Bladder Cancer in 2020

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Disclosures (A)

- Consulting/Honoraria: Astellas, AstraZeneca, Janssen, Merck, Pfizer, Roche
- Research Funding: Pfizer, Janssen
- Educational Support: Roche

- Clinical Trials (Institution): >300 trials open per year with a wide variety of industrial and cooperative sponsors

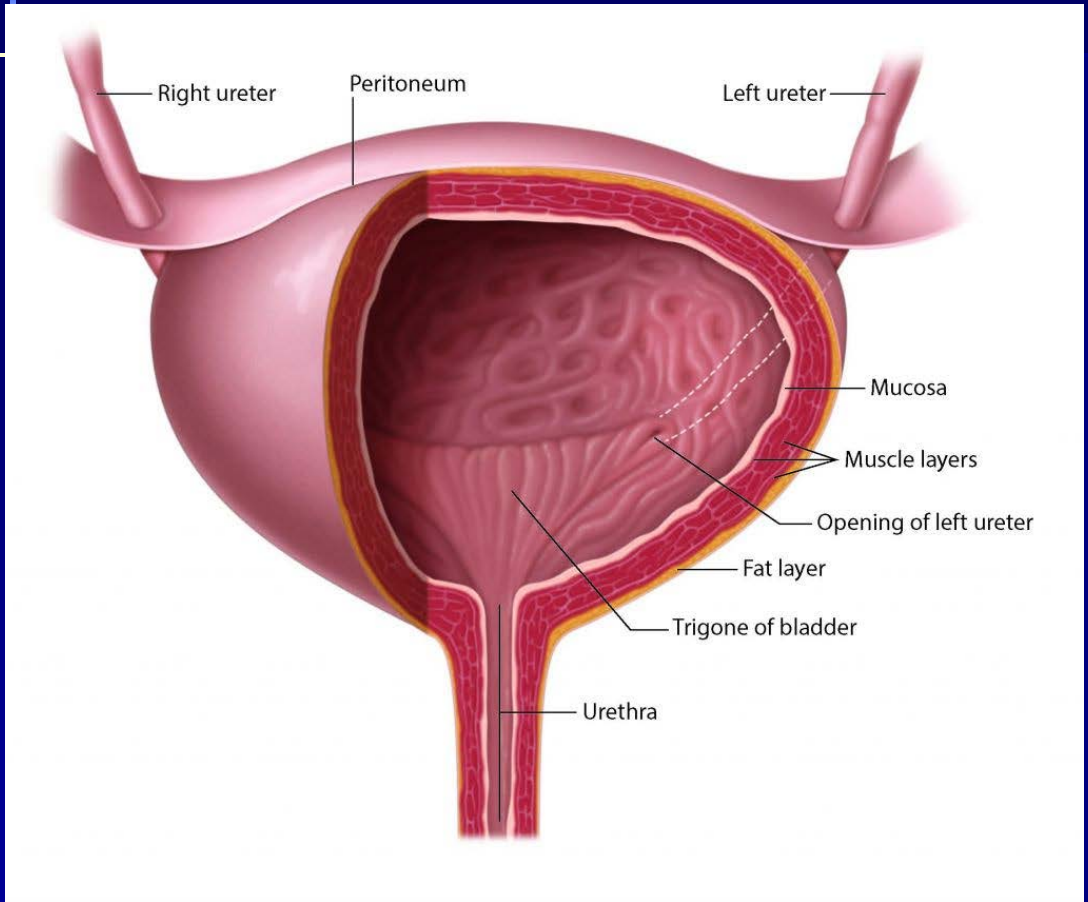
Disclosures (B)

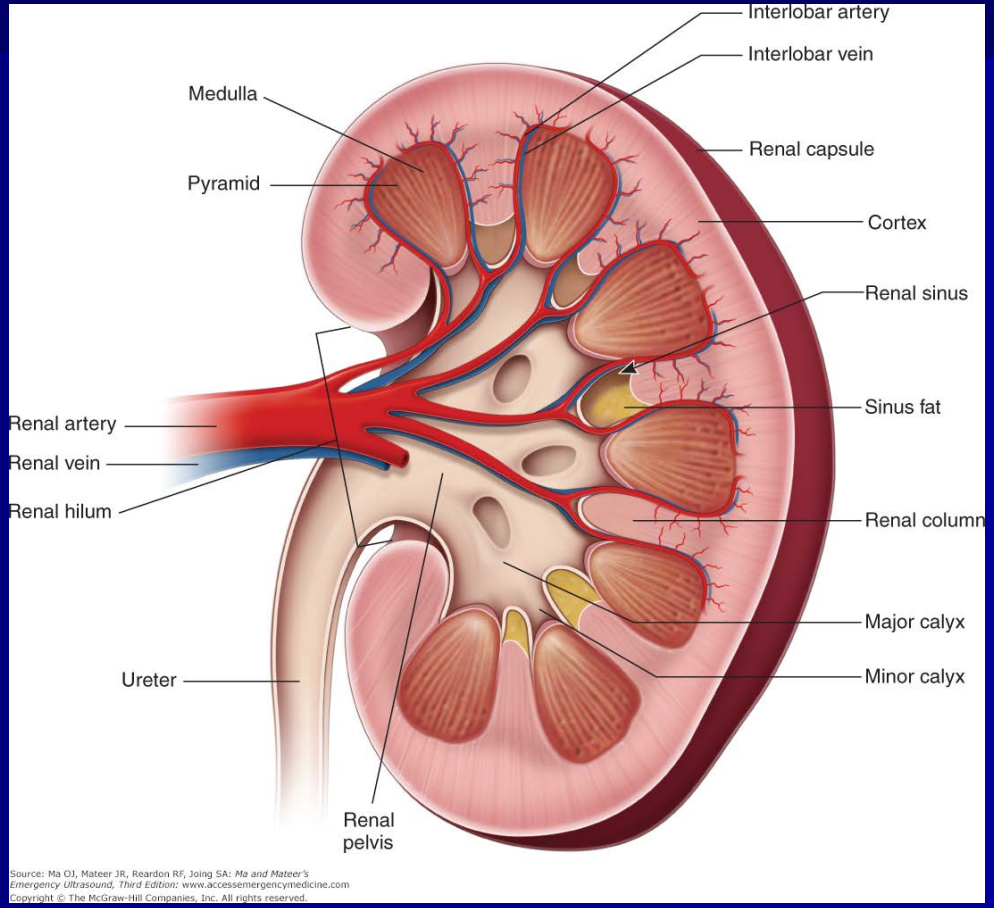
- I am not a urologist. My expertise is in the management of advanced bladder cancer, so my comments on management of localized disease are ”text-book”

Overview

- What is bladder cancer (aka Urothelial Carcinoma)?
- Basic epidemiology
- Clinical Presentation
- Diagnostic assessment
- Molecular Subtypes
- Management of:
  - Non-Muscle Invasive Bladder Cancer (NMIBC)
  - Muscle Invasive Bladder Cancer (MIBC)
  - Metastatic Bladder Cancer (mUC)

Anatomy of the Urinary Tract





What is urothelial cancer?

- Cancer arising from the transitional cell epithelium (lining) of the urinary tract structures:
  - Renal pelvis
  - Ureter
  - Bladder
  - Urethra

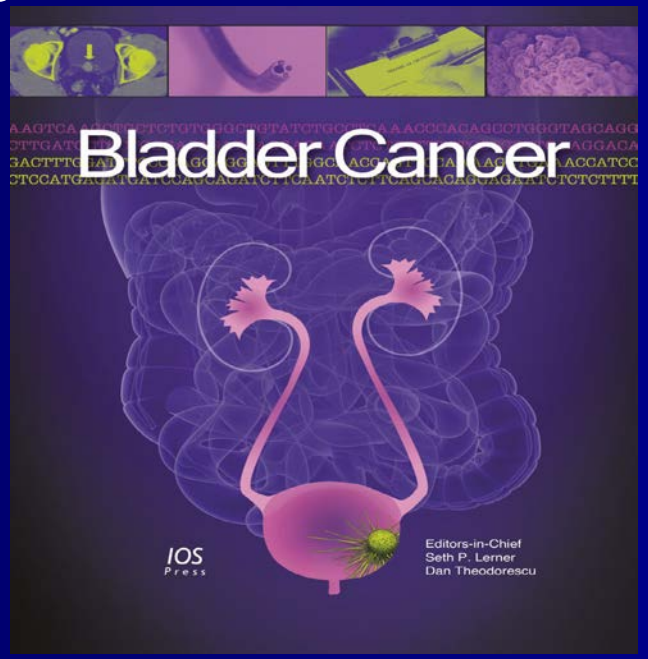
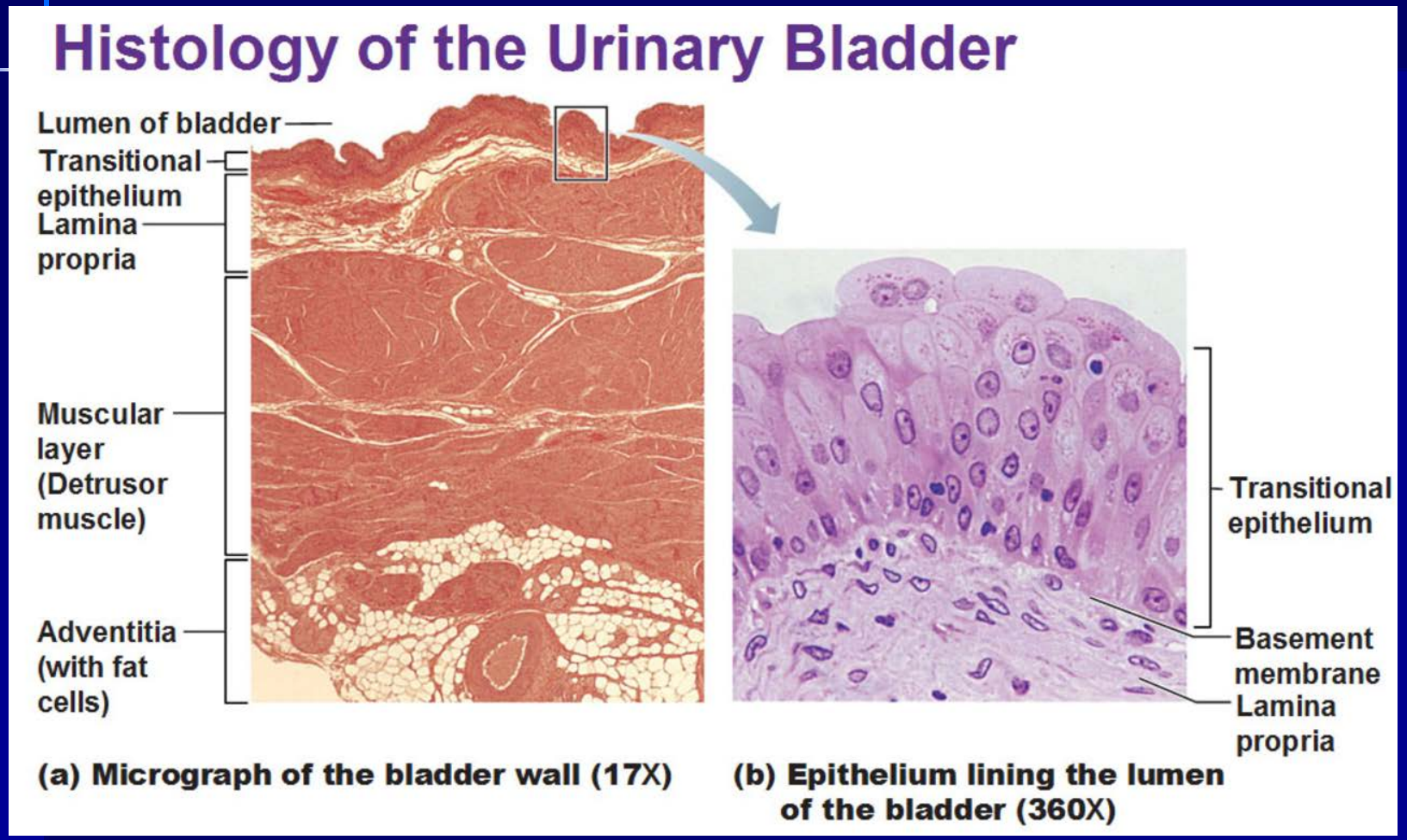


Image: www.bladdercancerjournal.com

Types of bladder cancer



Types of bladder cancer:

- **Transitional cell carcinoma (TCC/UC)**
- **Squamous cell carcinoma**
- **Small-cell carcinoma (rare)**
- **Adenocarcinoma (very rare)**
- **Sarcoma (very rare)**

A little bit about epidemiology

- Men – median age at diagnosis = 69
- Women – median age at dx = 71
- Male:female nearly 2:1
- 2019 – CDN 11,800 new cases – 2,500 will die of the disease
  - Male #4 cause, #7 death
  - Female #11 cause, #11 death
- Majority of cases occur in developing regions of world (smoking/shisto/occupational)

Worldwide Bladder Cancer Statistics*				
	Global[1]	EU[1]	Asia[1]	US[2]
New Cases, n	**429,793**	**124,118**	**148,568**	**76,960**
Deaths, n	**165,084**	**40,635**	**69,294**	**16,000**

2012 data

Risk Factors

- Smoking 35-50% of cases
  - Second hand smoke increases risk in women (1.5-2X)
- Aromatic amines:
  - 2-naphthylamine, benzidine, 4-aminobiphenyl, 4-nitrobiphenyl, and 2-amino-1-naphthol
- Occupations:
  - metal workers, painters, rubber industry, leather workers, textile workers, firefighters, miners cement workers, manufacturing of carpets, paints, plastics...
- Arsenic (e.g. Chile & Taiwan)

Risk Factors (non-TCC)

- Chronic cystitis
- Spinal cord injury – catheters
- Calculi
- Schistosomiasis

Staging of Bladder Cancer (abridged)

- TaNoninvasive papillary carcinoma
- TisCarcinoma in situ: "flat tumor“
- T1 Tumor invades subepithelial connective tissue
- ***T2 Tumor invades muscle***
- T2a Tumor invades superficial muscle (inner half)
- T2b Tumor invades deep muscle (outer half)
- T3 Tumor invades perivesical tissue
- T4 Tumor invades any of the following: prostate, uterus, vagina, pelvic wall, abdominal wall
- T4a Tumor invades prostate, uterus, vagina
- T4b Tumor invades pelvic wall, abdominal wall
- **Regional lymph nodes (N)**
  - Regional lymph nodes are those within the true pelvis; all others are distant lymph nodes.
- **Distant metastasis (M)**
- M0 No distant metastasis
- *M1* Distant metastasis (a-node, b-visceral)

Incidence, Recurrence and Progression by Stage

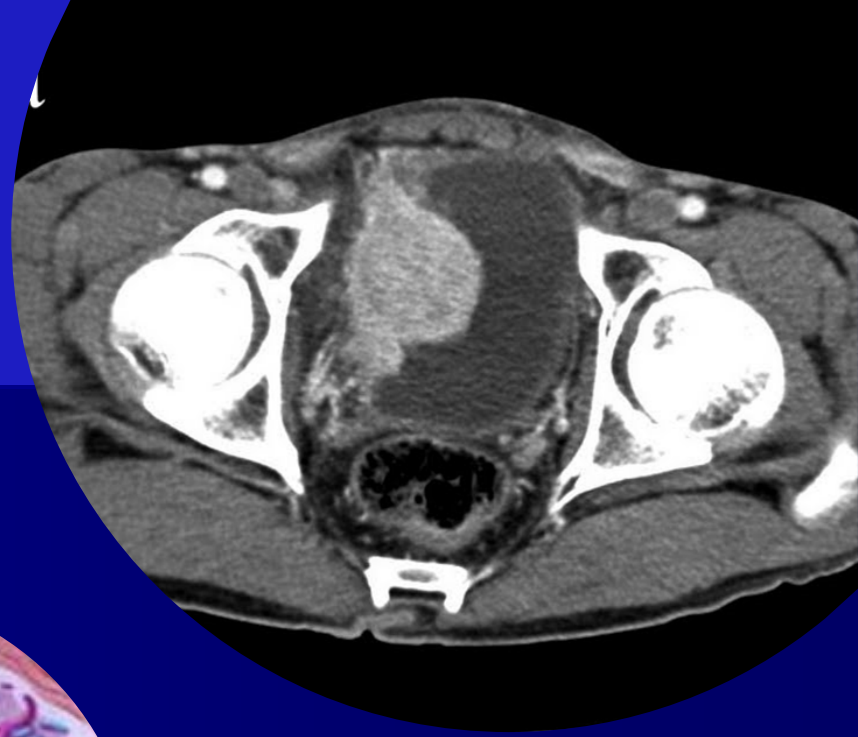
Classification	Incidence/Stage	5-Year Survival
NMIBC	~ 70% of cases at diagnosis	86-98%
- 31-78% will recur - 10-20% will progress **MIBC**	**~ 25%** of cases at diagnosis	50% (30-63%)
- 20-70% will recur - 50% will progress mUC	~ 4% of cases at diagnosis	<10%

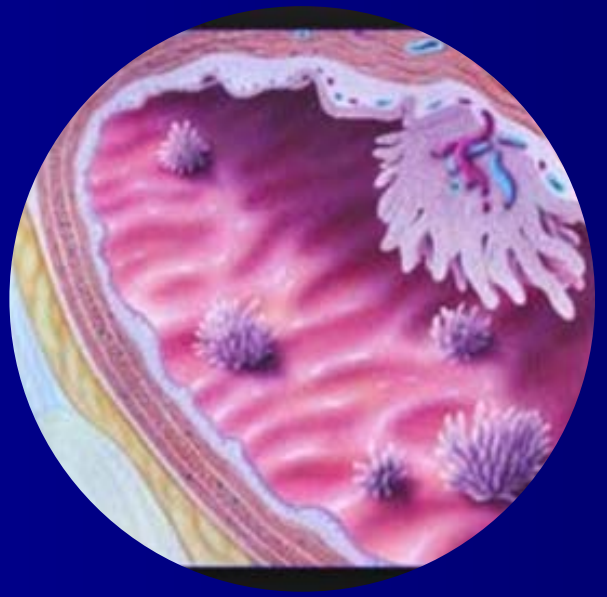
NMIBC: Non-Muscle Invasive Bladder Cancer
MIBC: Muscle Invasive Bladder Cancer
mUC: Metastatic Urothelial Carcinoma

Urothelial Carcinoma

Diagnostic assessment

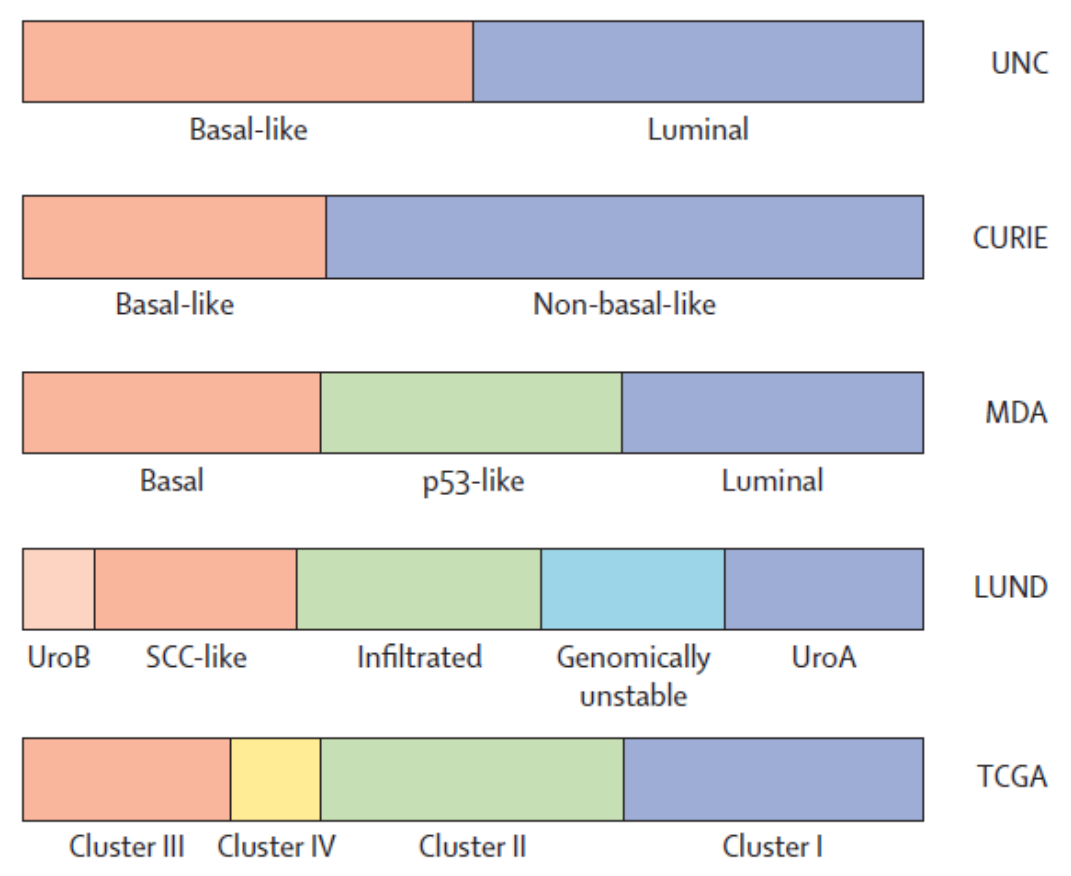
- Symptoms
  - Blood in the urine
  - Urinary frequency
  - Painful urination
  - Lower back pain
- Routine evaluations
  - History and physical exam
  - Urinalysis
- Further evaluations:
  - Urine cytology
  - Cystoscopy
  - CT urography





Molecular Subtype Classification

Bladder cancer



TCGA=The Cancer Genome Atlas. **UNC**=University of North California.
CURIE=Institut Curie. **SCC**=squamous cell carcinoma.
LUND=Lund University. **UroB**=Orobasal B

- Several institutions have established subtypes based upon gene expression profiling. This is becoming relevant for management decisions.
- E.g.
  - Basal subtypes often have squamous differentiation and are more often metastatic at diagnosis, respond to chemo
  - Luminal subtype are enriched for papillary features and more often have FGFR3 mutations (we have FGFR3 inhibitors now)
- The color bars indicate the subtype classification made by each institution.
- This is not yet a standard of care approach.

Non-Muscle-Invasive Bladder Cancer (NMIBC)

Risk stratification and treatment

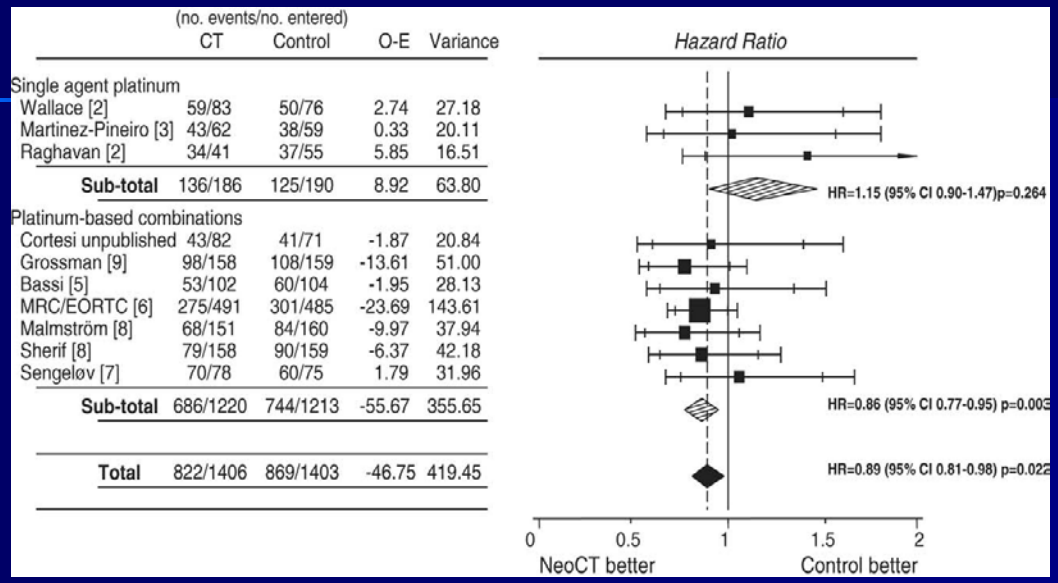
- NMIBC can be classified as low risk, intermediate risk, or high risk according to risk of recurrence and progression, and risk categories have been used to guide management.[6]

Risk	Risk Subtype	Recommend Treatment
Low-risk NMIBC (low-grade Ta tumor)		Single immediate postoperative instillation of intravesical chemotherapeutic drug
Intermediate-risk NMIBC (multifocal or multirecurrent low-grade Ta tumors)	None of the following factors: multiple tumors, tumor ≥3 cm, >1 recurrence per year, recurrence within 1 year after transurethral resection	Same as treatment for low-risk NMIBC
	One or two of the following factors: multiple tumors, tumor ≥3 cm, >1 recurrence per year after transurethral resection	Single immediate postoperative instillation of intravesical chemotherapeutic drug; induction plus maintenance treatment (1 year) with either an intravesical chemotherapeutic drug or BCG
	Three or more of the following factors: multiple tumors, tumour ≥3 cm, >1 recurrence per year, recurrence within 1 year after transurethral resection	Same as treatment for high-risk NMIBC
High-risk NMIBC (T1 [invasive into lamina propria], carcinoma in situ, or any high-grade tumor)		Restaging transurethral resection in 4–6 weeks; induction plus maintenance treatment (3 years) with BCG; consider early cystectomy if high-grade T1 tumor with any of the following: multiple tumors or large tumor, micropapillary histological variant, concomitant carcinoma in situ in bladder or prostatic urethra, or presence of lymphovascular invasion

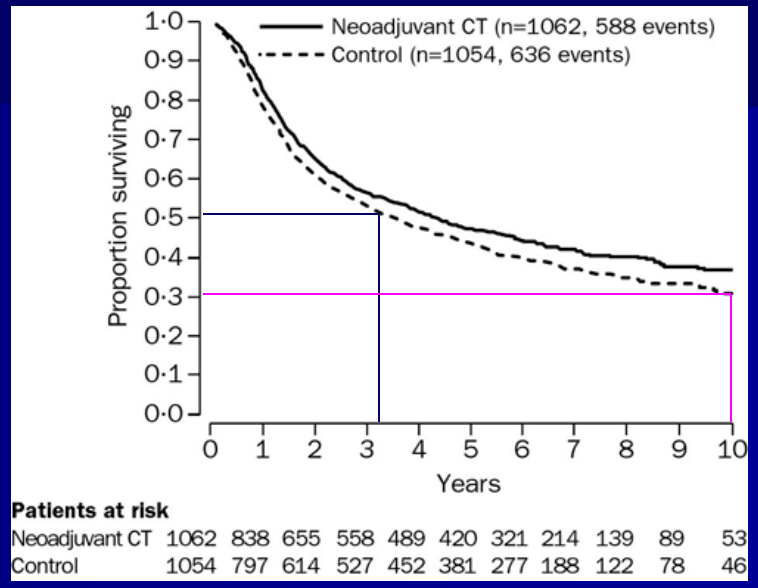
Muscle Invasive Bladder Cancer

- T2 to T4a disease (N0)
  - Invasion through the muscle layer of the bladder or deeper into perivesical tissues
    - Can no longer be managed by local means
    - Neoadjuvant chemotherapy
    - Cystectomy is the mainstay of local therapy
    - Trimodality therapy (TURBT plus chemo/radiotherapy) for bladder sparing approach is also an option in selected patients.

Bladder Cancer – Neoadjuvant Chemotherapy
Metaanalysis of 11 trials (~3000 pts)



	(no. events/no. entered) CT	Control	O-E	Variance
Single agent platinum				
Wallace [2]	59/83	50/76	2.74	27.18
Martinez-Pineiro [3]	43/62	38/59	0.33	20.11
Raghavan [2]	34/41	37/55	5.85	16.51
Sub-total	136/186	125/190	8.92	63.80
Platinum-based combinations				
Cortesi unpublished	43/82	41/71	-1.87	20.84
Grossman [9]	98/158	108/159	-13.61	51.00
Bassi [5]	53/102	60/104	-1.95	28.13
MRC/EORTC [6]	275/491	301/485	-23.69	143.61
Malmström [8]	68/151	84/160	-9.97	37.94
Sherif [8]	79/158	90/159	-6.37	42.18
Sengeløv [7]	70/78	60/75	1.79	31.96
Sub-total	686/1220	744/1213	-55.67	355.65
Total	822/1406	869/1403	-46.75	419.45



Benefit for neoadjuvant cisplatin-based combination chemotherapy

13% reduction in risk of death; 5-6.5% absolute benefit at 5 years; HR 0.87

ABC Metaanalysis Colloboration Lancet 2003
Winquist et al. J Urol 2004

Locally Advanced Bladder Cancer

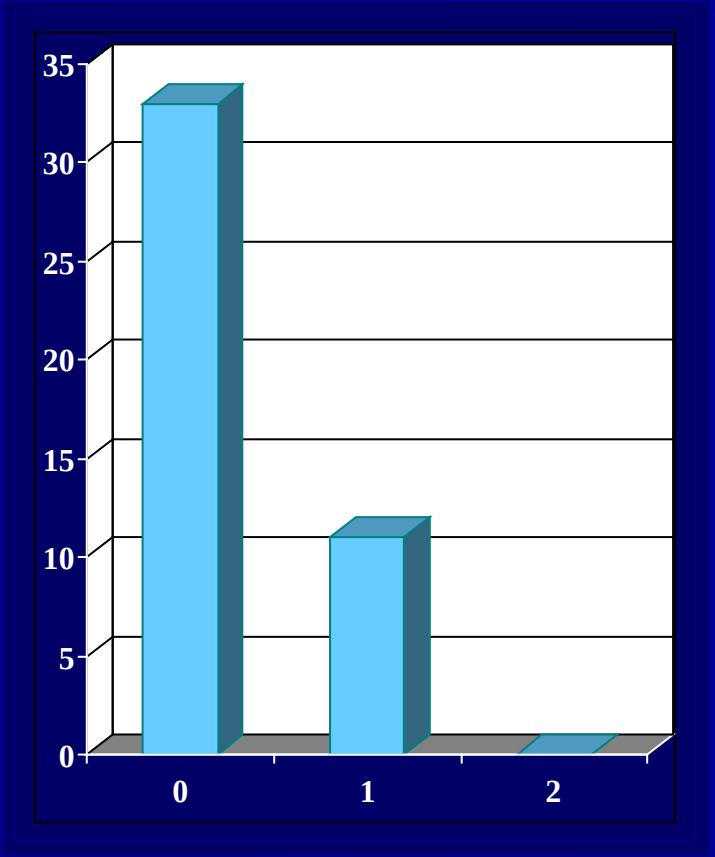
- T4b
- Multi disciplinary approach and individualized therapy
- Management includes chemotherapy, +/- radiation, +/- surgery
- Goal: decrease eventual morbidity of pelvic progression

Metastatic Disease: What is my prognosis, Doc?

Risk factors

Risk score	KPS	Visceral mets.	Median OS (mo)	5-y-OS	10-y-OS
0	≥ 80	No	33.0	33%	24%
1	≥80 < 80	Yes No	13.4	11%	6%
2	< 80	Yes	9.2	0	0

5-y-OS by No. RF



Bajorin et al. JCO 1998

When would we use chemotherapy for Bladder Cancer?

	Neo-Adjuvant	Adjuvant	Palliative
Early	No	No	N/A
Muscle invasive	Yes	Maybe	N/A
Metastatic	N/A	N/A	Yes

Metastatic Bladder Cancer (mUC)

- Untreated/Best Supportive Care:
  - Median OS is ~6-8 mo
- With Chemo:
  - median OS is still only ~12-14 mo!
- Challenges:
  - Elderly patients with comorbidities
  - Frequent renal impairment (age related, hydronephrosis)
  - Patients are often unwell due to the cancer

Treatment options for mUC are rapidly evolving!

- Current standards
- First Line:
  - Chemotherapy:
    - Platinum based (cisplatin preferable over carboplatin), most centers use Gemcitabine/Cisplatin
- Second Line:
    - Immunotherapy (current standard is pembrolizumab)
- Third line:
    - No established standard. Fit patients may get chemo (taxane) but no survival benefit
    - BUT: Enfortumab Vedotin, FGFR targeted therapies (e.g. erdafitinib), and combinations will likely soon be available.

Cisplatin-based chemo for mUC

Methotrexate/Vinblastine/Adriamycin/Cisplatin

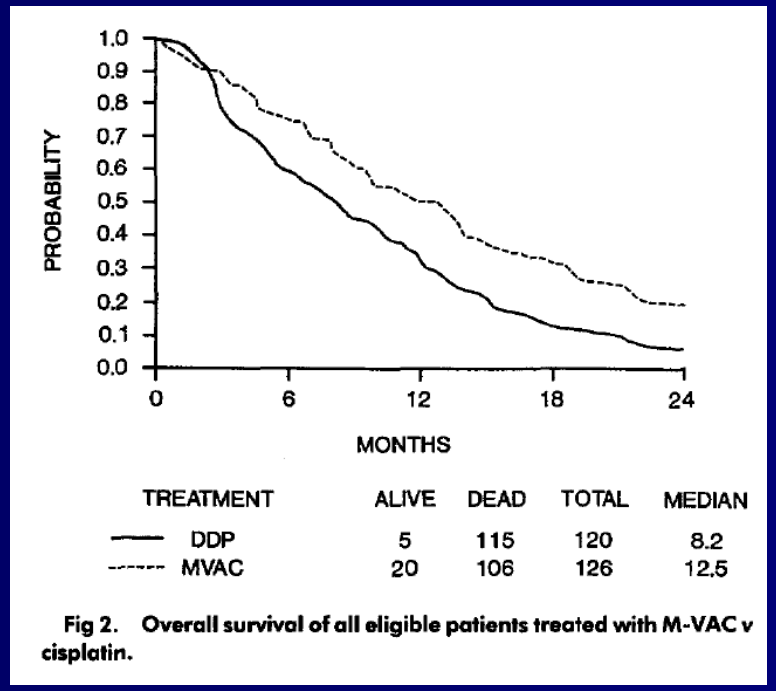
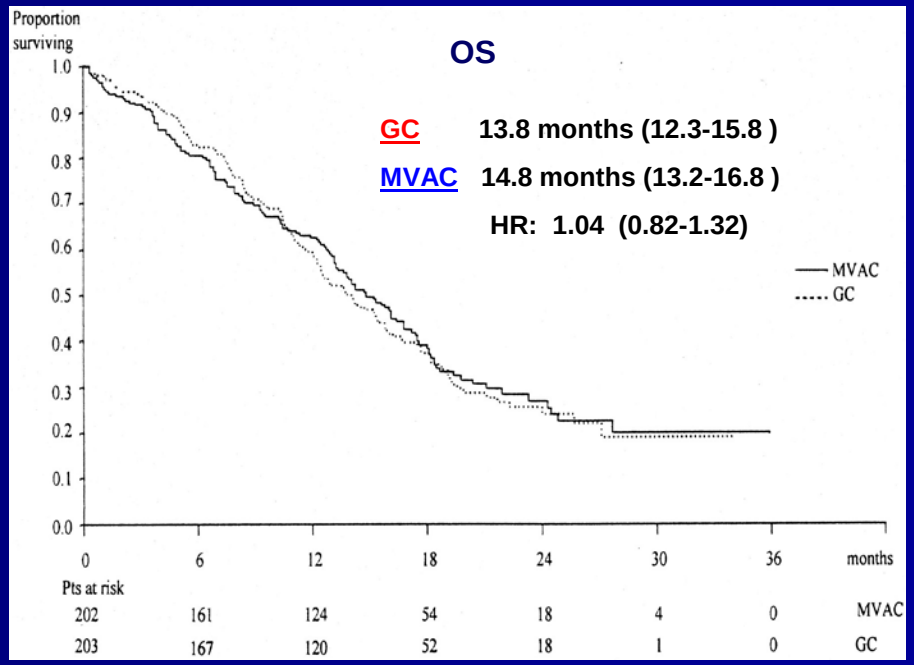


Fig 2. Overall survival of all eligible patients treated with M-VAC v cisplatin.

- 50% with visceral disease
- Overall response rate: 39%
- Complete response rate: 13%

Loehrer, JCO 1992

Gemcitabine/Cisplatin



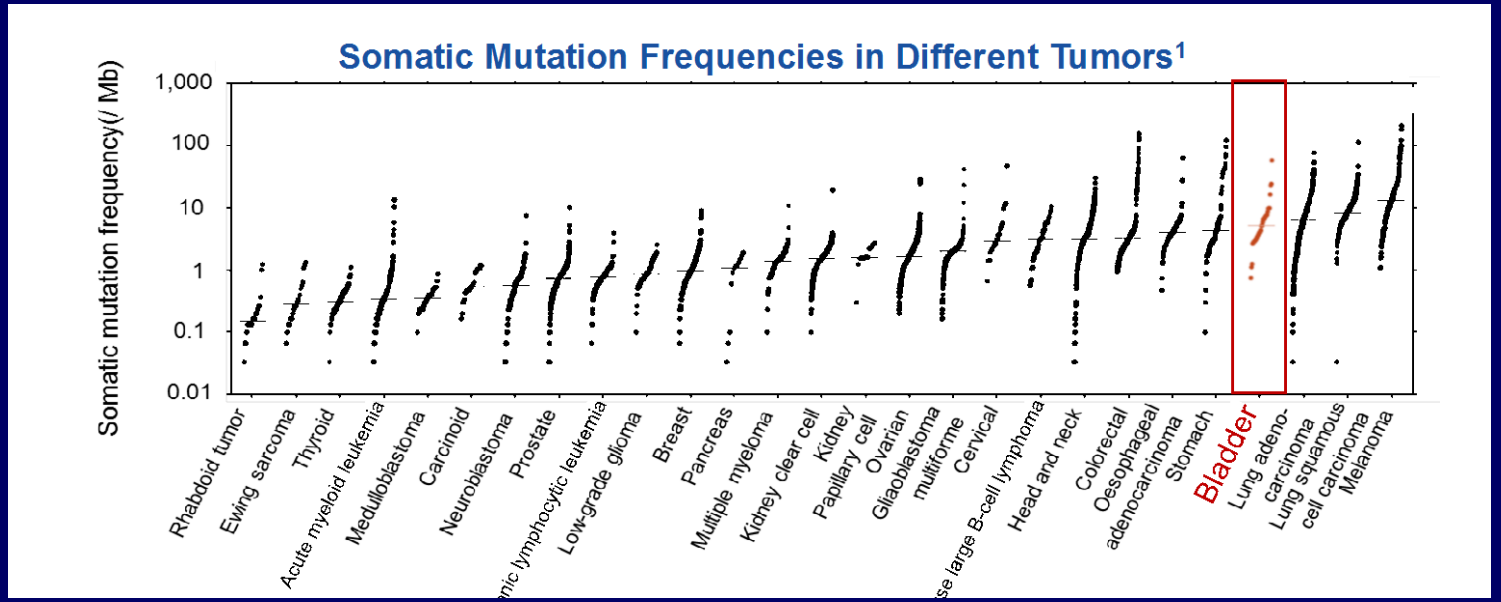
- 50% with visceral disease
- Overall response rate: 49.4% vs. 45.7%
- Complete response rate: 12.2% vs. 11.9%

Van der Maase JCO 2000

What are the toxicities of Cisplatin and Gemcitabine?

	World Health Organization Toxicity Grades			
	GC (% of patients)		MVAC (% of patients)	
Toxicity	3	4	3	4
Hematologic				
Anemia	23.5	3.5	15.5	2.1
Thrombocytopenia	28.5	28.5	7.7	12.9
Neutropenia	41.2	29.9	17.1	65.2
Nonhematologic				
Mucositis	1.0	0	17.7	4.2
Nausea/vomiting	22.0	0	19.2	1.6
Alopecia	10.5	0	54.2	1.0
Infection	2.0	0.5	9.9	5.2
Diarrhea	3.0	0	7.8	0.5
Pulmonary	2.5	0.5	2.6	3.1
Hematuria	4.5	0	2.3	0
Constipation	1.5	0	2.6	0.5
Hemorrhage	2.0	0	2.1	0
State of consciousness	0.5	0	3.1	0.5
Fever	0	0	3.1	0

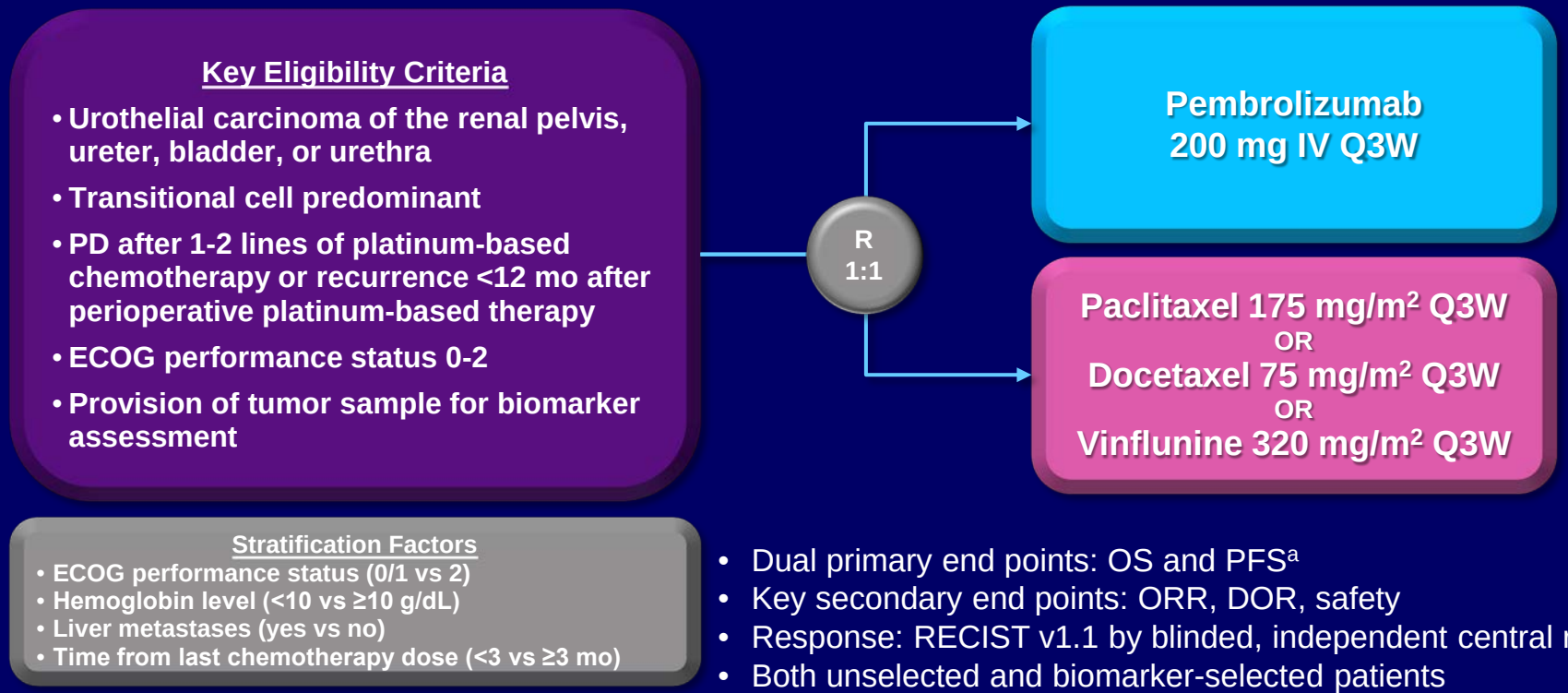
Immunotherapy - The Wave of Change



- High mutation burden = more antigens and immunogenicity

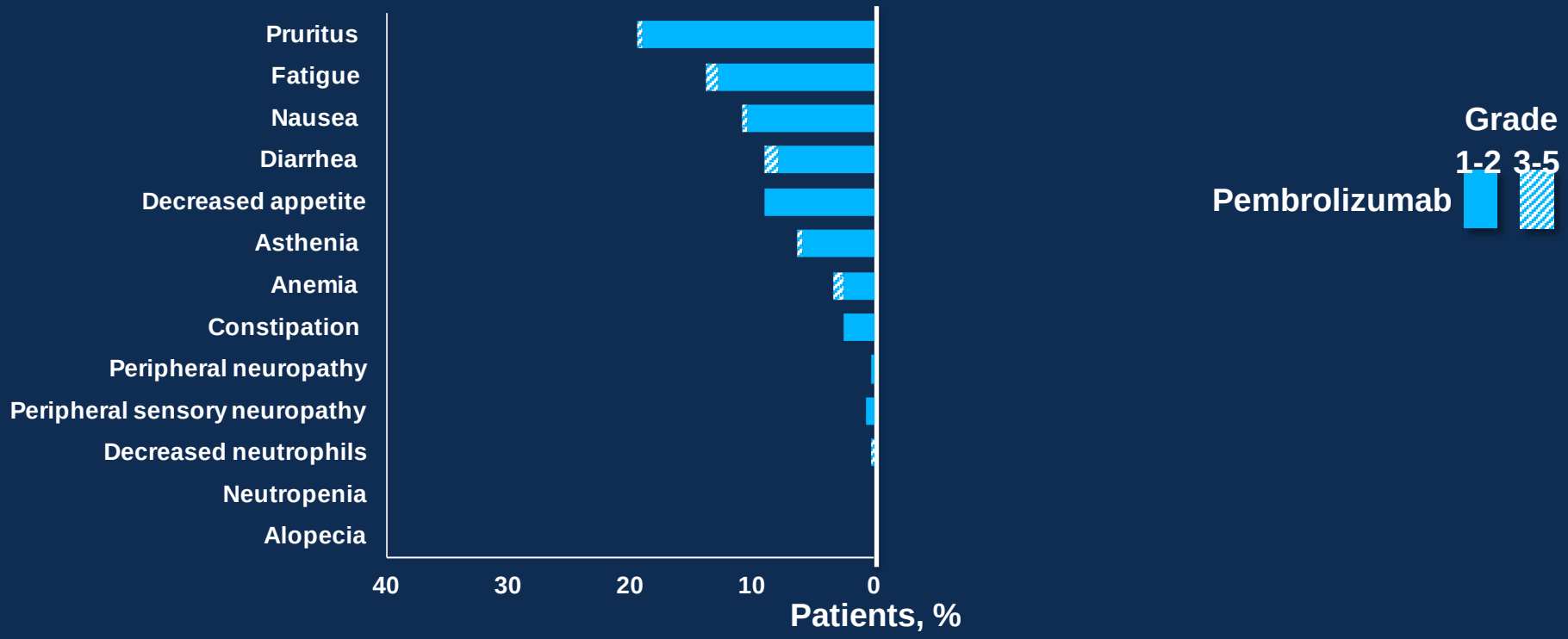
- Alexandrov Nature 2013

Pembrolizumab: KEYNOTE-045

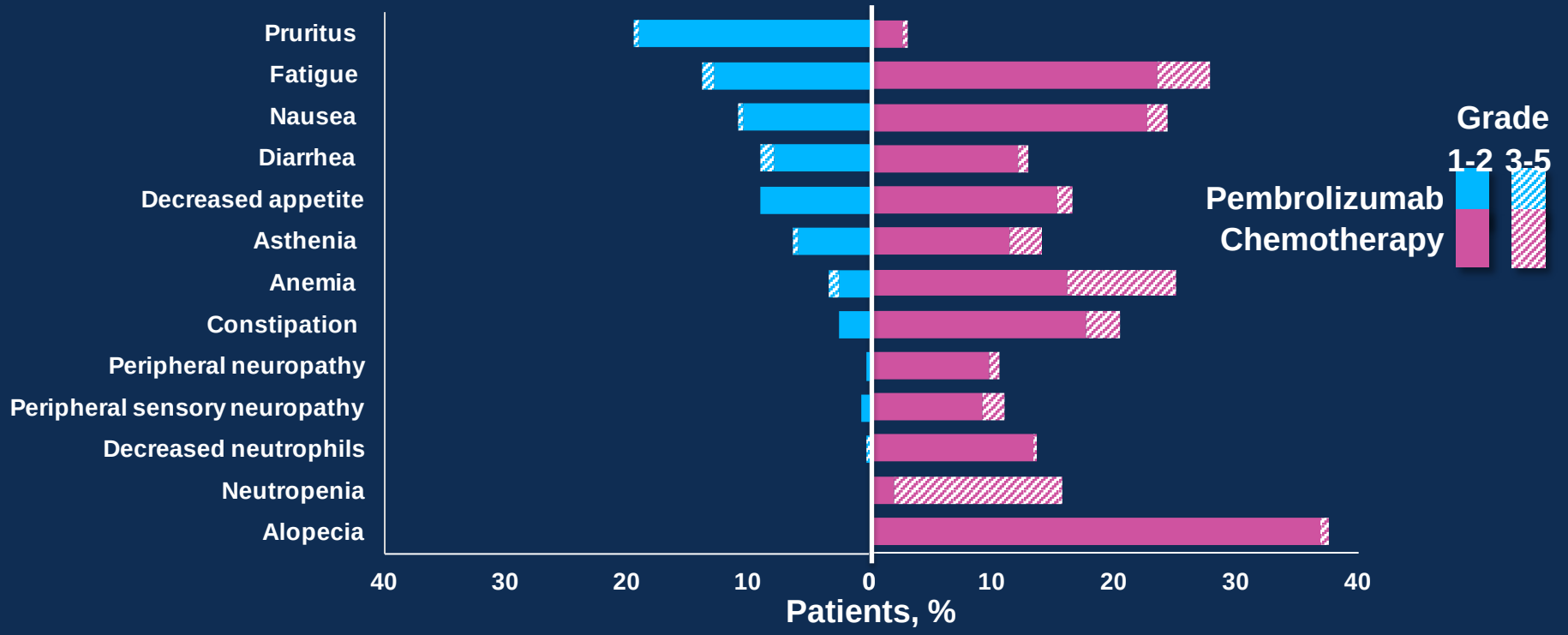


- Dual primary end points: OS and PFS[a]
- Key secondary end points: ORR, DOR, safety
- Response: RECIST v1.1 by blinded, independent central review
- Both unselected and biomarker-selected patients

Treatment-Related AEs Occurring in ≥10% Patients[a]

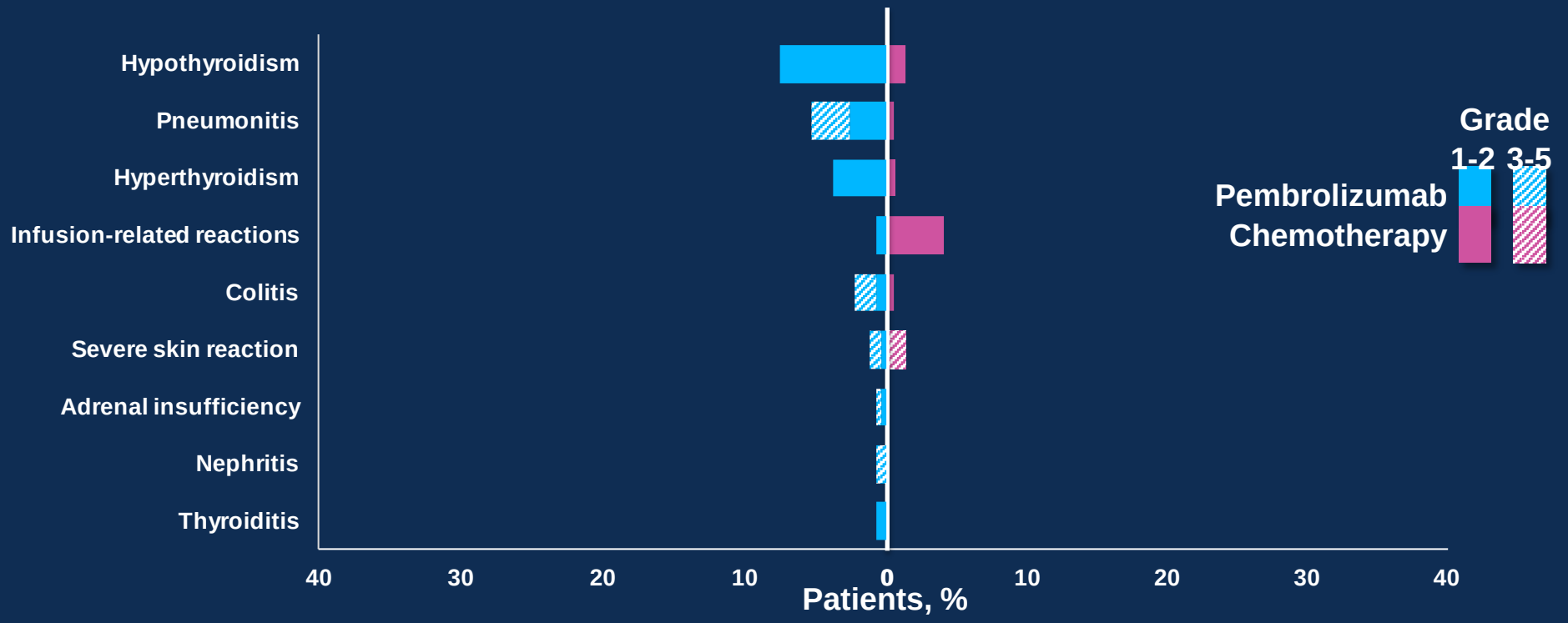


Treatment-Related AEs Occurring in ≥10% Patients[a]



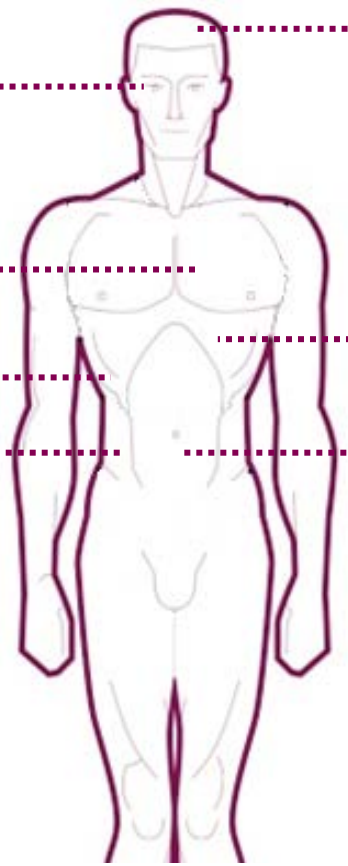
[a]Of patients in either treatment arm.
7.5% febrile neutropenia in the chemotherapy arm.
Data cutoff date: January 18, 2017.

AEs of Interest[a] Occurring in ≥2 Patients[b]



[a]Based on a list of terms specified by the sponsor and included regardless of attribution to study treatment or immune relatedness by the investigator; related terms included. [b]In either treatment arm.
Data cutoff date: January 18, 2017.

Most common imAEs in anti-PD-L1 / PD-1 studies in UC[3-6]



Eye
- Uveitis
- Conjunctivitis
- Scleritis, episcleritis
- Blepharitis
- Retinitis

Cardiovascular
- Myocarditis
- Pericarditis
- Vasculitis

Hepatic
- Hepatitis

Renal
- Nephritis
- Renal failure

Skin
- Rash
- Pruritus
- Psoriasis
- Vitiligo
- DRESS
- Stevens-Johnson syndrome
- Toxic epidermal necrosis

Musculoskeletal
- Arthritis
- Dermatomyositis

Neurological
- Encephalitis
- Guillain-Barré
- Myelopathy
- Meningitis
- Myasthenia gravis
- Neuropathy

Endocrine
- Hyperthyroidism
- Hypothyroidism
- Hypophysitis
- Adrenal insufficiency
- Diabetes

Respiratory
- Pneumonitis
- Interstitial lung disease
- Pleuritis
- Sarcoid-like granulomatosis

Gastrointestinal
- Colitis
- Ileitis
- Pancreatitis
- Gastritis

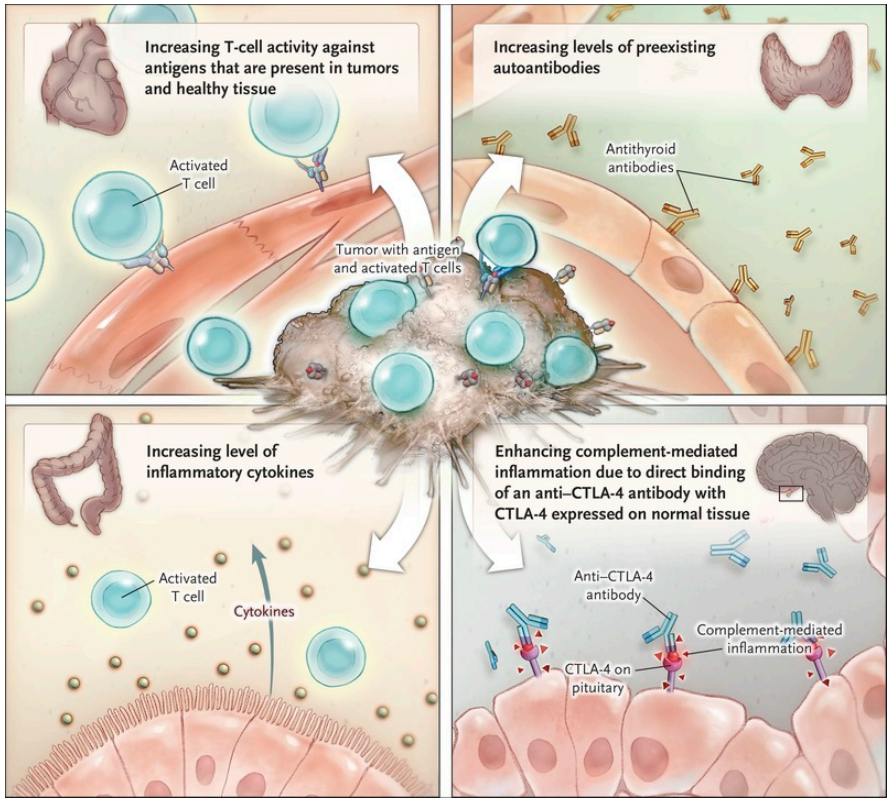
Blood
- Haemolytic anaemia
- Thrombocytopenia
- Neutropenia
- Haemophilia

DRESS, drug reaction with eosinophilia and systemic symptoms; imAEs, immune-mediated adverse events; PD-1, programmed cell death-1; PD-L1, programmed cell death ligand-1; UC, urothelial carcinoma

1. Michot JM, et al. *Eur J Cancer* 2016;54:139–148. 2. Champiat S, et al. *Ann Oncol* 2016;27:559–574. 3. Rosenberg JE, et al. *Lancet* 2016;387:1909–1920. 4. Balar AV, et al. *Lancet Oncol* 2017;18:1483–1492. 5. Powles T, et al. *JAMA Oncol* 2017;3:e172411. 6. Sharma P, et al. *Lancet Oncol* 2017;18:312–322.

Resources for understanding IO toxicities

Postow et al. NEJM 2018; 378:158-168



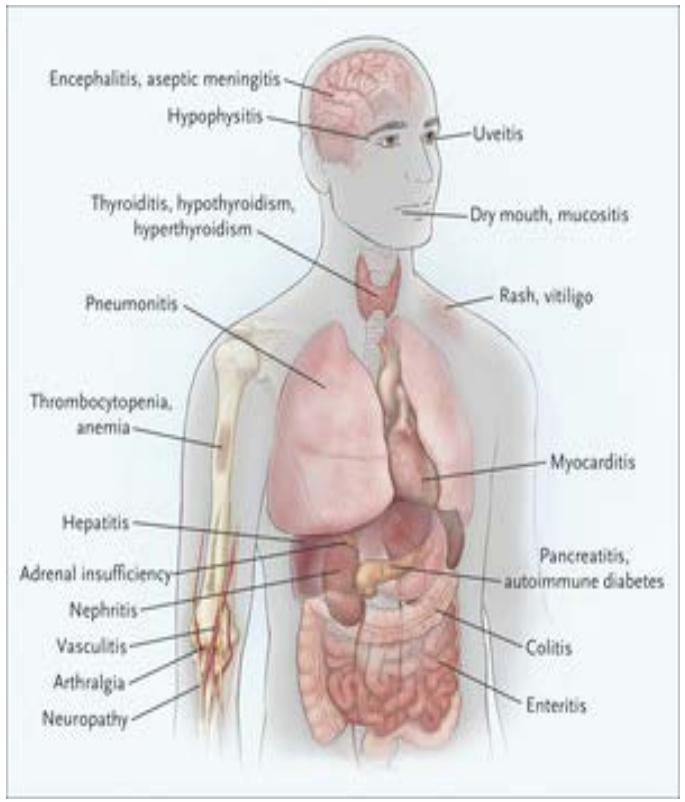
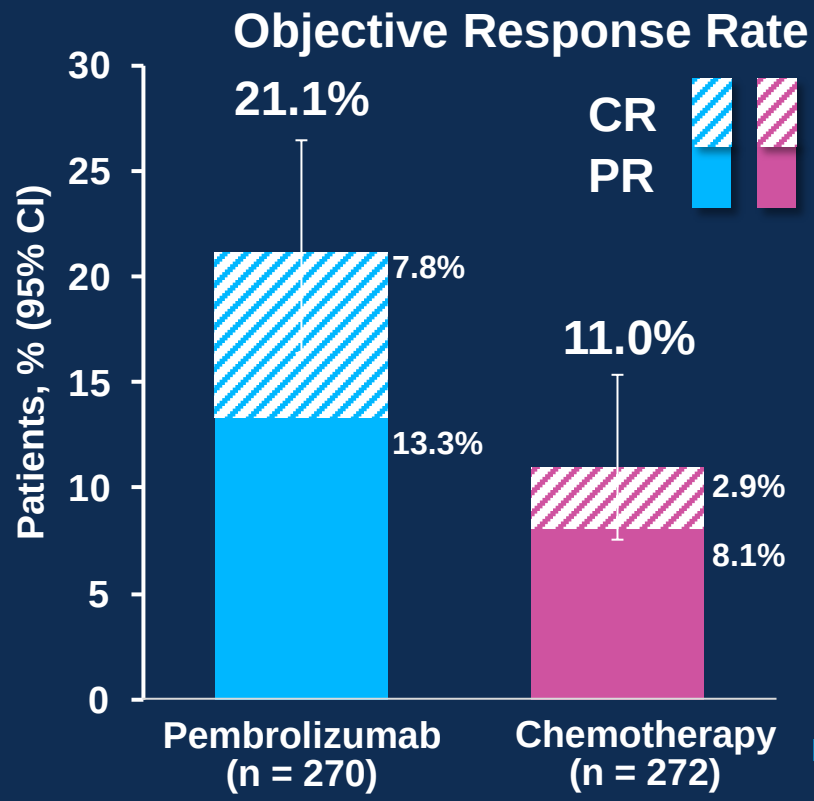
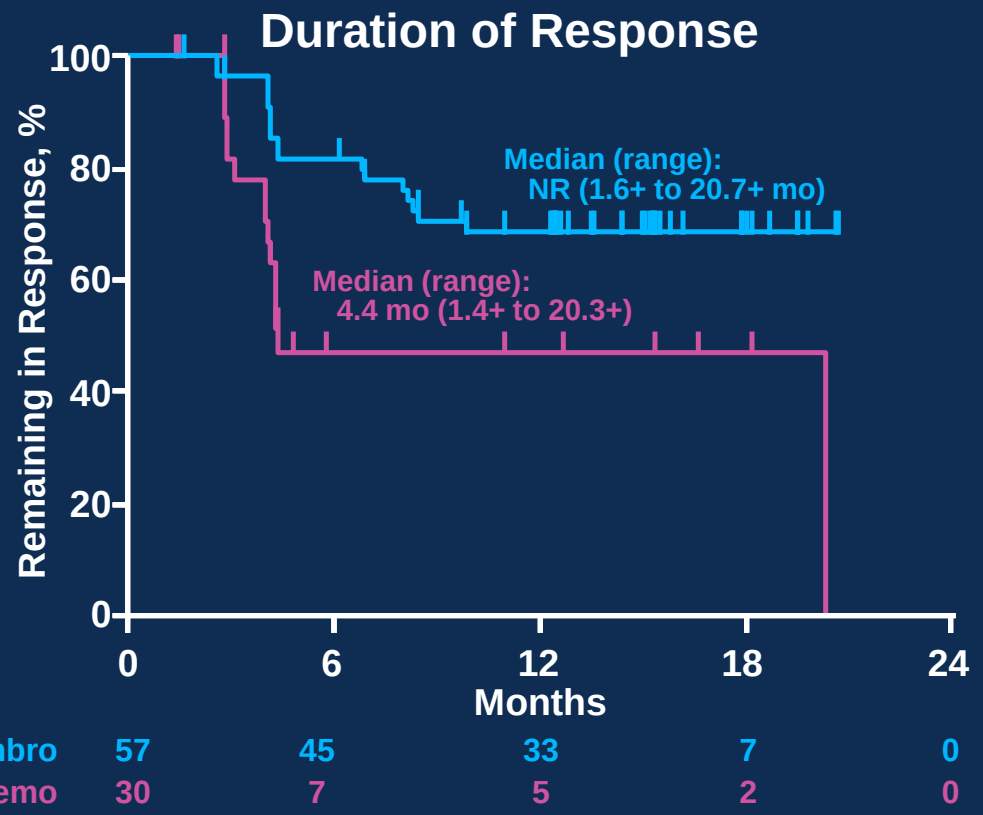


Table 2. Ten Questions Relevant to the Management of Immune-Related Adverse Events in Patients Treated with Immune Checkpoint Blockade.

Questions about Immune-Related Adverse Events	Comments
Why do they occur?	The precise pathophysiology is unknown. Translational studies in patients with immune-related adverse events have shown that T-cell, antibody, and cytokine responses may be involved.
How are they generally treated?	No prospective trials have defined the best treatment approaches, and recommendations are based on consensus opinion. Immunosuppression is used to reduce the excessive state of temporary inflammation. Glucocorticoids are usually the first-line immunosuppressive agent. Additional immunosuppressive agents can be used if glucocorticoids are not initially effective.
When do they occur?	Immune-related adverse events usually start within the first few weeks to months after treatment but can occur anytime, even after treatment discontinuation. Dermatologic adverse events are usually the first to appear.
Why do they occur in some patients and not others?	The reason for the occurrence of immune-related adverse events only in certain patients is unknown. Some studies are investigating whether such factors as germline genetics and the composition of host microbiota are related to risk.
Are they associated with the efficacy of immune checkpoint blockade?	Conflicting data are available regarding whether the occurrence of immune-related adverse events is associated with improved treatment efficacy. The development of immune-related adverse events is not required for treatment benefit. Specific adverse events (e.g., vitiligo) may be more clearly associated with treatment efficacy.
Does immunosuppression to treat such adverse events reduce the antitumor efficacy of treatment?	Clinical outcomes are similar in patients who require immunosuppression to treat immune-related adverse events and in those who do not require such treatment. Beneficial responses can persist despite the use of immunosuppression to treat immune-related adverse events.
Are there unintended effects of immunosuppression to treat adverse events?	Side effects of glucocorticoid use (e.g., hyperglycemia, edema, anxiety, and iatrogenic adrenal insufficiency) can occur. Immunosuppression is a risk factor for subsequent opportunistic infections.
Is it safe to restart treatment after a major adverse event?	Retrospective studies have shown that immune-related adverse events associated with one class of agent (e.g., anti–CTLA-4) may not necessarily recur during subsequent treatment with another agent (e.g., anti–PD-1). The safety of retreatment probably depends on the severity of the initial immune-related adverse event.
Is it necessary to restart treatment after resolution of an adverse event?	Retrospective data suggest that patients who have had a favorable response to immune checkpoint blockade and then discontinue treatment because of immune-related adverse events generally maintain responses. Prospective data are needed to address whether restarting immunotherapy is necessary.
Is it safe to treat patients at potentially increased risk for such adverse events?	Patients at increased risk for immune-related adverse events (e.g., preexisting autoimmune disease) may still benefit from immune checkpoint blockade. Age alone should not be used to exclude patients from treatment, since benefit appears to be similar regardless of age.

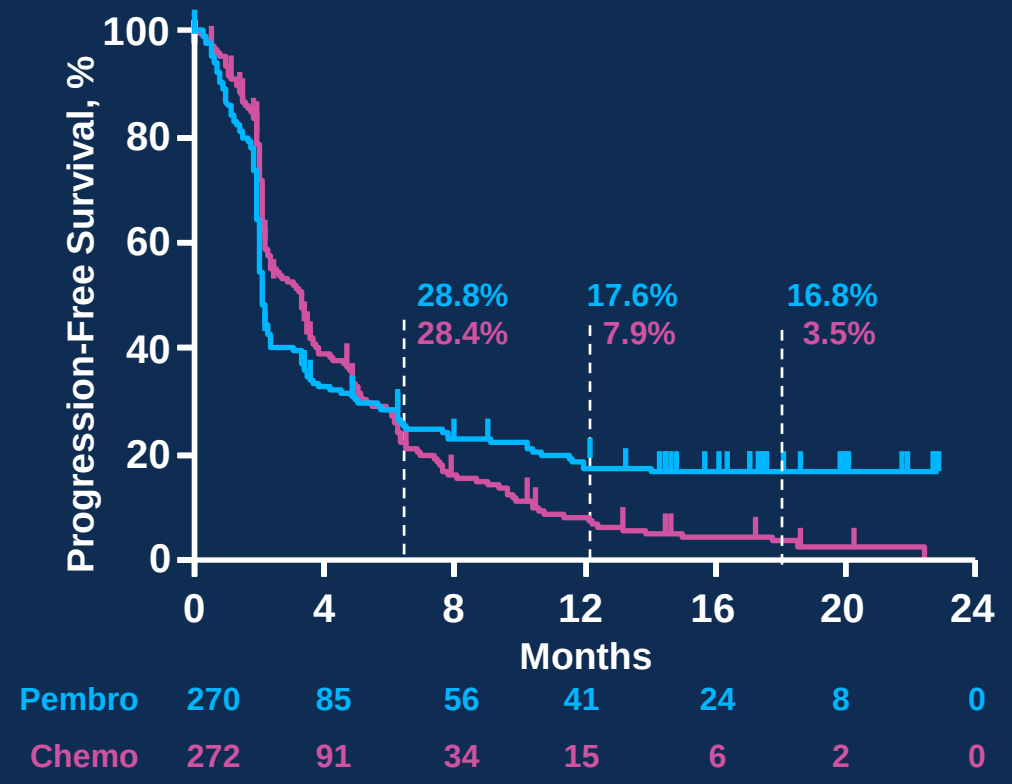
Objective Response and Response Duration





Assessed per RECIST v1.1 by blinded, independent central review.
Data cutoff date: January 18, 2017.

Progression-Free Survival: Total

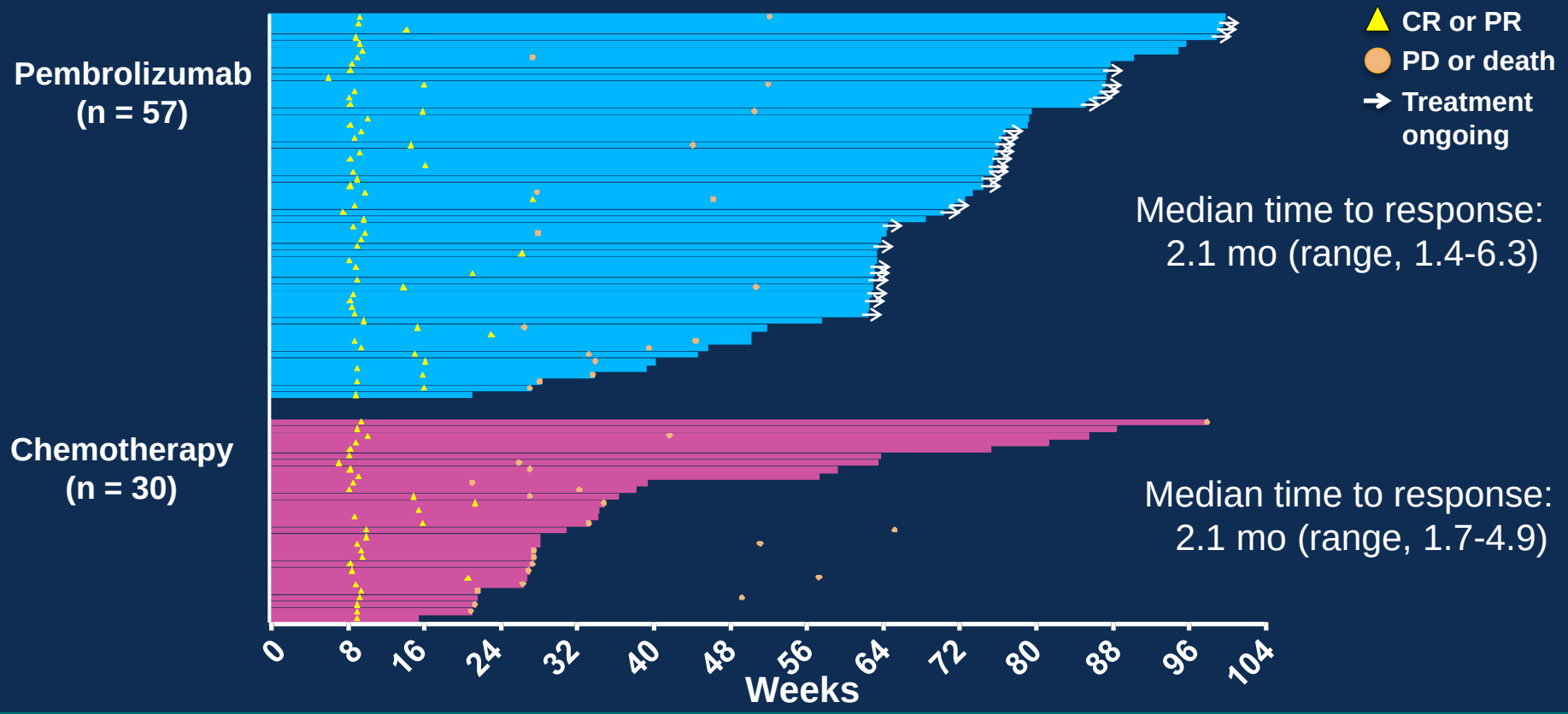


	Events, n	HR (95% CI)	*P*
Pembro	270	0.96 (0.79-1.16)	0.32
Chemo	272		

Median (95% CI):
2.1 mo (2.0-2.2)
3.3 mo (2.4-3.5)

Assessed per RECIST v1.1 by blinded, independent central review.
Data cutoff date: January 18, 2017.

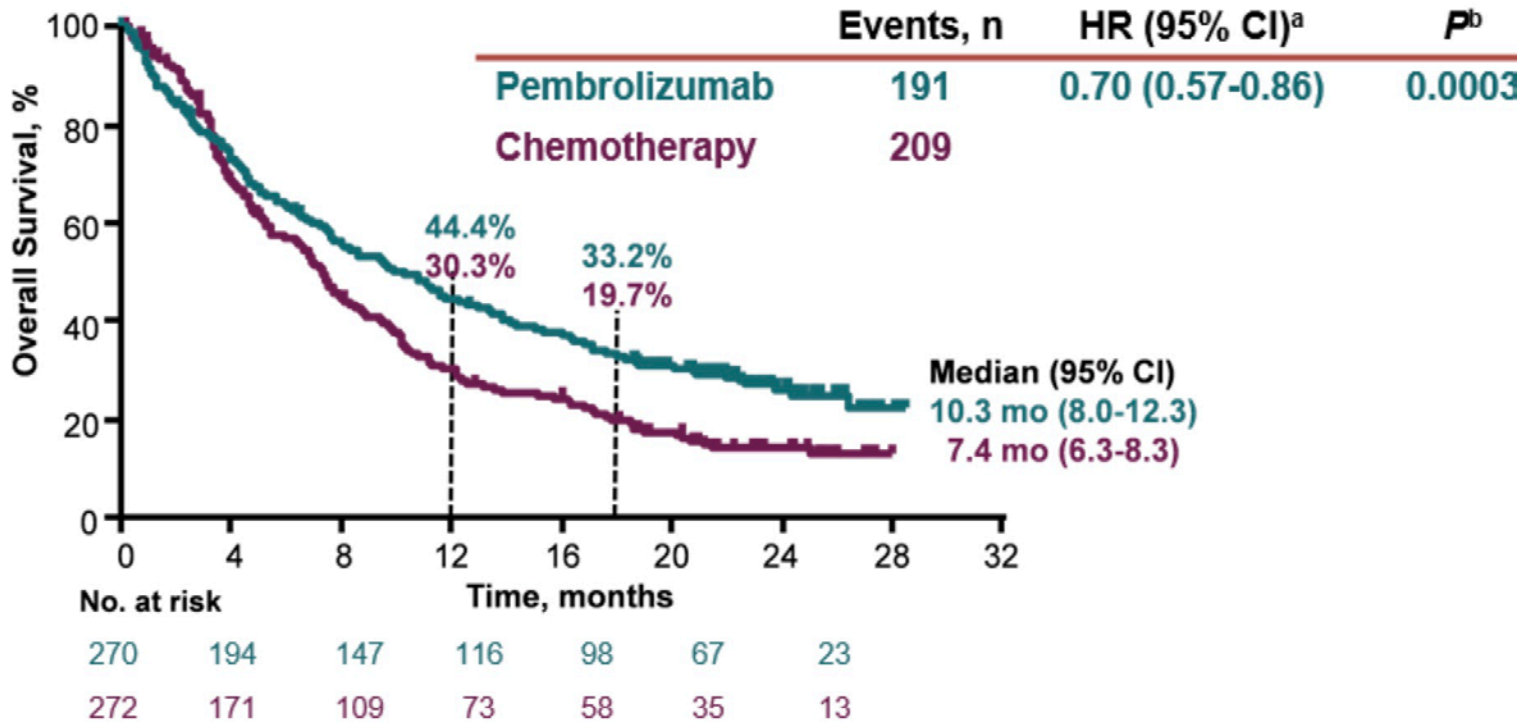
Time to Response[a]



[a]For patients who achieved a complete or partial response.
Data cutoff date: January 18, 2017.

de Wit et al., LBA37_PR, Mature Results from KEYNOTE-045

KEYNOTE-045
Overall Survival – updated analysis



Data cutoff: May 19, 2017.
[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/d
and time from completion of chemotherapy (<3 vs ≥3 mo).
[b]One-sided *P* value based on stratified log-rank test.

Bottom Line on 2nd Line

- Level I data for pembrolizumab OS benefit
  - BUT only a 20% response rate
- Promising activity for other PD-X agents
- Excellent tolerability
- QOL benefits also seen

Conclusion

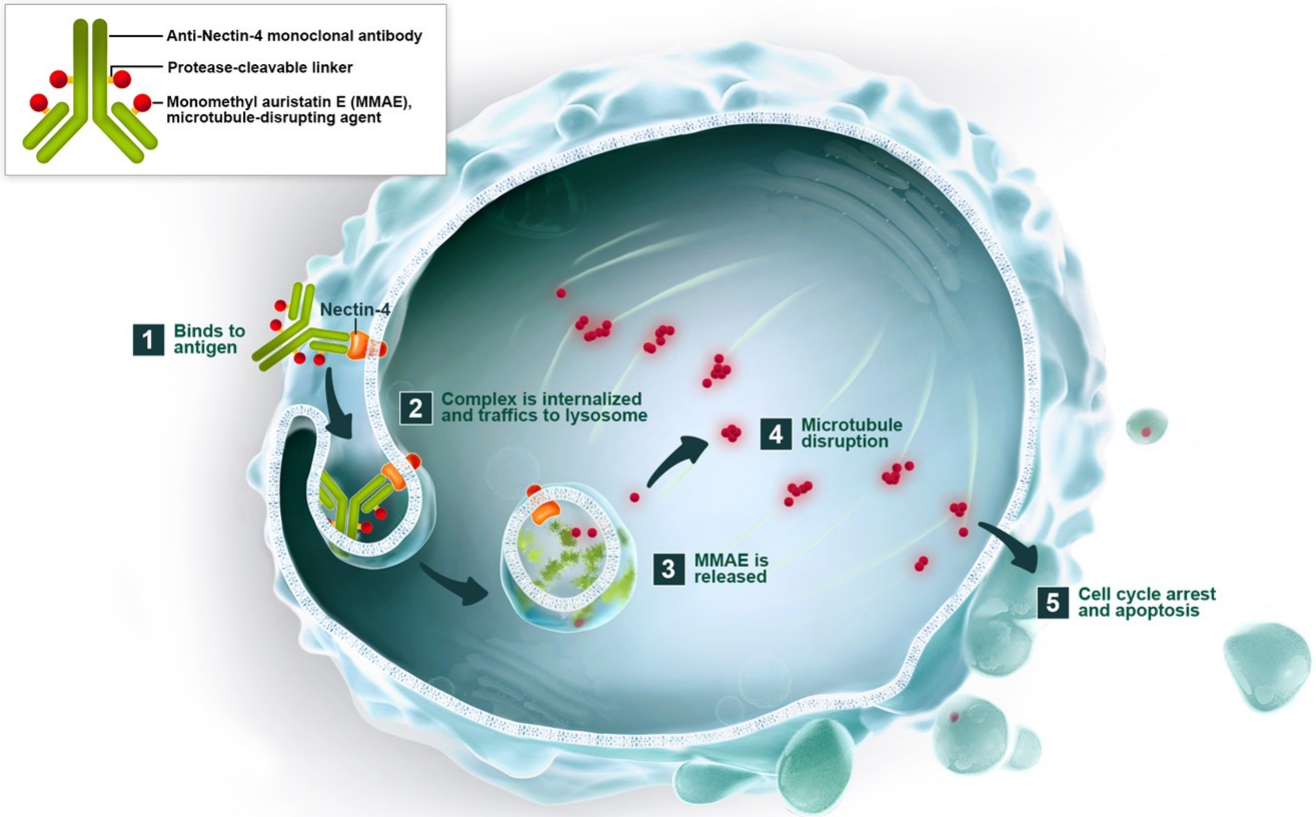
- Bladder Cancer is a common disease
  - Risk factor modification will be important in decreasing incidence
- Localized disease has a very high cure/control rate
  - Early detection/management is key
- Management is highly multidisciplinary
- Immunotherapy and other emerging treatments are changing outcomes!

Thank you!

Emerging Therapies

Enfortumab Vedotin: Nectin-4 Targeted Therapy

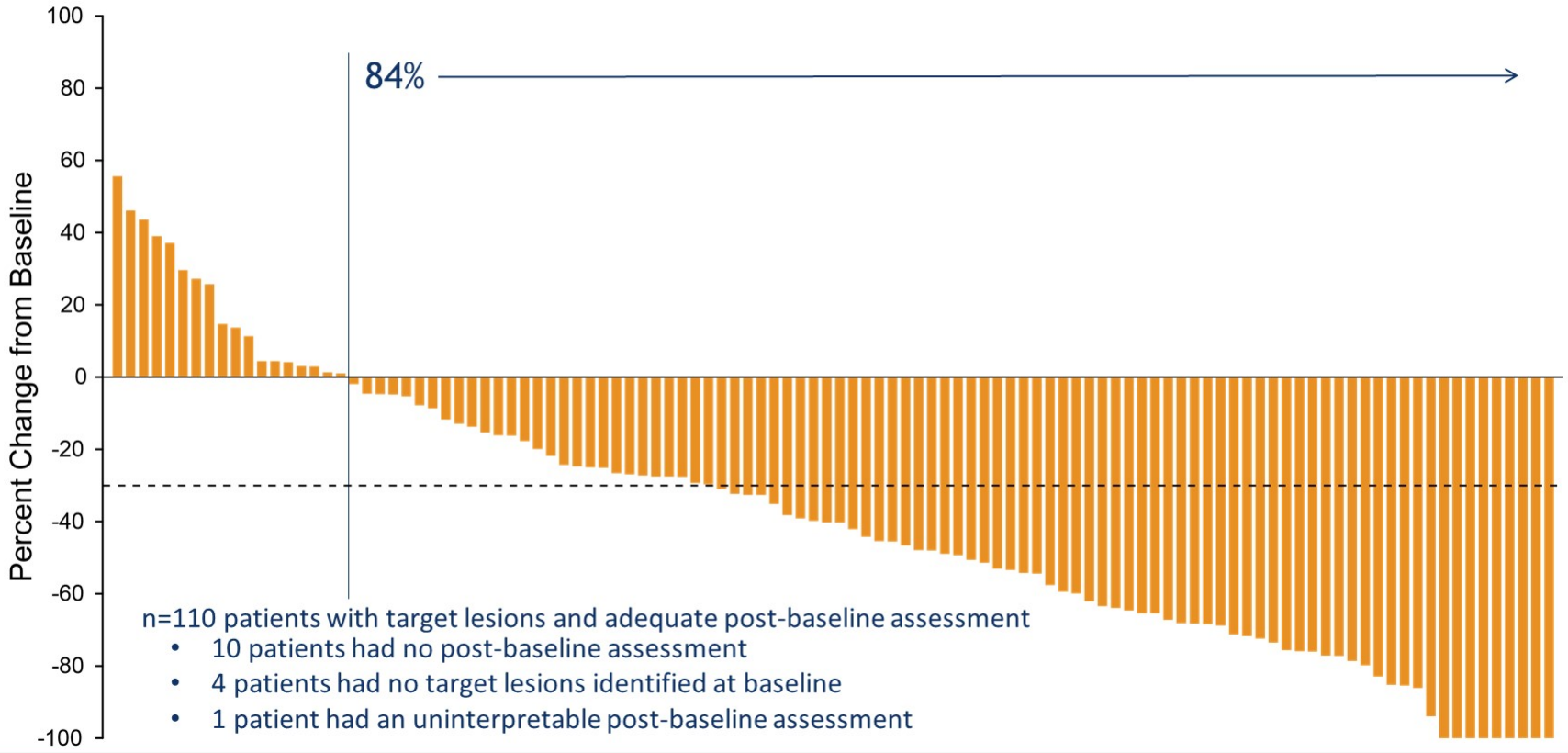
Proposed Mechanism of Action



Enfortumab vedotin (ASG-22ME) is an investigational agent, and its safety and efficacy have not been established.
Enfortumab vedotin is being developed in collaboration with Astellas Pharma Inc.

Presented By Daniel Petrylak at 2019 ASCO Annual Meeting

EV-201: Cohort 1 Change in Tumor Measurements per BICR



n=110 patients with target lesions and adequate post-baseline assessment

- 10 patients had no post-baseline assessment
- 4 patients had no target lesions identified at baseline
- 1 patient had an uninterpretable post-baseline assessment

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