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Overview of and current indications for the use of immune checkpoint inhibitors in urothelial carcinoma

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Disclosures

Advisory Committee	Astellas Pharma Global Development Inc, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Bristol-Myers Squibb Company, EMD Serono Inc, Genentech BioOncology, Inovio Pharmaceuticals Inc, Gritstone Oncology, Lilly, Merck, Roche Laboratories Inc, Sanofi Genzyme
Contracted Research	Genentech BioOncology, Incyte Corporation, Novartis

Current FDA approvals for bladder cancer

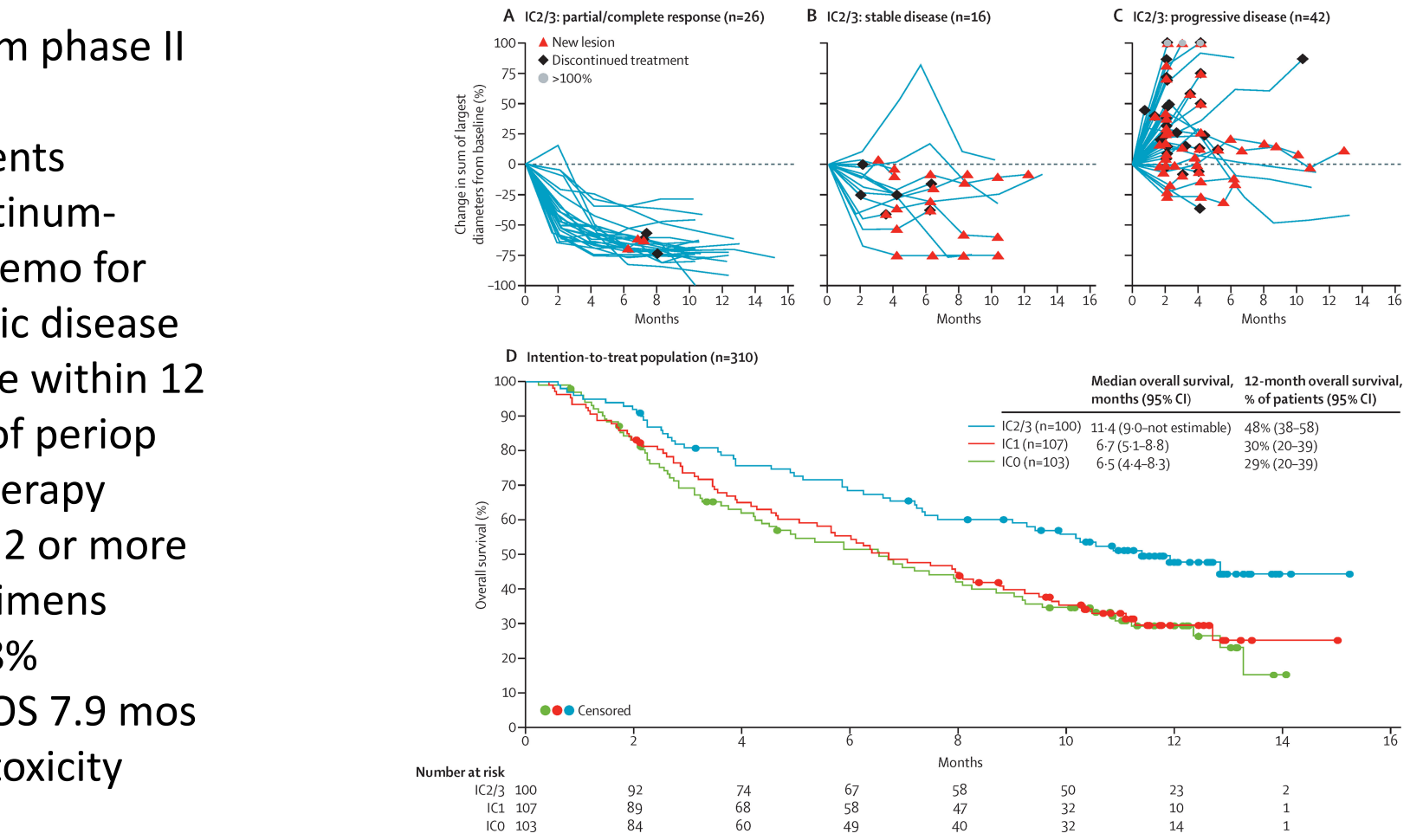
Agent	Indication	N	Overall Response Rate (%)	DOR (mos)	Overall Survival (mos)	Randomized
Atezolizumab	1st-line cis-ineligible	310	14.8% (11.1, 19.3)	NR	7.9 (6.7, 9.3)[1]	No
	Prior platinum	119	23.5% (16.0, 31.0)	NR	15.9 (10.4, NR)[2]	No
Nivolumab	Prior platinum	270	19.6% (15.1, 24.9)	NR	8.7 (6, NR)[3]	No
Durvalumab	Prior platinum	182	17.0% (11.9, 23.3)	NR	Not reported	No
Avelumab	Prior platinum	242	16.1% (≥6 mos follow-up)	Not estimable	Not reported	No

1. Rosenberg, et al. *Lancet* 2016
2. Balar, et al. *Lancet* 2017
3. Sharma, et al. *Lancet Oncology* 2017
4. Avelumab package insert

NR: Not Reached

Atezolizumab approved for prior platinum-treated patients

- Single arm phase II study
- 310 patients
- Prior platinum-based chemo for metastatic disease or relapse within 12 months of periop chemotherapy
- 40% had 2 or more prior regimens
- ORR 14.8%
- Median OS 7.9 mos
- Modest toxicity



Rosenberg, et al. *The Lancet* 2016

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Update on Phase III study of atezolizumab in patients with previously treated advanced bladder cancer

May 9, 2017

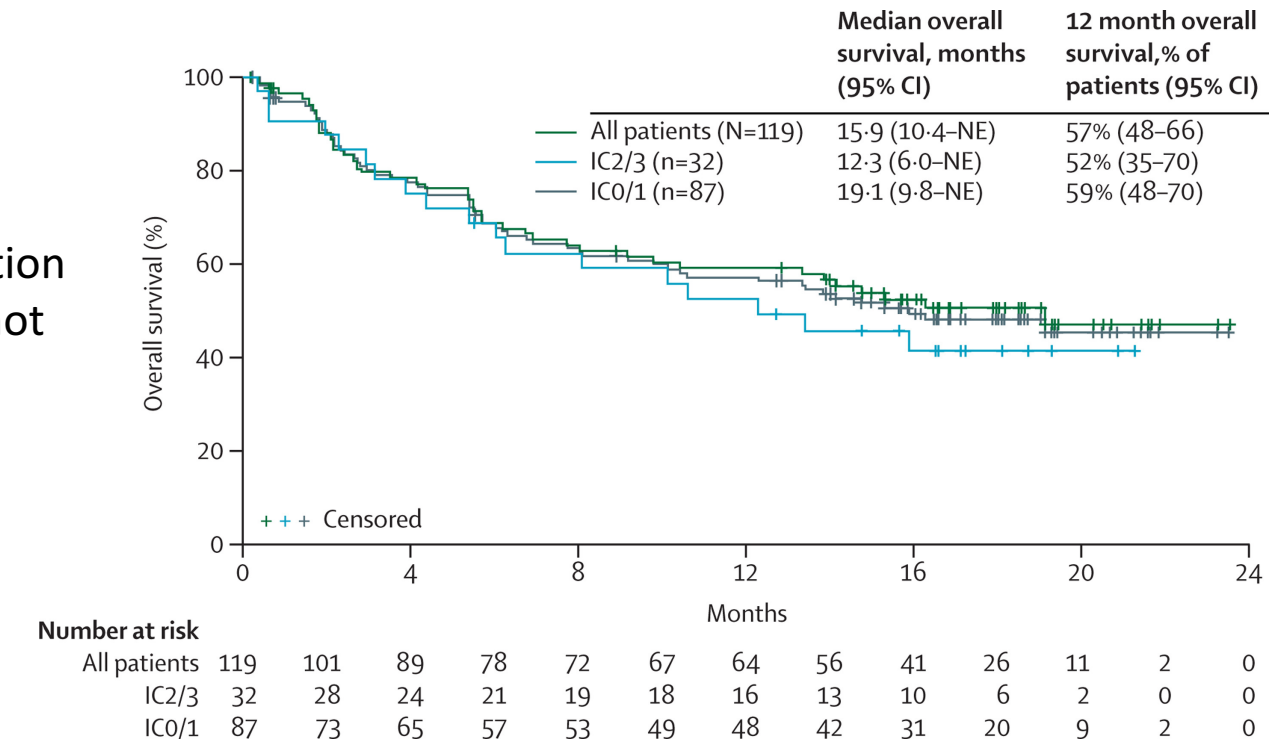
The Phase III IMvigor211 study that evaluated atezolizumab in people with locally advanced or metastatic urothelial cancer whose disease progressed during or after treatment with a platinum-based chemotherapy (previously treated) did not meet its primary endpoint of overall survival compared to chemotherapy. The safety profile observed in IMvigor211 was consistent with what has been previously observed for atezolizumab.

https://www.gene.com/media/press-releases/14665/2017-05-09/genentech-provides-update-on-phase-iii-s

Atezolizumab: cisplatin-unfit (n=119)

	IC2/3 (n = 32)	IC1/2/3 (n = 80)	All Patients (N = 119)	IC1 (n = 48)	IC0 (n = 39)
ORR[a] (95% CI)	28% (14, 47)	24% (15, 35)	23% (16, 31)	21% (10, 35)	21% (9, 36)
CR	12%	10%	9%	8%	8%
PR	16%	14%	14%	13%	13%

Median duration of response not reached



Balar AV et al. *Lancet* 2016

US FDA approved April 2017

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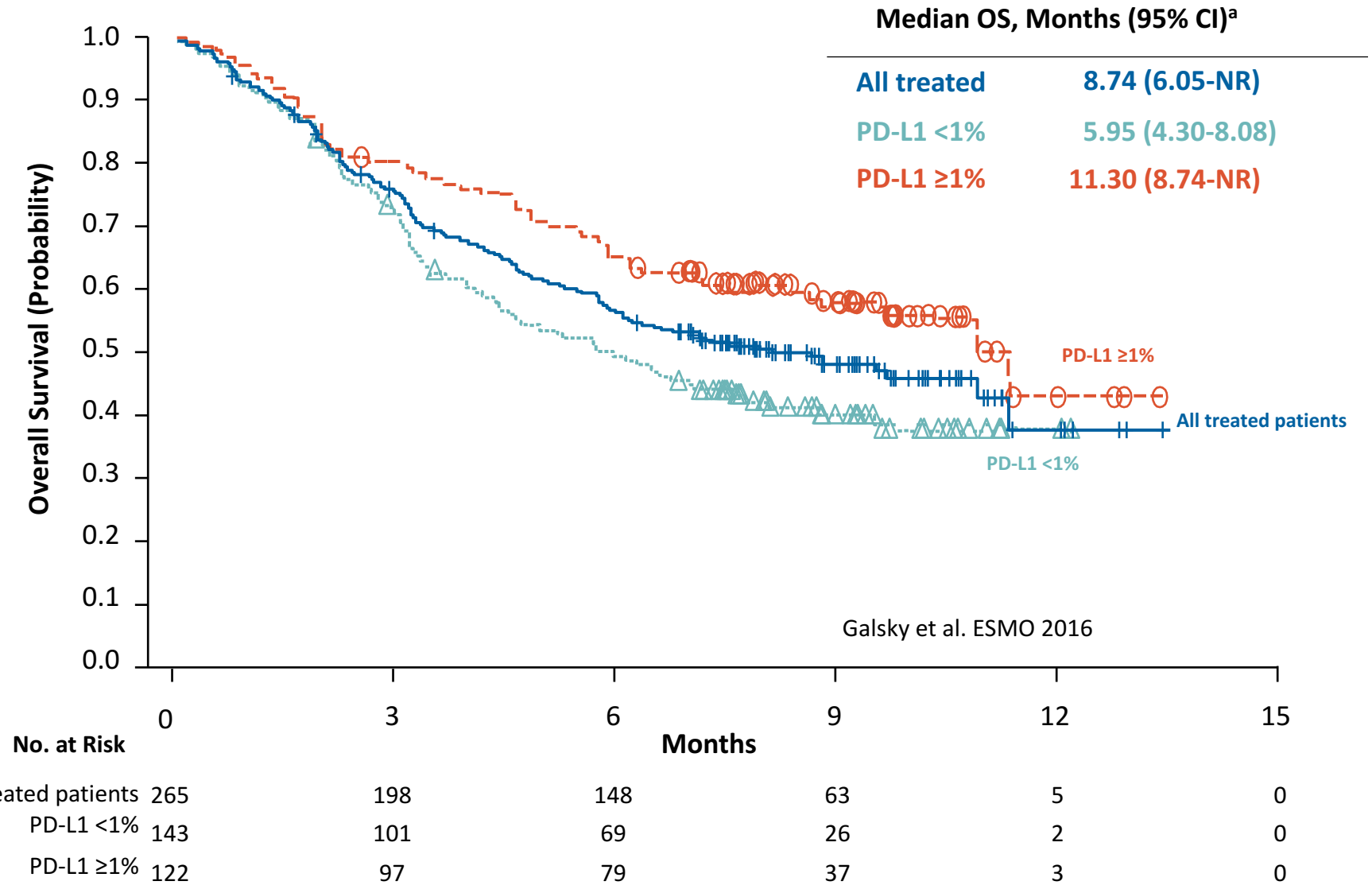
Checkmate 275: Activity of nivolumab in previously platinum-treated locally advanced or metastatic UC

Outcome, %	All N=265	PD-L1 <1% n=143	PD-L1 ≥1% n=122	PD-L1 ≥5% n=81
Confirmed ORR	19.6	16.1	23.8	28.4
95% CI	15.0–24.9	10.5–23.1	16.5–32.3	18.9–39.5
Best overall response				
Complete response	2.3	<1	4.1	4.9
Partial response	17.4	15.4	19.7	23.5
Stable disease	22.6	17.5	28.7	28.4
Progressive disease	39.2	46.9	30.3	25.9
Unable to determine	18.5	19.6	17.2	17.3

- PD-L1 measured on tumor cells
- Median follow-up was 7 months (minimum of 6 months)

Sharma, et al. *Lancet Oncology* 2017

Nivolumab 2nd-line: Overall survival



Sharma, et al. *Lancet Oncology* 2017

Durvalumab approved for platinum-treated advanced UC

- Single-arm Phase I/II Study 1108
- 182 pts
- Previously treated UC w/ platinum-based chemo or relapse ≤1 y of (neo)adjuvant chemo

	All patients (n = 182)	PD-L1 high (n = 95)	PD-L1 low (n = 73)	PD-L1 unknown (n = 14)
ORR by blinded review	31 (17.0%)	25 (26.3%)	3 (4.1%)	3 (21.4%)
CR	5 (2.7%)	3 (3.16%)	1 (1.4%)	1 (7.1%)
PR	26 (14.3%)	22 (23.16%)	2 (2.7%)	2 (14.3%)
Median DoR	Not reached	Not reached	12.3 mo	Not reached

Median follow-up = 5.6 mo

VENTANA (SP263) assay approved as complementary diagnostic test

Press Release: May 01, 2017

Avelumab approved for platinum-treated advanced UC

- Single-arm JAVELIN Phase I study
- 242 pts
- Previously treated UC with platinum-based chemo or relapse ≤1 y of (neo)adjuvant chemo

Response	Follow-up of ≥13 weeks (n = 226)	Follow-up of ≥6 months (n = 161)
Confirmed ORR	30 (13.3%)	26 (16.1%)
CR	9 (4%)	9 (5.6%)
PR	21 (9.3%)	17 (10.6%)
Median DoR	Not reached	Not reached

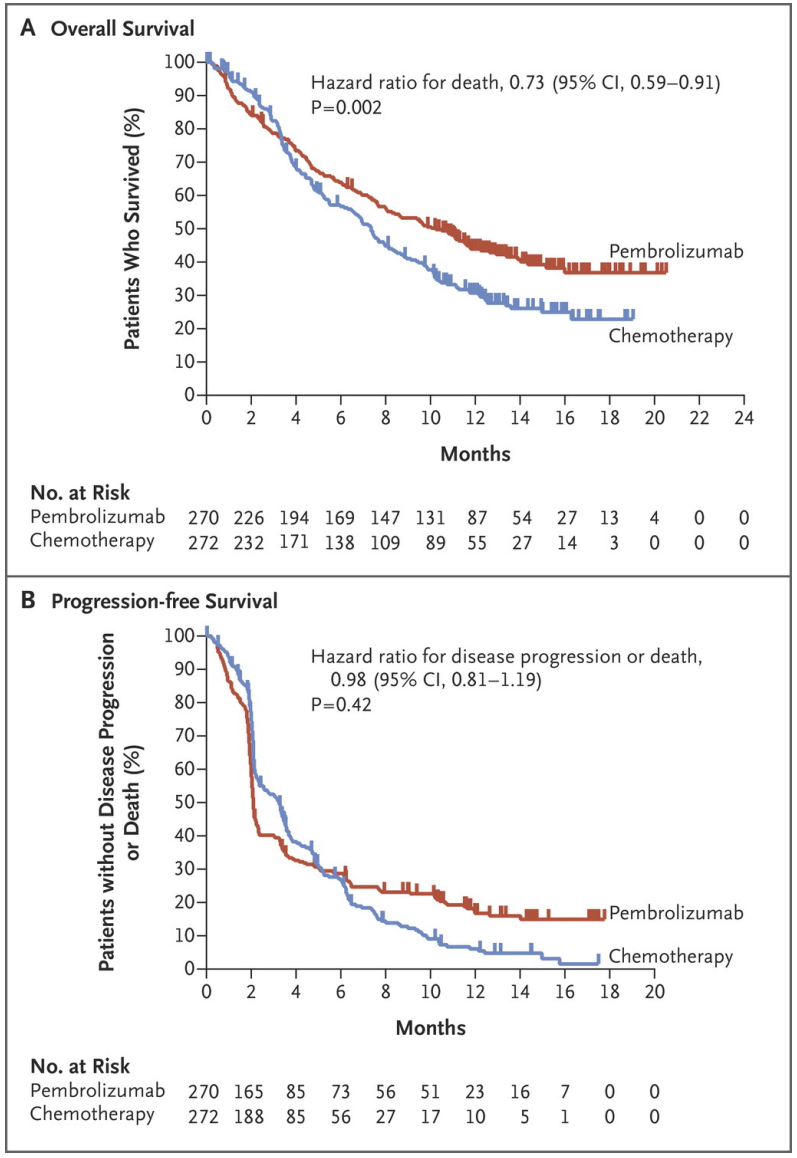
Adverse Events (AEs)	N = 242
Deaths due to AEs	6%
Occurrence of serious AEs	41%

Infusion-related reactions were noted in >20% of pts, requiring premedications (antihistamines and acetaminophen)

Press Release: May 09, 2017

KEYNOTE 045 – Pembrolizumab improves overall survival vs. salvage chemotherapy

- Dealers choice chemotherapy
  - Docetaxel, paclitaxel, or vinflunine
- Median OS 10.3 months for pembro vs. 7.4 for chemo (HR 0.73)
- PFS short, and not different between the two arms



Bellmunt J et al. *NEJM* 2017;376(11):1015-26.

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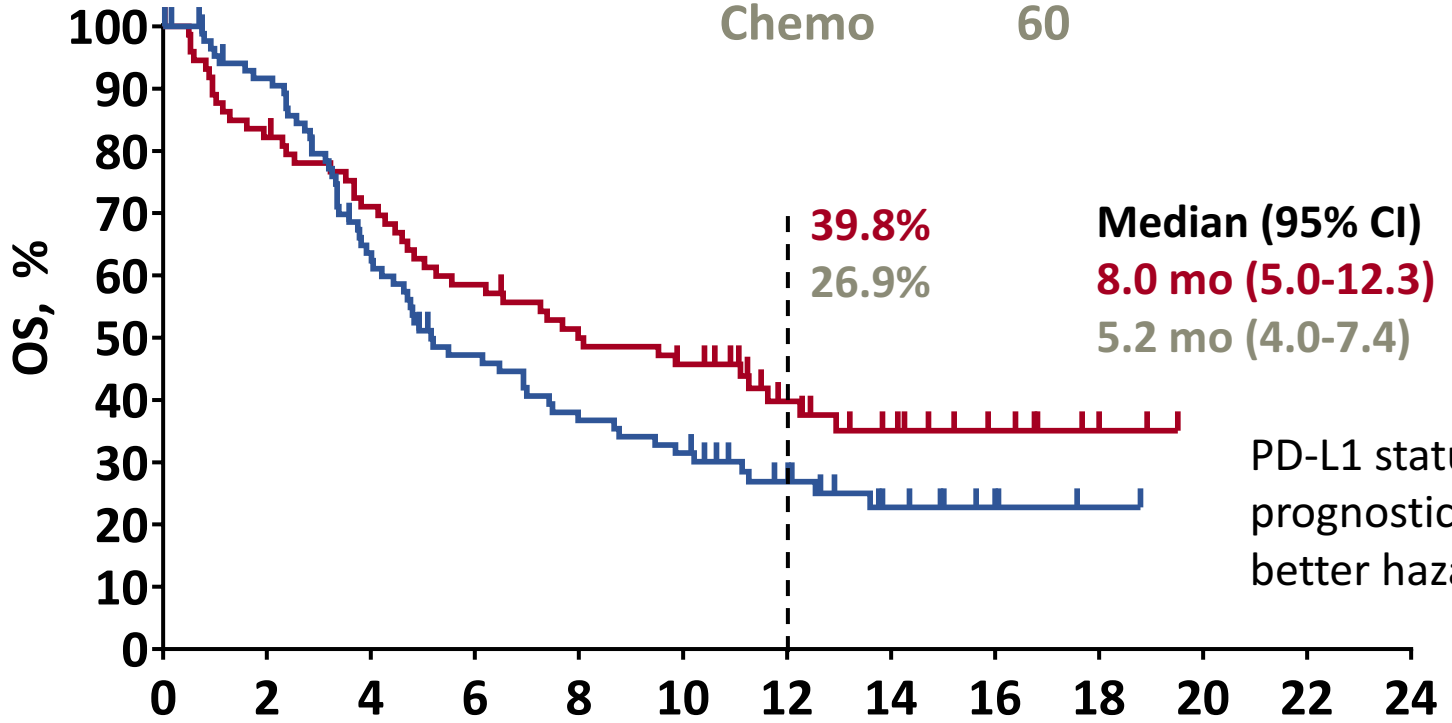
Overall Survival:
PD-L1 Combined Positive Score ≥10%

	Events, n	HR (95% CI)	*P*
Pembro	44	0.57 (0.37-0.88)	0.0048
Chemo	60		



PD-L1 status is negative prognostic factor, but predicts better hazard ratio

No. at risk

74	60	51	42	35	31	18	12	7	3	0	0	0
90	76	51	36	28	24	16	8	4	1	0	0	0

Data cutoff date: Sep 7, 2016.

Bellmunt, et al. SITC 2016

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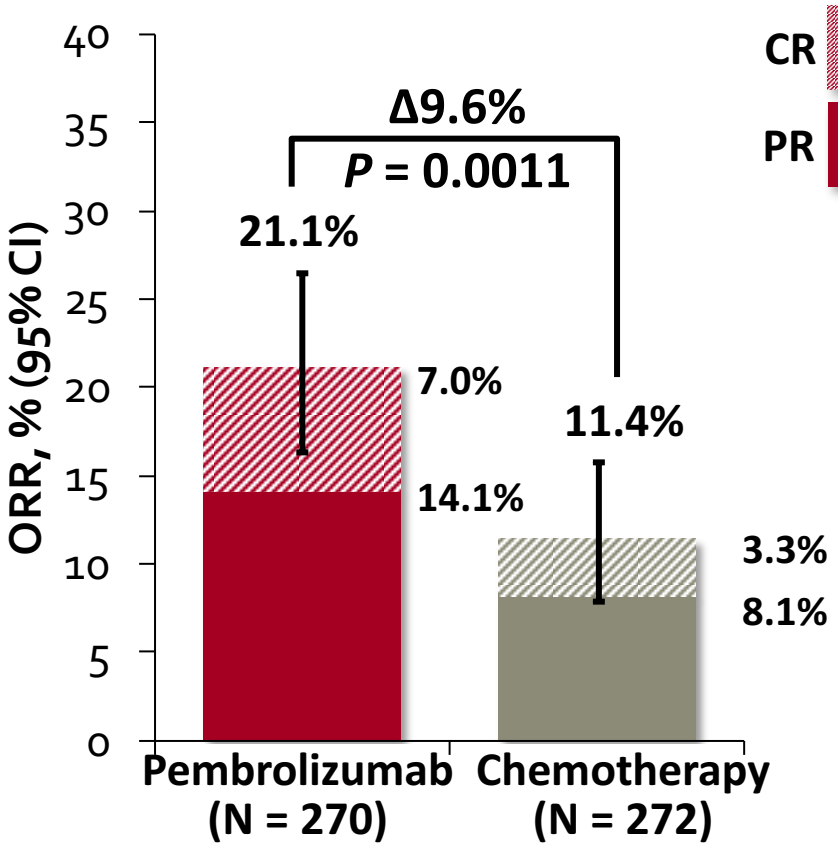
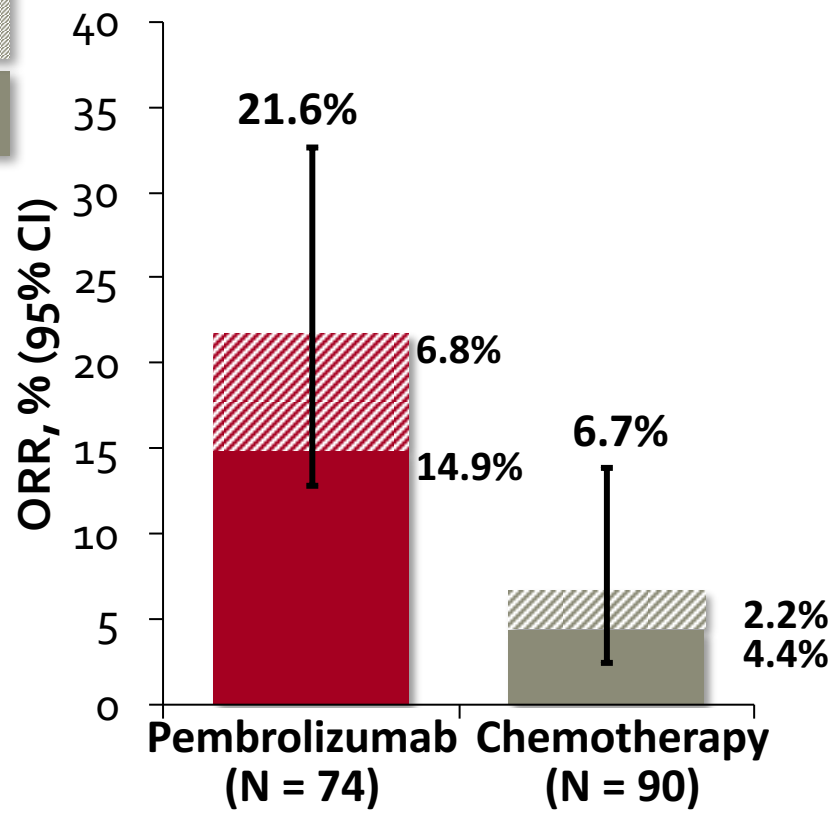
Confirmed Objective Response Rate

Total Population



CPS ≥10% Population



CPS = combined positive score

Bellmunt J et al., SITC 2016

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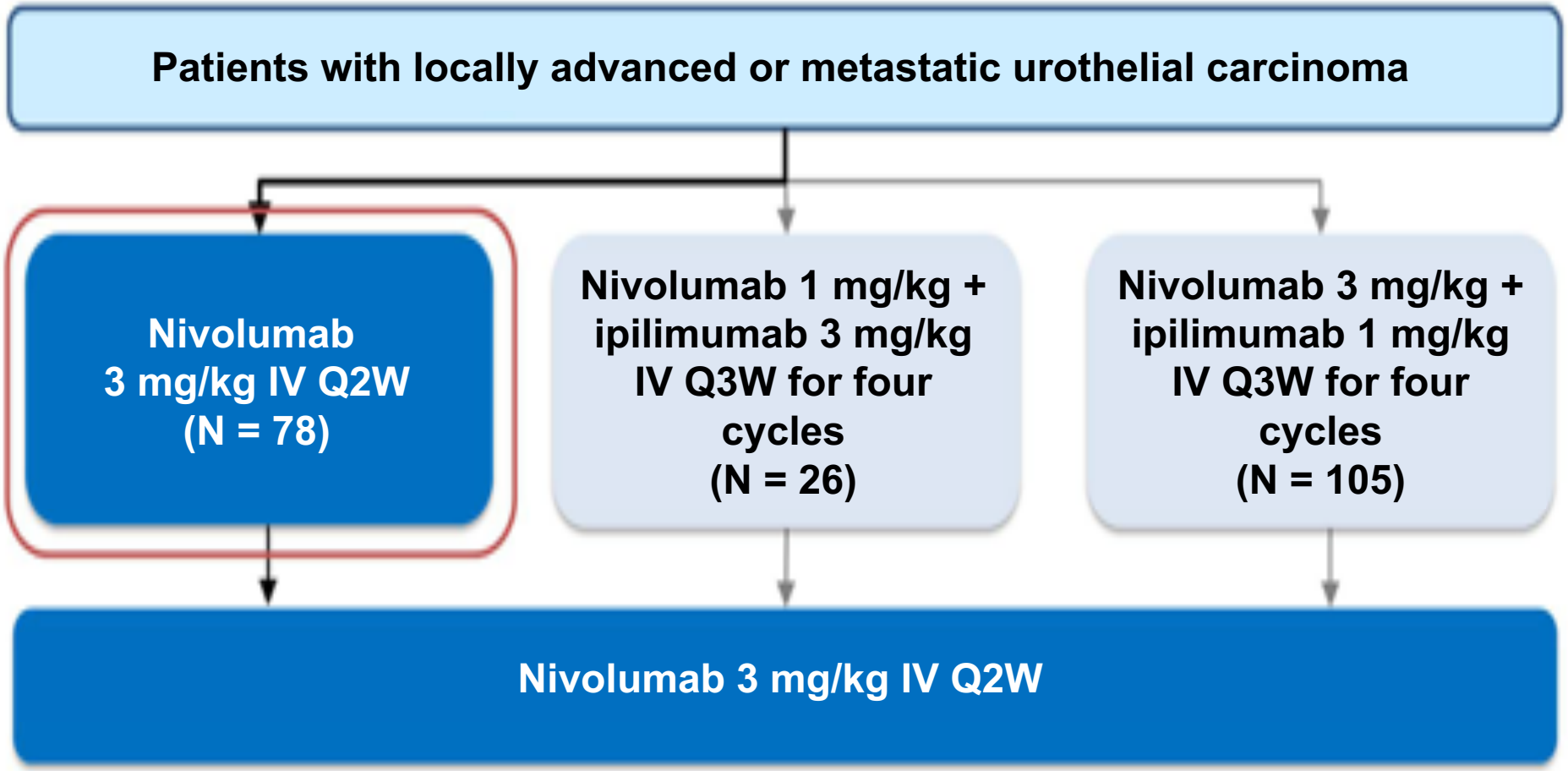
CheckMate 032: Ongoing Phase I/II trial of nivolumab +/- ipilimumab in advanced urothelial carcinoma



Primary endpoint: Objective response rate (ORR)

Sharma P et al. *Proc ASCO* 2016;Abstract 4501.

CheckMate 032: Response and survival

Outcome	Nivo 1 mg/kg + Ipi 3 mg/kg (n = 26)	Nivo 3 mg/kg + Ipi 1 mg/kg (n = 104)
Disease control rate	57.7%	51%
ORR	38.5%	26%
CR	3.8%	2.9%
Median PFS	4.3 mo	2.6 mo
Median OS	10.2 mo	7.3 mo

Sharma P et al. SITC 2016;Abstract 03.

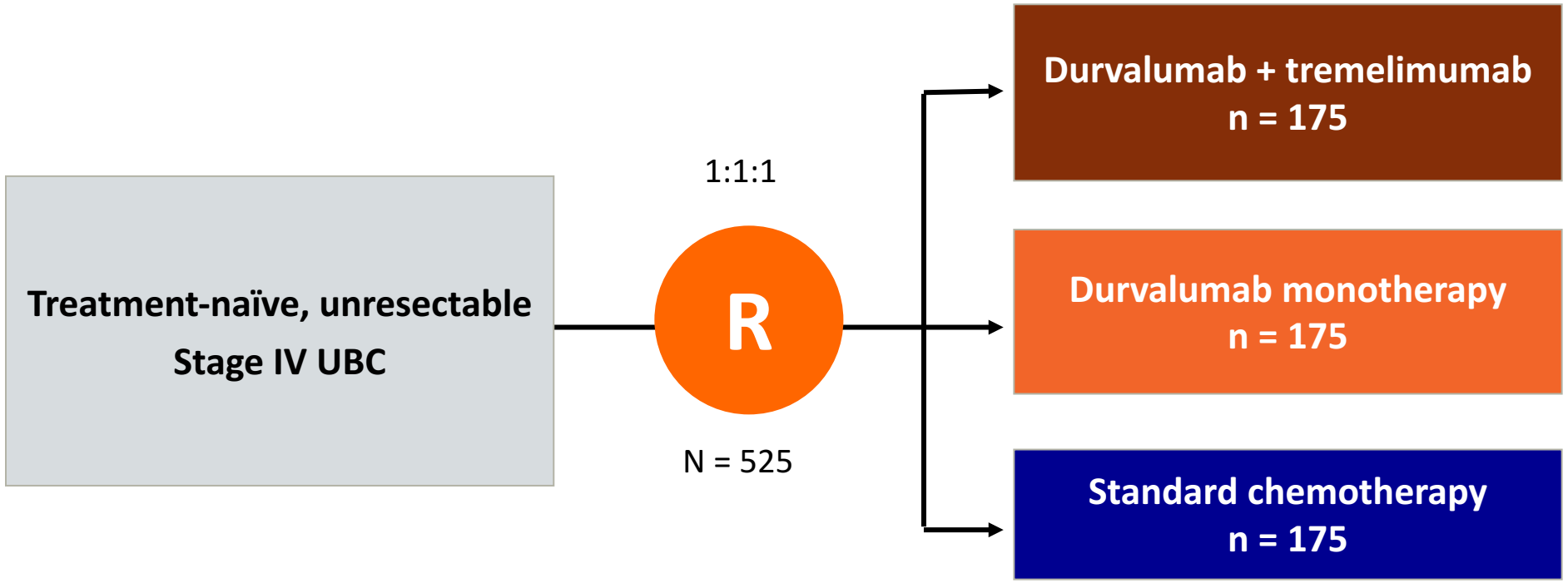
CheckMate 032: Adverse events

Grade ≥3	Nivo 1 mg/kg + Ipi 3 mg/kg (n = 26)	Nivo 3 mg/kg + Ipi 1 mg/kg (n = 104)
All	30.8%	31.7%
Diarrhea	7.7%	4.8%
Pneumonitis	3.8%	<1%
Increased ALT	NR	5.8%
Increased AST	NR	3.8%
Colitis	NR	3.8%

NR = not reported

Sharma P et al. SITC 2016;Abstract 03.

DANUBE: Phase III trial of first-line durvalumab ± tremelimumab in unresectable metastatic urothelial bladder cancer



Primary endpoint: Progression-free survival

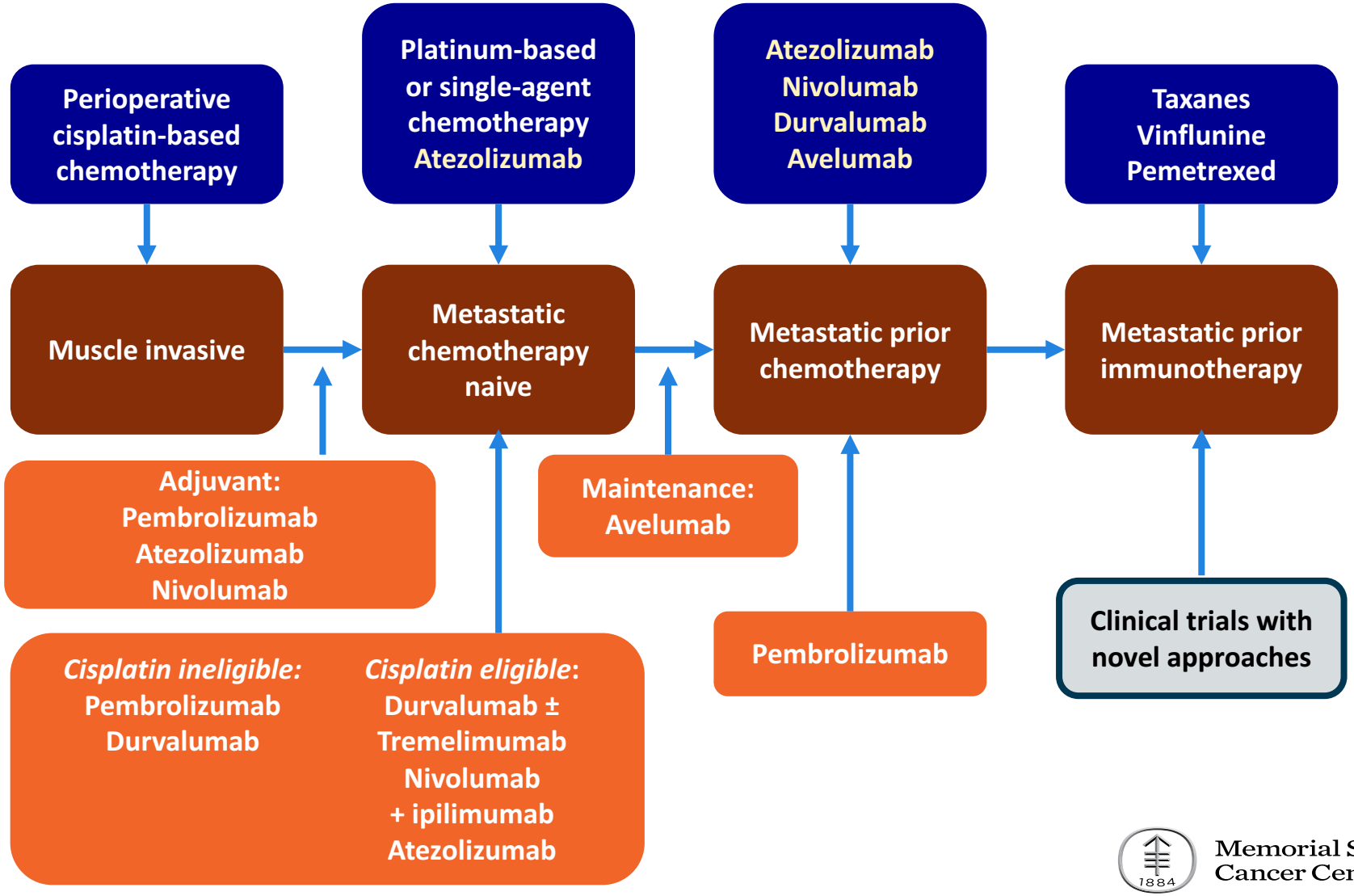
Powles T et al. *Proc ASCO* 2016;Abstract TPS4574.

Ongoing Phase III Trials of Immune Checkpoint Inhibitor Combinations in Urothelial Cancer

Trial name	Phase	N	Treatment
NCT02516241	III	1,005	• Durvalumab • Durvalumab + tremelimumab • SOC chemotherapy
CheckMate 901 (NCT03036098)	III	690	• Nivolumab + ipilimumab • SOC chemotherapy

SOC = standard of care

Current Status of Systemic Therapy for Bladder Cancer



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Immune checkpoint blockade in urothelial carcinoma

- 4 agents approved for locally advanced or metastatic patients previously treated with platinum-based chemotherapy
  - Nivolumab (anti-PD1)
  - Atezolizumab (anti-PD-L1)
  - Durvalumab (anti-PD-L1)
  - Avelumab (anti-PD-L1)
- 1 agent approved for cisplatin-ineligible first-line therapy
  - Atezolizumab (anti-PD-L1)
- Responses often occur quickly and are frequently durable
- Only a minority of patients respond, and new approaches are warranted.