THE MANAGEMENT OF UROTHELIAL BLADDER CANCER IN THE (MODERN) ERA OF CANCER IMMUNOTHERAPY

NYU Langone Health

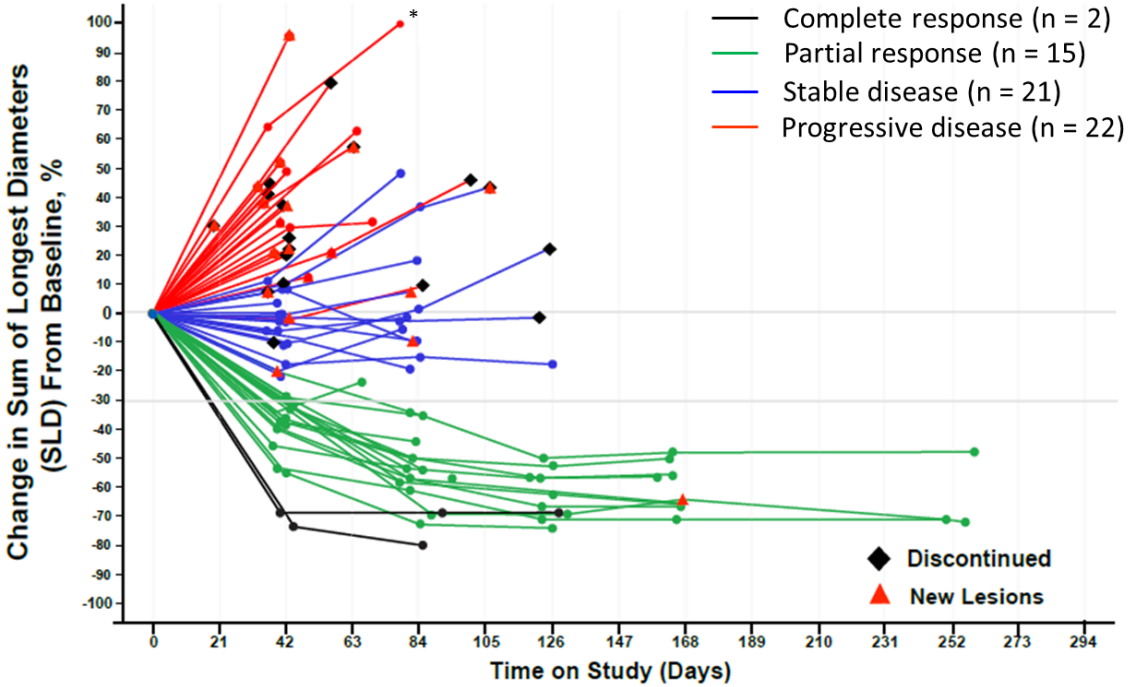
Arjun Balar, M.D.
Associate Professor of Medicine
Perlmutter Cancer Center
Director - Genitourinary Medical Oncology Program

Invasive and Metastatic Urothelial Cancer: Historical Context

- Platinum-based chemotherapy has historically been the standard of care
  - Cisplatin most active and improves survival (~10% cures)
  - Why? - potentially deleterious alterations in genes involved in DNA damage repair (e.g. ERCC2)
  - Other chemotherapy agents are active, but less so
    - Reserved for patients predicted to be harmed by cisplatin (PS 2, Poor renal function)
    - Carboplatin-based therapy SOC
      - Median OS 9 months, 0% 5-year survival
  - Lesson: Toxicity ~ Efficacy
  - A major breakthrough warranted a shift from targeting weakness/vulnerabilities in the cancer toward strengths/opportunities in the host.

PD-1/PD-L1 Antibodies in Urothelial Cancer

Atezolizumab: Phase Ia in Metastatic UBC



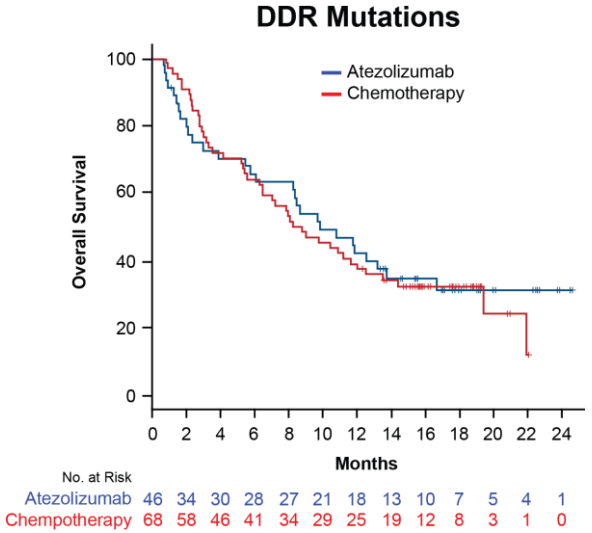
- Median time to first response was 42 days (range, 38 to 85 days)
- Median duration of response has not been reached
  - 0.1+ to 30.3+ weeks IHC (IC) 2 or 3 and 0.1+ to 6.0+ weeks for IHC (IC) 0 or 1

Powles et al, ASCO Annual Meeting 2014

Urothelial Cancer Elicits a Host Immune Response

- Driven by mutations which generate neoepitopes
  - Carcinogen-induced tumors likely accumulate many mutations
    - NSCLC, Melanoma, H&N and Urothelial Cancer
  - Are deficiencies in DDR genes linked (i.e are biomarkers for cisplatin-sensitivity similar to immune-biomarkers)
    - Controversial
    - MSKCC Cohort (N=30): DDR alterations associated with ORR (Teo et al JCO 2018)

IMVigor211: 2nd Line Chemo vs Atezo



Adapted: Powles et al GU ASCO 2018

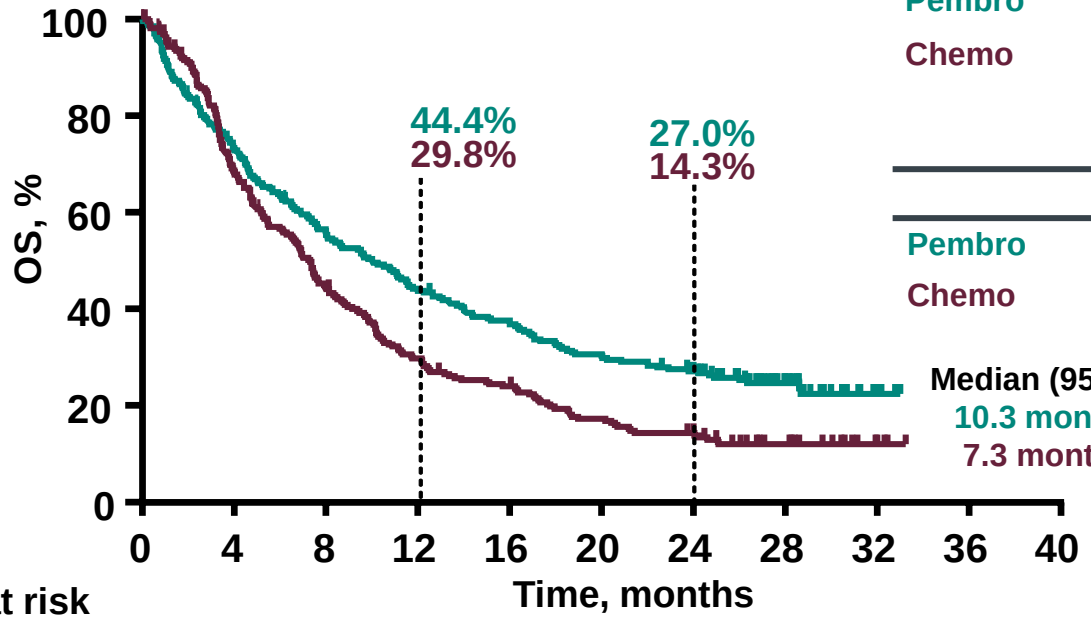
Checkpoint Inhibitors Approved for Use in Urothelial Carcinoma

Setting	Antibody (Study)	N	ORR	Median OS
Platinum-pretreated	Atezolizumab[1] (Imvigor210, Cohort 2)	310	15%	7.9 months
	Nivolumab[2] (CheckMate 275)	265	20%	8.74 months
	Durvalumab[3] (Study 1108)	191	18%	18.2 months
	Avelumab[4] (JAVELIN Solid Tumor)	242	16%	7.7 months
	Pembrolizumab[5] (KEYNOTE-045 [Ph 3])	270[a]	21%	10.3 months

[a]Pembrolizumab arm

[1]Rosenberg et al. *Lancet*. 2016; [2]Sharma et al. *Lancet Oncol*. 2017;18:312; [3]Hahn et al. ASCO 2017; Abstract 4525;
[4]Apolo et al. ESMO 2017; Abstract 856P; [5]Bajorin et al. ASCO 2017, Abstract 4501.

KN045: Overall Survival



No. at risk

Pembro	270	194	147	116	98	80	67	32	6	0	0
Chemo	272	173	109	73	58	41	33	18	4	0	0

14.1 months of follow-up

	Events, n	HR (95% CI)[a]	*P*[b]
Pembro	155	0.73 (0.59-0.91)	0.0022
Chemo	179		

27.7 months of follow-up

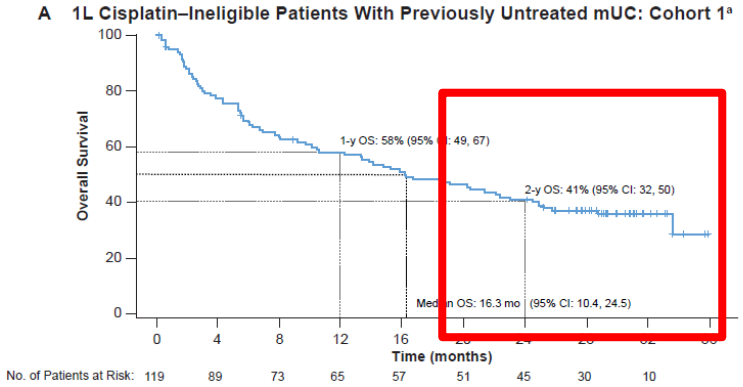
	Events, n	HR (95% CI)[a]	*P*[b]
Pembro	199	0.70 (0.57–0.85)	0.00017
Chemo	218		

Median (95% CI):
10.3 months (8.0–12.3)
7.3 months (6.1–8.1)

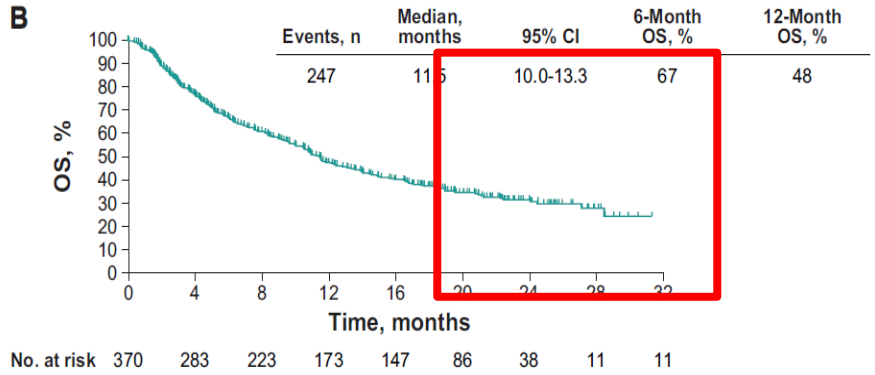
60.6% at 24 months in the chemotherapy arm received an immunotherapeutic agent, including those who received pembrolizumab as part of the cross over.

[a]Based on Cox regression model with treatment as a covariate stratified by ECOG performance status (0/1 vs 2), liver metastases (yes vs no), hemoglobin (<10 vs ≥10 g/dL), and time from completion of chemotherapy (<3 vs ≥3 months). [b]One-sided *P* value based on stratified log-rank test.
Data cutoff date: October 26, 2017.
Bellmunt J et al. *N Engl J Med*. 2017;376:1015-1026.

Cisplatin-ineligible Patients and First-line Immunotherapy



Balar et al J Clin Oncol 36, 2018 (suppl; abstr



Vuky et al ASCO 2018

- Enthusiasm for activity in second-line inspired testing in first-line cisplatin-ineligible
- Two single arm studies (IMVigor 210 C1 and KN052)
  - Accelerated approval based on response (including durability) and safety
- Immediately expanded the treatable population with advanced urothelial cancer
  - Chemo-ineligible patients now have an option
- Safety alerts (KN361 and IMVigor130) have better defined appropriate patients for therapy

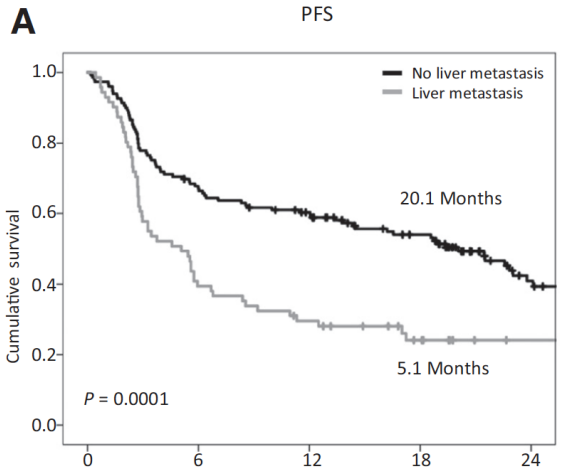
NYU Langone Health

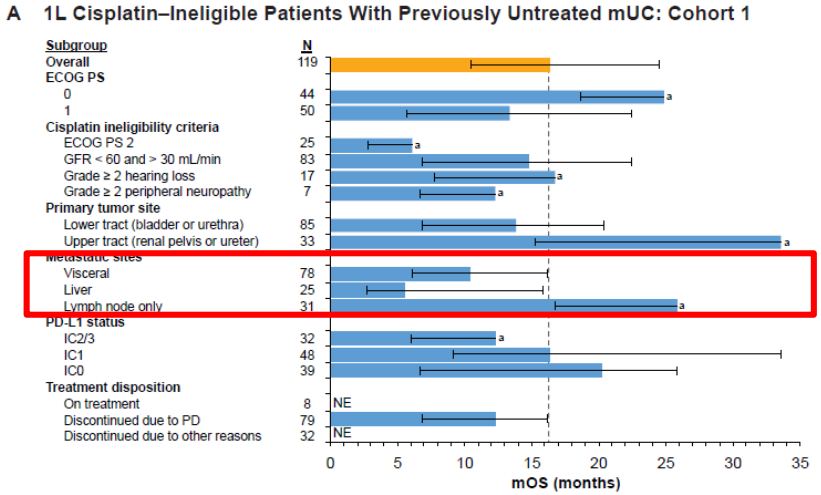
SPECIAL POPULATIONS, NOVEL COMBINATIONS AND NOVEL SETTINGS

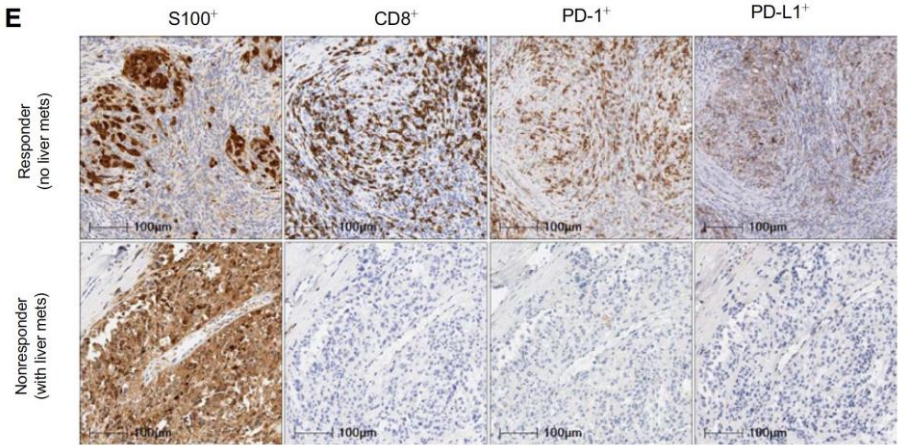
NYU Langone Health

Special Populations

- Liver metastases in Urothelial Cancer
  - Uniformly a poor predictor of outcomes (with any therapy)
  - Mechanisms of immune exclusion not entirely clear, but possibly shared across tumor types





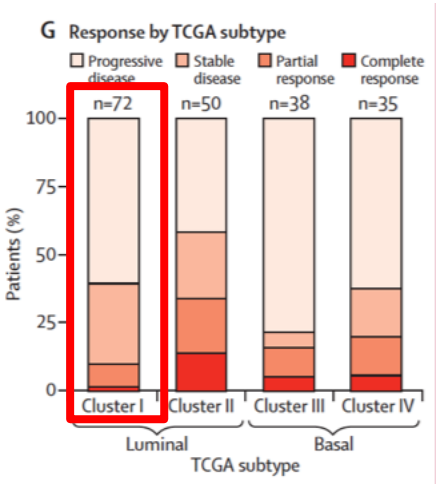


Tumeh et al CIR 2017 DOI: 10.1158/2326-6066.CIR-16-0325

FGFR3 Mutations

- Activating mutations present in 15-20% of HG Invasive Urothelial Cancer
- Oncologic drivers – therapeutic benefit to FGFR3 inhibitors
- Thought to be associated with immune exclusion (enriched in luminal 1 tumors)
- A more focused analysis of CM-275 suggests otherwise:

IMVigor 210 C2 (Atezolizumab)



%CD8 in WT vs Mut

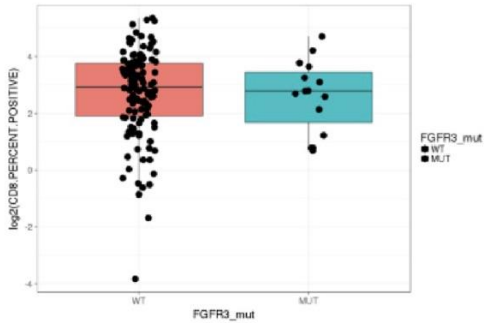
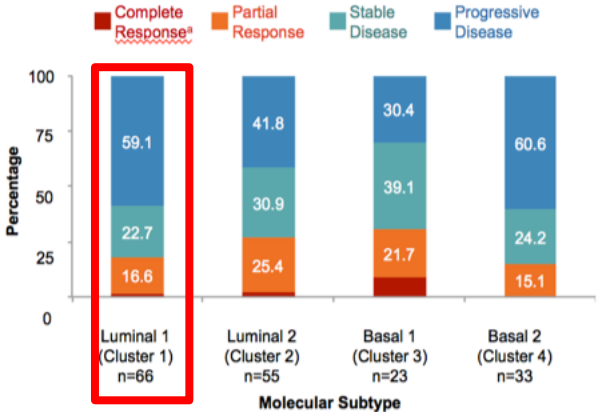


Table 1. BOR with Nivolumab in FGFR3 Wild Type versus Mutant Tumors

FGFR3	Response	N (%)
WT	PD + SD + NE	99 (80%)
WT	CR + PR	25 (20%)
Mutant	PD + SD + NE	12 (80%)
Mutant*	CR + PR	3 (20%)

*CR=S249C, PR=S249C, PR=Y375C

CM-275 (Nivolumab)

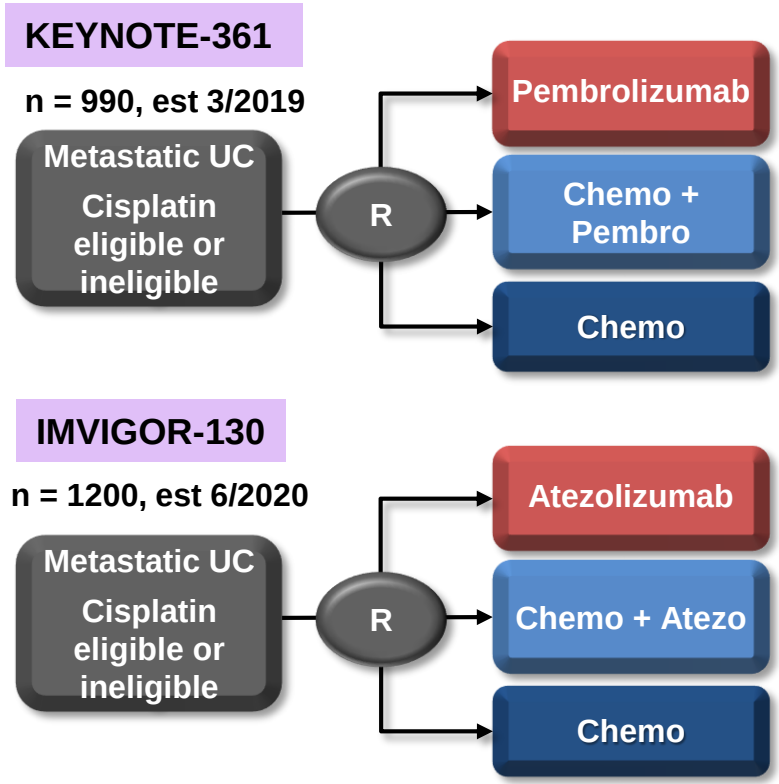


Galsky et al GU ASCO 2018

Novel Combinations: Chemotherapy

- KEYNOTE-189 and 407 in NSCLC: Platinum+IO better than Platinum alone
- Similar outcomes expected in mUC and platinum-IO likely be a new standard of care

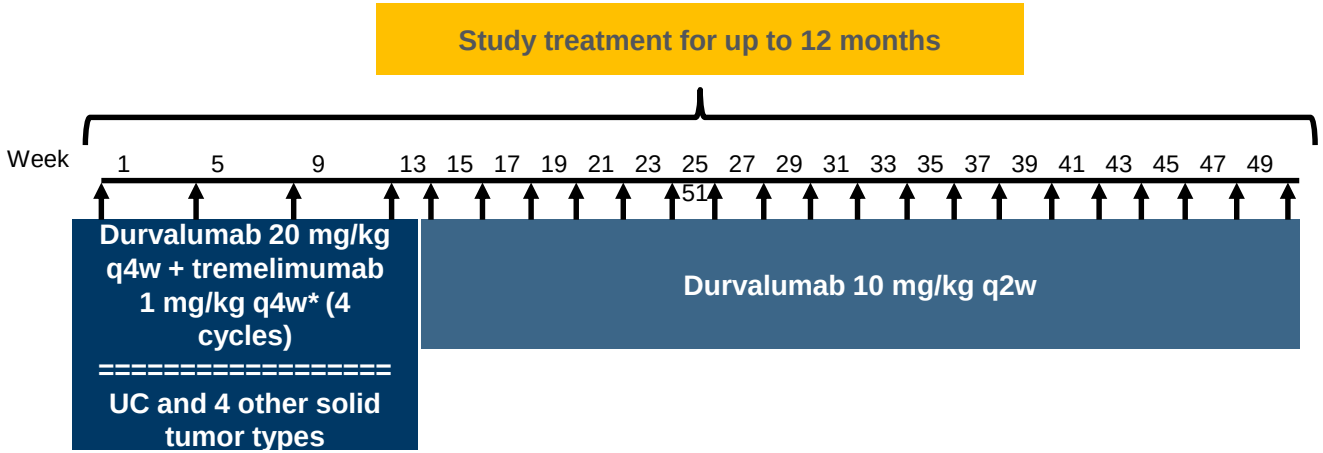
- For platinum-eligible patients (cis *OR* carbo), reduces anxiety of ”waiting” for an immune response
- Does not address chemo-ineligible patients



CTLA-4 plus PD-1 Axis Inhibition

2nd line Durvalumab and Tremelimumab in mUC: Study 10

- Dose expansion part of a multicenter, open-label, phase 1b study in advanced solid tumors
- mUC cohort enrolled patients who progressed after 1–2 prior treatments, including a platinum-based therapy
- Tumor cell (TC) and immune cell (IC) PD-L1 expression (fresh biopsy or archival sample within 6 months) were assessed using the Ventana PD-L1 (SP263) assay and categorized as ≥25% expression in TCs or ICs or <25% expression in both TCs and ICs



Primary objectives

- Safety and tolerability
- Antitumor activity in PD-L1 <25% subgroup

Secondary objective

- Antitumor activity in all patients and in PD-L1 ≥25% subgroup

*Based on dose escalation in Study 006 in NSCLC (Antonia S, et al. Lancet Oncol 2016;17:299–308).

Balar et al AACR 2018

Investigator-assessed antitumor activity (RECIST v1.1)

Response and survival	PD-L1 ≥25% (n=68)	PD-L1 <25% (n=86)	Total* (N=168)
Confirmed ORR (CR+PR) (95% CI), %	29.4 (19.0–41.7)	**15.1 (8.3–24.5)**	20.8 (15.0–27.8)
Disease control rate (CR+PR+SD≥24 weeks) (95% CI), %	32.4 (21.5–44.8)	24.4 (15.8–34.9)	29.2 (22.4–36.7)

ORR 5% for Durvalumab monotherapy in PD-L1 <25% in Study 1108[1]

*14 patients had unknown PD-L1 expression

[1] Powles et al JAMA Oncol 2017 Sep 14;3(9):e172411

Balar et al AACR 2018

CheckMate 032: Nivolumab plus Ipilimumab in mUC

Outcome, %	NIVO 1 + IPI 3 (n = 26)	NIVO 3 + IPI 1 (n = 104)	NIVO Monotherapy (n = 78)
Confirmed ORR, %	**38.5**	26.0	24.4
95% CI	20.2-59.4	17.9-35.5	15.3-35.4
Best overall response, %			
Complete response	3.8	2.9	6.4
Partial response	34.6	23.1	17.9
Stable disease	19.2	25.0	28.2
Progressive disease	26.9	41.3	38.5

Sharma P, et al. Presented at SITC. 2016.

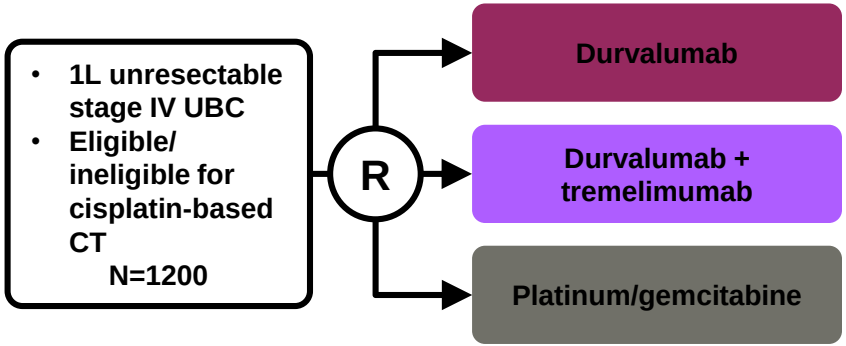
CheckMate 032: Nivolumab plus Ipilimumab: ESMO 2018 Update

Characteristic	NIVO3 (N = 78)	NIVO3+IPI1 (N = 104)	NIVO1+IPI3 (N = 92)
Confirmed ORR, % 95% CI	25.6 16.4–36.8	26.9 18.7–36.5	**38.0** **28.1–48.8**
Best overall response, %			
Complete response	10.3	7.7	6.5
Partial response	15.4	19.2	31.5
Stable disease	26.9	23.1	25.0
Progressive disease	38.5	42.3	21.7
Unable to determine	9.0	7.7	13.0
Not reported	0	0	2.2
PD-L1 <1%	25.6 (13.5-41.2)	25.0 (14.4-38.4)	23.8 (12.1-39.5)

Adapted:Rosenberg et al ESMO 2018

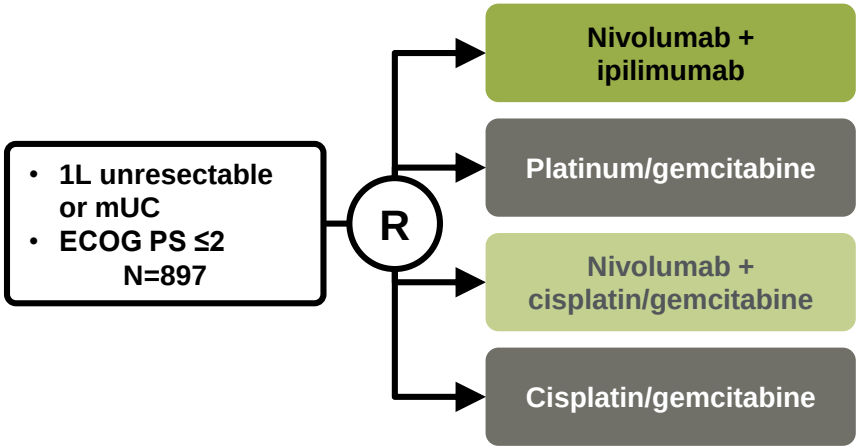
CTLA-4 + PD-1/L1 Combinations in 1-line mUC

DANUBE (NCT02516241)[1]



Primary endpoint: OS (ITT and PD-L1+ populations)
Estimated primary completion date: 23 September 2019

CheckMate 901 (NCT03036098)[2]



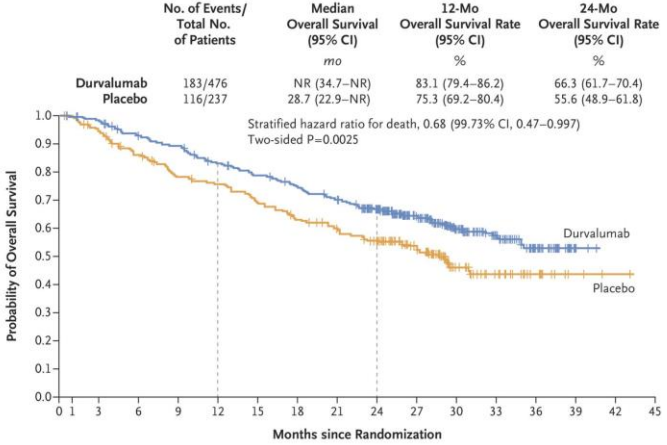
Co-primary endpoints: PFS and OS (cisplatin-ineligible)
Estimated primary completion date: 26 April 2020

1. https://clinicaltrials.gov/ct2/show/NCT02516241
2. https://clinicaltrials.gov/ct2/show/record/NCT03036098

Novel Settings: Early Stage Disease

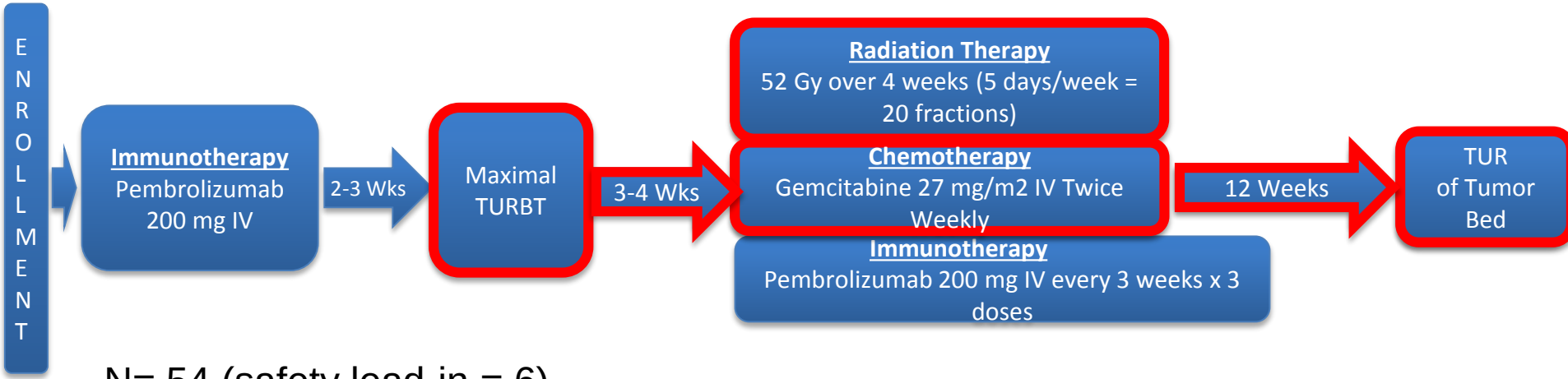
- Too many trials to count, vast majority on-going
- Localized (Curable) Muscle-Invasive Disease
  - Provocative data for PD-1/L1 in two pre-surgical studies (ABACUS[1] and PURE-01[2]) demonstrating 30-40% pCR rate (enriched in PD-L1 positives)
  - Immunotherapy added to chemoradiation
    - PACIFIC Study (ChemoRT -> Durvalumab vs Placebo) showed a significant PFS and OS benefit in Stage III NSCLC[3]
    - Chemoradiation historically reserved for non-surgical candidates
    - Rates of cure similar if done appropriately (Tri-Modality) and in appropriate patients[4]

PACIFIC: ChemoRT -> Durva/Placebo



[1]Powles et al ASCO 2018, [2]Necchi et al ASCO 2018, [3]Antonia et al N Engl J Med. 2018 Sep 25. doi: 10.1056/NEJMoa1809697
[4]Kulkarni GS J Clin Oncol. 2017 Jul 10;35(20):2299-2305.

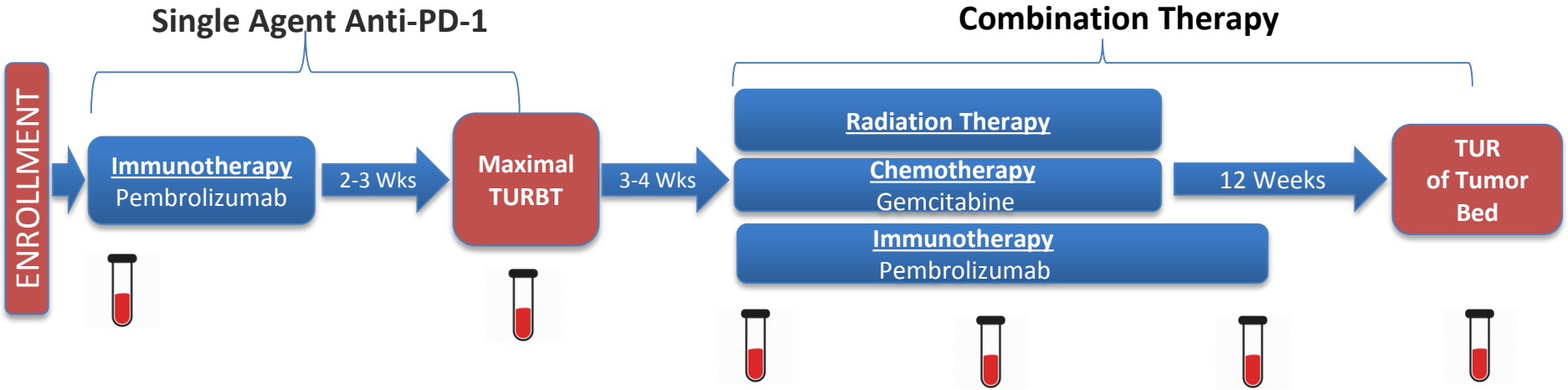
NYU Phase II Trial of Pembrolizumab, Gemcitabine and Hypofractionated RT as Bladder Sparing Treatment for MIBC



N= 54 (safety lead-in = 6)
Primary Endpoint: BIDFS
Participating Sites: 4

PI: Balar (NYU); NCT02621151

Biospecimen Collection Schema



= Blood collection

= Tumor collection

Participating Sites: U-Chicago, U-Michigan, UNC, MSKCC

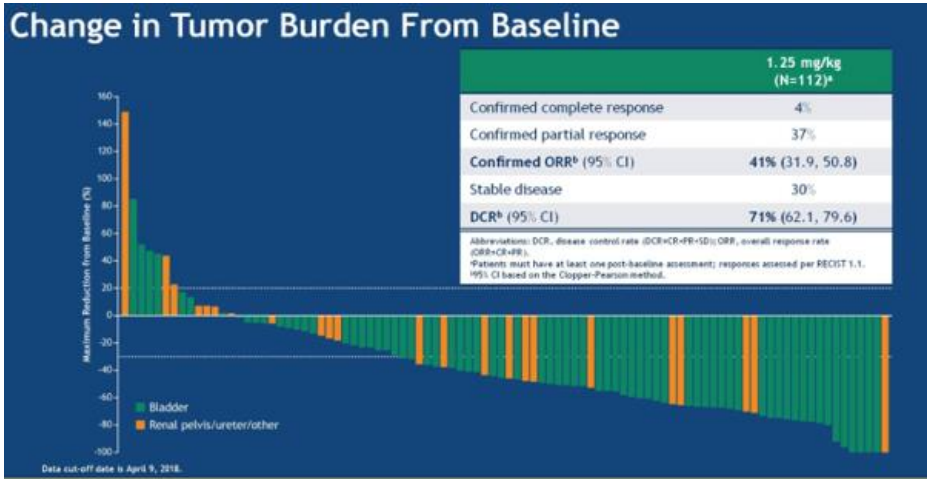
Current: **22 enrolled of 54 planned**

WHILE WE WAIT FOR THE NEXT IO BREAKTHROUGH: MANAGING PROGRESSION AFTER PD-1

ADCs Most Viable Option post-PD-1

- Two ADCs in development:
  - Enfortumab Vedotin
    - Target Nectin-4, Payload MMAE
  - Sacituzumab Govitecan
    - Target Trop-2, Payload SN-38
  - ORRs up to 40%[1] (EV)
- PD-1 progressors declared most often on first-scan and not subtle
  - Need rapid response
- Phase II/III studies are ongoing

EV 101: Phase I in 2nd and 3rd line mUC[1]



Clinical Response With Enfortumab Vedotin in mUC Patients With or Without Prior CPI or Liver Metastases

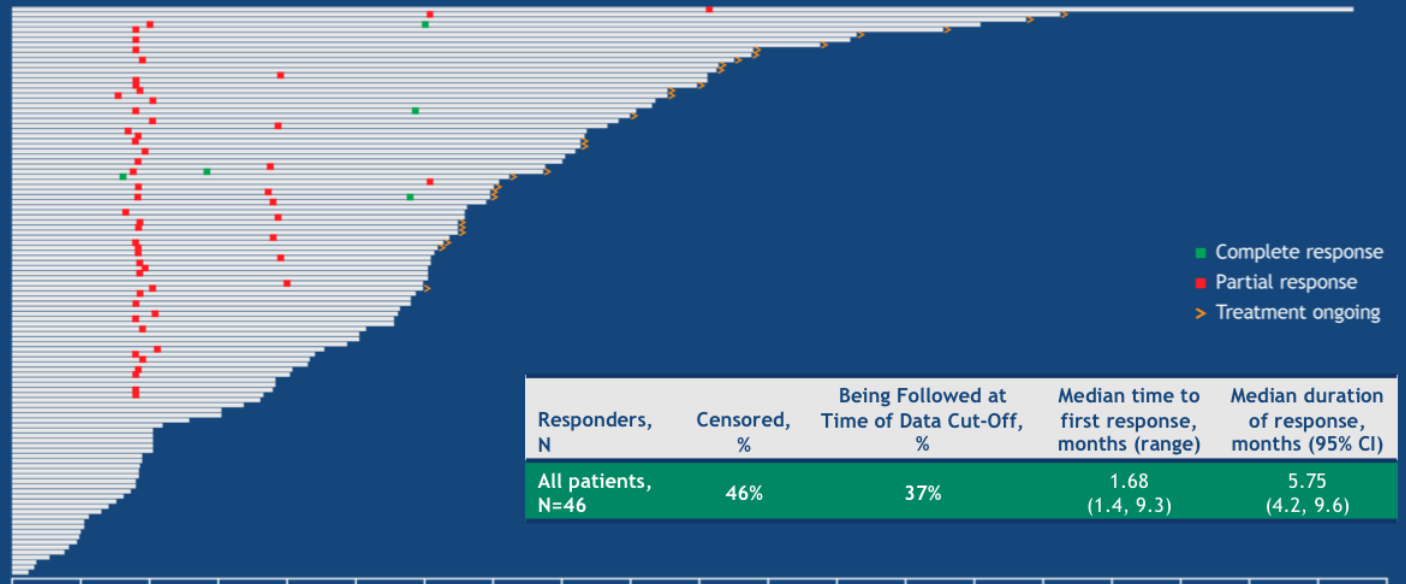
	Prior CPI Treatment[a] 1.25 mg/kg (n=89)	CPI-Naïve[a] 1.25 mg/kg (n=23)	Liver Metastases[a] 1.25 mg/kg (n=33)
Confirmed complete response	3%	9%	0
Confirmed partial response	37%	35%	39%
Confirmed ORR[b] (95% CI)	40% (30.2, 51.4)	43% (23.2, 65.5)	39% (22.9, 57.9)
Stable disease	34%	17%	21%
DCR[b] (95% CI)	74% (63.8, 82.9)	61% (38.5, 80.3)	61% (42.1, 77.1)

Abbreviations: CPI, checkpoint inhibitor; DCR, disease control rate (DCR=CR+PR+SD); ORR, overall response rate (ORR=CR+PR).
Data rounded to the nearest whole percent.
[a]Evaluable patients must have at least one post-baseline assessment or discontinued treatment without any disease assessment; responses assessed per RECIST 1.1.
[b]Data presented as % (95% CI); 95% CI based on the Clopper-Pearson method.

[1]Rosenberg et al ASCO 2018

EV 101: Response Durability

Duration of Response



Responders, N	Censored, %	Being Followed at Time of Data Cut-Off, %	Median time to first response, months (range)	Median duration of response, months (95% CI)
All patients, N=46	46%	37%	1.68 (1.4, 9.3)	5.75 (4.2, 9.6)

Data cut-off date is April 9, 2018.

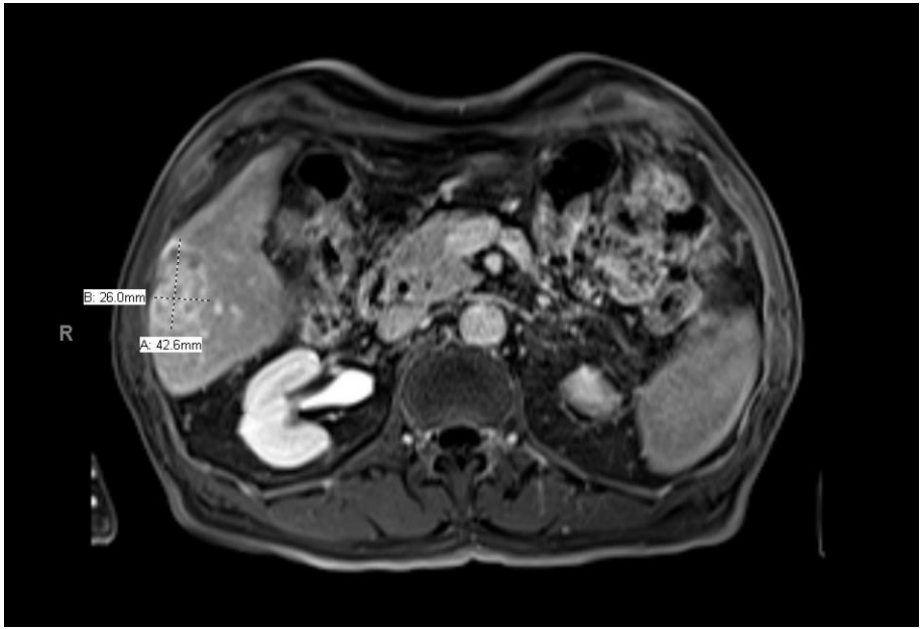
Rosenberg J, et al. 2018 ASCO Annual Meeting. Abstract 4504.

Case

- 64 year old former smoker
- Hematuria in 2008, diagnosed with NMIBC, treated with BCG
- Progressed to MIBC with pelvic nodal involvement in November 2010
- Neoadjuvant Gem/Cis x 3 cycles (1/21/2011 - 4/18/2011);
- Cisplatin/RT (8/2011 - 9/2011) to the bladder
- Recurred with distant metastases in 2015
- Gemcitabine/Cisplatin x 6 cycles 2015
- **PD-L1/CTLA-4 (10/31/2016 - 4/3/2017) – Best Response SD**
- Paclitaxel weekly (4/17/2017 - 8/7/2017); enfortumab vedotin x 4 cycles (12/6/2017 - 3/22/2018) – both achieving a near CR, followed by progression in liver

Subsequent PD-1 Re-Challenge

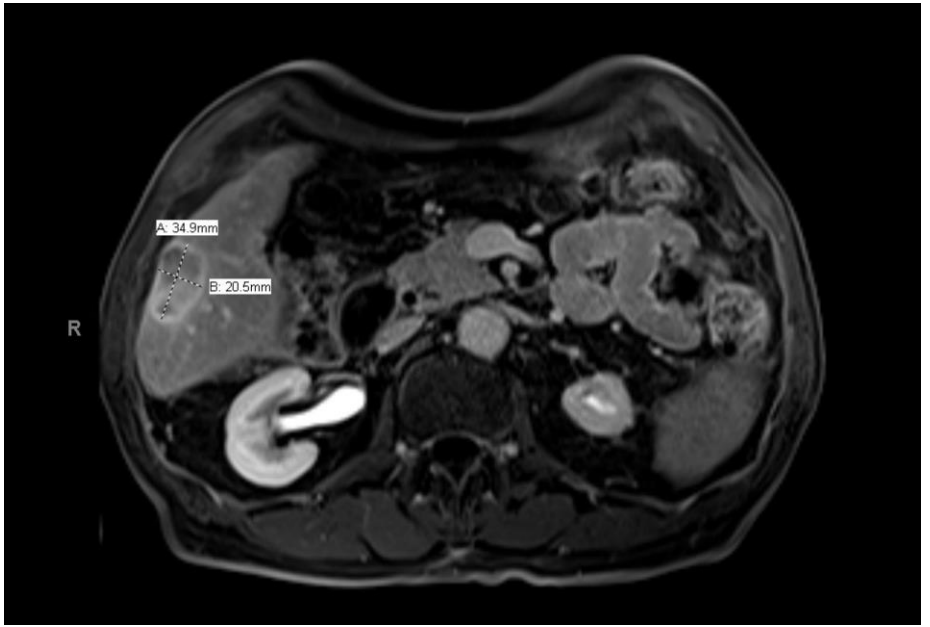
April 2018



4.2 cm

After 3 cycles

June 2018



3.4 cm

Summary

- PD-1 pathway inhibitors have revolutionized bladder cancer management and how we think about the disease
- New questions and challenges have emerged
  - Special populations defined clinically and molecularly may warrant unique approaches
- Novel combinatorial strategies (Chemo-based, IO-IO-based) in the near-term could lead to new standards of care and may be broadly applicable
- Cytotoxics still have a role and ADCs have improved therapeutic index
  - Enfortumab vedotin and sacituzumab govitecan poised to be excellent options post-IO
  - Questions remain re: immune-synergy
- The most significant impact is yet-to-come.
  - Early-stage disease (MIBC and NMIBC)