Immunotherapy for Bladder Cancer

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Disclosures

- Research collaboration with Tempus labs
- Participated in advisory boards with Seagen/Astellas (declined compensation)
- Consulting with Janssen (declined compensation)

- I will be discussing non-FDA approved indications during my presentation.

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72 year-old man with new diagnosis of metastatic urothelial carcinoma with lymph node and lung metastases. Patient has ECOG PS 1, CrCl 45, no heart disease, hearing loss or neuropathy. How would you treat patient?

A. Cisplatin and Gemcitabine
B. Carboplatin and Gemcitabine
C. Carboplatin, Gemcitabine and Atezolizumab
D. Pembrolizumab

72 year-old man with new diagnosis of metastatic urothelial carcinoma with lymph node and lung metastases, ECOG PS 1, CrCl 45. Patient is treated with carboplatin and gemcitabine x 6 cycles with imaging showing partial response. How would you treat patient now?

A. Maintenance Avelumab
B. Best supportive care / surveillance
C. Continue carboplatin/gemcitabine
D. Consolidation radiation to bladder and pelvic lymph nodes

Bladder Cancer Epidemiology

- ~80,000 cases / year in the USA
  - 4th most common cancer in men and 8th leading cause of cancer death
- 3x higher incidence in males vs females
- 2x higher incidence in White men vs Black men

Figure 3. Leading Sites of New Cancer Cases and Deaths – 2022 Estimates

Estimated New Cases

Male			Female		
Prostate	268,490	27%	Breast	287,850	31%
Lung & bronchus	117,910	12%	Lung & bronchus	118,830	13%
Colon & rectum	80,690	8%	Colon & rectum	70,340	8%
Urinary bladder	61,700	6%	Uterine corpus	65,950	7%
Melanoma of the skin	57,180	6%	Melanoma of the skin	42,600	5%
Kidney & renal pelvis	50,290	5%	Non-Hodgkin lymphoma	36,350	4%
Non-Hodgkin lymphoma	44,120	4%	Thyroid	31,940	3%
Oral cavity & pharynx	38,700	4%	Pancreas	29,240	3%
Leukemia	35,810	4%	Kidney & renal pelvis	28,710	3%
Pancreas	32,970	3%	Leukemia	24,840	3%
All sites	**983,160**		**All sites**	**934,870**	

Estimated Deaths

Male			Female		
Lung & bronchus	68,820	21%	Lung & bronchus	61,360	21%
Prostate	34,500	11%	Breast	43,250	15%
Colon & rectum	28,400	9%	Colon & rectum	24,180	8%
Pancreas	25,970	8%	Pancreas	23,860	8%
Liver & intrahepatic bile duct	20,420	6%	Ovary	12,810	4%
Leukemia	14,020	4%	Uterine corpus	12,550	4%
Esophagus	13,250	4%	Liver & intrahepatic bile duct	10,100	4%
Urinary bladder	12,120	4%	Leukemia	9,980	3%
Non-Hodgkin lymphoma	11,700	4%	Non-Hodgkin lymphoma	8,550	3%
Brain & other nervous system	10,710	3%	Brain & other nervous system	7,570	3%
All sites	**322,090**		**All sites**	**287,270**	

Estimates are rounded to the nearest 10, and cases exclude basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder. Estimates do not include Puerto Rico or other US territories. Ranking is based on modeled projections and may differ from the most recent observed data.

American Cancer Society. Cancer Facts & Figures 2022. Atlanta: American Cancer Society; 2022

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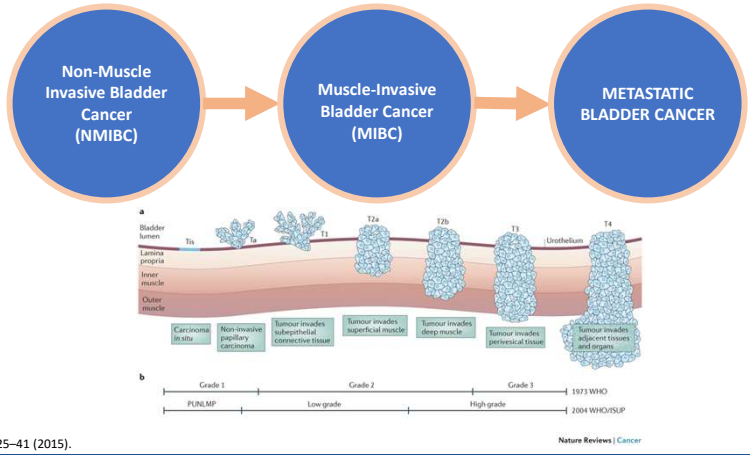
Bladder Cancer Disease States



Knowles, M., Hurst, C. *Nat Rev Cancer* **15**, 25–41 (2015).

Nature Reviews | Cancer

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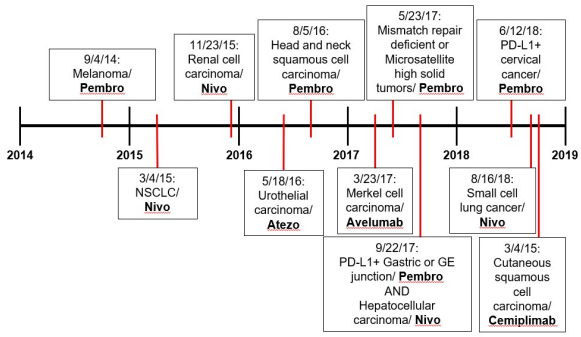
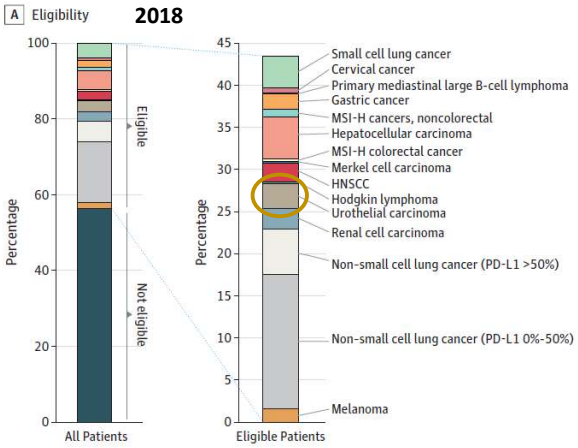
Immune checkpoint inhibitors





Haslam A, et al. JAMA Netw Open. 2019 May 3;2(5):e192535. PMID 31050774

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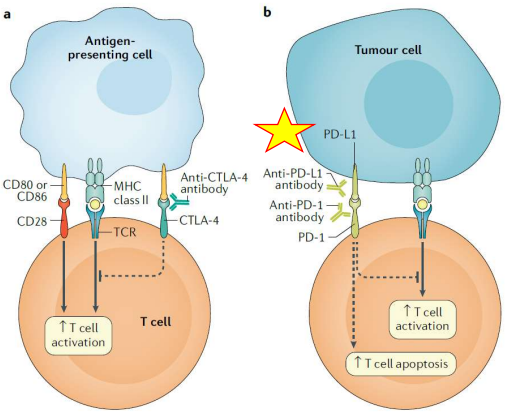
Immune checkpoint inhibitors



Ramos-Casals M, et al. Nat Rev Dis Primers. 2020 May 7;6(1):38. PMID 32382051

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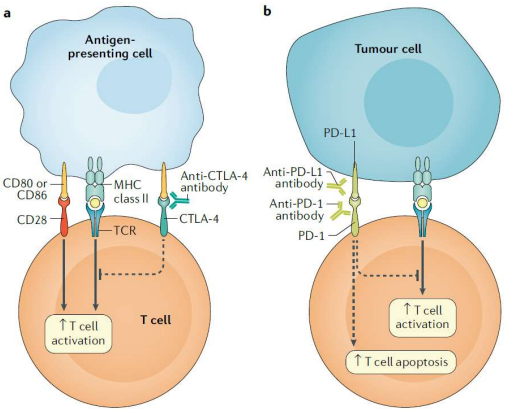
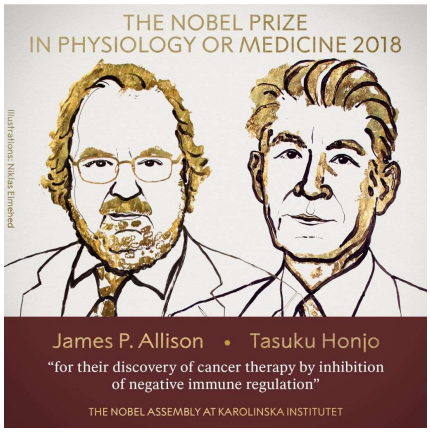
Immune checkpoint inhibitors





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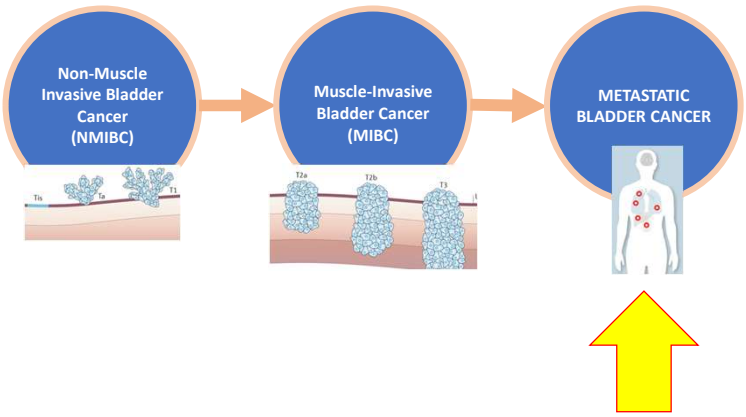

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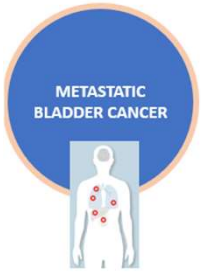
Prior to immunotherapy in bladder cancer



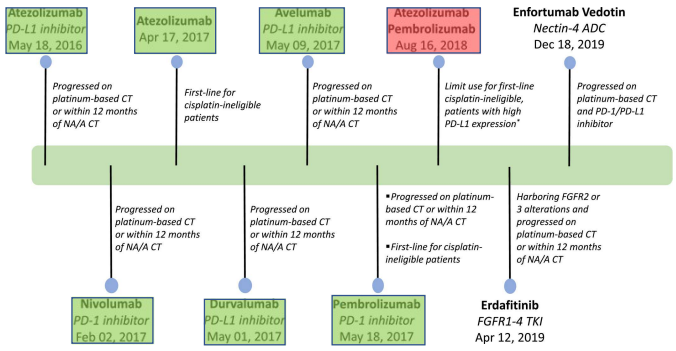
Platinum-based chemotherapy → Salvage chemotherapy (taxanes)

Cisplatin Ineligible Criteria[1]

- ECOG PS 2+
- Creatinine clearance < 60mg/min
- Grade 2+ Hearing loss
- Grade 2+ Peripheral Neuropathy
- NYHA Class III Heart Failure

[1] Galsky MD, et al. J Clin Oncol. 2011 Jun 10;29(17):2432-8

Five different Immune checkpoint inhibitors initially approved for bladder cancer



CA A Cancer J Clinicians, Volume: 70, Issue: 5, Pages: 404-423, First published: 07 August 2020, DOI: (10.3322/caac.21631)

Cisplatin and Platinum eligibility

Cisplatin Ineligible Criteria[1]

- ECOG PS 2+
- Creatinine clearance < 60mg/min
- Grade 2+ Hearing loss
- Grade 2+ Peripheral Neuropathy
- NYHA Class III Heart Failure

Carboplatin Ineligible Criteria[2]

- ECOG PS 3+
- Creatinine clearance < 30 ml/min
- ECOG PS 2 AND CrCl < 30ml/min
- Grade 3+ Peripheral Neuropathy
- NYHA Class IV Heart Failure

[1] Galsky MD, et al. J Clin Oncol. 2011 Jun 10;29(17):2432-8
[2] Gupta S, et al. J Clin Oncol. 2019;37(7_suppl):451

Checkpoint Inhibitors Initially Approved for Platinum-Treated Patients with Urothelial Cancer

Drug	Target	N	ORR (%)	CR (%)	PFS (mos)	OS (mos)	Any grade AE (%)	Grade 3-5 AE (%)	Duration of response
Atezolizumab[1]	PDL1	310	13 (15)	3 (5)	2.1	8.6	69% (89% for chemo)	24.6% (36.6% for chemo)	21.7 mo
Pembrolizumab[2]	PD1	542	26	11	2.1	10.3	60.9% (90.2% for chemo)	15% (49.4% for chemo)	68% at least 12mo
Nivolumab[3]	PD1	265	20	2	2	8.7	64%	18%	NR with med FU 7mo
Durvalumab[4]	PDL1	191	18	4	1.5	18.2	58.2%	9.5%	50% at least 6mo
Avelumab[5]	PDL1	249	17	6	3	6.5	67%	20%	96% at least 24 weeks

[1]Powles T et al. Lancet 2018; 391:748-57; [2]Bellmunt J et al. N Engl J Med; 2017;376:1015-26; [3]Sharma P et al. Lancet Oncol 2017; 18:312-22;
[4]Powles T et al. JAMA Oncol 2017; 3:e172411; [5]Patel MR et al. Lancet Oncol 2018; 19:51-64.

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Modest ORR (15-20%)
Durable responses
Favorable toxicity

[1]Powles T et al. Lancet 2018; 391:748-57.
[2]Bellmunt J et al. N Engl J Med; 2017;376:1015-26.
[3]Sharma P et al. Lancet Oncol 2017; 18:312-22.
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[5]Patel MR et al. Lancet Oncol 2018; 19:51-64.

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. 2019 Jun 1;30(6):970-976.

Pembrolizumab after platinum chemotherapy (Keynote 045)

Key Eligibility Criteria
- UC of the renal pelvis, ureter, bladder, or urethra
- Predominantly transitional cell histology
- PD after 1-2 lines of platinum-based chemotherapy or recurrence <12 months after perioperative platinum-based therapy
- ECOG PS 0-2
- Measurable disease per RECIST v1.1
- Tumor sample for biomarker assessment

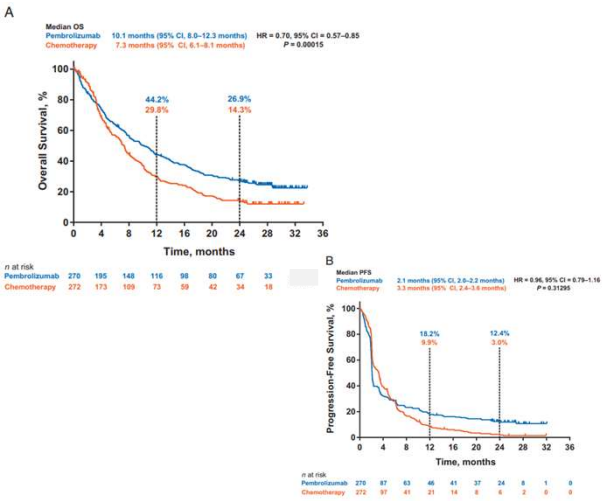
R (1:1) N = 542

n = 270 → Pembrolizumab 200 mg IV Q3W up to 2 years

n = 272 → Paclitaxel 175 mg/m² Q3W or Docetaxel 75 mg/m² Q3W or Vinflunine 320 mg/m² Q3W

Stratification Factors
- ECOG PS (0 or 1 vs 2)
- Hemoglobin level (<10 vs ≥10 g/dL)
- Liver metastases (yes vs no)
- Time from last chemotherapy dose (<3 vs ≥3 months)

- Dual primary end points: OS and PFS[a]
- Key secondary end points: ORR, DOR, safety
- Response: RECIST v1.1 by blinded independent central review



Bellmunt J, et al. N Engl J Med. 2017 Mar 16;376(11):1015-1026. PMID 28212060.
Fradet Y, et al. Ann Oncol. 2019 Jun 1;30(6):970-976. PMID 31050707

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Anti-PD1/PD-L1 checkpoint inhibitors show durable activity after platinum chemotherapy

What about combinations?

- Anti-PD1/PD-L1 + Chemotherapy
- Anti-PD1/PD-L1 + Anti-CTLA4

IMvigor130: Platinum Chemo ± Atezolizumab

IMvigor130 study design

- 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)

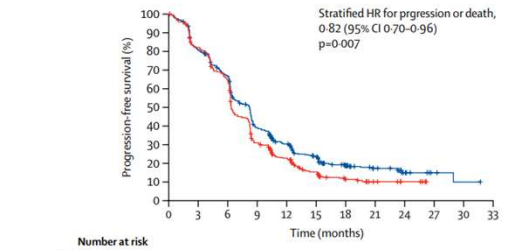
Co-primary endpoints:
- INV-assessed PFS[a] and OS (Arm A vs C)
- OS (Arm B vs C, hierarchical approach)

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

Progression-free Survival

A

	Number of events/ number of patients	Median progression-free survival (95% CI), months
Atezolizumab + platinum-based chemotherapy (group A)	334/451	8·2 (6·5–8·3)
Placebo + platinum-based chemotherapy (group C)	326/400	6·3 (6·2–7·0)



Number at risk (number censored)												
Atezolizumab + platinum-based chemotherapy (group A)	451 (0)	345 (22)	282 (27)	160 (34)	111 (49)	74 (62)	42 (81)	22 (98)	10 (108)	4 (114)	2 (115)	NE
Placebo + platinum-based chemotherapy (group C)	400 (0)	317 (13)	246 (14)	116 (19)	73 (31)	40 (45)	18 (58)	11 (63)	4 (70)	NE	NE	NE

Galsky MD et al. Lancet. 2020 May 16;395(10236):1547-1557.

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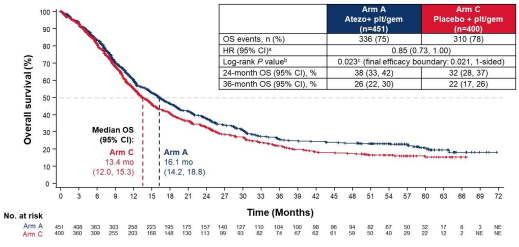
- PFS[a] and OS (Arm B vs C; PD-L1 IC2/3 subgroup)
- Safety

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)



Clinical cutoff: Aug 31, 2022. Median survival follow-up: 13.4 months. NE, not estimable. [a]Stratified by PD-L1 status, Bajorin risk factors and/or liver metastases, investigator's choice of plt/gem and enrollment stage. [b]*P* value is 1-sided. [c]Not statistically significant (final efficacy boundary was adjusted from prior analyses).

ASCO Genitourinary Cancers Symposium #GU23 — Grande E. IMvigor130 Arms A/C Final OS [abs LBA440] https://bit.ly/3kuBVUS @drenriquegrande #IMvigor130 ASCO

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Grande E. ASCO GU 2023. LBA 440

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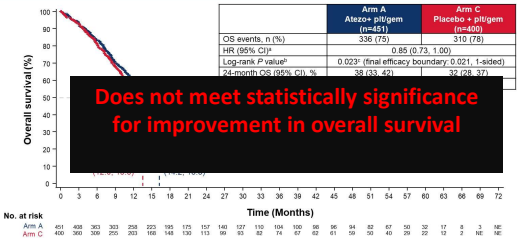

Does not meet statistically significance for improvement in overall survival

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Only 25% of patients in chemotherapy control arm received subsequent checkpoint inhibitor

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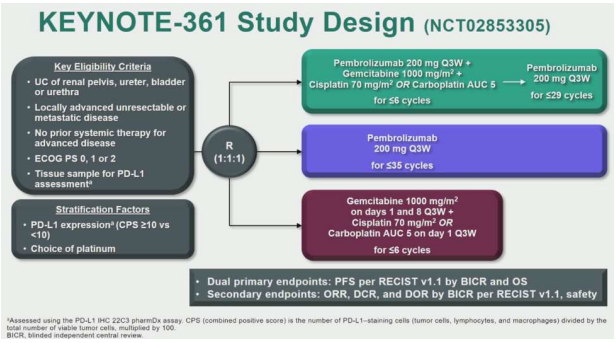
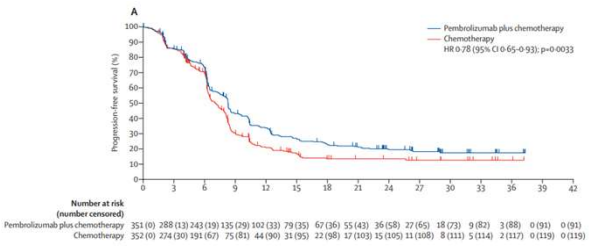
Keynote 361: Platinum Chemo ± Pembrolizumab



Progression-free Survival



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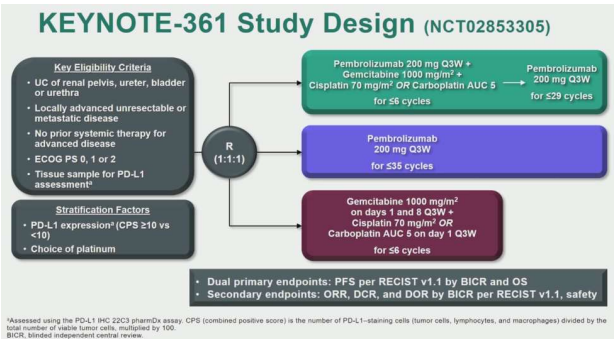
Keynote 361: Platinum Chemo ± Pembrolizumab



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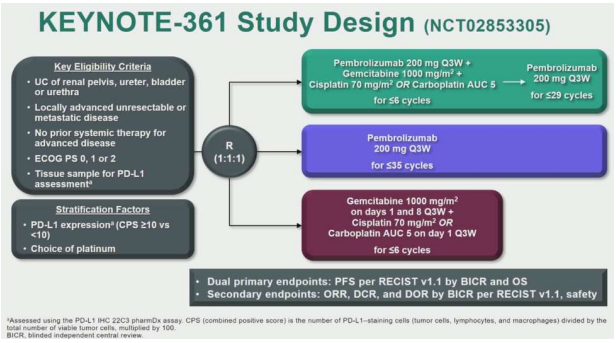
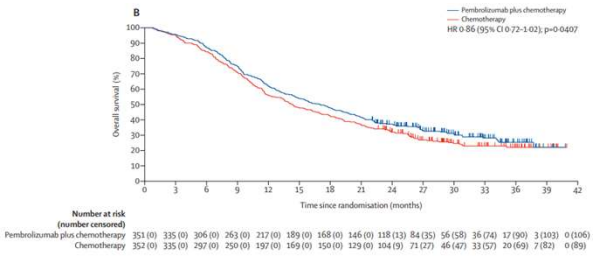


Overall Survival



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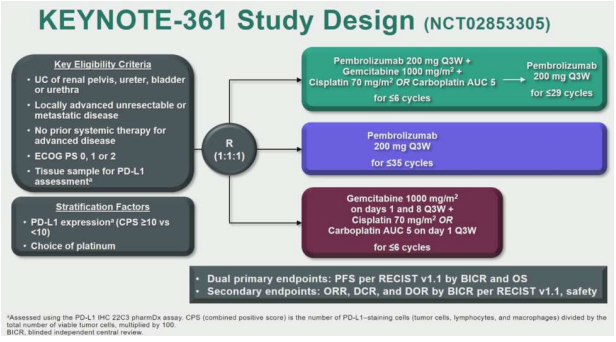

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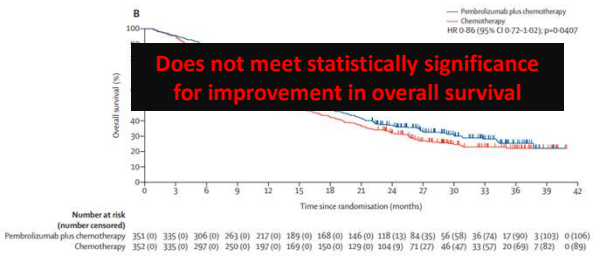

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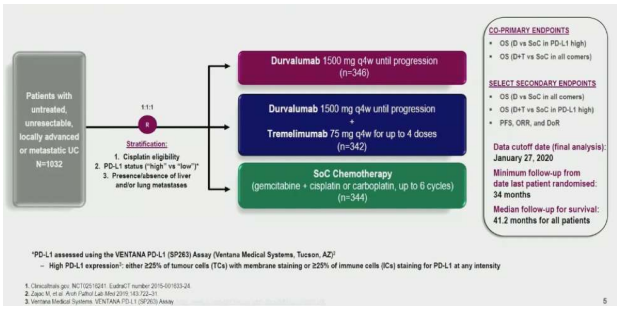
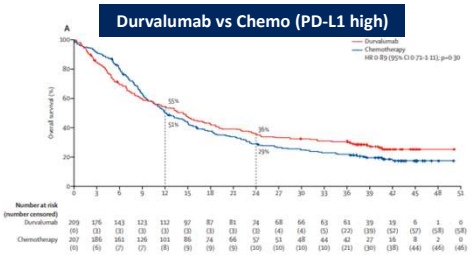
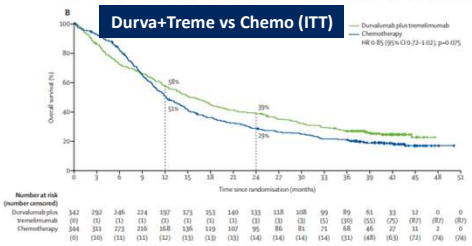
DANUBE: Durvalumab ± Tremelimumab vs Platinum Chemo



Durvalumab vs Chemo (PD-L1 high)



Durva+Treme vs Chemo (ITT)



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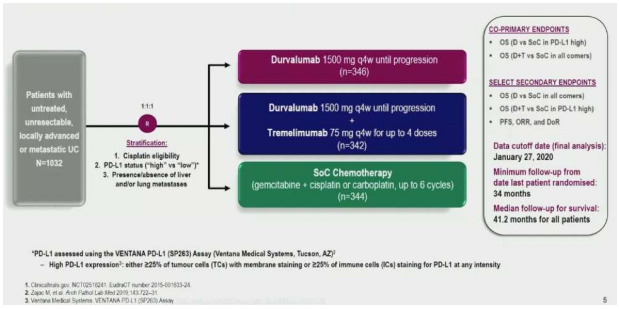
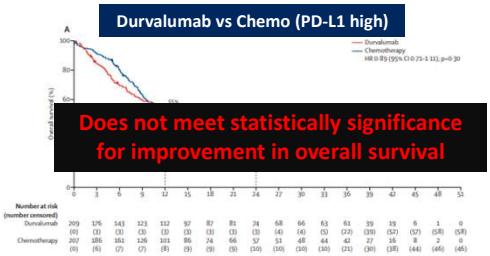
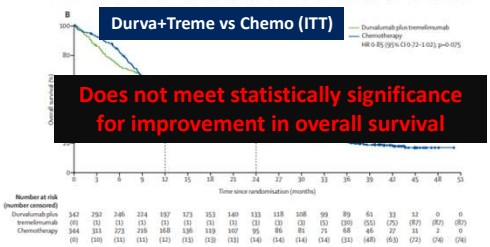


Durvalumab vs Chemo (PD-L1 high)



Does not meet statistically significance for improvement in overall survival

Durva+Treme vs Chemo (ITT)



Does not meet statistically significance for improvement in overall survival

Only 31% of patients in chemotherapy control arm received subsequent checkpoint inhibitor

Powles T et al. Lancet Oncol. 2020 Dec;21(12):1574-1588.

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Other Combination Studies

Checkmate-901

Checkmate-901 (NCT03036098) N=897
- First-line unresectable or metastatic UC
- ECOG PS ≤ 1
- Co-primary endpoints: PFS and OS

R → Nivolumab + Ipilimumab
R → Nivolumab + Cisplatin-gemcitabine
R → Cisplatin-gemcitabine or Carboplatin-gemcitabine

NILE

NILE study (NCT03682068) N=885
- First-line unresectable or metastatic UC
- ECOG PS ≤ 1
- Co-primary endpoints: PFS and OS

R → Durvalumab + Cisplatin-gemcitabine or Durvalumab + Carboplatin-gemcitabine
R → Durvalumab + Tremelimumab + Cisplatin-gemcitabine Durvalumab + Tremelimumab + Carboplatin-gemcitabine
R → Cisplatin-gemcitabine or Carboplatin-gemcitabine

Nadal R and Bellmunt J. Cancer Treat Rev. 2019 Jun;76:10-21.

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Other Combination Studies

Checkmate-901

Bristol Myers Squibb Provides Update on CheckMate -901 Trial Evaluating (nivolumab) Plus (ipilimumab) as First-Line Treatment for Patients with Unresectable or Metastatic Urothelial Carcinoma

05/16/2022

CATEGORY: Corporate/Financial News

PRINCETON, N.J.--(BUSINESS WIRE)-- Bristol Myers Squibb (NYSE: BMY) today announced the Phase 3 CheckMate -901 trial, comparing (nivolumab) plus (ipilimumab) to standard-of-care chemotherapy as a first-line treatment for patients with untreated unresectable or metastatic urothelial carcinoma, did not meet the primary endpoint of overall survival (OS) in patients whose tumor cells express PD-L1 ≥1% at final analysis. The company remains blinded to the data, and an independent Data Monitoring Committee recommended that the trial continue to assess other primary and secondary endpoints. No new safety signals were observed at the time of the analysis.

Checkmate-901 (NCT03036
- First-line unresectable
- ECOG PS ≤ 1
- Co-primary endpoints:

ilimumab
in-gemcitabine
rboplatin-gemcitabine

NILE

NILE study (NCT03682068) N=885
- First-line unresectable or metastatic
- ECOG PS ≤ 1
- Co-primary endpoints: PFS and OS

To be reported

Durvalumab + Cisplatin-gemcitabine or
b + Carboplatin-gemcitabine
remelimumab + Cisplatin-gemcitabine
melimumab + Carboplatin-gemcitabine
Cisplatin-gemcitabine or Carboplatin-gemcitabine

Nadal R and Bellmunt J. Cancer Treat Rev. 2019 Jun;76:10-21.

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Anti-PD1/PD-L1 checkpoint inhibitors show durable activity after platinum chemotherapy

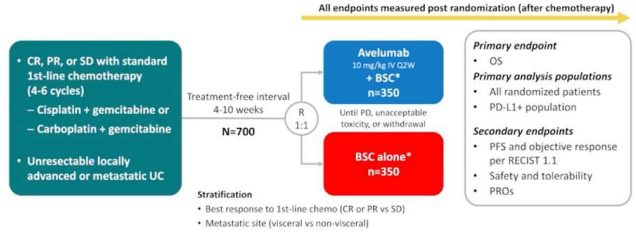
What about combinations?

- ~~Anti-PD1/PD-L1 + Chemotherapy~~
- ~~Anti-PD1/PD-L1 + Anti-CTLA4~~

→ Switch Maintenance Immunotherapy

Javelin Bladder-100: Maintenance avelumab vs best supportive care

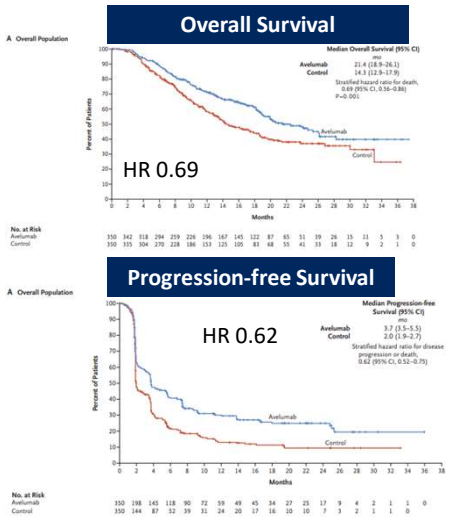
JAVELIN Bladder 100 study design (NCT02603432)



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

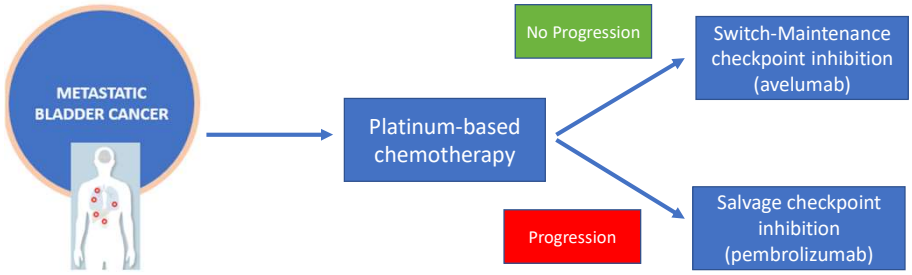
*BSC (eg, antibiotics, nutritional support, hydration, or pain management) was administered per local practice based on patient needs and clinical judgment; other systemic antitumor therapy was not permitted, but palliative local radiotherapy for isolated lesions was acceptable



Only 43.7% of patients in best supportive care control arm received subsequent checkpoint inhibitor

Powles T, et al. N Engl J Med 2020;383:1218-30.

Metastatic bladder cancer treatment



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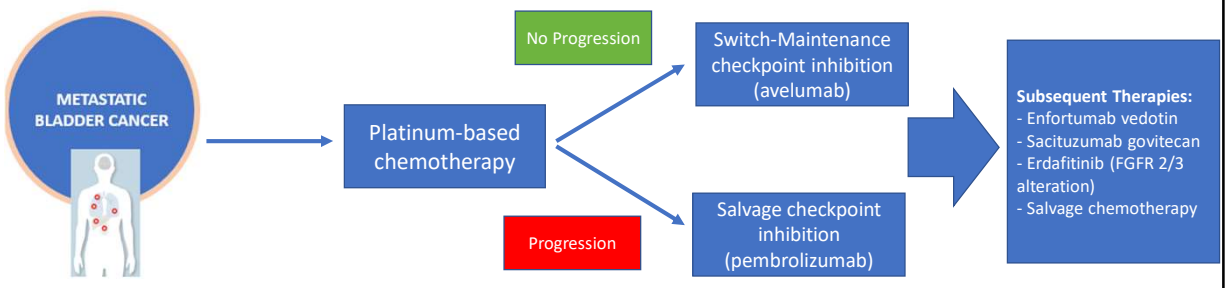
Metastatic bladder cancer treatment



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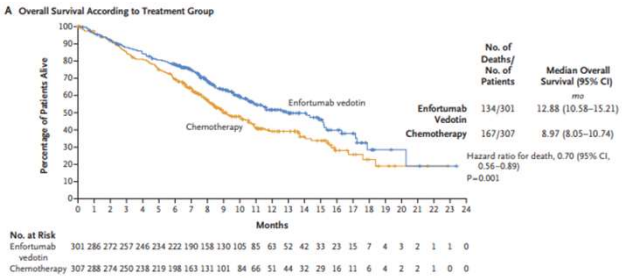
Novel Combinations

33

Enfortumab vedotin

Enfortumab vedotin extended overall survival in EV-301 trial in patients previously treated with platinum chemotherapy and immunotherapy



Powles T, et al. N Engl J Med 2021; 384:1125-1135.

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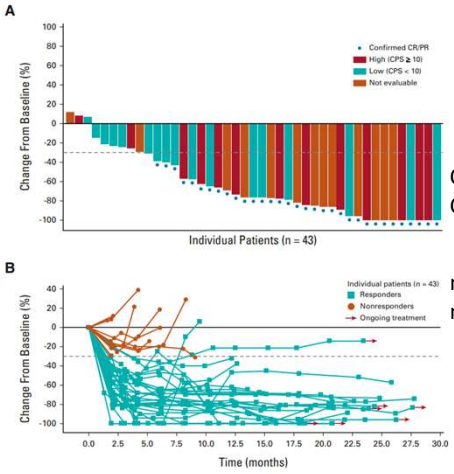
Enfortumab Vedotin + Pembrolizumab

EV-103 Cohort A

(Phase Ib/II Dose Escalation and dose expansion cohort)

First-line therapy, Cisplatin-ineligible



ORR 73%
CR 16%

mDOR 26 months
mOS 26 months

Hoimes CJ, et al. J Clin Oncol 41:22-31.

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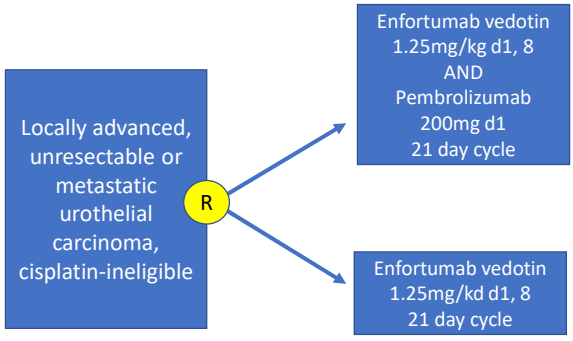
Enfortumab Vedotin + Pembrolizumab

EV-103 Cohort K



	EV+P (N=76)	EV Mono (N=73)
Confirmed ORR, n (%) (95% CI)	49 (64.5) (52.7, 75.1)	33 (45.2) (33.5, 57.3)
Best overall response, n (%)		
Complete Response	8 (10.5)	3 (4.1)
Partial Response	41 (53.9)	30 (41.1)
Stable Disease	17 (22.4)	25 (34.2)
Progressive Disease	6 (7.9)	7 (9.6)
Not Evaluable	3 (3.9)	5 (6.8)
No Assessment	1 (1.3)	3 (4.1)
Median time to objective response (range), mos	2.07 (1.1, 6.6)	2.07 (1.9, 15.4)
Median number of treatment cycles (range)	11.0 (1, 29)	8.0 (1, 33)

Data cutoff: 10Jun2022
BICR: Blinded Independent Central Review; cORR: Confirmed Objective Response Rate; NR: Not Reached

EV+P
- 41/49 (85.7%) of responses observed at first assessment (week 9±1 wk)
- cORRs were consistent across all pre-specified subgroups
- 7/13 (53.8%) cORR observed in patients with liver metastases

EV monotherapy
- Activity is consistent with prior results in 2L+ la/mUC

Rosenberg JE, et al. Ann of Oncol (2022) 33 (suppl_7): S808-S869.

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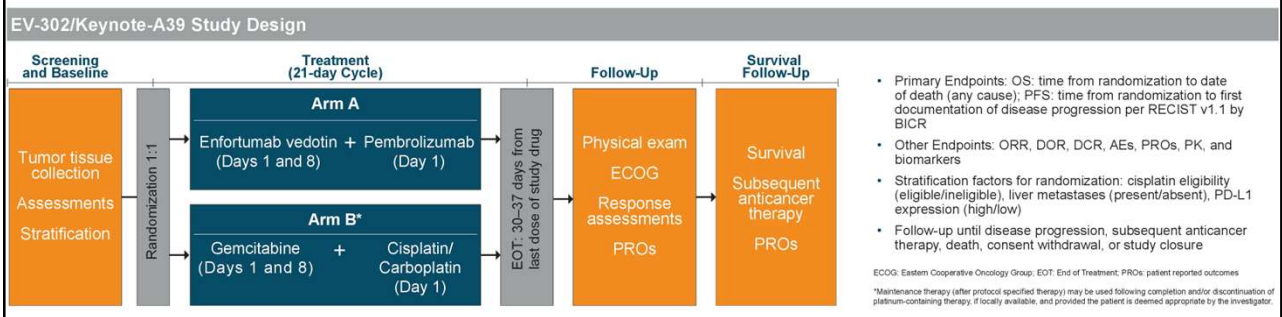
Enfortumab Vedotin + Pembrolizumab

EV-302 ongoing trial

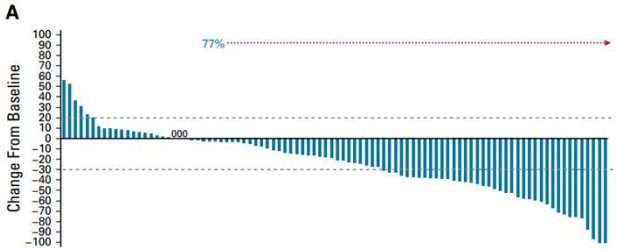


Van der Heijden MS, et al. J Clin Oncol. 2022;40(6_suppl):TPS589

Sacituzumab govitecan

- Sacituzumab govitecan received accelerated approval based on TROPHY-U-01 cohort 1

(Post-platinum chemo and checkpoint inhibitor)



- ORR 28%, CR 5%
- Duration of response 7 months

Tagawa ST, et al. J Clin Oncol. 2021 Aug 1;39(22):2474-2485.

Sacituzumab govitecan + Pembrolizumab

TROPHY-U-01 Cohort 3

Checkpoint inhibitor naïve metastatic urothelial carcinoma, **Progression on platinum chemotherapy**

→

Sacituzumab govitecan 10mg/kg d1, 8
AND
Pembrolizumab 200mg d1
21 day cycle

Table 3. Best Overall Responses, per Independent Review

	Cohort 3 (N=41)
Best overall response, n (%)	
Complete response	8 (20)
Partial response	9 (22)
Stable disease	9 (22)
Progressive disease	10 (24)
Not evaluable	3 (7)
Not assessed[a]	2 (5)
Objective response rate (CR + PR), n (%) [95% CI]	17 (41) [26.3-57.9]
Clinical benefit rate (CR + PR + SD ≥6 months), n (%) [95% CI]	19 (46) [30.7-62.6]

[a]Three patients had no post-baseline radiologic tumor assessments.
CR, complete response; PR, partial response; SD, stable disease.

Figure 3. Best Change in Target Lesions, per Independent Review[a]

ORR 41%
CR 20%

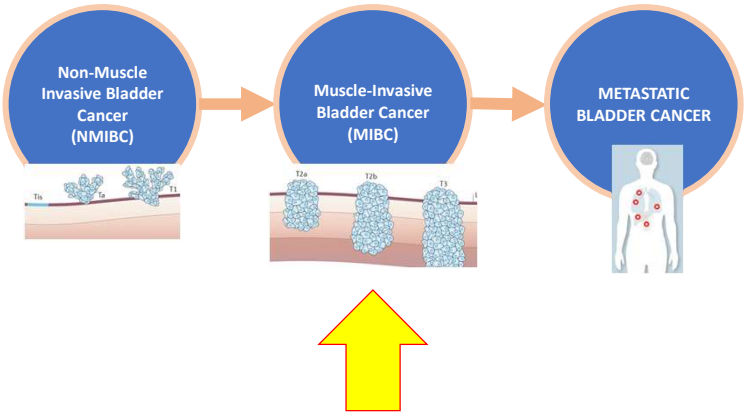
Grivas P, et al. J Clin Oncol. 2023;41(6_suppl):518

Other molecularly targeted combinations

- FGFR inhibitors + checkpoint inhibitors (cisplatin-ineligible 1L)
  - NORSE[1]: erdafitinib + avelumab (ORR 52%) vs erdafitinib
  - FORT-2[2]: rogaratinib + atezolizumab (ORR 54%) vs atezolizumab
- HER2
  - Disitamab vedotin (RC-48) ± pembrolizumab (ORR 75% with anti-PD-1 toripalimab[3])

[1] NCT03473743; Siefker-Radtke AO, et al. Ann of Oncol (2020) 31 (suppl_4): S584-S85.
[2] NCT03473756; Rosenberg JE, et al. J Clin Oncol. 2022;40(16_suppl):4521
[3] Sheng X, et al. J Clin Oncol. 2022;40(16_suppl):4518

Bladder Cancer Disease States



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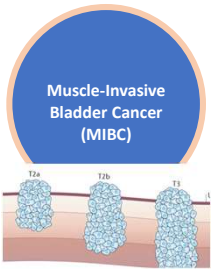
Muscle Invasive Bladder Cancer Treatment

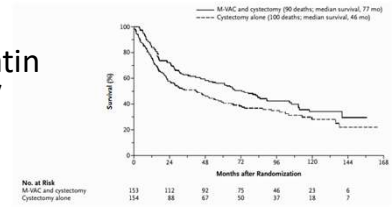


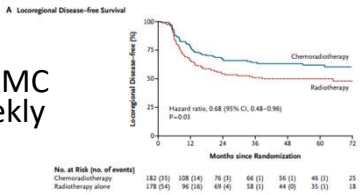
T2-T4a

- Neoadjuvant cisplatin-based chemotherapy (gemcitabine/cisplatin OR dose-dense MVAC) followed by radical cystectomy[1]

OR

- Radiation therapy with radiation-sensitizing chemotherapy[2] (5-FU+MMC or twice weekly gemcitabine or weekly cisplatin)





[1] Grossman HB et al. N Engl J Med 2003; 349:859-866
[2] James ND et al. N Engl J Med. 2012 Apr 19;366(16):1477-88.

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Immunotherapy in MIBC

- Neoadjuvant (pre-operative) setting
  - Checkpoint inhibitor monotherapy
  - Chemotherapy-checkpoint inhibitor combination therapy
  - Other combinations (e.g. EV + Pembro)
- Adjuvant (post-operative) setting
  - Checkpoint inhibitor monotherapy

Neoadjuvant Immunotherapy

Neoadjuvant Chemo-IO shows activity in cisplatin-eligible MIBC

	BLASST-1[1] (N=41)	HCRN GU 14-188[2] (N=43)	LCCC1520[3] (N = 39)	MSKCC[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
Pathological complete response (pT0), %	49* (includes pTis)	44	36	41	34
Relapse-free survival	85% (1yr)	82% (18 mo)	89% (1yr)	Not reported	84% (2yr)

1 Gupta S et al. J Clin Oncol. 2020;38(6_suppl):439; 2 Brown J et al. J Clin Oncol. 2023;41(6_suppl):448;
3 Rose TL et al. J Clin Oncol. 2021;39:3140-3148; 4 Funt SA et al. J Clin Oncol 40:1312-1322.
5 Cathomas R et al. J Clin Oncol. 2022;40(16_suppl):4515

Slide adapted from Shilpa Gupta ASCO GU 2023 presentation

Neoadjuvant immunotherapy also show activity in MIBC

	PURE-01[1] (N=114)	ABACUS[2] (N=95)	NABUCCO [3] (N = 24) [all Stage III pts]	AURA[4] (N = 28)	MDACC[5] (N = 28)	DUTRENEO[6] (N=23) ["Hot" Tumors]
Immunotherapy	Pembrolizumab	Atezolizumab	Ipilimumab + Nivolumab	Avelumab	Durvalumab + Tremelimumab	Durvalumab + Tremelimumab
Pathological complete response (pT0), %	37	31	46	25	38	35
Relapse-free survival	74% (3yr EFS)	79% (1yr)	92% (1yr)	Not reported	83% (1yr)	Not reported

Enfortumab vedotin with **pT0 36%** in EV-103 cohort H[7]

1 Necchi A et al. Eur Urol. 2020 Apr;77(4):439-446.; 2 Powles T et al. Nat Med. 2019 Nov;25(11):1706-1714;
3 Van Dijk N et al. Nat Med. 2020 Oct;26:1839-1844; 4 Martinez Chanza N et al. J Clin Oncol. 2022;40(16_suppl):4517
5 Gao J et al. Nat Med. 2020 Oct;26:1845-1851; 6 Grande E et al. J Clin Oncol. 2020;38(15_suppl):5012
7 Petrylak DP et al. J Clin Oncol. 2022;40(6_suppl):435

Slide adapted from Shilpa Gupta ASCO GU 2023 presentation

Ongoing phase 3 neoadjuvant immunotherapy trials

	Clinical Trial	N	Treatment Arms
Cisplatin-eligible	**KEYNOTE-866**	870	Pembrolizumab + Gem-Cis VS Gem-Cis
	KEYNOTE-B15/EV-304	784	Pembrolizumab + Enfortumab vedotin (EV) VS Gem-Cis
	NIAGARA	1050	Durvalumab + Gem-Cis VS Gem-Cis
	ENERGIZE	1200	Nivolumab + Gem-Cis VS Gem-Cis
Cisplatin-INeligible	**KEYNOTE-905/EV-303**	836	Radical Cystectomy VS Pembrolizumab + EV VS Pembrolizumab
	VOLGA	830	Radical Cystectomy VS Durvalumab-Tremelimumab+EV VS Durvalumab + EV
	SWOG GAP	196 (Phase 2)	Radical Cystectomy VS Gem-Carbo+Avelumab

Slide adapted from Shilpa Gupta ASCO GU 2023 presentation

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Perioperative Ongoing phase 3 ~~neoadjuvant~~ immunotherapy trials

	Clinical Trial	N	Treatment Arms
Cisplatin-eligible	**KEYNOTE-866**	870	Pembrolizumab + Gem-Cis VS Gem-Cis
	KEYNOTE-B15/EV-304	784	Pembrolizumab + Enfortumab vedotin (EV) VS Gem-Cis
	NIAGARA	1050	Durvalumab + Gem-Cis VS Gem-Cis
	ENERGIZE	1200	Nivolumab + Gem-Cis VS Gem-Cis
Cisplatin-INeligible	**KEYNOTE-905/EV-303**	836	Radical Cystectomy VS Pembrolizumab + EV VS Pembrolizumab
	VOLGA	830	Radical Cystectomy VS Durvalumab-Tremelimumab+EV VS Durvalumab + EV
	SWOG GAP	196 (Phase 2)	Radical Cystectomy VS Gem-Carbo+Avelumab

Slide adapted from Shilpa Gupta ASCO GU 2023 presentation

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Neoadjuvant Immunotherapy

- Checkpoint inhibitors show activity (~pCR to chemo)
- Further studies ongoing to confirm efficacy (e.g. improved RFS, OS vs neoadjuvant chemotherapy)

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Adjuvant Immunotherapy

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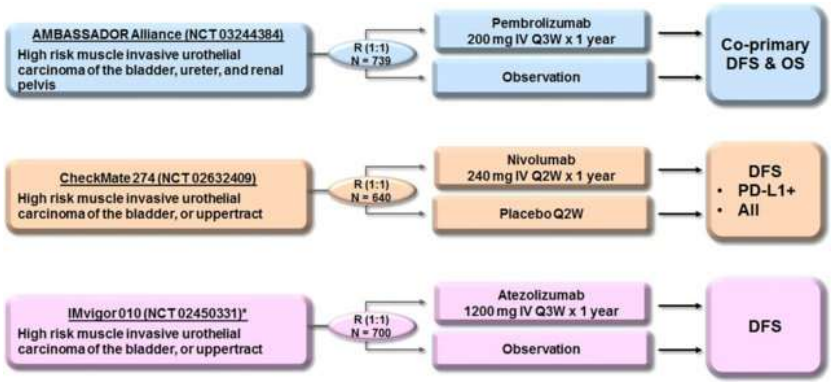
Adjuvant Immunotherapy trials



Nadal R and Apolo A. Curr. Treat. Options in Oncol. (2018) 19: 36

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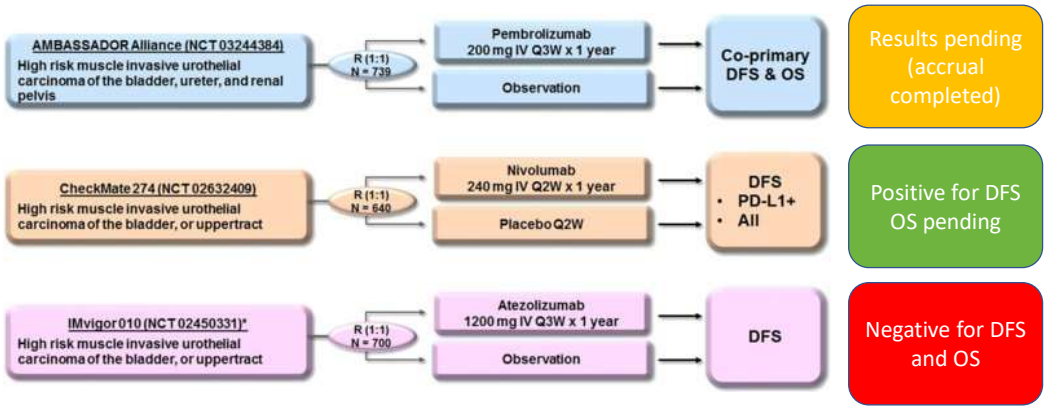
Adjuvant Immunotherapy trials



Nadal R and Apolo A. Curr. Treat. Options in Oncol. (2018) 19: 36

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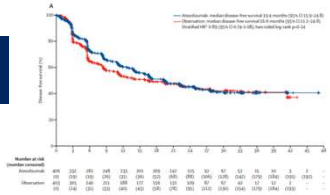
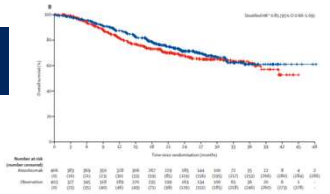
Adjuvant immunotherapy

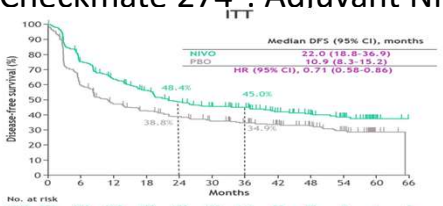
IMvigor 010[1]: Adjuvant Atezolizumab Checkmate 274[2]: Adiuvant Nivolumab

Disease-free Survival

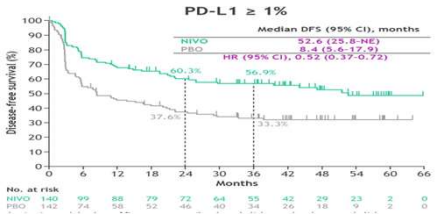


Overall Survival





Intention-to-treat



PD-L1 Expression ≥ 1%

1 Bellmunt J et al. Lancet Oncol. 2021 Apr;22(4):525-537; 2 Galsky MD et al. J Clin Oncol. 2023;41(6_suppl):LBA443

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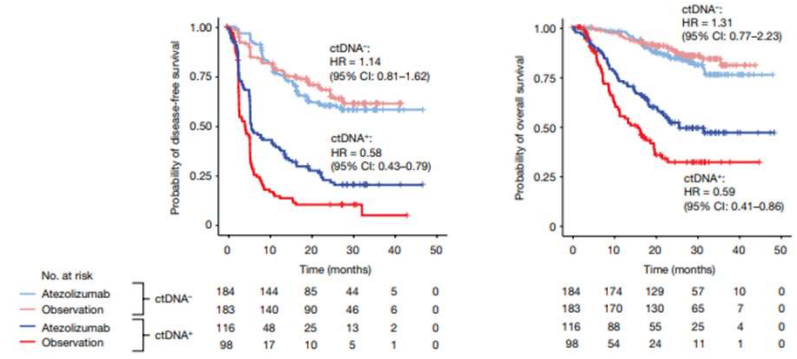
ctDNA may be useful predictive biomarker

IMvigor 010
exploratory analysis



Powles T et al. Nature. 2021 Jul;595(7867):432-437.

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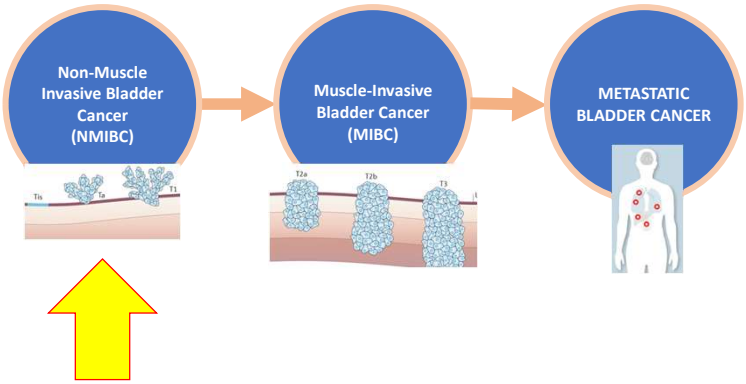
Bladder Cancer Disease States



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NMIBC Treatment

AUA Risk Stratification for Non-Muscle Invasive Bladder Cancer*

Low Risk	Intermediate Risk	High Risk
• Papillary urothelial neoplasm of low malignant potential • Low grade urothelial carcinoma ‣ Ta and ‣ ≤3 cm and ‣ Solitary	• Low grade urothelial carcinoma ‣ T1 or ‣ >3 cm or ‣ Multifocal or ‣ Recurrence within 1 year • High grade urothelial carcinoma ‣ Ta and ‣ ≤3 cm and ‣ Solitary	• High grade urothelial carcinoma ‣ CIS or ‣ T1 or ‣ >3 cm or ‣ Multifocal • Very high risk features (any): ‣ BCG unresponsive[l] ‣ Variant histologies[m] ‣ Lymphovascular invasion ‣ Prostatic urethral invasion

Surveillance

Intravesical therapy OR Surveillance

BCG

Cystectomy OR Intravesical chemotherapy

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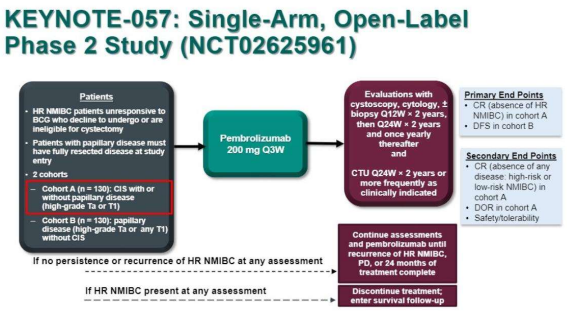
Keynote 057: Pembrolizumab in BCG-refractory NMIBC

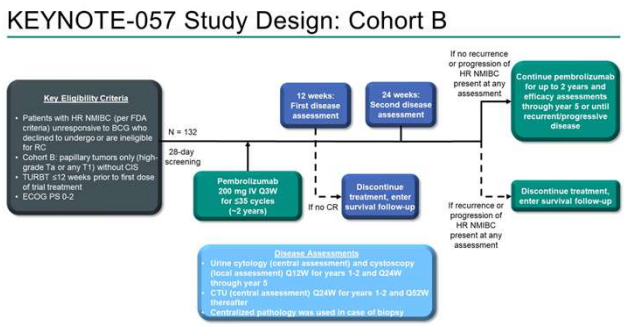


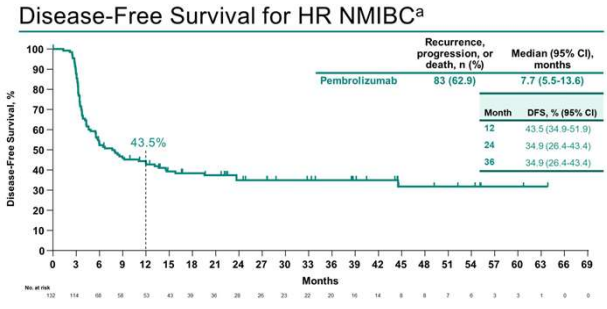
Cohort A: BCG-unresponsive Carcinoma in situ (N=96)

- Complete response at month 3: 41%
- Complete response at 1 year: 19%
- Median duration of response: 16 months

Balar AV et al. Nature. 2021 Jul;595(7867):432-437.

Keynote 057 Cohort B





Necchi A et al. J Clin Oncol. 2023;41(6_suppl):LBA442

Biomarkers?

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Molecular Biomarkers

- **PD-L1 testing by immunohistochemistry:** variable assays, variable cut-points, inconsistent predictive properties; may have role with adjuvant nivolumab (Checkmate 274)
- **Tumor mutation burden (TMB):** Potential predictive biomarkers, optimal cutpoint?
- **Circulating tumor DNA (ctDNA):** may have role with adjuvant therapy, immunotherapy monitoring
- IFN-γ signatures, TGF-β, RNA expression sub-types (TCGA), etc. still ongoing development and validation

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Advanced Urothelial Ca treated with ICIs: a multi-institutional initiative (P. Grivas)

- 'Real-world' (off trial) data
- 26 sites from US & Europe

1360 pts

UCLA
UCSF
UCSD
University of Iowa
University of Utah
Cleveland Clinic Foundation
Tulane University
Cleveland Medical Center
University of Michigan
Winship Cancer Institute, Emory University
Dana Farber Cancer Institute
University of Oklahoma
University of Virginia
University of Zagreb, Croatia
University of Athens, Greece
Imperial College, UK
Hospital Universitario 12 de Octubre, Spain
Val d'Hebron Institute of Oncology, Spain
Hospital Universitario Marques de Valdecilla, Spain
Oncology University of Molise and ASL
Hospital del Mar, Spain
Sidney Kimmel Comprehensive Cancer Center
Montefiore Medical Center
Pennsylvania State University


Ali Raza Khaki, MD


Rafee Talukder, MD


Dimitra Bakaloudi, MD


Leonidas Diamantopoulos MD


Dimitrios Makrakis MD


Petros Grivas, MD, PhD

NIH National Institutes of Health
Funding support under NIH training grant award #T32CA009515

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Real world data for advanced urothelial carcinoma

- ECOG PS 2+ (vs ECOG 0-1) with comparable ORR but shorter OS[1]
- Mixed histology UC with similar ORR, PFS, OS vs pure UC but neuroendocrine mixed variant with shorter PFS and OS[2]
- Upper tract UC with similar ORR, PFS, OS vs lower tract UC[3]
- Prior BCG exposure not associated with worse ORR, PFS, OS[4]
- Prior radical cystectomy with higher ORR, longer PFS and OS for patients receiving salvage ICIs[5]
- Presence of bone and liver metastases associated with lower ORR, shorter PFS and OS; LN-only metastases associated with higher ORR, longer PFS and OS[6]
- Time to 2L ICI<3 months associated with shorter PFS and OS[7]
- Case series reporting outcomes with ICI re-challenge (ORR 13%)[8]
- **Developed new prognostic risk score for patients with aUC treated with first-line checkpoint inhibitors (ECOG 2+, Albumin<3.5g/dL, NLR>5 and liver metastasis)[9]**

1. Khaki AR, Li A, Diamantopoulos LN, et al. *Cancer*. 2020 Mar 15;126(6):1208-1216.
2. Miller NJ*, Khaki AR*, Diamantopoulos LN, et al. *J Urol*. 2020 Jul;204(1):63-70.
3. Esagian SM*, Khaki AR*, Diamantopoulos LN, et al. *BJU Int*. 2021 Aug;128(2):196-205.
4. Talukder R, Makrakis D, Diamantopoulos LN, et al. *Clin Genitourin Cancer*. 2022 Apr;20(2):165-175.
5. Makrakis D, Talukder R, Diamantopoulos L, et al. *BJU Int*. 2021 Nov;130(5):592-603.
6. Makrakis D, Talukder R, Lin GI, et al. *Clin Genitourin Cancer*. 2022 Oct;20(5):e440-e452.
7. Makrakis D, Talukder R, Lin GI, et al. *Clin Genitourin Cancer*. 2022 Dec;20(6):558-567.
8. Makrakis D, Bakaloudi DR, Talukder R, et al. Clin *Genitourin Cancer*. 2022 Nov. Online ahead of print.
9. Khaki AR, Li A, Diamantopoulos LN, et al. *Eur Urol Oncol*. 2021 Jun;4(3):464-472.

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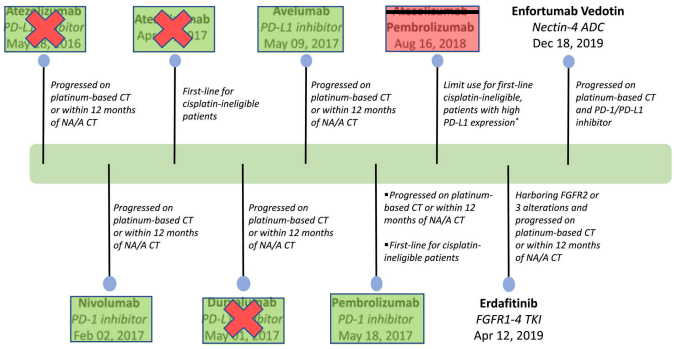
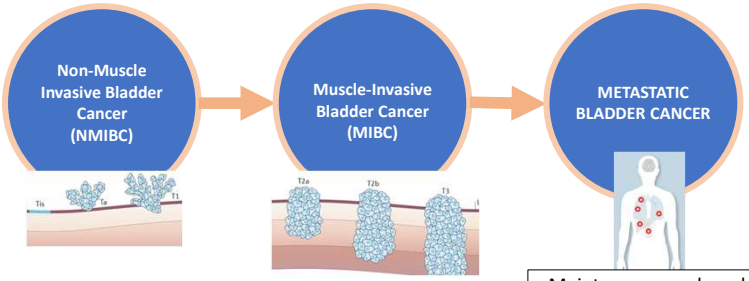
Five different Immune checkpoint inhibitors initially approved for bladder cancer



CA A Cancer J Clinicians, Volume: 70, Issue: 5, Pages: 404-423, First published: 07 August 2020, DOI: (10.3322/caac.21631)

Bladder Cancer Disease States and Treatment



FDA-approved immunotherapy	Pembrolizumab for BCG-refractory CIS	Adjuvant nivolumab	- Maintenance avelumab - Salvage pembrolizumab - Pembro/Atezo for platinum-ineligible disease
Investigational immunotherapy	- Pembrolizumab for BCG-refractory papillary - Novel agents (e.g. N-803)	- Neoadjuvant combinations - Bladder preservation	Novel combinations Novel targets

72 year-old man with new diagnosis of metastatic urothelial carcinoma with lymph node and lung metastases. Patient has ECOG PS 1, CrCl 45, no heart disease, hearing loss or neuropathy. How would you treat patient?

A. Cisplatin and Gemcitabine
B. Carboplatin and Gemcitabine
C. Carboplatin, Gemcitabine and Atezolizumab
D. Pembrolizumab

65

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72 year-old man with new diagnosis of metastatic urothelial carcinoma with lymph node and lung metastases, ECOG PS 1, CrCl 45. Patient is treated with carboplatin and gemcitabine x 6 cycles with imaging showing partial response. How would you treat patient now?

A. Maintenance Avelumab
B. Best supportive care / surveillance
C. Continue carboplatin/gemcitabine
D. Consolidation radiation to bladder and pelvic lymph nodes

67

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Thank You!

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