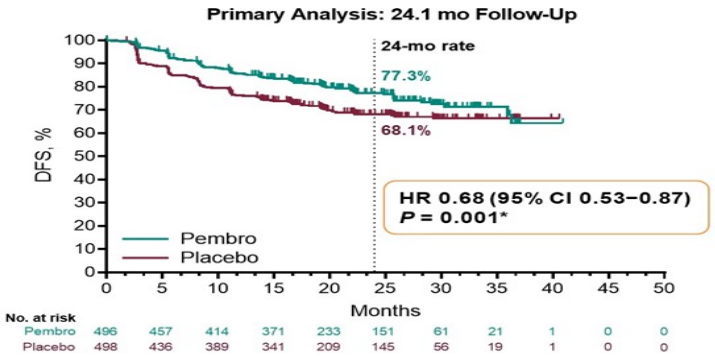
Stratification Factors
- M0 vs M1 NED
- M0 group further stratified:
  - ECOG PS 0 vs 1
  - US vs non-US

R (1:1)

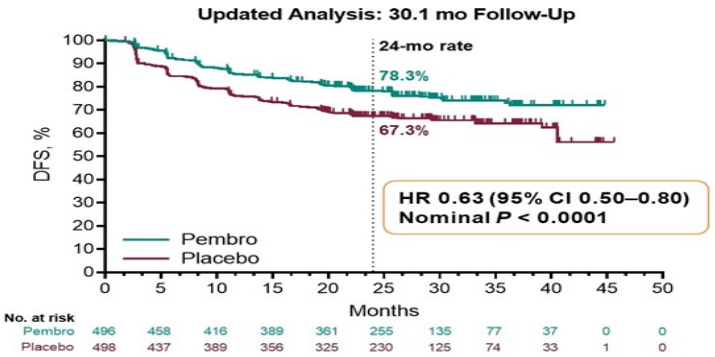
- Pembrolizumab 200 mg Q3W for ~1 year[a]
- Placebo Q3W for ~1 year[a]

- Primary end point: DFS per investigator
- Key secondary end point: OS
- Other secondary end points: Safety





	Pts w/ Event	Median, mo (95% CI)
Pembro	109	NR (NR–NR)
Placebo	151	NR (NR–NR)



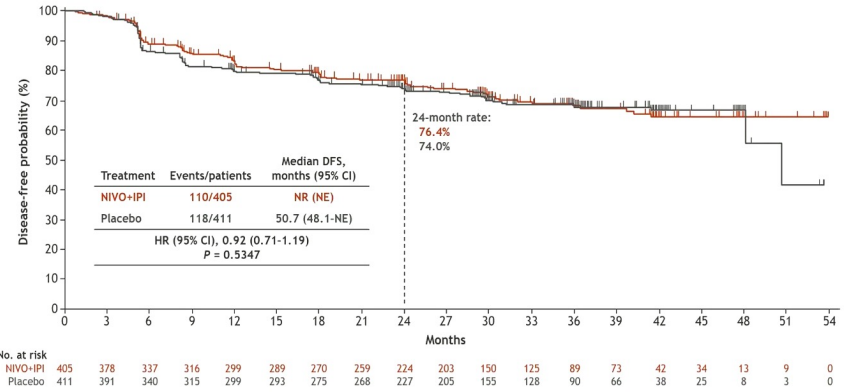
	Pts w/ Event	Median, mo (95% CI)
Pembro	114	NR (NR–NR)
Placebo	169	NR (40.5–NR)

* denotes statistical significance.
ITT population included all randomized participants. DFS, disease-free survival; NR, not reached. Primary analysis data cutoff date: December 14, 2020. Updated analysis data cutoff date: June 14, 2021.

Data cutoff at updated analysis: June 14, 2021.

Powles T, et al. *Lancet Oncol*. 2022;23;1133-1144; Choueiri TK, et al. ASCO GU 2022. Abstract 290; Choueiri TK et al. *N Engl J Med*. 2021;385:683-694; Choueiri TK et al. 2021 ASCO Annual Meeting. Abstract LBA5.

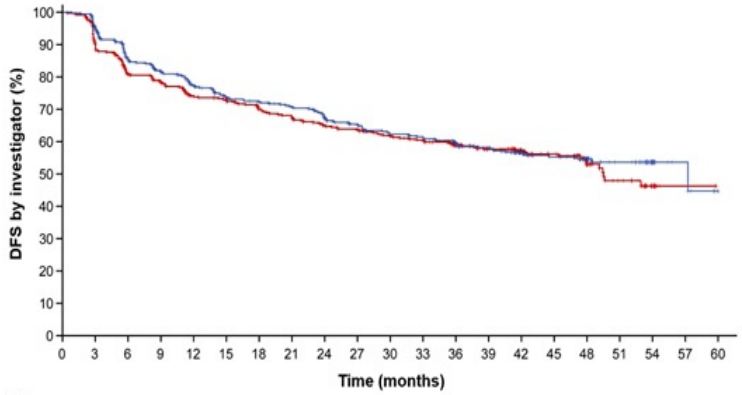
CheckMate-914



Median (range) follow-up, 37.0 (15.4-58.0) months.
As the DFS endpoint was not met, no formal analysis of OS was performed (in total, there were 33 deaths in the NIVO+IPI arm and 28 deaths in the placebo arm).

Treatment	Events/patients	Median DFS, months (95% CI)
NIVO+IPI	110/405	NR (NE)
Placebo	118/411	50.7 (48.1-NE)
HR (95% CI), 0.92 (0.71-1.19) *P* = 0.5347		

IMmotion010



Data cutoff: 3 May 2022. Minimum follow-up, 38.6 months; Median follow-up, 44.7 months (range, 0-62.6).
NE, not estimable.
[a] Stratified for disease status and PD-L1 status. [b] Not significant at α=0.05.

Bex.

	Atezolizumab (n=390)	Placebo (n=388)
DFS events, n (%)	164 (42)	168 (43)
Median DFS (95% CI), mo	57.2 (44.6, NE)	49.5 (47.4, NE)
24-month DFS (95% CI), %	67% (63, 72)	65% (60, 70)
Stratified HR (95% CI)[a]	0.93 (0.75, 1.15); *P*=0.4950[b]	

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National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2023
Kidney Cancer

NCCN Guidelines Index
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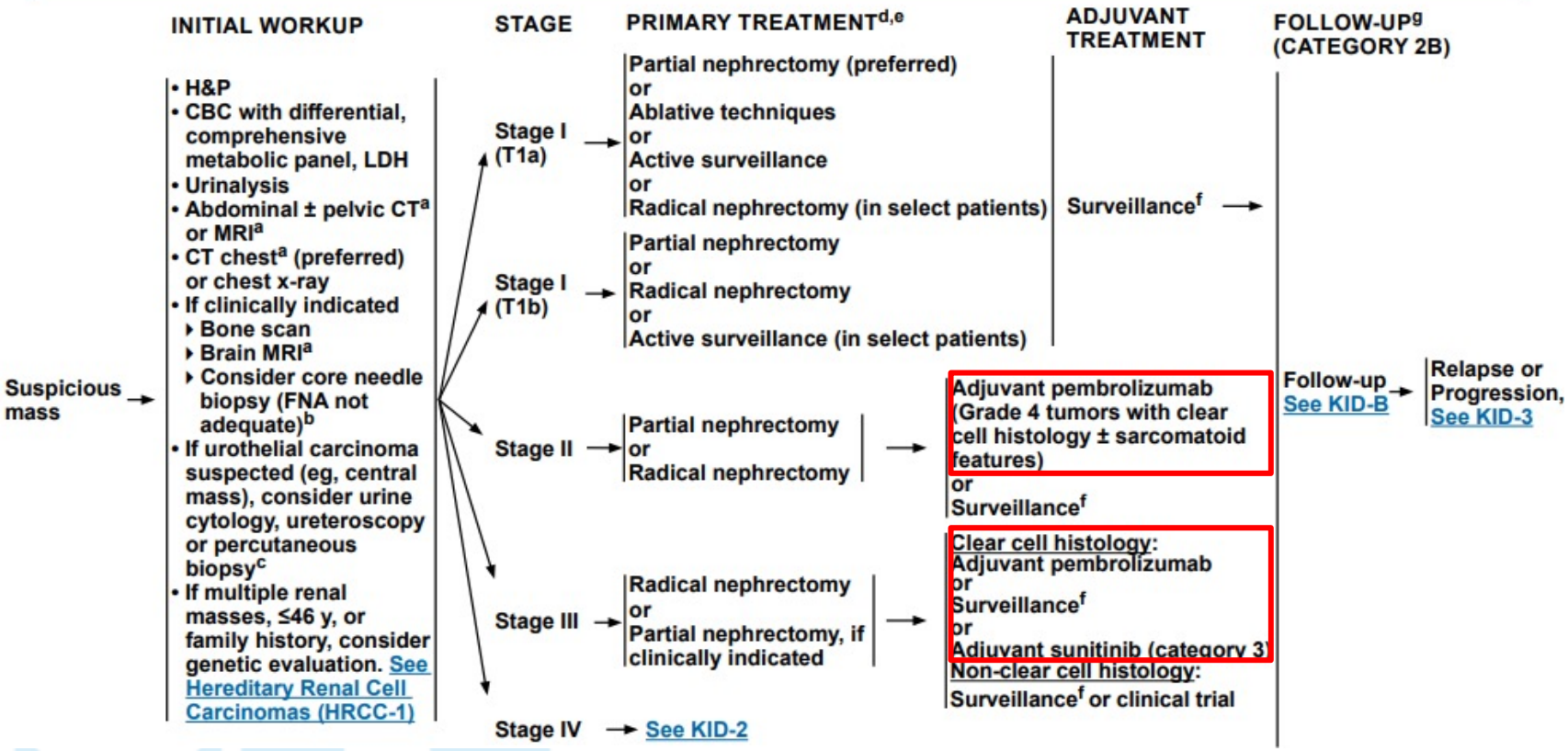

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First-line IO Combination Trials in mRCC

	CheckMate 214 (Ipi/Nivo) [1] (n=550 vs n=546)	KEYNOTE-426 (Axi/Pembro)[2] (n=432 vs n=429)	CheckMate 9ER (Cabo/Nivo)[3] (n=323 vs n=328)	CLEAR (Len/Pembro)[4] (N=355 vs n=357)
mOS, months HR (CI)	NR vs 38.4 **0.69** (0.59–0.81)	45.7 vs 40.1 **0.73** (0.60-0.88)	NR vs 29.5 **0.66** (0.50–0.87)	NR vs NR **0.66** (0.49-0.88)
Landmark OS 12 mo Landmark OS 24 mo	**83%** vs. 78% **71%** vs. 61%	**90%** vs. 79% **74%** vs. 66%	**86%** vs. 76% **72%** vs 60% (est.)	**90%** vs 79% (est.) **79%** vs. 70%
mPFS, months HR (CI)	**12.2** vs 12.3 0.89 (0.76–1.05)	**15.7** vs 11.1 0.68 (0.58–0.80)	**17.0** vs 8.3 0.52 (0.43–0.64)	**23.9** vs 9.2 0.39 (0.32-0.49)
ORR, %	**39** vs 32	**60** vs 40	**55** vs 27	**71** vs 36
CR, %	**11** vs 3	**10** vs 4	**9** vs 4	**16** vs 4
Med f/u, months	**55**	**42.8**	**23.5**	**27**
Prognostic risk, % Favorable Intermediate Poor	 23 61 17	 32 55 13	 23 58 19	 31 59 9
Prior nephrectomy	82%	83%	69%	74%
Subsequent systemic therapies for sunitinib arm, %	Overall (69%) IO (42%)	Overall (69%) IO (48%)	Overall (40%) IO (29%)	Overall (71%) IO (53%)

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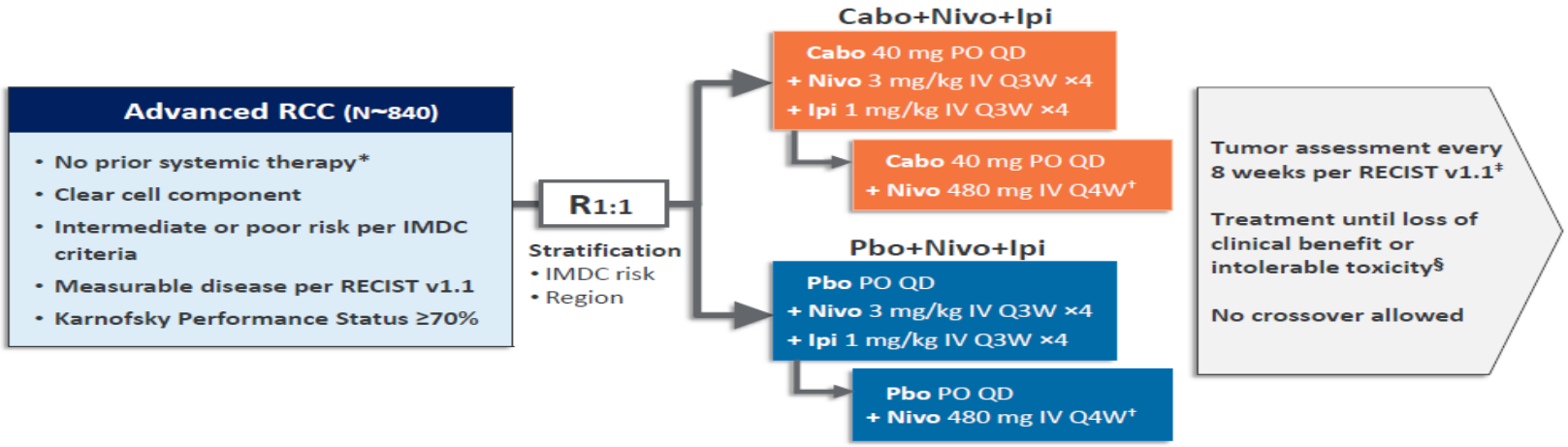
COSMIC-313

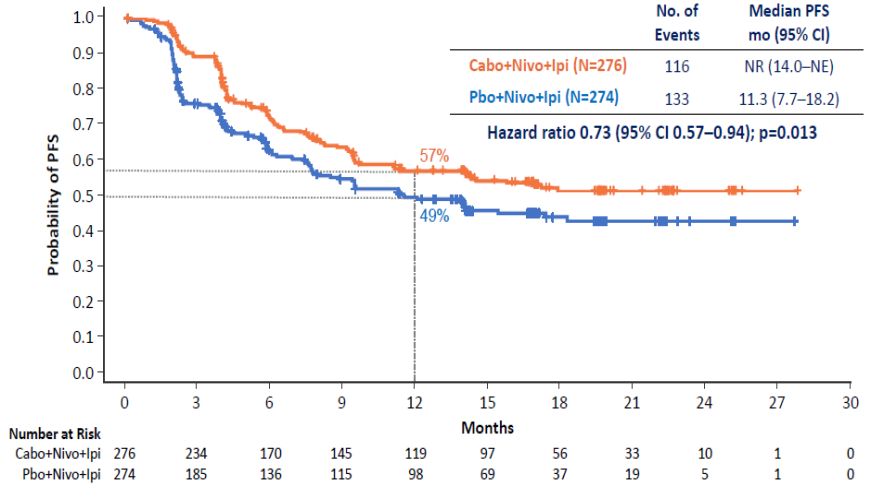
COSMIC-313 Study Design



Tumor Response (PITT Population)

	Cabo+Nivo+Ipi (N=276)	Pbo+Nivo+Ipi (N=274)
Objective response rate (95% CI), %	43 (37.2–49.2)	36 (30.1–41.8)
Best overall response, n (%)		
Complete response	7 (3)	9 (3)
Partial response	112 (41)	89 (32)
Stable disease	119 (43)	100 (36)
Progressive disease	23 (8)	55 (20)
Not evaluable	15 (5)	21 (8)
Disease control rate, %	86	72
Median time to objective response (range), mo	2.4 (1.5–17.1)	2.3 (1.9–16.8)
Median duration of response (95% CI), mo	NR (20.2–NE)	NR (NE–NE)

Progression-Free Survival: Final Analysis (PITT Population)



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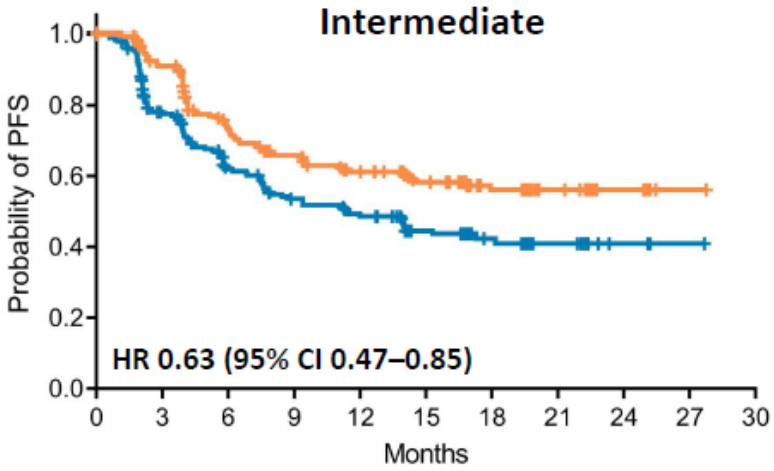
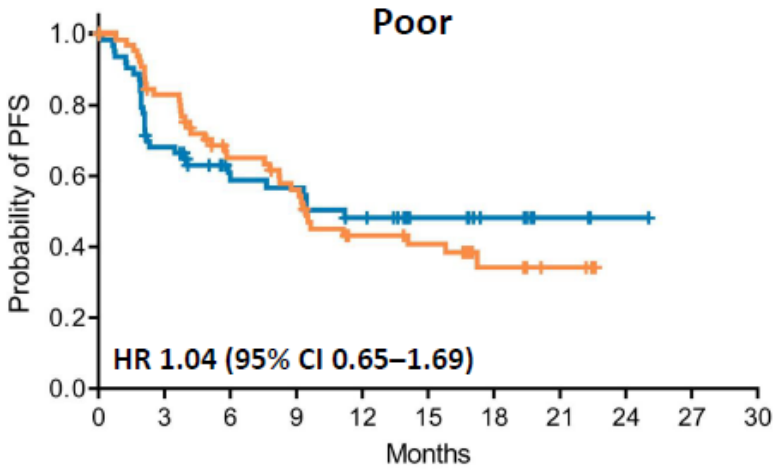
PFS and ORR by IMDC Risk Group (PITT Population)



	No. of Events	Median PFS mo (95% CI)
Cabo+Nivo+Ipi (N=209)	79	NR (16.9–NE)
Pbo+Nivo+Ipi (N=208)	103	11.4 (7.6–17.3)

ORR: 45% (95% CI, 38.1–52.0) for Cabo+Nivo+Ipi vs 35% (95% CI, 28.6–42.0) for Pbo+Nivo+Ipi



	No. of Events	Median PFS mo (95% CI)
Cabo+Nivo+Ipi (N=67)	37	9.5 (7.8–17.3)
Pbo+Nivo+Ipi (N=66)	30	11.2 (4.0–NE)

ORR: 37% (95% CI, 25.8–50.0) for Cabo+Nivo+Ipi vs 38% (95% CI, 26.2–50.7) for Pbo+Nivo+Ipi

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VEGF-IO in Refractory RCC

Tivozanib +nivolumab

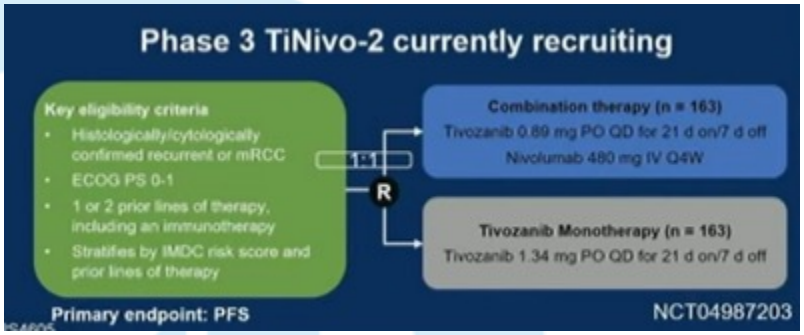
Phase 1/2 TiNivo: tivozanib + nivolumab in the first-line setting and beyond in patients with mRCC

- With a median follow-up of 19.0 mo, mPFS was 18.9 mo in treatment-naïve patients; not reached for previously treated patients

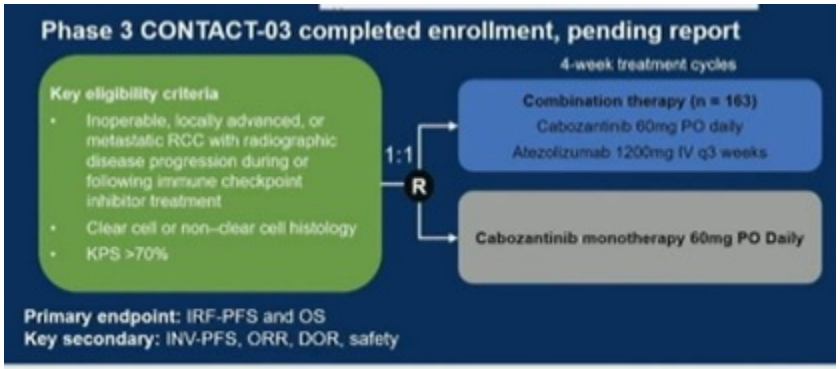
Cabozantinib + atezolizumab

- **Phase 1/2 COSMIC-021:** cabozantinib + atezolizumab in the refractory mRCC setting
  - Objective response rate 58%

Phase 3 TiNivo-2 currently recruiting



Phase 3 CONTACT-03 completed enrollment, pending report



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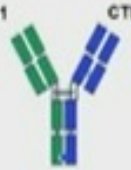
Bispecifics to combine immune targets? Phase 1/2 of MEDI5752

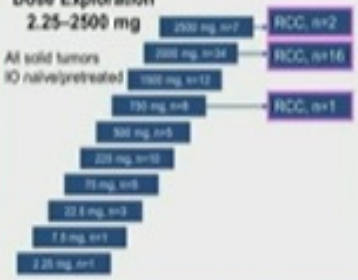
MEDI5752: A monovalent bispecific antibody



- Affinity to human CTLA-4: 0.42 nM
- Affinity to human PD-1: 0.81 nM
- Fc isotype: human IgG1-TM (reduced antibody-dependent cellular cytotoxicity)
- CTLA-4 arm = Tremelimumab arm

Cohort	Dose Exploration 750–2500 mg	Dose Expansion 1500 mg	Dose Expansion 750 mg*	TOTAL
Enrolled, N	19	27	32	78
Median age, years (range)	63.0 (31–78)	61.0 (41–83)	59.0 (36–78)	61.0 (31–83)
Tumor type				
Clear cell RCC	17 (89.5)†	26 (96.3)†	32 (100)	75 (96.2)
PD-L1 <1% (SP263), n (%)	12 (63.2)	18 (66.7)	19 (59.4)	49 (62.8)
Study treatment line of therapy, n (%)				
1L	5 (26.3)	13 (48)	32 (100)	50 (64.1)
2L	9 (47.4)	14 (52)	-	23 (29.5)
3–4L	5 (26.3)	-	-	5 (6.4)
IMDC category, n (%)				
Intermediate/Poor risk, n (%)	4/5 1L (80.0)	9/13 1L (69.3)	N/A	N/A
Prior nephrectomy, n (%)	13 (68.4)	17 (63)	16 (50)	46 (59)
Prior VEGFR-TKI therapy, n (%)	14 (73.7)	14 (51.9)	0	28 (35.9)

Dose Exploration 2.25–2500 mg



RCC Dose Expansion

Clear cell RCC 1–2L, IO naive	Clear cell RCC 1L, IO naive; VEGFR-TKI naive	
1500 mg n=27	750 mg n=32	500 mg n=30, ongoing

Data included in presentation (DCO 10 April 2022, unless otherwise specified)

	Dose Exploration	Dose Expansion 1500 mg		Dose Expansion 750 mg
Response-evaluable, N	1–4L, n=19	1L, n=12	2L, n=14	1L, n=32
Median follow-up, months (range)	13.1 (0.7–29.8)	18.4 (0.5–23.6)		6.9 (1.4–10.9)
Overall response rate, n (%)	7 (36.8)	7 (58.3)	3 (21.4)	Data immature*
CR + PR + uPR, n (%)	-	-	-	14 (43.8)*
CR	0	1 (8.3)	1 (7.1)	1(3.1)*
PR	7 (36.8)	6 (50.0)	2 (14.3)	10(31.3)*
uPR, pending confirmation	-	-	-	3(9.4)*
Stable disease, n (%)	5 (26.3)	4 (33.3)	5 (35.7)	14(43.8)*
Progressive disease/NE, n (%)	7 (36.9)	1 (8.3)	6 (42.9)	4(12.5)*

*Clinical database review 16 May 2022

Albiges L et al, ASCO 2022

ASCO Genitourinary Cancers Symposium #GU23

PRESENTED BY: Tian Zhang, MD, MHS

@tiansterzhang

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY
KNOWLEDGE CONQUERS CANCER

Courtesy Slide Tian Zhang GU ASCO 2023

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Is cellular therapy coming to RCC?
COBALT-RCC: CD70-targeted CAR-T cell Trial

Phase 1, open-label, multicenter, international, single-arm study (NCT04438083) evaluating the safety and efficacy of CTX130, an investigational, allogeneic CAR T cell targeting CD70

Informed consent form

CTX130 infusion (D +1):

DL1	DL2	DL3	DL4
3×10^7 cells	1×10^8 cells	3×10^8 cells	9×10^8 cells

Screening

D42 Assessment and Follow-up

Flu 30mg/m² + Cy 500mg/m² for 3 days (D –5, –4, –3)

Key inclusion criteria

- Age ≥18 years and body weight ≥42 kg
- Unresectable or metastatic clear cell RCC
- Prior exposure to both check point and VEGF inhibitorw/ documented progression, Adequate renal, liver, cardiac, and pulmonary organ function

Key exclusion criteria

- Prior treatment with any anti-CD70 targeting agents
- Prior treatment with any CAR T cells or any other modified T or natural killer (NK) cells
- History of certain central nervous system (CNS), cardiac or pulmonary conditions
- Prior solid organ transplantation or bone marrow transplant

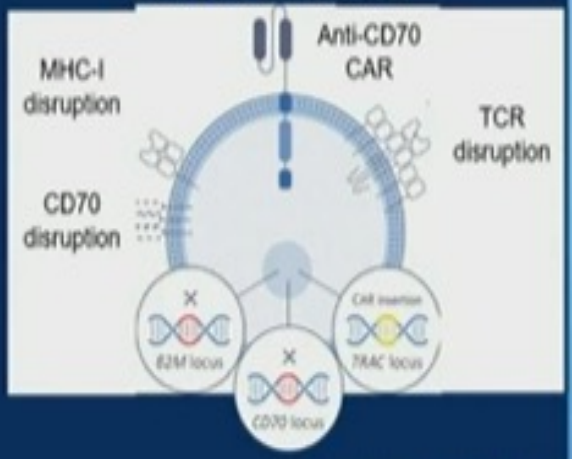
Primary endpoint

- Part A (Dose Escalation): Incidence of AEs and DLTs
- Part B (Cohort Expansion): Objective response rate by RECIST criteria

Secondary endpoints

- Best overall response
- Progression-free survival
- Overall survival

CTX130 Construct



Pal SK et al, SITC 2022

Courtesy Slide Tian Zhang GU ASCO 2023

MOFFITT CANCER CENTER

Is cellular therapy coming to RCC?
COBALT-RCC: CD70-targeted CAR-T cell Trial

Phase 1, open-label, multicenter, international, single-arm study (NCT04438083) evaluating the safety and efficacy of CTX130, an investigational, allogeneic CAR T cell targeting CD70

Informed consent form

CTX130 infusion (D +1):

DL1	DL2	DL3	DL4
3×10^7 cells	1×10^8 cells	3×10^8 cells	9×10^8 cells

Scre… Flu…

	DL1 3×10^7 N=3	DL2 1×10^8 N=3	DL3 3×10^8 N=4	DL4 9×10^8 N=3	Total N=13
Overall Response Rate	1 (33)	0	0	0	**1 (8)**
Stable Disease	2 (67)	2 (67)	2 (50)	3 (100)	**9 (69)**
Disease Control Rate (DCR = CR + PR + SD)	3 (100)	2 (67)	2 (50)	3 (100)	**10 (77)**

Refractory population

No Grade >3 CRS events

77% disease control
1 patient with PR

Key inclusion criteria

- Age ≥18 years and body weight ≥42 k…
- Unresectable or metastatic clear cell…
- Prior exposure to both check point and VEGF inhibitor(s), documented progression, Adequate renal, liver, cardiac, and pulmonary organ function

Key exclusion criteria

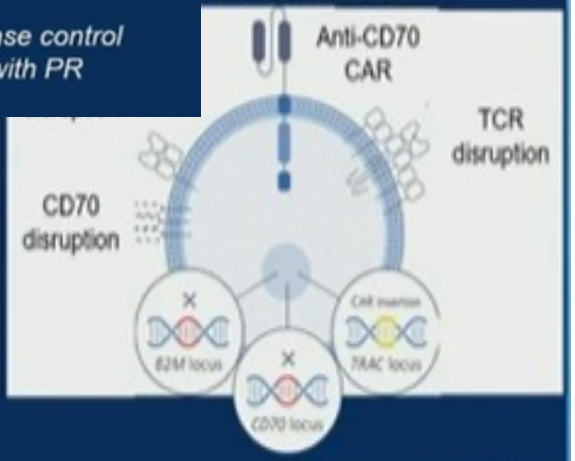
- Prior treatment with any anti-CD70 targeting agents
- Prior treatment with any CAR T cells or any other modified T or natural killer (NK) cells
- History of certain central nervous system (CNS), cardiac or pulmonary conditions
- Prior solid organ transplantation or bone marrow transplant

- Part A (Dose Escalation): Incidence of AEs and DLTs
- Part B (Cohort Expansion): Objective response rate by RECIST criteria

Secondary endpoints

- Best overall response
- Progression-free survival
- Overall survival

…30 Construct



Pal SK et al, SITC 2022

Courtesy Slide Tian Zhang GU ASCO 2023

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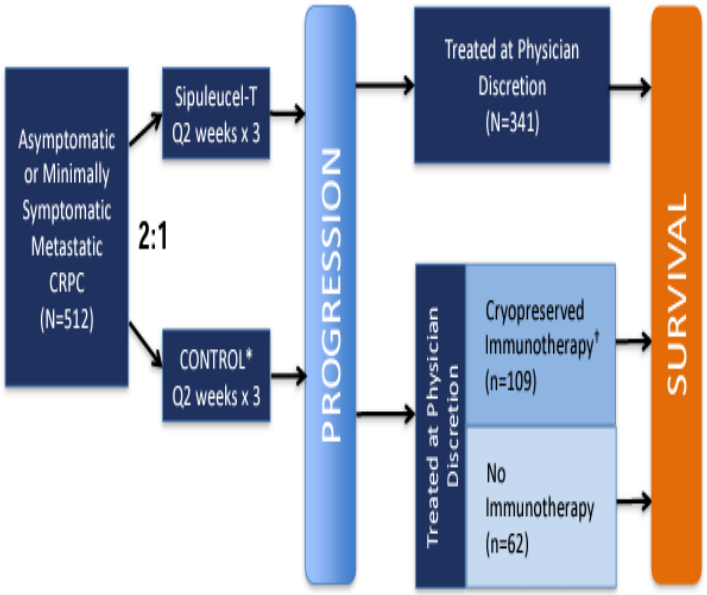
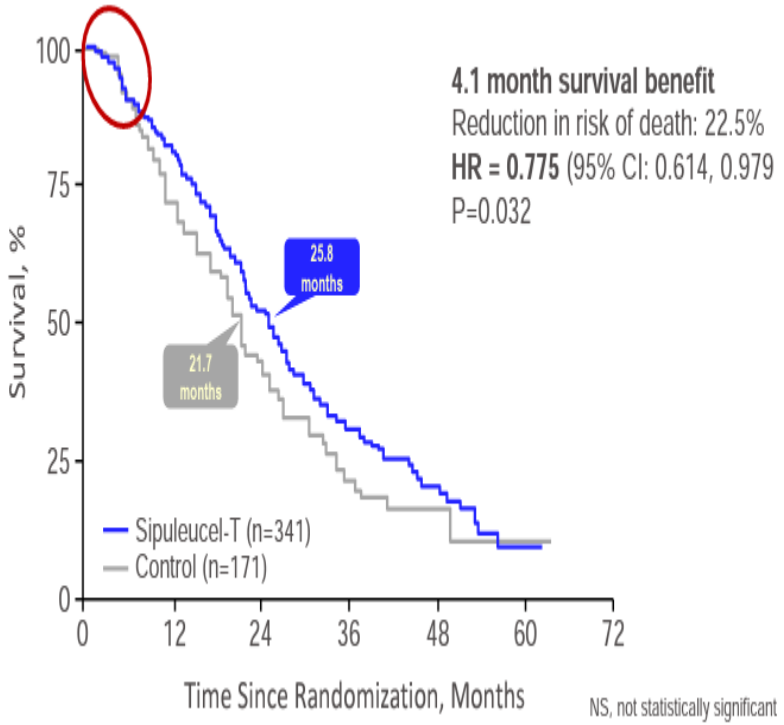
Immunotherapy in Prostate cancer



Primary endpoint: Overall survival

Secondary endpoint: Time to objective disease progression



Kantoff P et al NEJM 2010

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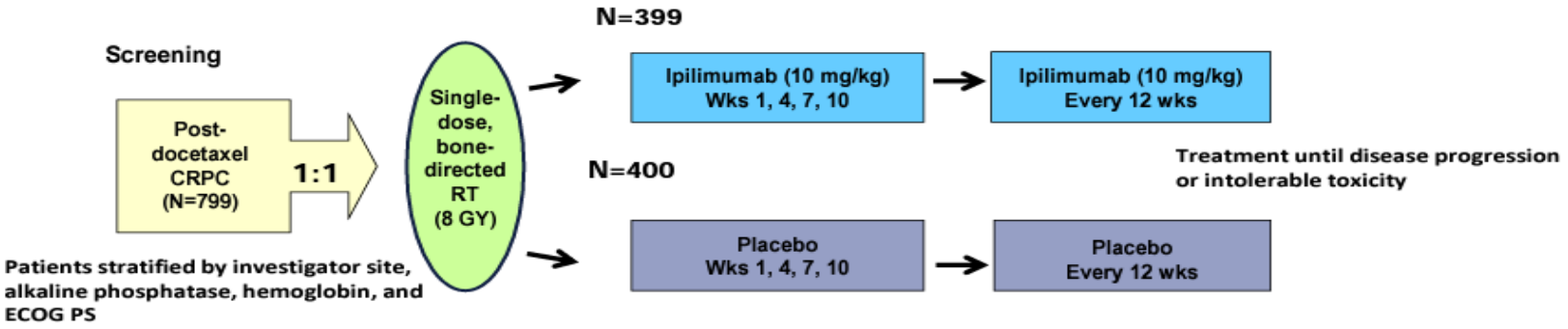
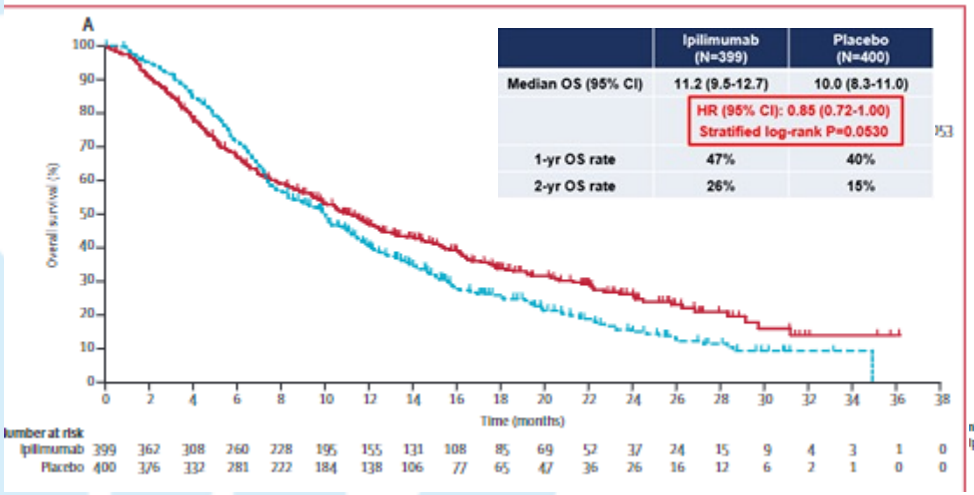
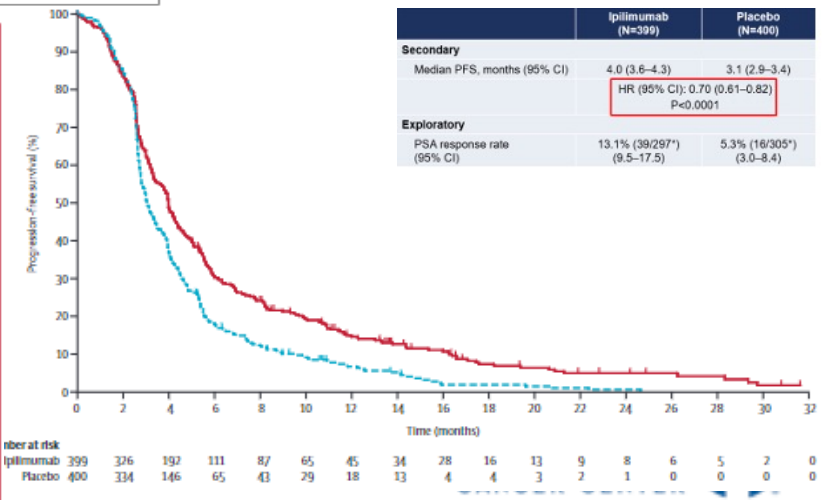
Ipilimumab –Phase 3 Trial

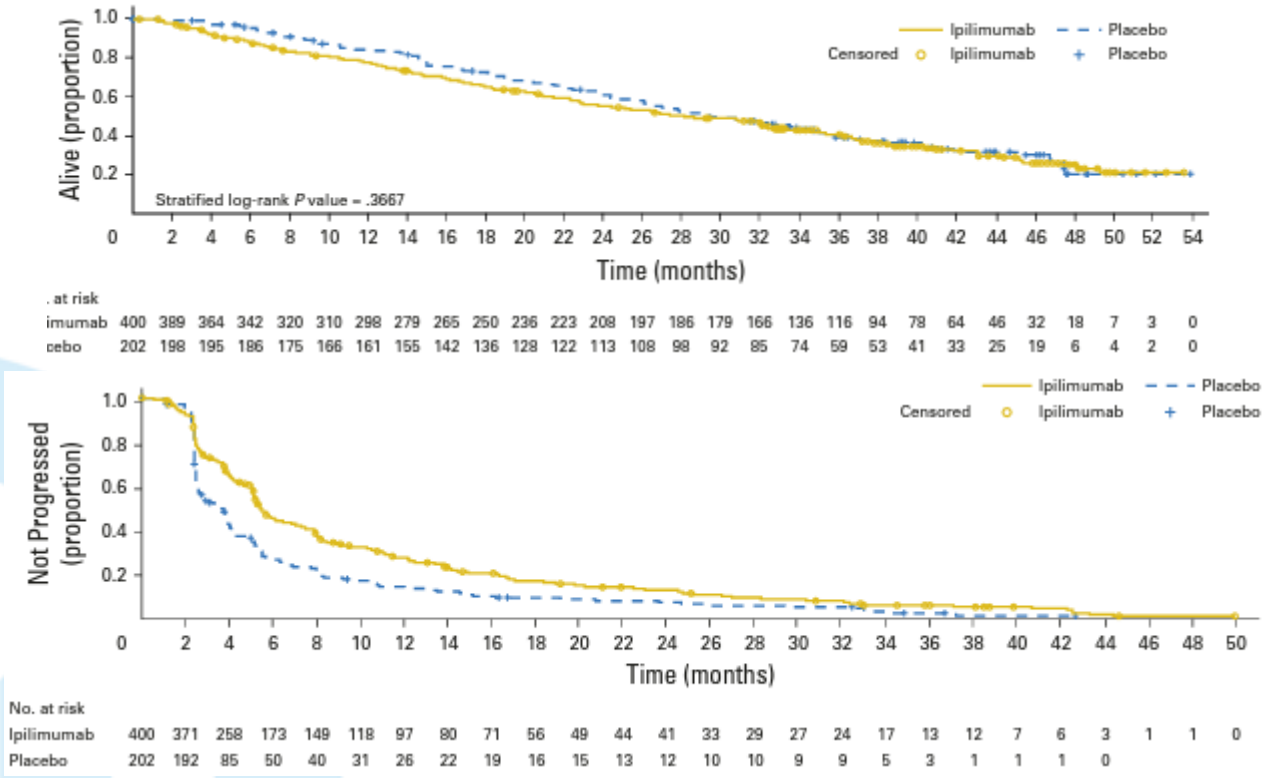


- Primary endpoint: overall survival (OS)
- Secondary endpoints: progression-free survival, safety
- Exploratory endpoint: PSA response rate





Ipilimumab in Docetaxel Naïve CRPC

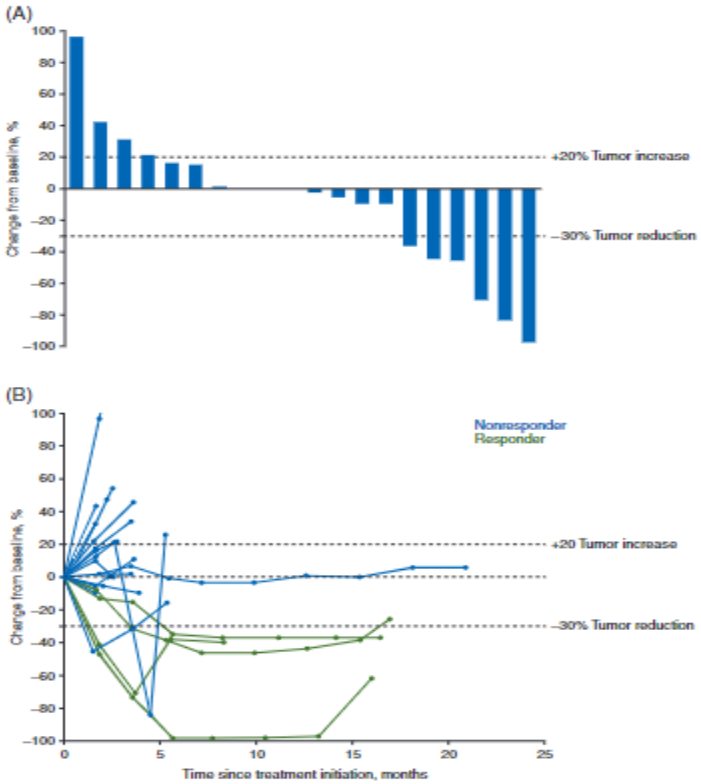


Tomasz et al JCO 2017

MOFFITT CANCER CENTER

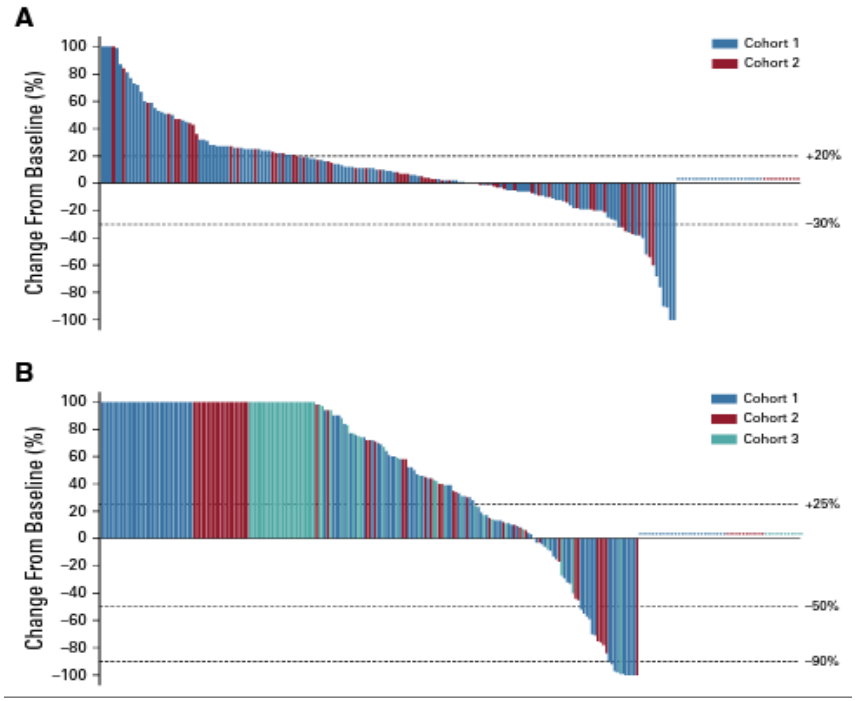
Pembrolizumab

KEYNOTE 028



Hansen A R 2019 Annals of Onco

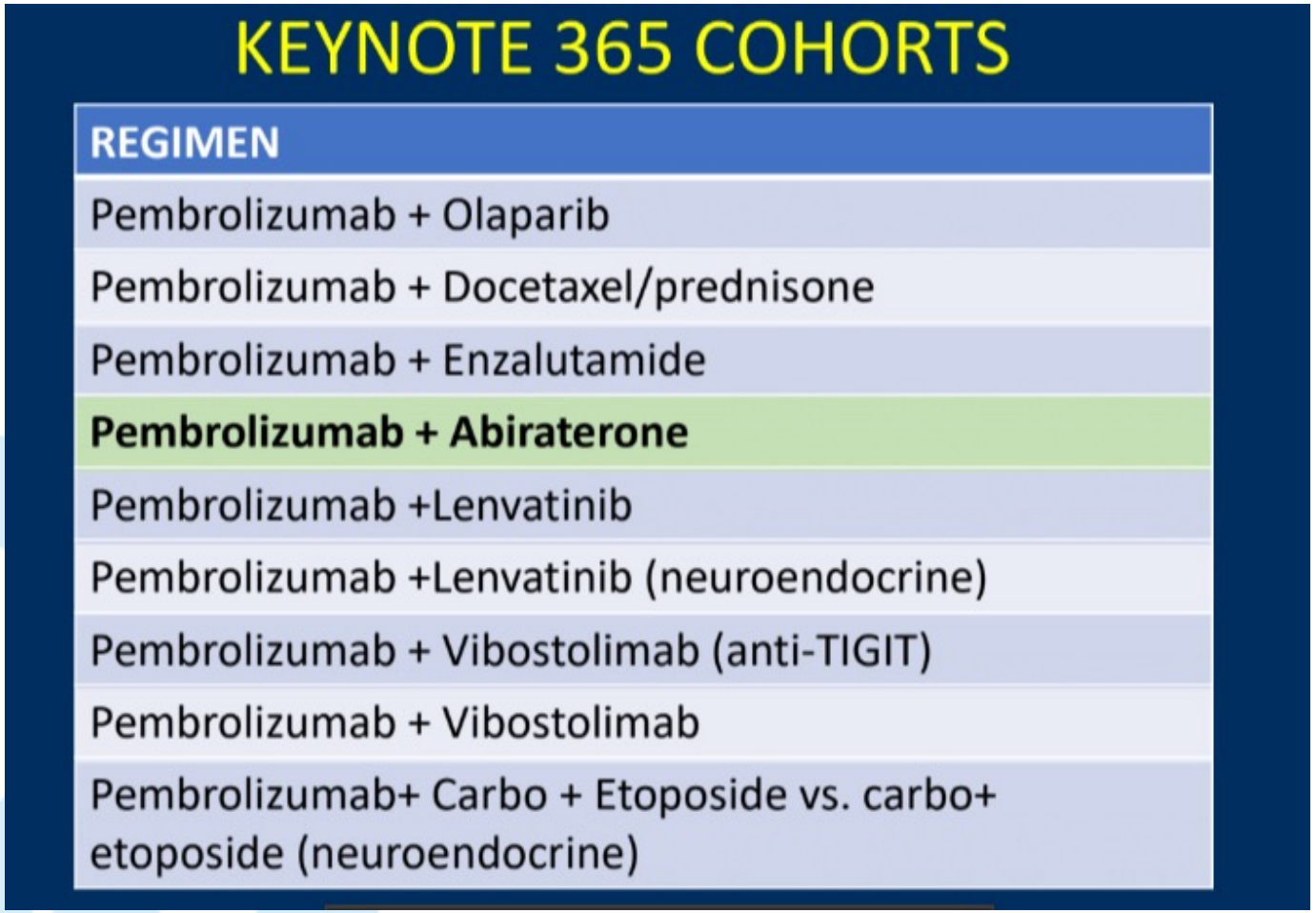
KEYNOTE-199



Antonarakis E JCO 2019

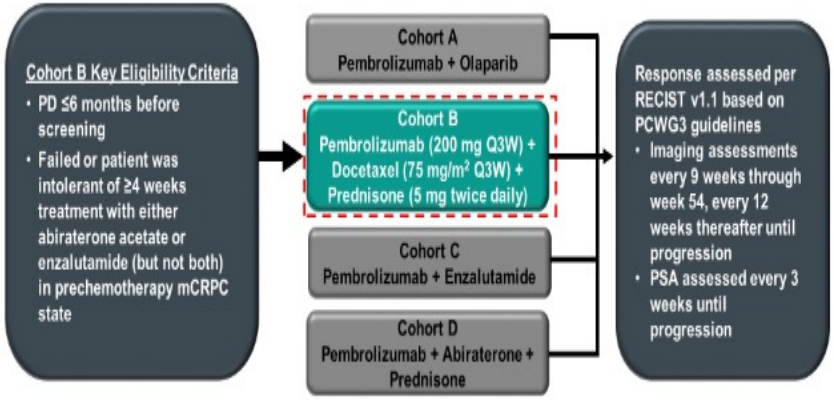
MOFFITT CANCER CENTER

KEYNOTE 365



KEYNOTE-365

KEYNOTE-365 Study Design



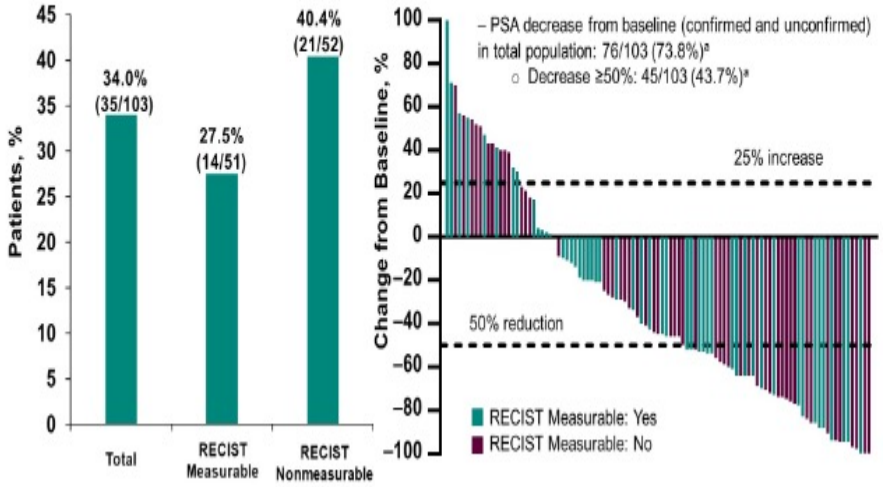
Median Time From Enrollment to Data Cutoff in Cohort B
- **All patients**: 32.4 months (range, 13.9-40.3)

Primary End Points
- Safety
- PSA response rate
- ORR by RECIST v1.1 (BICR)

Secondary End Points
- DCR
- rPFS by PCWG-modified RECIST v1.1
- OS

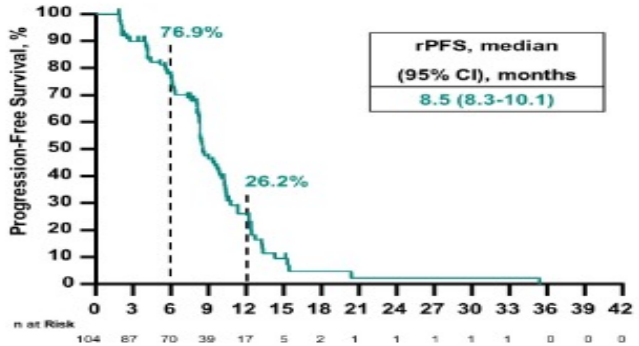
Data cutoff: July 9, 2020.

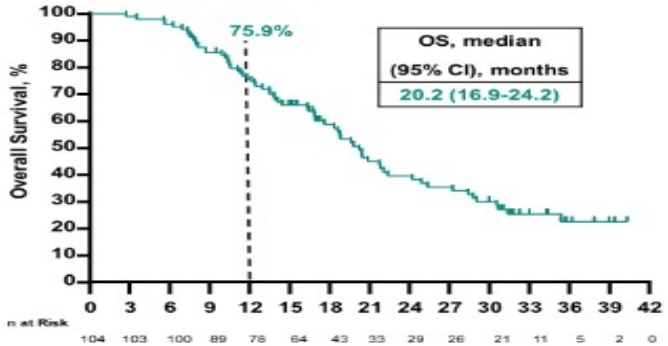
Confirmed PSA Response Rate (≥50% Reduction)[a] and Percentage Change From Baseline[b]



[a]Calculation is based on patients who had nonmissing PSA measurements at baseline; ≥50% PSA decline confirmed by subsequent value ≥3 weeks later. [b]Plot is based on patients who had a

Kaplan-Meier Estimates of rPFS per PCWG3-Modified RECIST v1.1 and OS





Appleman L et al GU ASCO 2021

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KEYNOTE-921

KEYNOTE-921 Study (NCT03834506)

- Phase 3, randomized, double-blind study of pembrolizumab + docetaxel vs docetaxel for participants with previously treated mCRPC

Key Eligibility Criteria
- Confirmed mCRPC
- Failure of or intolerance to 1 prior NHA therapy for mHSPC or mCRPC
- ECOG PS 0 or 1
- Tissue sample for biomarker assessment

R 1:1

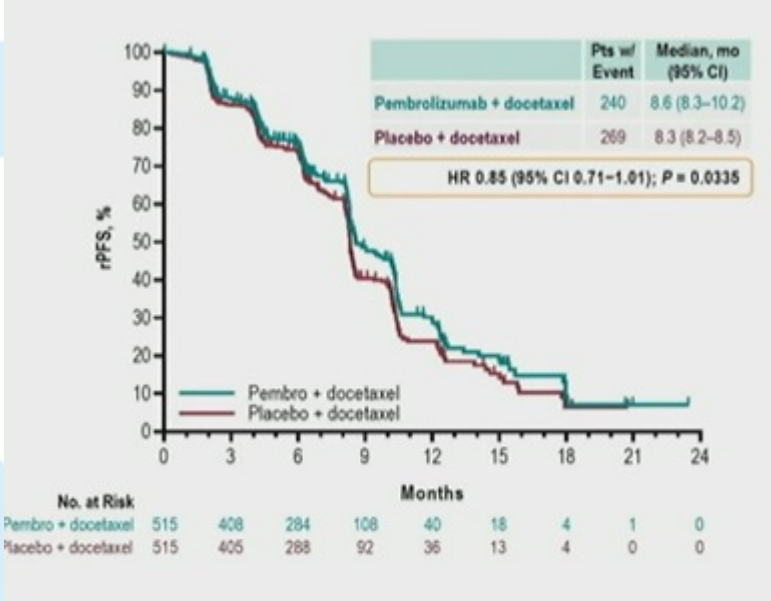
N = 515: **Pembrolizumab** 200 mg Q3W for ≤35 cycles + **Docetaxel** 75 mg/m² Q3W for ≤10 cycles + **Prednisone** 5 mg BID[a]

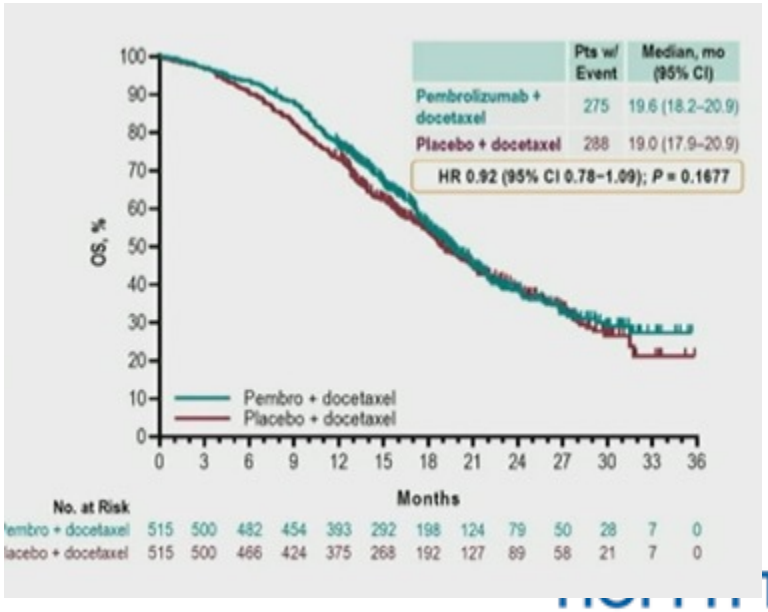
N = 515: **Placebo** Q3W for ≤35 cycles + **Docetaxel** 75 mg/m² Q3W for ≤10 cycles + **Prednisone** 5 mg BID[a]

Stratification Factors
- Prior abiraterone: yes vs no
- Metastases: bone only vs liver vs other

Dual Primary Endpoints
- rPFS by BICR per PCWG-modified RECIST v1.1
- OS

Secondary Endpoints
- TFST (key secondary)
- ORR
- Safety





Petrylak D GU ASCO 2023

KEYLYNK-010 Study (NCT03834519)

- Phase 3, randomized, open-label study of pembrolizumab plus olaparib vs NHA for participants with previously treated mCRPC

Key Eligibility Criteria
- Histologically or cytologically confirmed mCRPC
- PD after abi or enza (but not both) and docetaxel
- ECOG PS 0 or 1
- Tissue sample for biomarker assessment

Stratification Factors
- Prior NHA treatment: abi vs enza
- Measurable disease at baseline: yes vs no

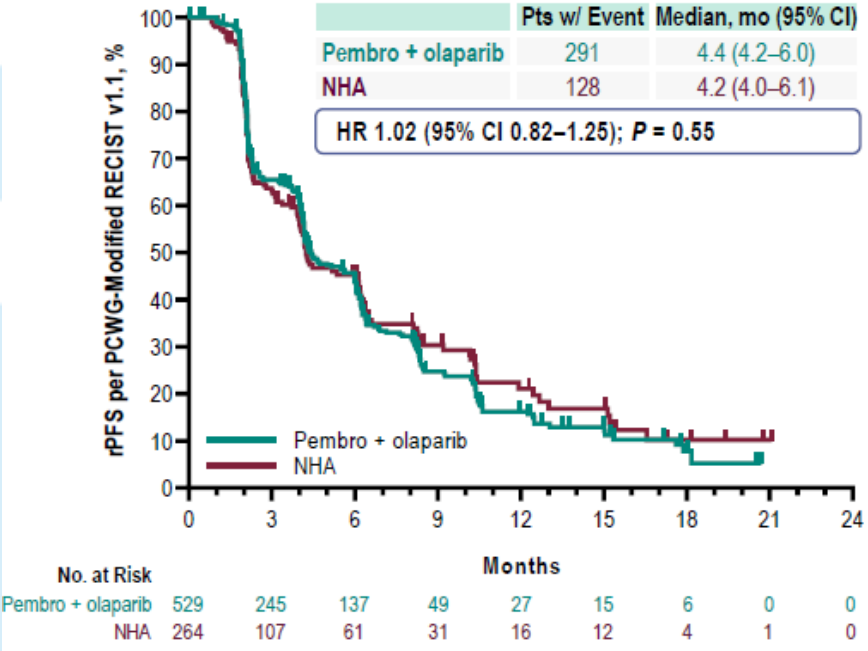
R 2:1

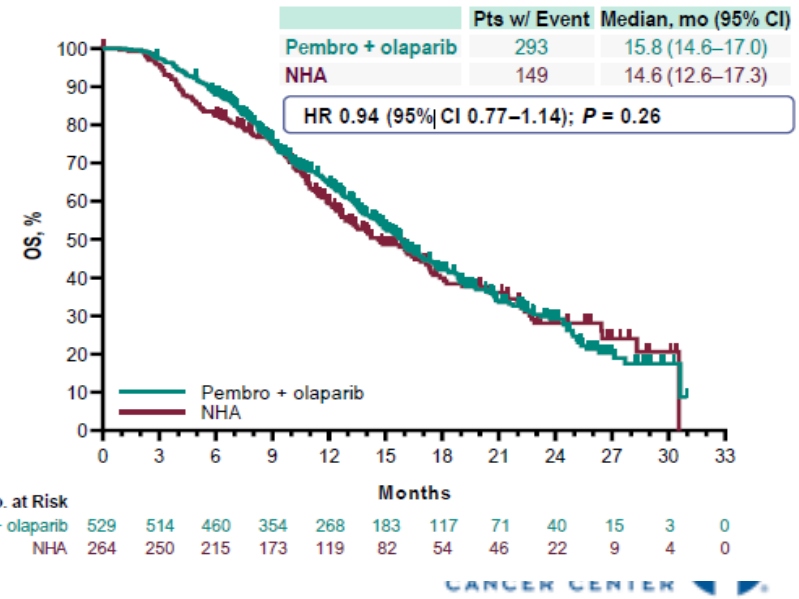
N = 529: **Pembrolizumab** 200 mg Q3W for ≤35 cycles + **Olaparib** 300 mg BID

N = 264: **Abi** 1000 mg QD (if prior enza) or **Enza** 160 mg QD (if prior abi)

Dual Primary Endpoints
- rPFS by BICR per PCWG-modified RECIST v1.1 (**IA1**)
- OS (**IA2**)

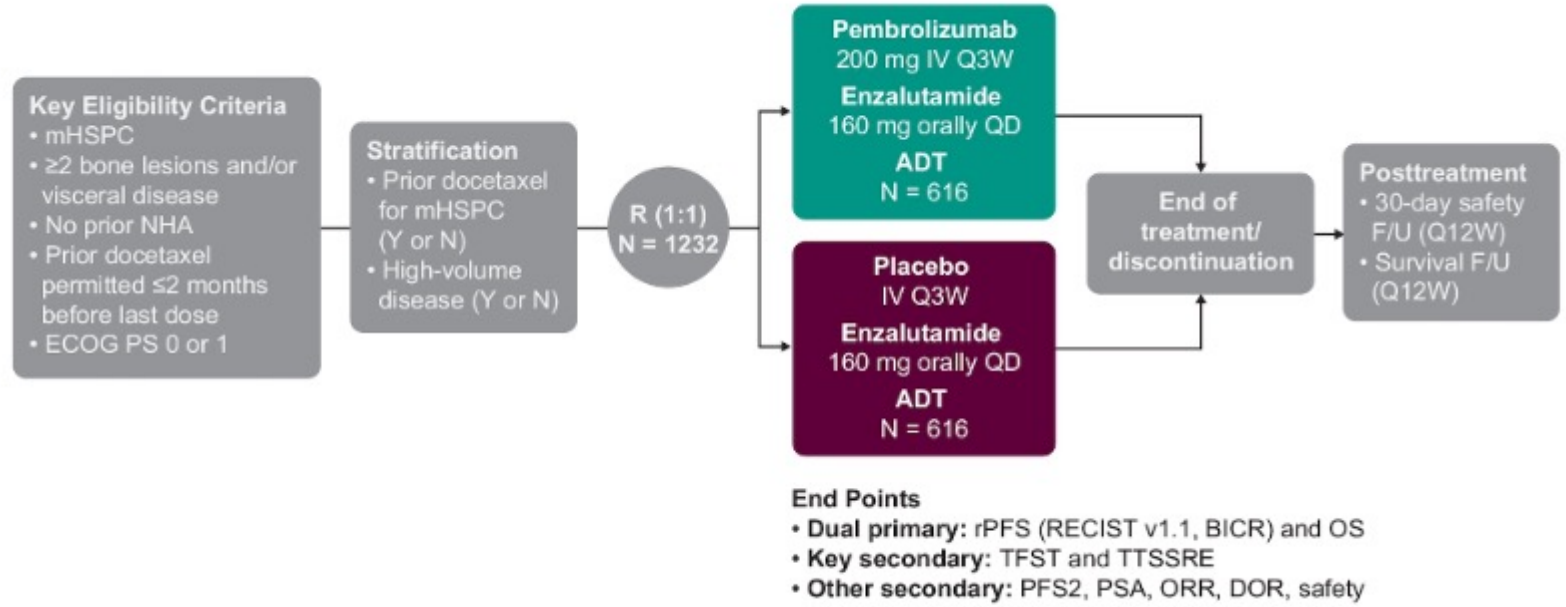
Secondary Endpoints
- TFST (key secondary; **IA1**)
- ORR by BICR per PCWG-modified RECIST v1.1 (**IA2**)
- Safety (**IA2**)





Yu E ESMO 2022

KEYNOTE 991



ECOG PS, Eastern Cooperative Oncology Group performance status; F/U, follow-up; NHA, next-generation hormonal agent; Q12W, every 12 weeks; R, randomization.

At the interim analysis, Pembrolizumab in combination with enzalutamide and ADT did not demonstrate an improvement in overall survival (OS) or radiographic progression-free survival (rPFS), the trial's dual primary endpoints, compared to placebo plus enzalutamide and ADT.

MERCK Press release Jan 2023

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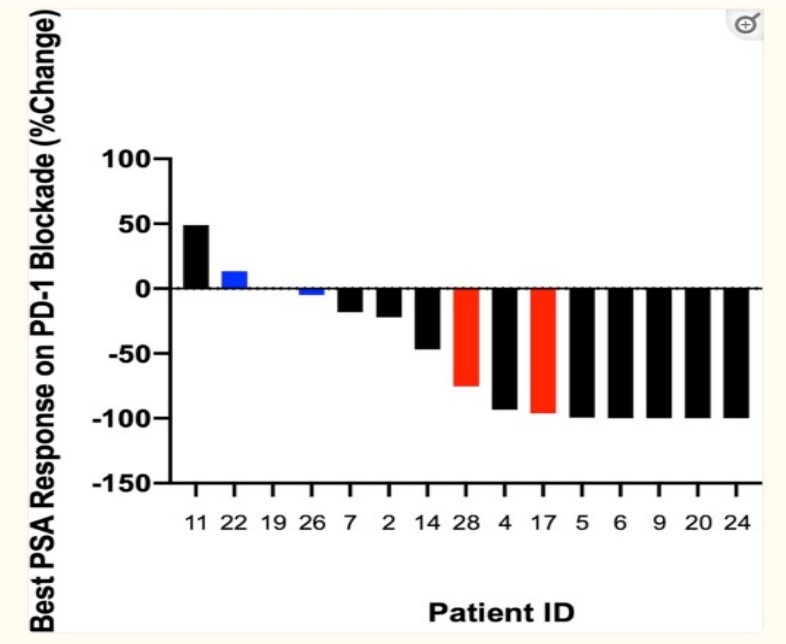
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

D.T. Le, J.N. Uram, H. Wang, B.R. Bartlett, H. Kemberling, A.D. Eyring, A.D. Skora, B.S. Luber, N.S. Azad, D. Laheru, B. Biedrzycki, R.C. Donehower, A. Zaheer, G.A. Fisher, T.S. Crocenzi, J.J. Lee, S.M. Duffy, R.M. Goldberg, A. de la Chapelle, M. Koshiji, F. Bhaijee, T. Huebner, R.H. Hruban, L.D. Wood, N. Cuka, D.M. Pardoll, N. Papadopoulos, K.W. Kinzler, S. Zhou, T.C. Cornish, J.M. Taube, R.A. Anders, J.R. Eshleman, B. Vogelstein, and L.A. Diaz, Jr.



Graham L et al Plos One 2020

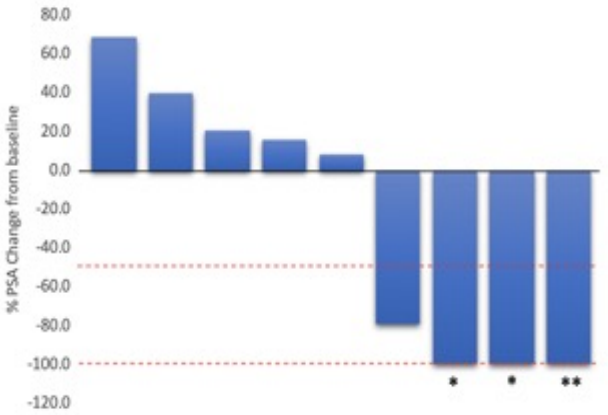


Figure 1 Best PSA change from baseline in mCRPC patients treated with pembrolizumab (N=9). *partial response, **complete response

Barata P JITC 2020

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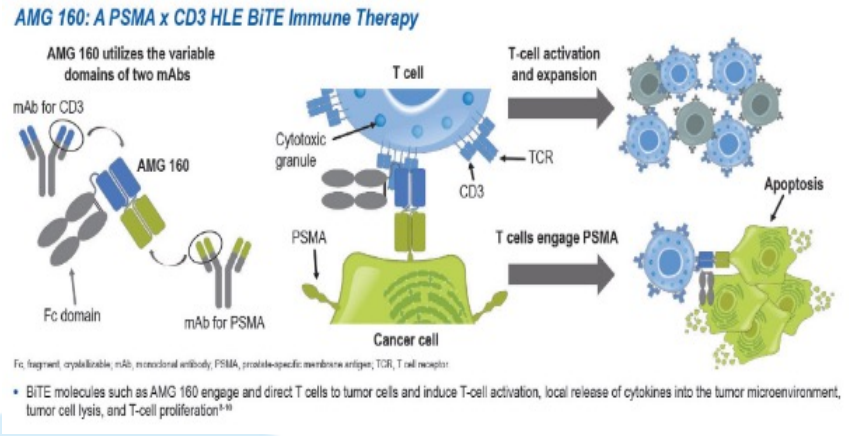
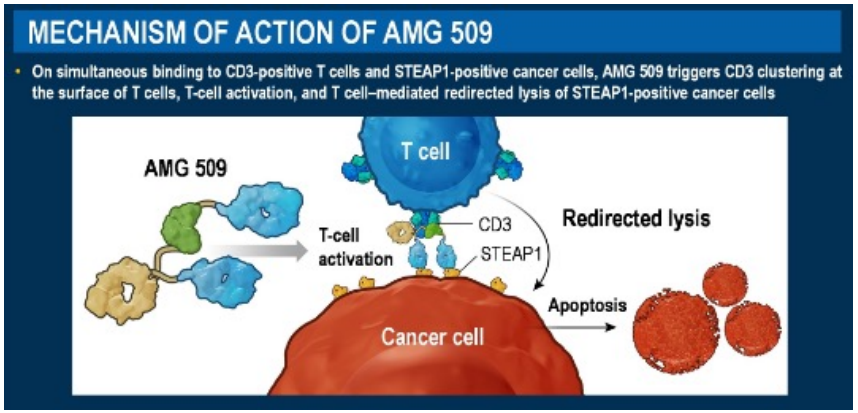
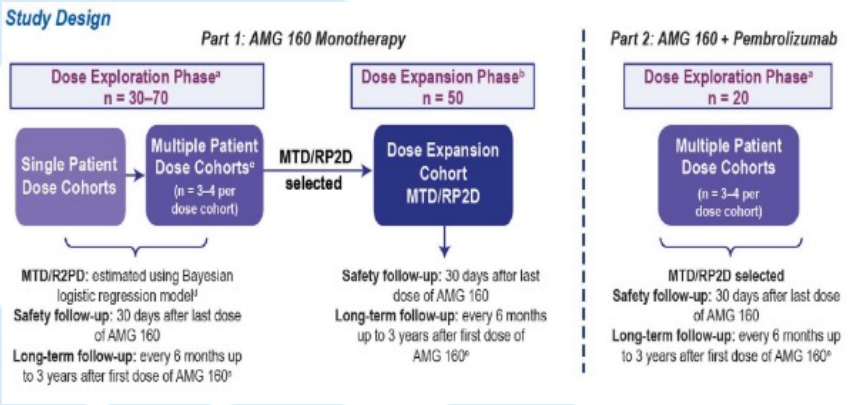
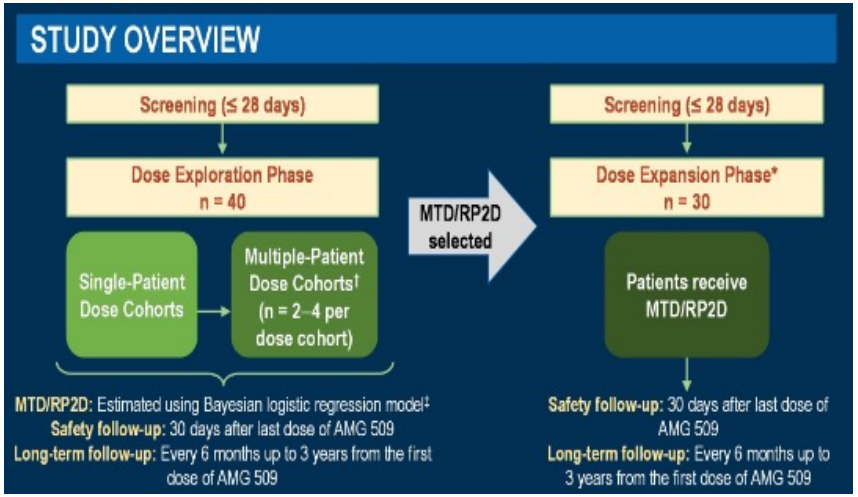
Bispecific T-Cell Engagers









Tran B et al GU ASCO 2020

Kelly W et al GU ASCO 2020

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Conclusions

- Immunotherapy has changed the treatment landscape in GU malignancies
- PD-1/PD-L1 inhibitors as monotherapy or in combination are being used either in neoadjuvant, adjuvant or metastatic settings
- Multiple trials using BiTe immunotherapy or cellular therapy are ongoing

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