SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Modena

I Tumori della Vescica

Inquadramento clinico

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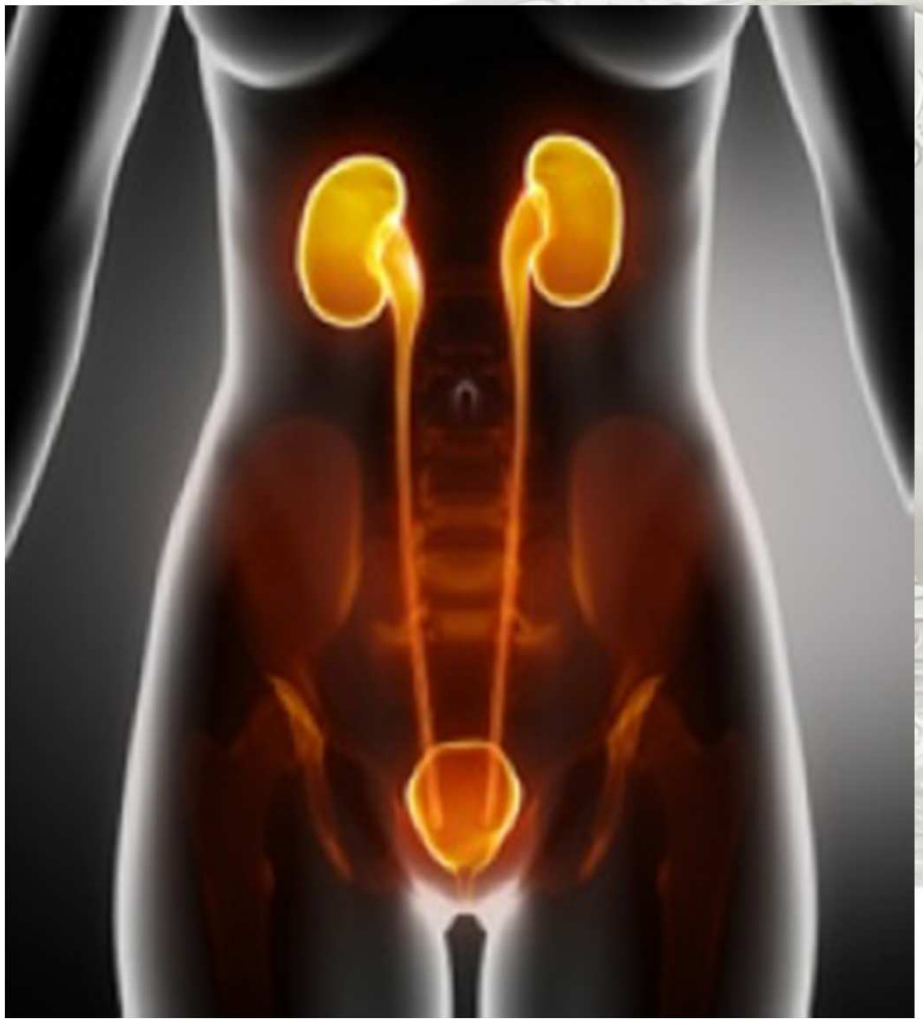
XII Corso di aggiornamento AIRTUM per operatori dei Registri Tumori
Reggio Emilia 28 settembre 2017

Genitourinary Malignancies



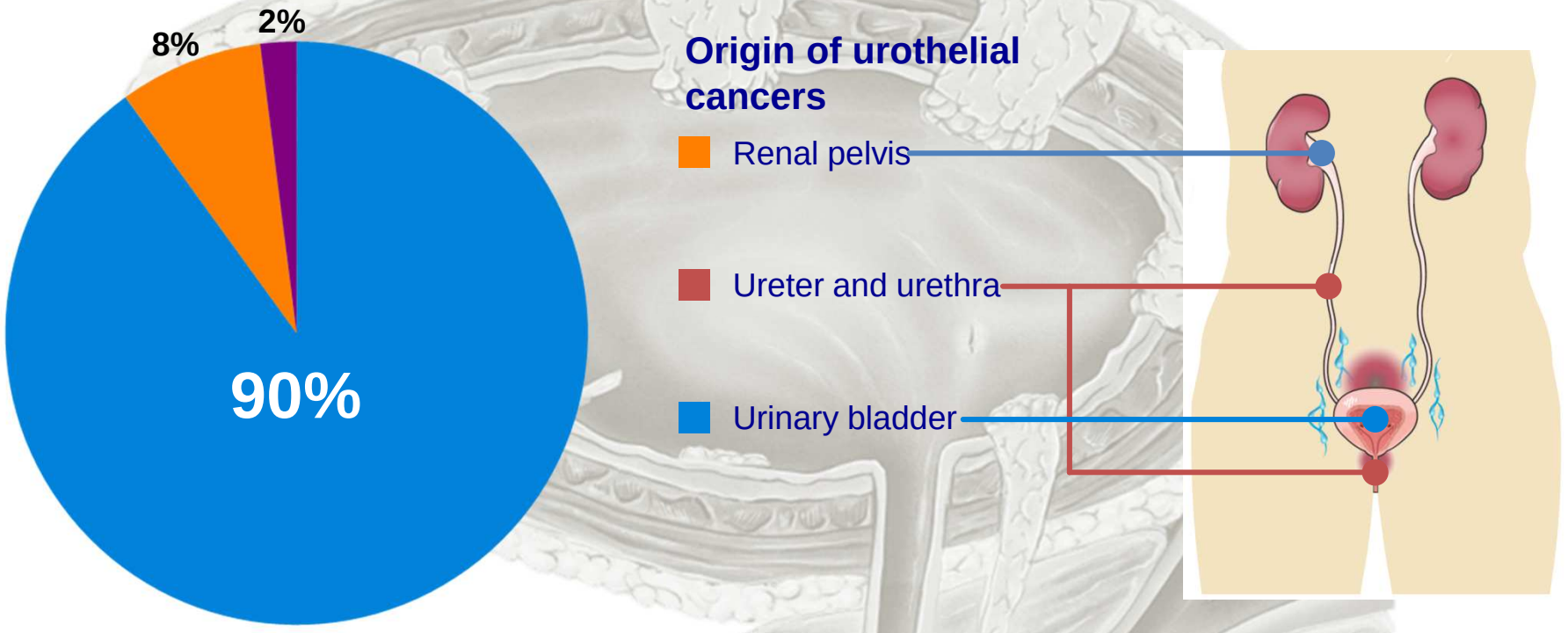
Urinary Bladder Cancer

In the area of the Italian Network of Cancer Registries there were, on yearly average, 70.7 new urinary bladder cancers per 100,000 men and 16.3 per 100,000 women.

It has been estimated that every year there are in Italy **15,987** new urinary bladder cancers diagnosed among males and **3,326** among females; as regards mortality, there were 4,158 deaths due to urinary bladder cancer among males and 1,080 among females in 2002.

90% of urothelial cancers originate in the bladder

The urothelium is the epithelial layer that lines the urethra, bladder, ureters and renal pelvis

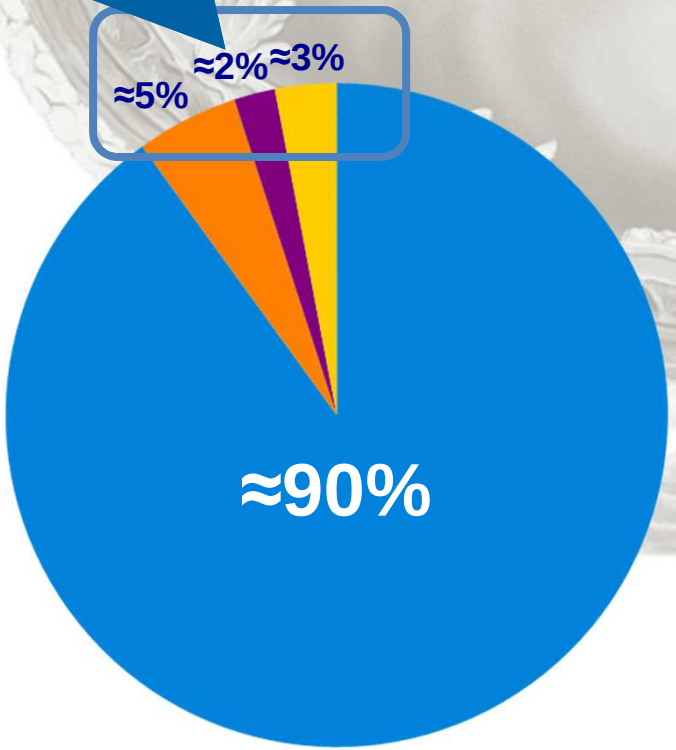


Bladder cancer is the most common form of urothelial cancer and is the focus of this module

- NCCN Guidelines – Bladder cancer v1.2015

Urothelial cell carcinoma is the most common histologic subtype of bladder cancer

In the developed world, squamous cell carcinoma, adenocarcinoma and other cell types (e.g. small-cell tumours, sarcoma) make up <10% of bladder cancers[1]



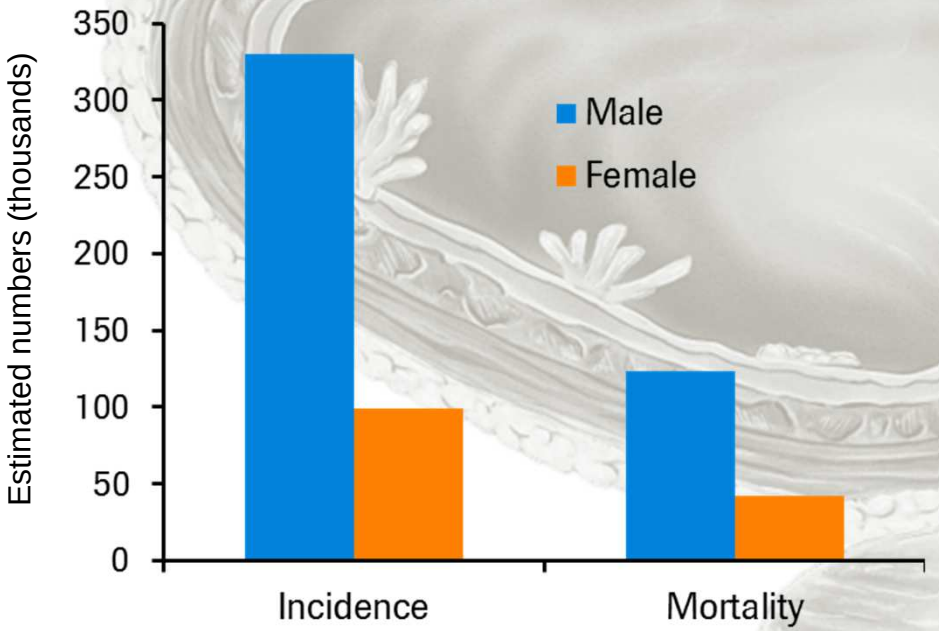
- Urothelial cell carcinoma (also known as transitional cell carcinoma)
- Squamous cell carcinoma
- Adenocarcinoma (pure glandular histology)
- Other cell types

- Urothelial cell carcinomas can show mixed histology
  - 17–22% with squamous histology[3]
  - up to 16% with glandular histology[3]
- Compared with pure urothelial cell carcinomas, tumours with mixed histology appear to have a poorer prognosis[3]

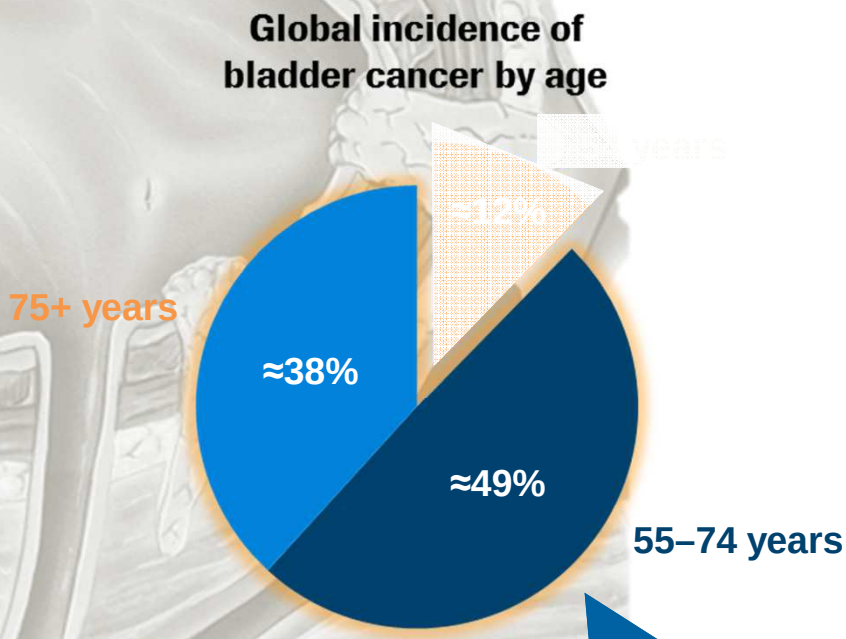
1. Kaufman DS, et al. Lancet 2009
2. NCCN Guidelines – Bladder cancer v1.2015
3. Chalasani V, et al. Can Urol Assoc J 2009

Bladder cancer is more common in males and in older patients

The rate of bladder-cancer-related deaths is higher in men than women (≈3:1)[1]



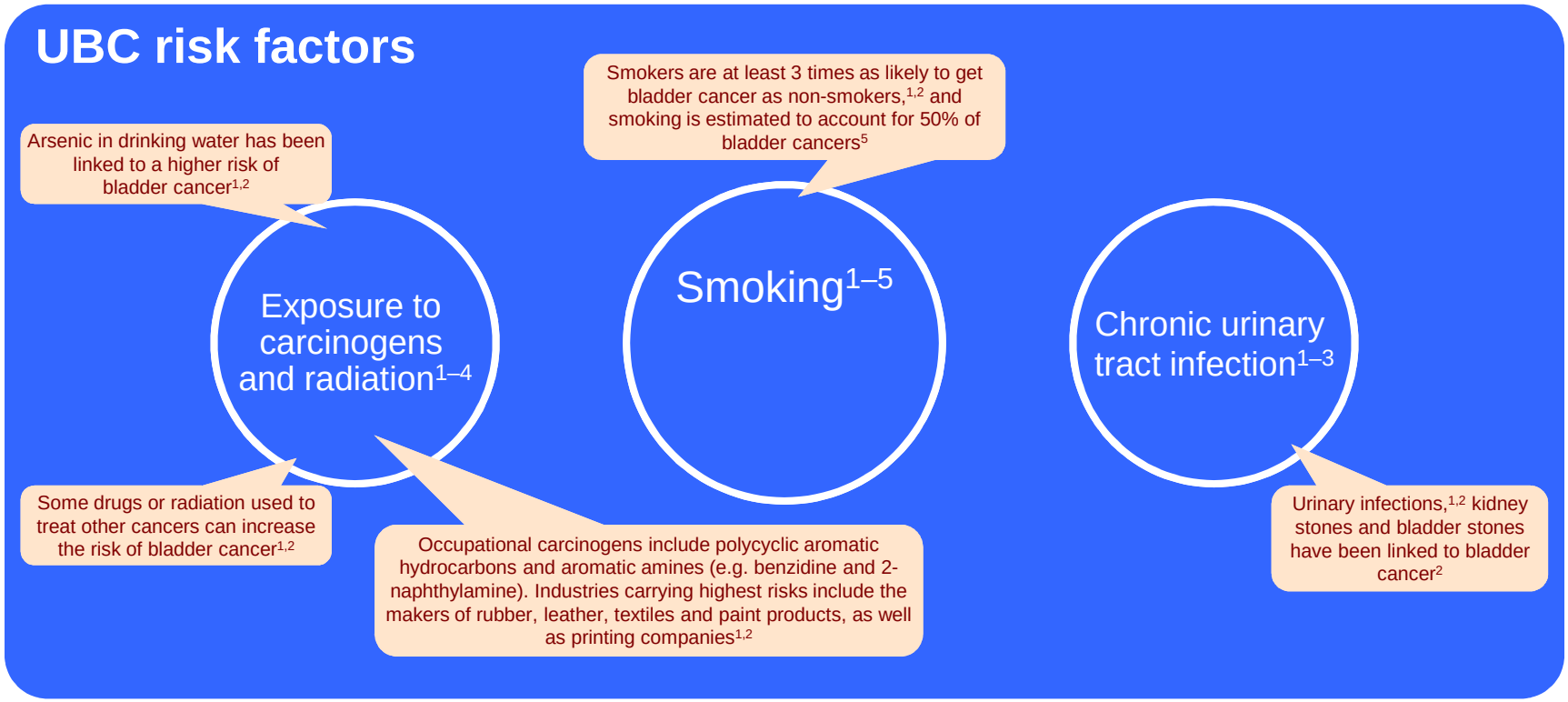
About 90% of patients with bladder cancer are aged >55 years[2]; average age at time of diagnosis is 73 years[2]



The majority of patients diagnosed with bladder cancer are aged >55 years

1. Ferlay J, et al. GLOBOCAN 2012
2. American Cancer Society 2014: Bladder Cancer Key Statistics

Smoking is the leading risk factor for bladder cancer, accounting for an estimated 50% of cases



In addition to the above risk factors, male gender and advanced age have also been linked to higher rates of bladder cancer[2,4,6]

Incidence of bladder cancer is strongly related to age[6]

Men are about 3 to 4 times more likely to get bladder cancer during their lifetime than women[2]

1. Cancer Research UK: Bladder Risk Factors
2. American Cancer Society 2014: Bladder Cancer Risk Factors
3. Sharma S, et al. Am Fam Physician 2009
4. Barocas DA, et al. Adv Urol 2012
5. Burger M, et al. Eur Urol 2013
6. Cancer Research UK: Bladder Cancer Incidence Statistics

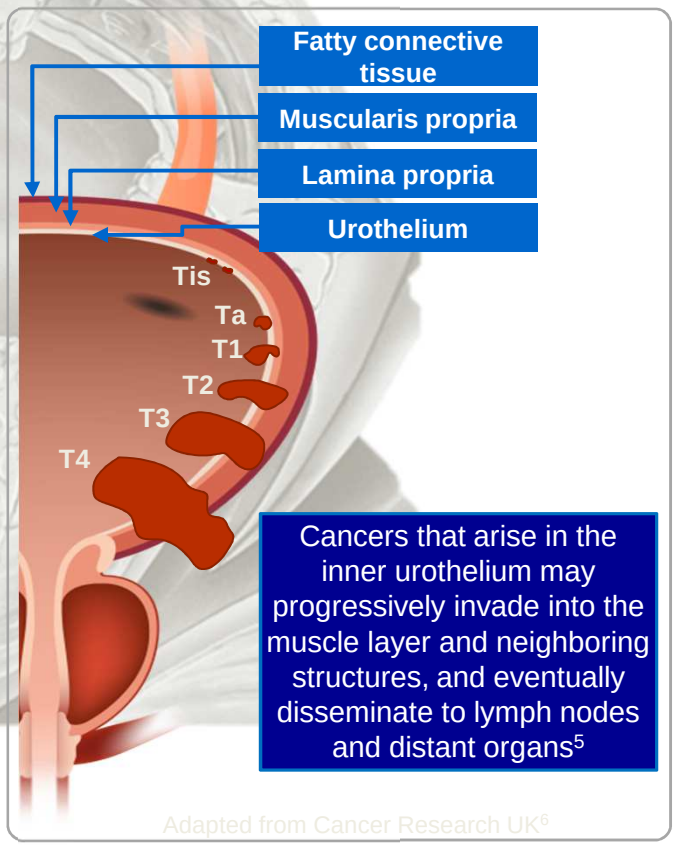
Staging Bladder Cancer: TNM

- Urothelial bladder cancer is staged using the tumor-node-metastasis (TNM) system
- Staging is based on the extent of penetration into the bladder wall, involvement of lymph nodes, and metastasis to distant organs[a1–3]
- Like tumor grade, tumor stage is prognostic for recurrence, progression, and survival[4]

T: Primary tumor[2]	
T0	No tumor evidence
Ta	Noninvasive papillary carcinoma
Tis	Carcinoma in situ (“flat tumor”)
T1	Invades connective tissue
T2a	Invades superficial muscularis propria
T2b	Invades deep muscularis propria
T3a	Invades perivesical tissue (microscopically observable)
T3b	Invades perivesical tissue (macroscopically observable)
T4a	Invades prostate, uterus, or vagina
T4b	Invades pelvic or abdominal wall

N: Regional lymph nodes[2]	
N0	No regional lymph node metastasis
N1	Single regional node metastasis in true pelvis
N2	≥2 lymph nodes in true pelvis
N3	Node metastasis to common iliac lymph nodes

M: Distant metastases[2]	
M0	No distant metastasis
M1	Distant metastasis

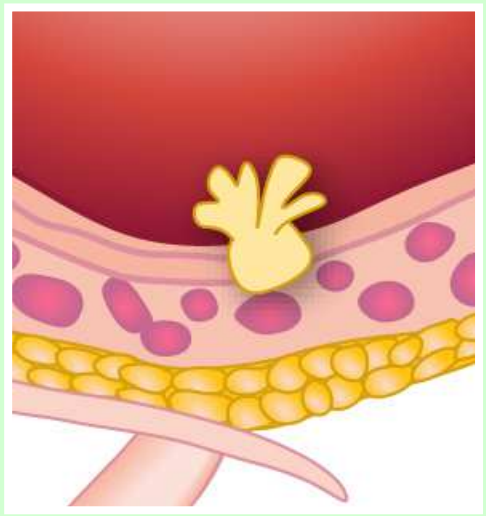


[a]The most common sites of metastases are lymph nodes, bone, lung, liver, and peritoneum.

References are listed in the speaker notes

Bladder cancer is generally categorised as non-muscle-invasive, muscle-invasive or metastatic

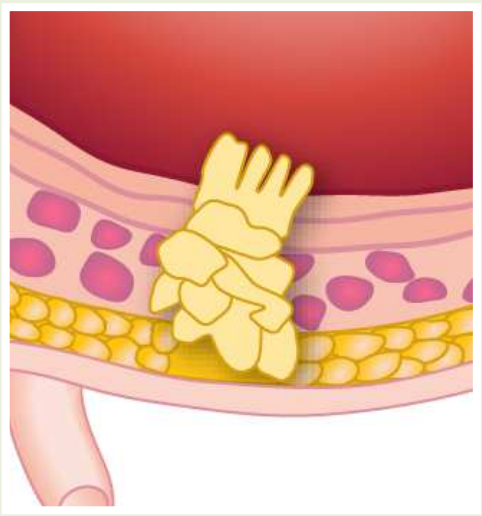
Non-invasive disease



Cancer that is restricted to the lining of the bladder is called **non-muscle-invasive bladder cancer (NMIBC)**

≈51–75% of patients are diagnosed at this stage[1–4]

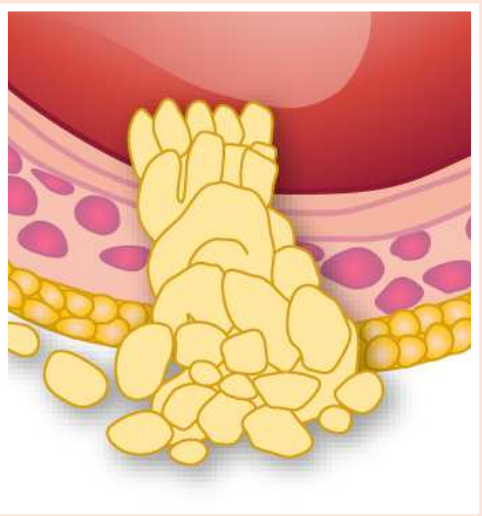
Locally invasive disease



Cancer that has spread through the muscle wall of the bladder is called **muscle-invasive bladder cancer (MIBC)**

≈30–42% of patients are diagnosed at this stage[1,4]

Metastatic disease



Cancer that has spread to other parts of the body is called **metastatic bladder cancer**

≈4% of patients are diagnosed at this stage[1,5]

1. Howlader N, et al. (eds). SEER Cancer Statistics Review 1975–2011
2. NCCN Guidelines – Bladder cancer v1.2015; 3. Sharma S, et al. Am Fam Physician 2009
4. Kaufman DS, et al. Lancet 2009; 5. American Cancer Society 2014: Bladder Cancer

Bladder cancer: high risk of recurrence for non-muscle-invasive and muscle-invasive disease and low 5-year survival for metastatic disease

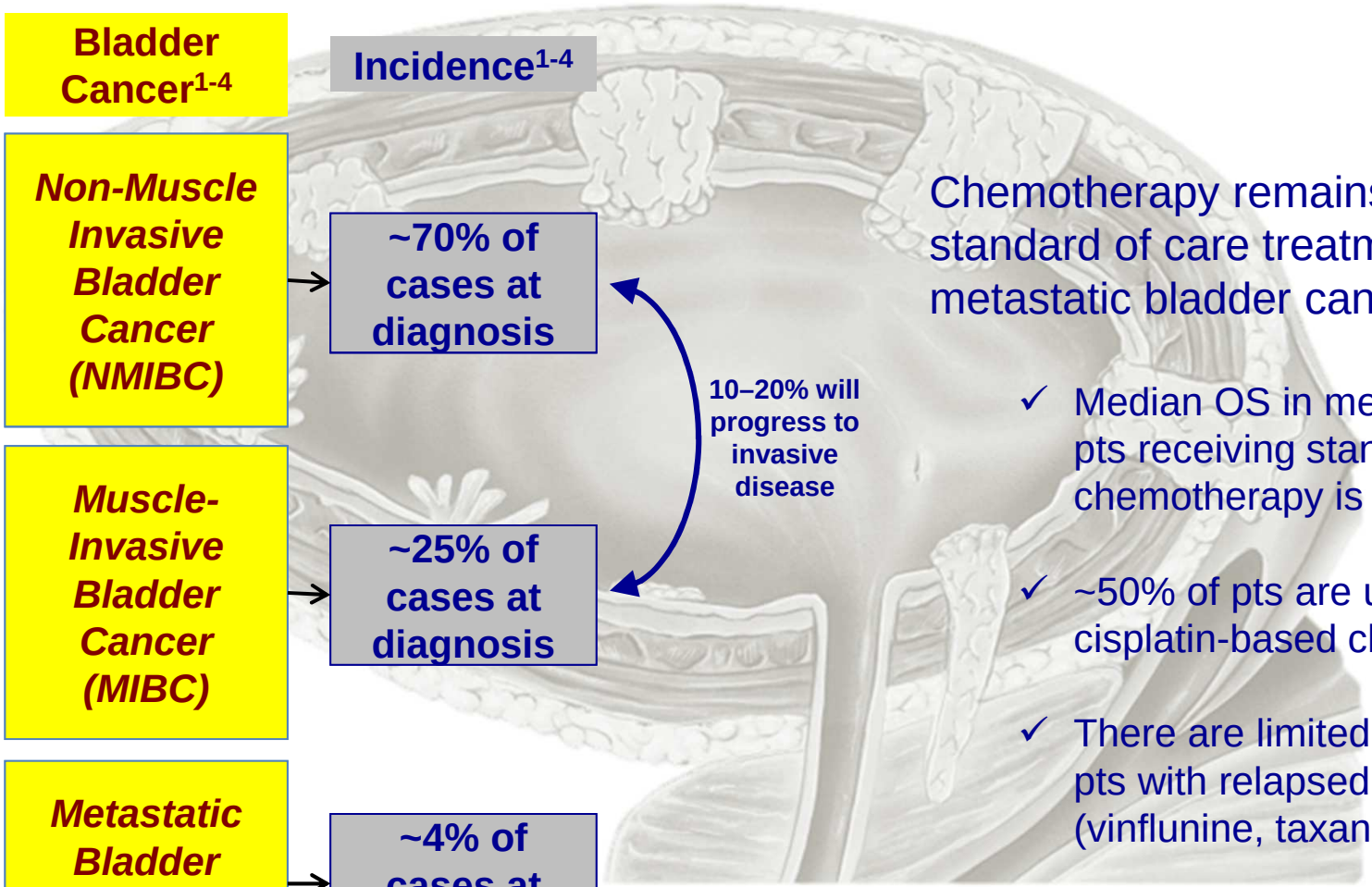
Classification	Stage at diagnosis	Proportion at diagnosis		5-year relative survival rate[1]	Probability of recurrence within 5 years
Non-muscle-invasive disease	Non-invasive (Ta, Tis and T1)	51–75%[1–4]		96%	50–90%[2,4]
Muscle-invasive disease	Localised (T2–4, N0)	35%[1]	30%[4]	69%	≈50%[6]
	Regional (Tx, N1)	7%[1]		34%	
Metastatic disease	Distant/metastatic (Tx, Nx, M1)	4%[1,5]		6%	NA

Low 5-year survival rate in patients with metastatic disease

High risk of recurrence in patients with non-muscle-invasive and muscle-invasive disease

1. Howlader N, et al. (eds). SEER Cancer Statistics Review, 1975–2011
2. NCCN Guidelines – Bladder cancer v1.2015; 3. Sharma S, et al. Am Fam Physician 2009
4. Kaufman DS, et al. Lancet 2009; 5. American Cancer Society 2014: Bladder Cancer
6. de Vos FY and de Wit R. Ther Adv Med Oncol 2010

Bladder Cancer History



Chemotherapy remains the standard of care treatment for metastatic bladder cancer[5,6]:

- ✓ Median OS in metastatic BC pts receiving standard chemotherapy is ~14 mos
- ✓ ~50% of pts are unfit for cisplatin-based chemotherapy
- ✓ There are limited options for pts with relapsed disease (vinflunine, taxane)

1. NCCN Guidelines. Bladder Cancer. V1.2015. 2. Kaufman DS et al. *Lancet.* 2009;274:239-249. 3. Yafi FA et al. *Urol Oncol.* 2011;18(1):e25-e34.
4. National Cancer Institute. SEER stat fact sheets: bladder cancer. http://seer.cancer.gov/statfacts/html/urinb.html. Accessed June 22, 2015.
5. Bellmunt J et al. *Ann Oncol*. 2014; 25(suppl 3):iii40-iii48. 6. Gartrell BA et al. *Exp Opin Emerging Drugs*. 2013;18:477-494.

Goals of treatment and treatment options vary by type of disease at diagnosis

	Non-muscle-invasive disease	Muscle-invasive disease	
Main goals of treatment	• Curative intent • Reduce recurrence • Prevent progression to more advanced stage	• Curative intent • Reduce recurrence • Prevent progression to more advanced stage	
Current treatment options	• TURBT • Intravesical therapy • Cystectomy	• TURBT • Partial or radical cystectomy • Neoadjuvant and adjuvant chemotherapy • Radiotherapy	

- NCCN Guidelines – Bladder cancer v1.2015

BLADDER CANCER: TREATMENT OF MUSCLE INVASIVE BLADDER CANCER (MIBC)

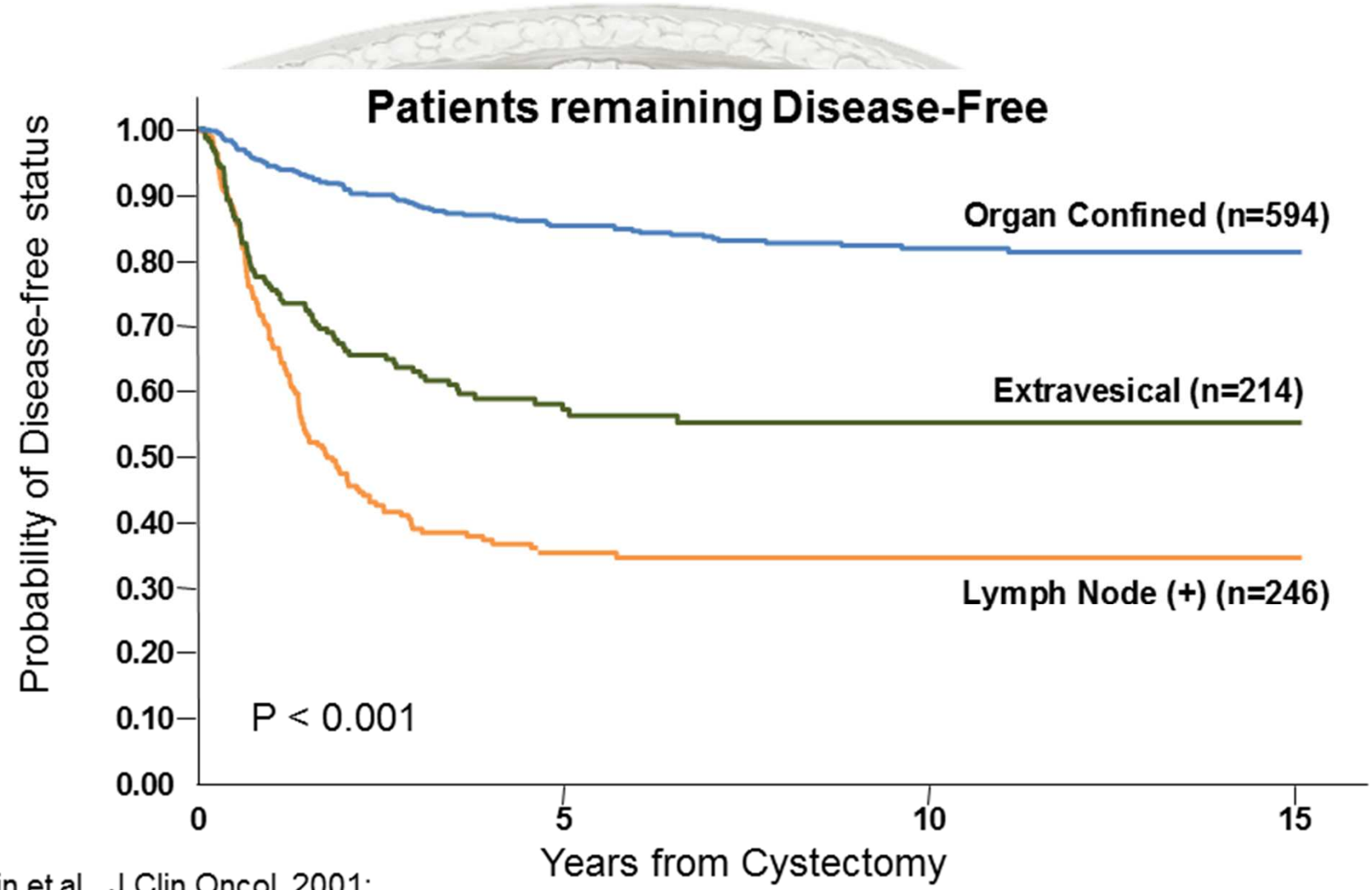
RADICAL CYSTECTOMY ➔ Removal in toto of the bladder, prostate, seminal vesicles (in men) and uterus and adnexa (in women) and pelvic lymph nodes.

- Traditionally radical cystectomy is recommended for patients with muscle-invasive bladder cancer T2-T4a, N0-Nx, M0.

- Other indications include high-risk and recurrent superficial tumours:
  1. BCG-resistant Tis,
  2. T1G3
  3. extensive papillary disease that cannot be controlled with TUR and intravesical therapy alone.

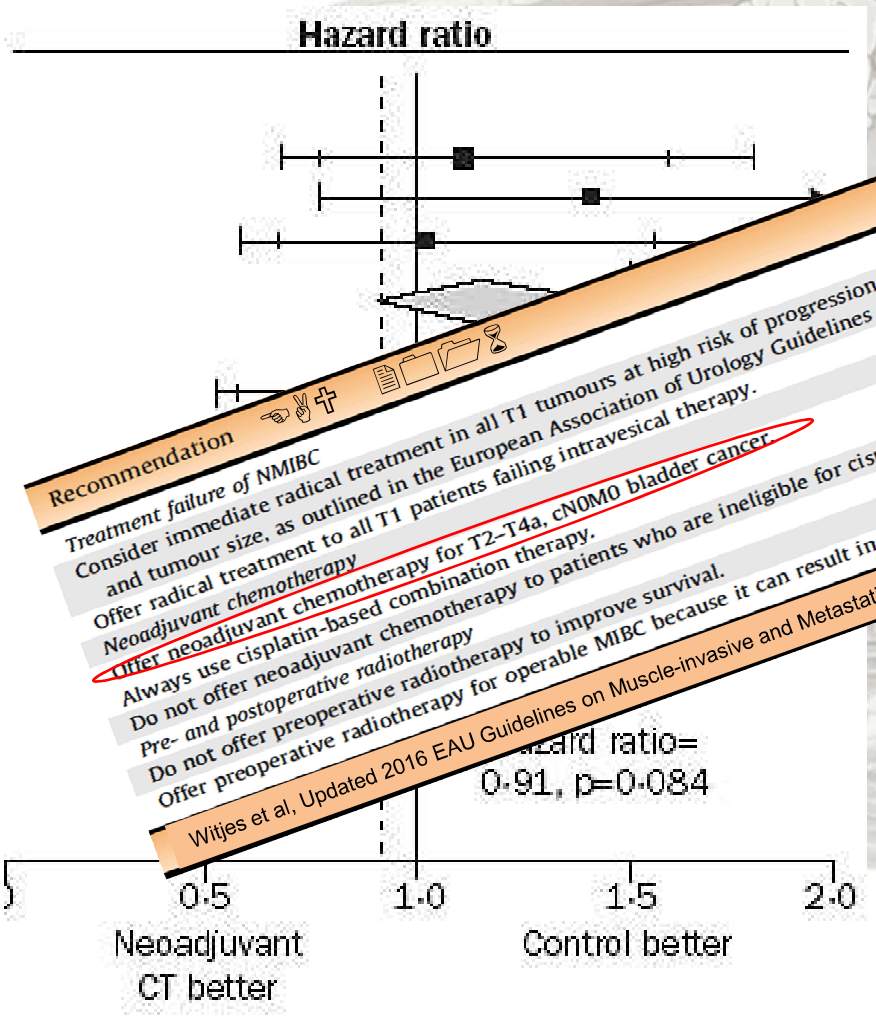
  - OPEN
  - *LAPAROSCOPIC/ROBOTIC-ASSISTED LAPAROSCOPIC CYSTECTOMY (RALC)*

USC Norris Cancer Center Data in 1,054 Patients



Stein et al. J Clin Oncol. 2001;

Neoadjuvant in Advanced Bladder Cancer: Meta-analysis



Recommendation	GR
Treatment failure of NMIBC	
Consider immediate radical treatment in all T1 tumours at high risk of progression (ie, high grade, multifocality, carcinoma *in situ*, and tumour size, as outlined in the European Association of Urology Guidelines for NMIBC [34]).	C
Offer radical treatment to all T1 patients failing intravesical therapy.	B
Neoadjuvant chemotherapy	
Offer neoadjuvant chemotherapy for T2–T4a, cN0M0 bladder cancer.	A
Always use cisplatin-based combination therapy.	A
Do not offer neoadjuvant chemotherapy to patients who are ineligible for cisplatin-based combination chemotherapy.	A
Pre- and postoperative radiotherapy	
Do not offer preoperative radiotherapy to improve survival.	C
Offer preoperative radiotherapy for operable MIBC because it can result in tumour downstaging after 4–6 wk.	

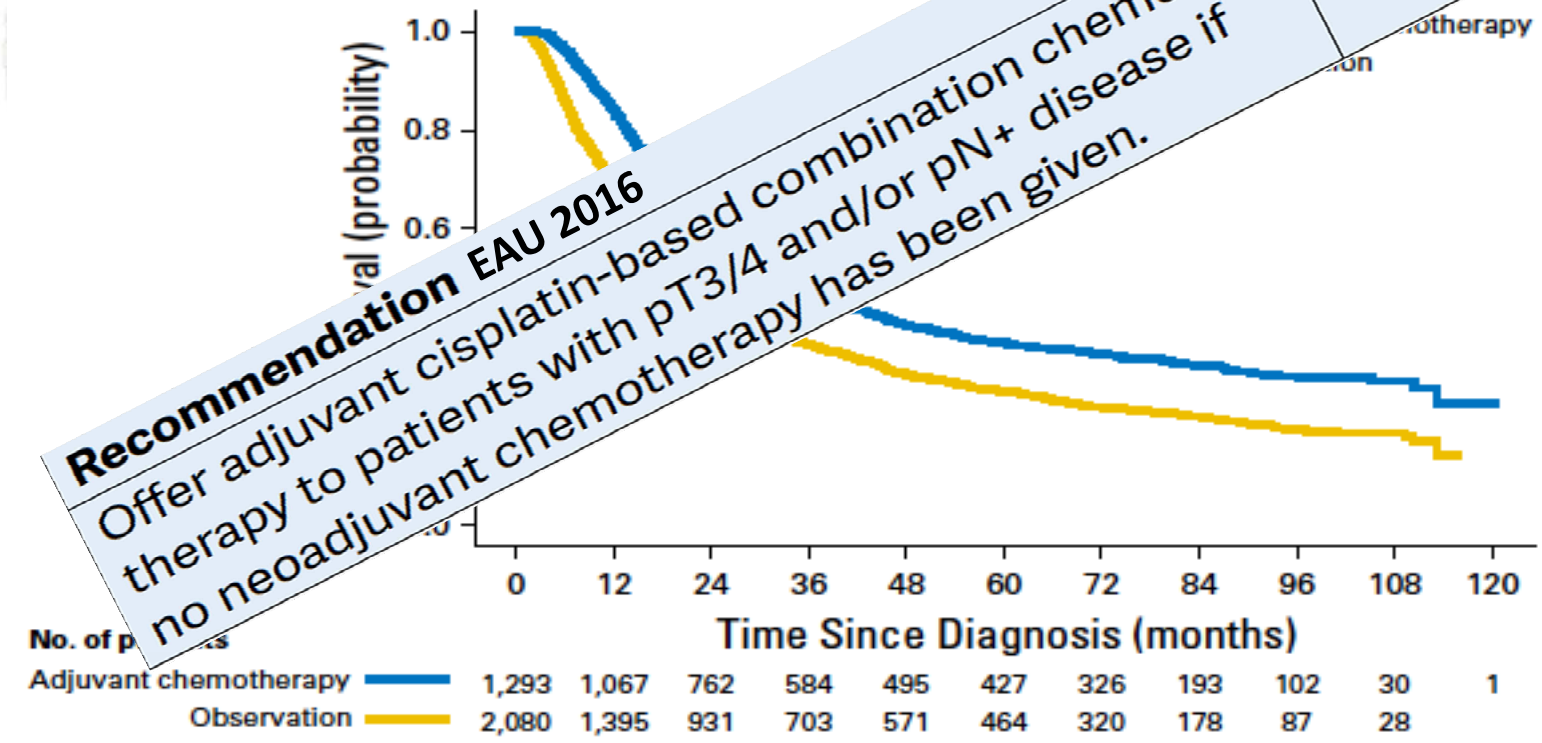
Witjes et al, Updated 2016 EAU Guidelines on Muscle-invasive and Metastatic BC

- Meta-a… …ials
  - …isk of death
    - …%
  - Absolute benefit at 5 yr
    - OS: 5% , p = 0.003
      - survival: 45% to 50%
    - DSS: 9%, p < 0.001

Lancet, 2003; Updated: European Urology, 2005

Effectiveness of Adjuvant Chemotherapy for Locally Advanced BC in pts with pathologic T3-4 and/or pathologic node+ BC using the National Cancer Data Base

A total of 5,653 patients met study inclusion
23% received adjuvant chemotherapy



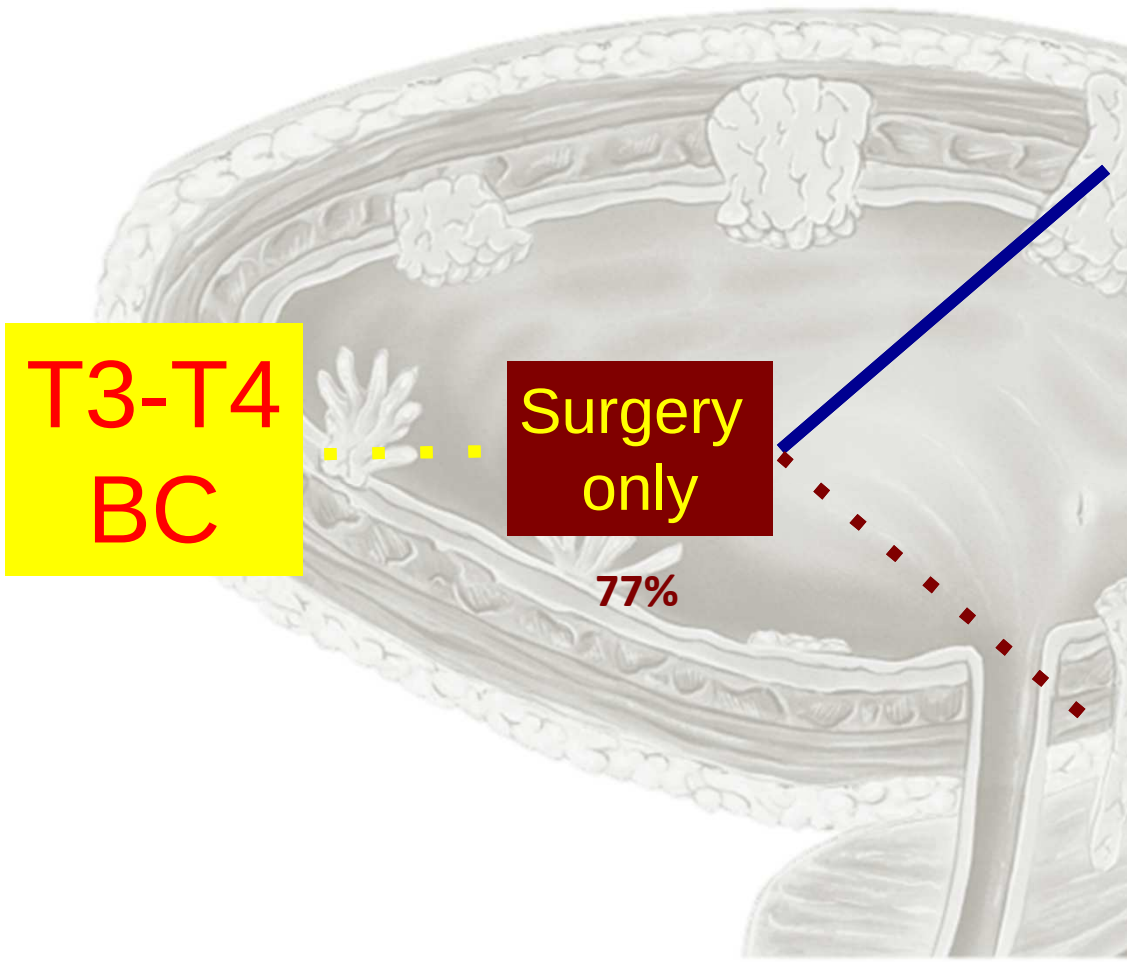
GR
C

Recommendation EAU 2016

Offer adjuvant cisplatin-based combination chemotherapy to patients with pT3/4 and/or pN+ disease if no neoadjuvant chemotherapy has been given.

Galsky MD, JCO 2016

Locally Advanced Bladder Cancer



ADJUVANT THERAPY IN MIBC (10%): POOR ACCRUAL, EARLY CLOSURE

NEOADJUVANT THERAPY IN MIBC (1%):

- Improved overall 10-year absolute survival by 6%
- Relative reduction in the risk of death resulting from bladder cancer by 16%
- Patients treated with surgery alone had a 66% greater likelihood of death resulting from bladder cancer

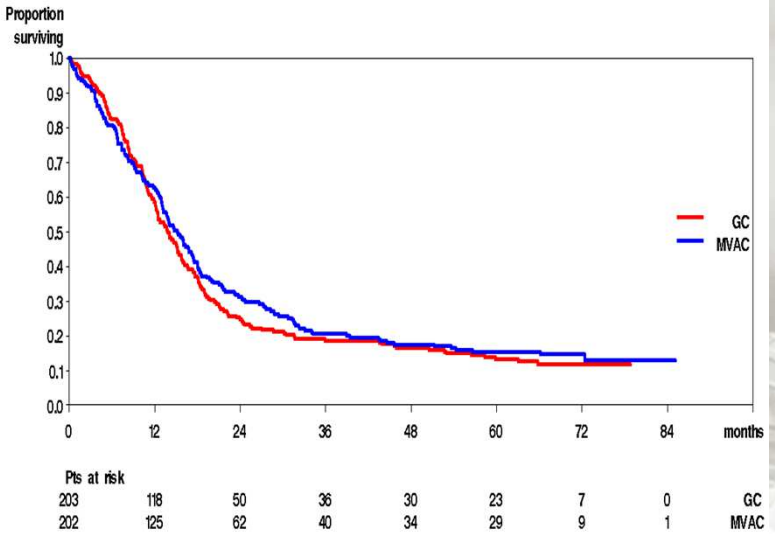
Goals of treatment and treatment options vary by type of disease at diagnosis

	Non-muscle-invasive disease	Muscle-invasive disease	Metastatic disease
Main goals of treatment	• Curative intent • Reduce recurrence • Prevent progression to more advanced stage	• Curative intent • Reduce recurrence • Prevent progression to more advanced stage	• Prolong quantity and quality of life
Current treatment options	• TURBT • Intravesical therapy • Cystectomy	• TURBT • Partial or radical cystectomy • Neoadjuvant and adjuvant chemotherapy • Radiotherapy	• Chemotherapy • Radiotherapy

- NCCN Guidelines – Bladder cancer v1.2015

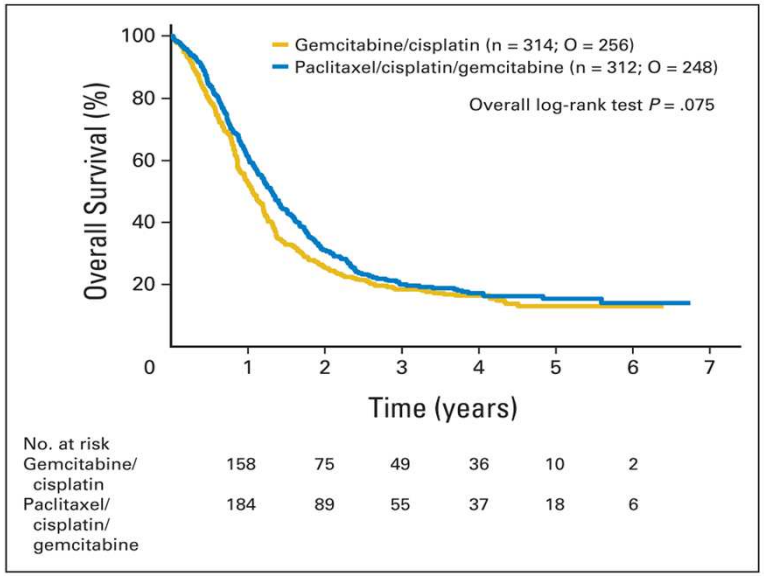
First-Line Chemotherapy in mUC

Gemcitabine-Cisplatin vs MVAC



GC: 14.0 months (12.3-15.5)
MVAC: 15.2 months (13.2-17.3)
HR: 1.09 (0.88-1.34)
von der Maase H, J Clin Oncol 2005

Paclitaxel added to GC



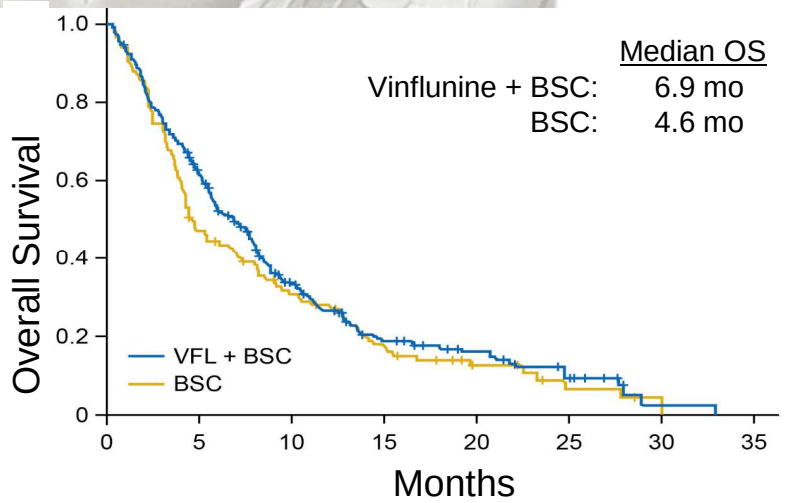
PCG: 15.8 months
CG: 12.7 months
p= .075

Bellmunt J, J Clin Oncol 2012

Treatment of cisplatin-failure mUC

- No global consensus for treatment following platinum-based chemotherapy exists
  - Taxanes are typically used in the US
  - Vinflunine (not approved in the US) is often used in Europe
    - In the registrational Phase III study leading to European approval, vinflunine did not demonstrate OS benefit in the ITT population[1]
    - More recent data suggest that clinical proficiency with vinflunine may be improving[2-5]
- More recently, checkpoint inhibitors[6-10] including atezolizumab[6] have been approved in the US and elsewhere for the treatment of mUC

2L Regimen[a]	ORR	mPFS	mOS
Paclitaxel (n = 31)	10%	2.2 mo	7.2 mo
Docetaxel (n = 30)	13%	—	9.0 mo
Vinflunine (n = 51)	18%	3.0 mo	6.6 mo
Vinflunine (n = 253)	9%	3.0 mo	6.9 mo

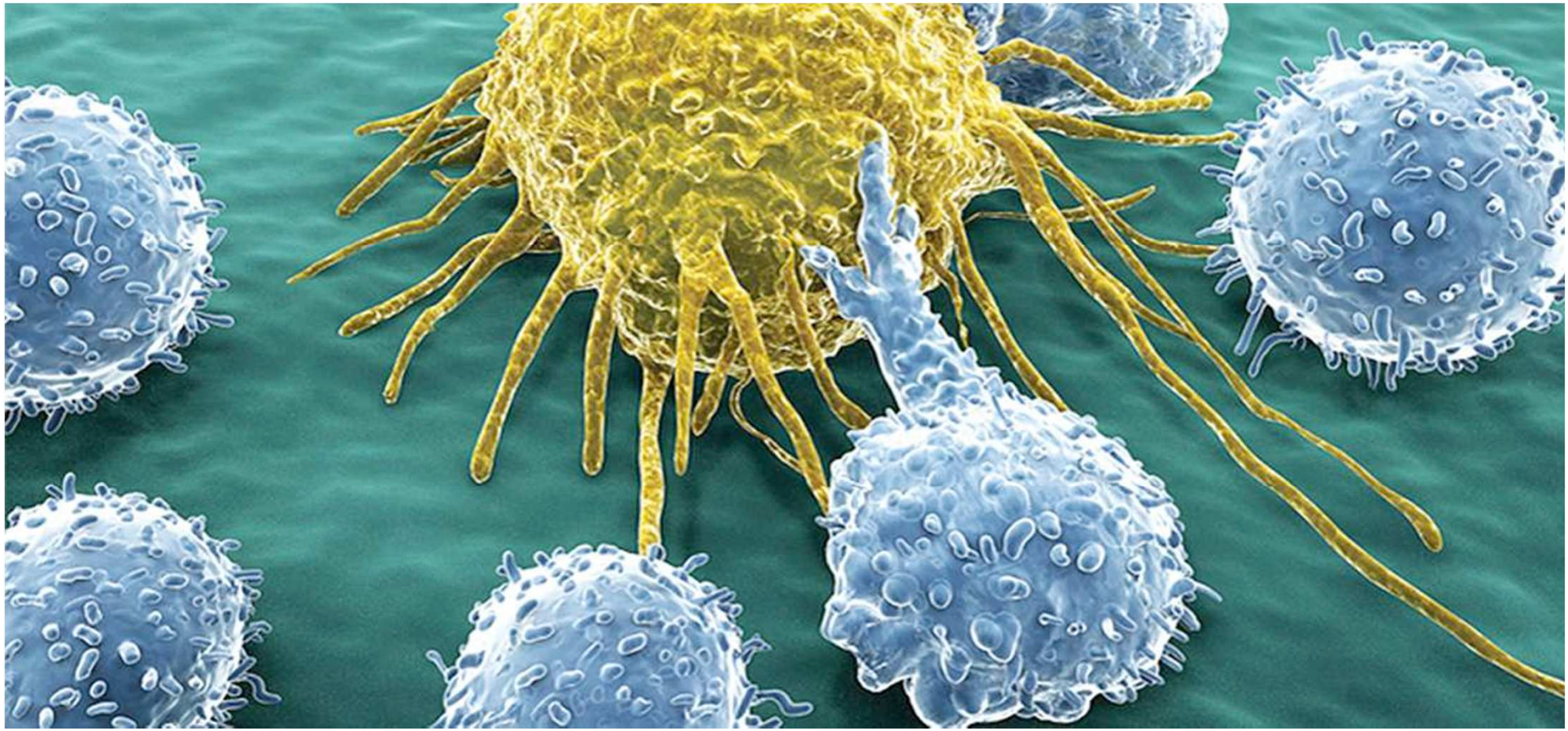


Bellmunt J, et al. *J Clin Oncol.* 2009;Reprinted with permission. © 2009 American Society of Clinical Oncology. All rights reserved.

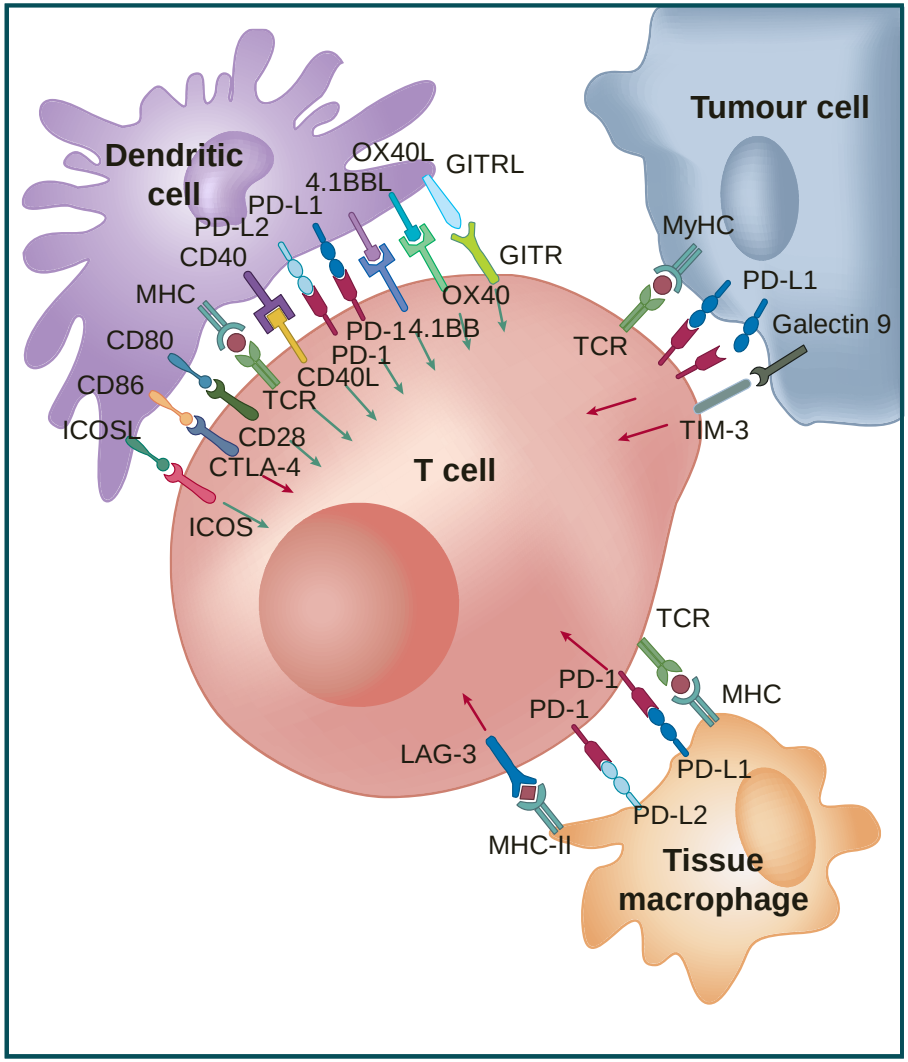
1. Bellmunt *J Clin Oncol* 2009. 2. Castellano *BMC Cancer* 2014. 3. Garcia-Donas *Lancet Oncol* 2017. 4. Medioni *BMC Cancer* 2016. 5. Pistamaltzian *Anticancer Drugs* 2016. 6. Rosenberg *Lancet* 2016. 7. Bellmunt *N Engl J Med* 2017. 8. Sharma *Lancet Oncol* 2017. 9. Masard *J Clin Oncol* 2016. 10. Apolo *J Clin Oncol* 2017.

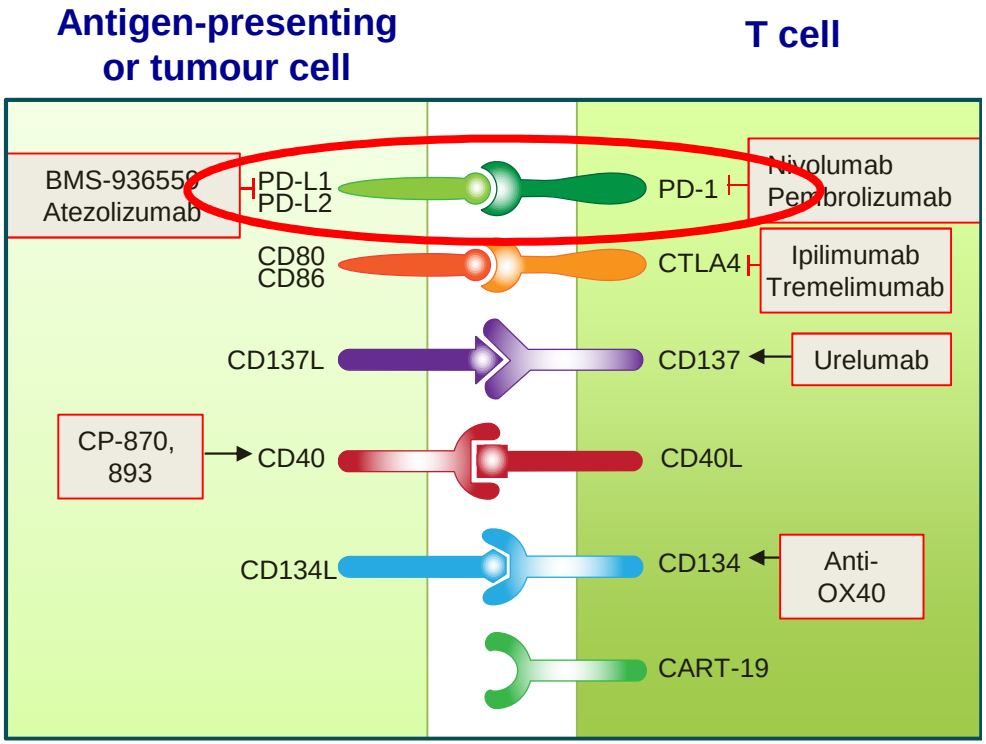
Powles T, et al. EAS 2017

Let’s start with some basic Immunology



Molecules regulating immune cell and cancer cell interactions





Ott PA, et al. Clin Cancer Res. 2013;19:5300.

IMvigor211 Study Design

Key Eligibility Criteria[a]

- mUC with progression during or following platinum-based chemotherapy
  - ≤ 2 prior lines of therapy
- Measurable disease per RECIST v1.1
- ECOG PS 0-1
- Evaluable sample for PD-L1 testing
- TCC histology as primary component

(N = 931)

Stratification Factors

- No. of risk factors[b] (0 vs. 1/2/3)
- Liver metastases (yes vs. no)
- PD-L1 status (0/1 vs. 2/3)
- Chemotherapy (vinflunine vs. taxanes)

R 1:1

Atezolizumab
1200 mg q3w

Chemotherapy
(investigator's choice)
- **Vinflunine** *q3w*
- **Docetaxel** *q3w*
- **Paclitaxel** *q3w*

Loss of clinical benefit

RECIST v1.1 progression

No crossover permitted per protocol

Survival follow-up

Primary endpoint

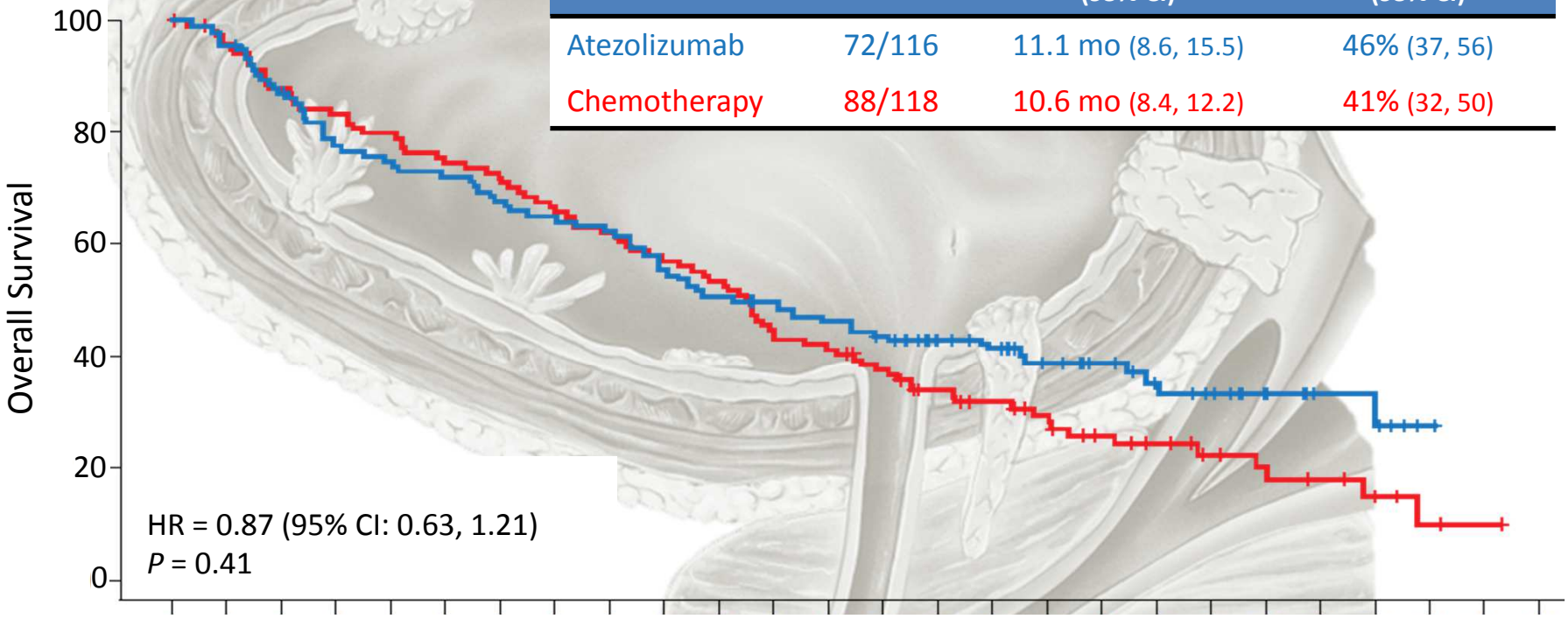
- OS, tested hierarchically in pre-specified populations

- **Additional endpoints**
  - Efficacy: RECIST v1.1 ORR, PFS and DOR[c]
  - Safety
  - PROs: EORTC QLQ-C30

Powles T, et al. EAS 2017

IMvigor211 OS Analysis: IC2/3 (25% of Population)

	Events/ Patients	Median OS (95% CI)	12-mo OS Rate (95% CI)
Atezolizumab	72/116	11.1 mo (8.6, 15.5)	46% (37, 56)
Chemotherapy	88/118	10.6 mo (8.4, 12.2)	41% (32, 50)



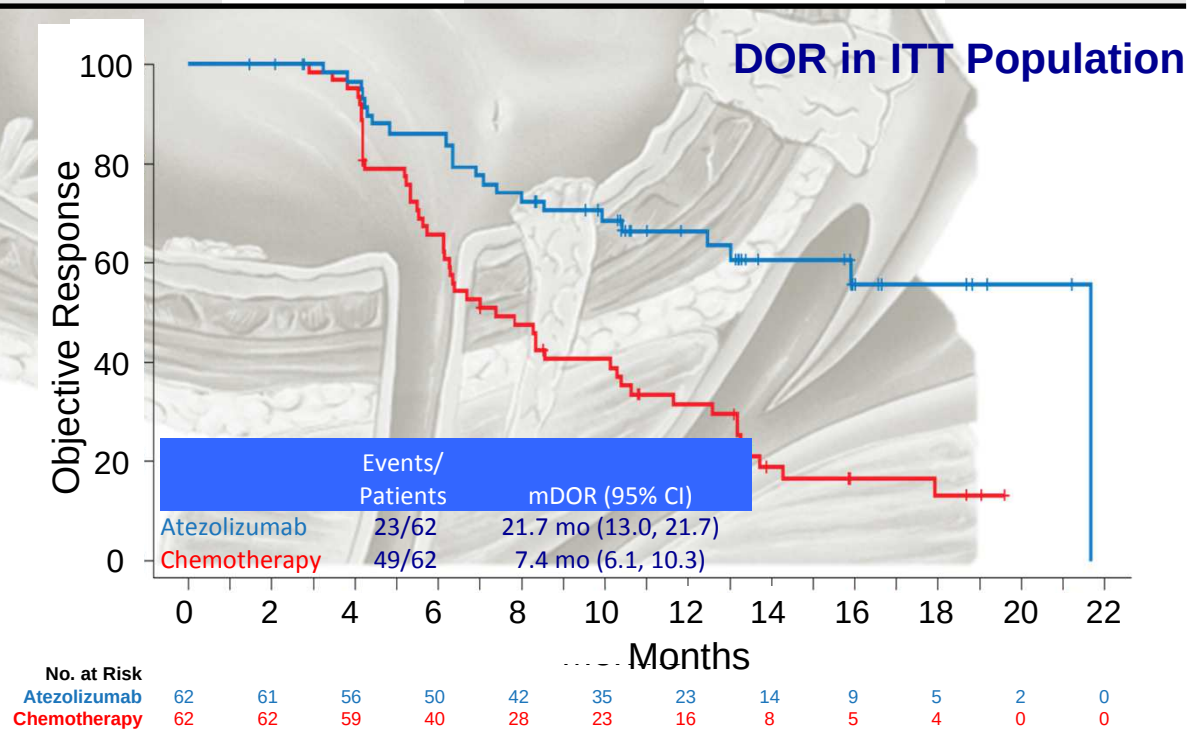
No. at Risk													
Atezolizumab	116	100	85	77	71	58	51	39	27	19	11	6	0
Chemotherapy	118	100	91	82	71	61	47	32	24	15	9	5	1

Powles T, et al. EAS 2017

IMvigor21: response by PD-L1 Subgroup

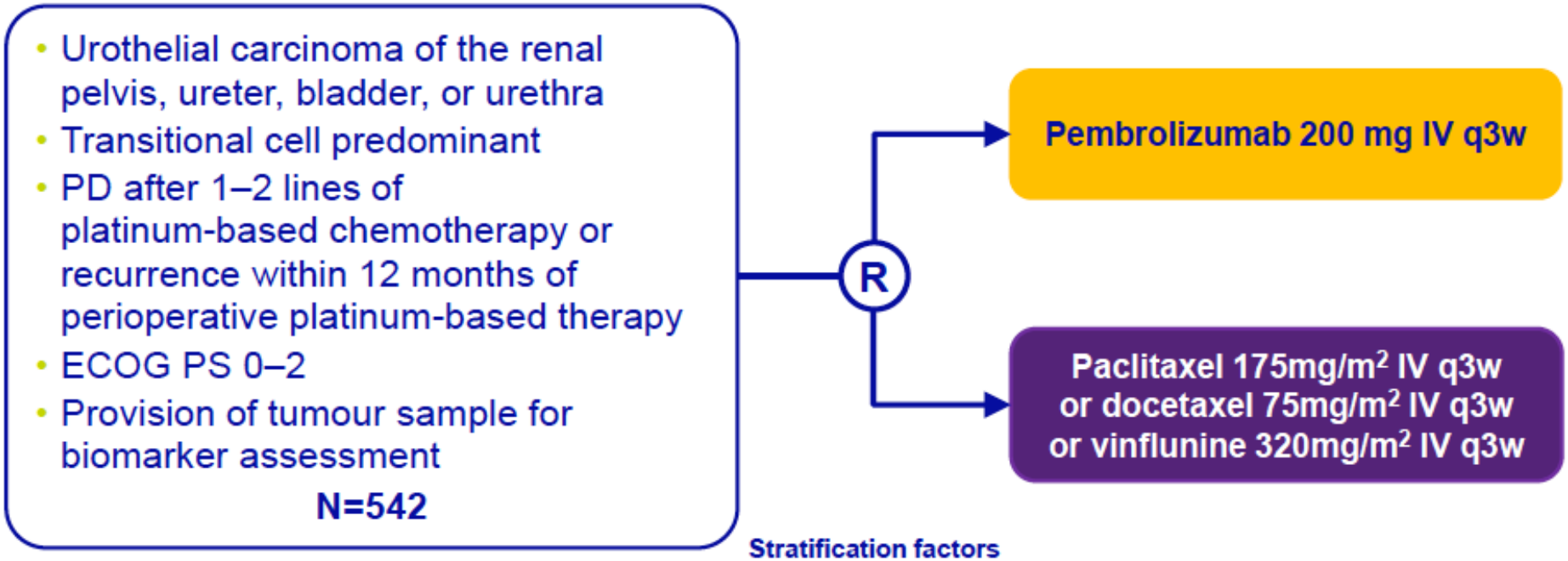
Confirmed ORR[a]	IC2/3		IC1/2/3		ITT	
	Atezo (n = 113)	Chemo (n = 116)	Atezo (n = 312)	Chemo (n = 306)	Atezo (n = 462)	Chemo (n = 461)
Responders, n (%)	26 (23%)	25 (22%)	44 (14%)	45 (15%)	62 (13%)	62 (13%)
95% CI, %	16, 32	15, 30	10, 19	11, 19	11, 17	11, 17
CR, n (%)	8 (7%)	8 (7%)	11 (4%)	13 (4%)	16 (3%)	16 (3%)

- Objective response was similar between arms
- Responses to atezolizumab were durable regardless of PD-L1 status
  - 63% of patients in the atezolizumab arm and 21% in the chemotherapy arm had ongoing responses at data cutoff



Powles T, et al. EAS 2017

KEYNOTE-045 study design

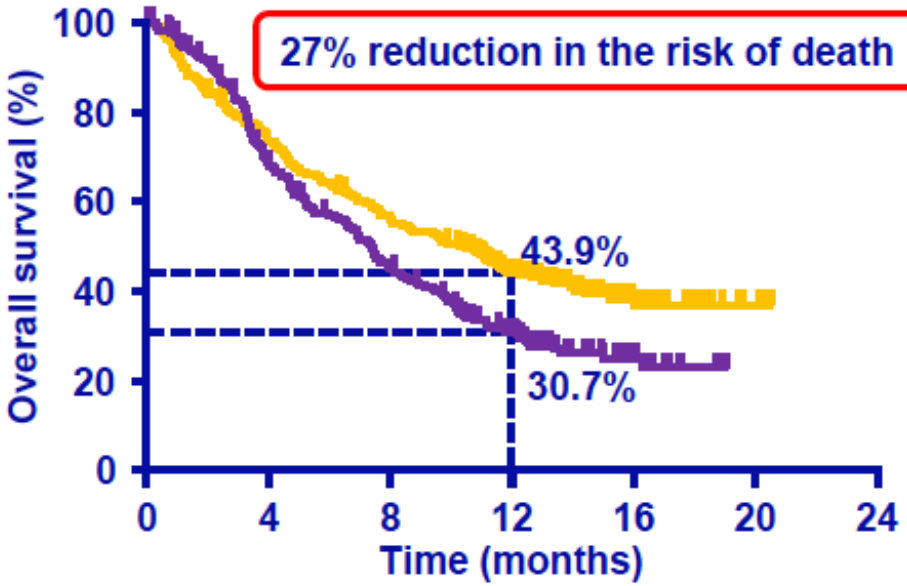


- **Co-primary endpoints**: OS and PFS in total and PD-L1 CPS ≥10% populations
- **Secondary endpoints**: ORR and DOR in total and PD-L1 CPS ≥10% populations; safety in total population

NCT02256436
Bellmunt J et al. N Engl J Med 2017 Mar 16;376(11):1015-1026

KEYNOTE-045 overall survival

Total population

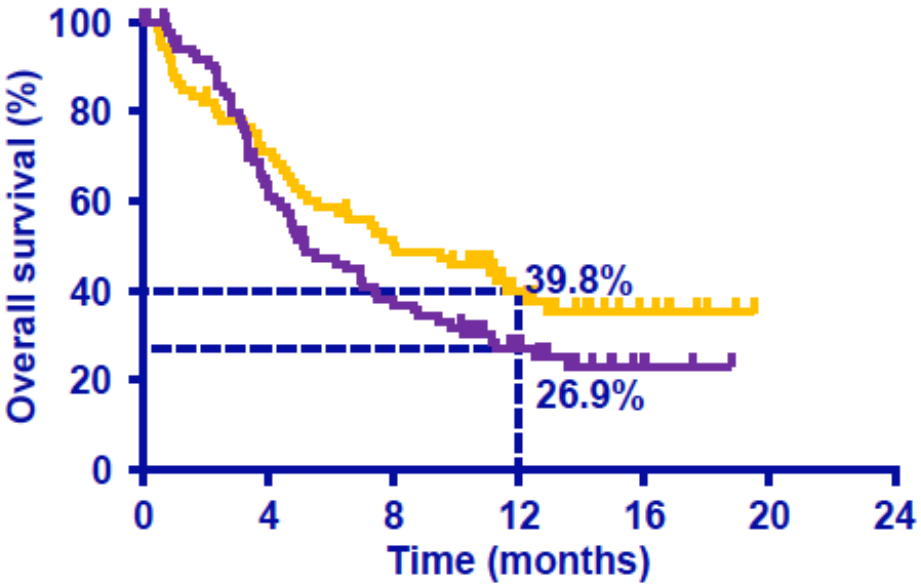


Number at risk

Pembro	270	226	194	169	147	131	87	54	27	13	4	0	0
Chemo	272	232	171	138	109	89	55	27	14	3	0	0	0

	Median OS months (95% CI)	HR (95% CI)	*P*
Pembrolizumab	10.3 (8.0–11.8)	0.73 (0.59–0.91)	0.0022
Chemotherapy	7.4 (6.1–8.3)		

High PD-L1 expression



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

	Median OS months (95% CI)	HR (95% CI)	*P*
Pembrolizumab	8.0 (5.0–12.3)	0.57 (0.37–0.88)	0.0048
Chemotherapy	5.2 (4.0–7.4)		

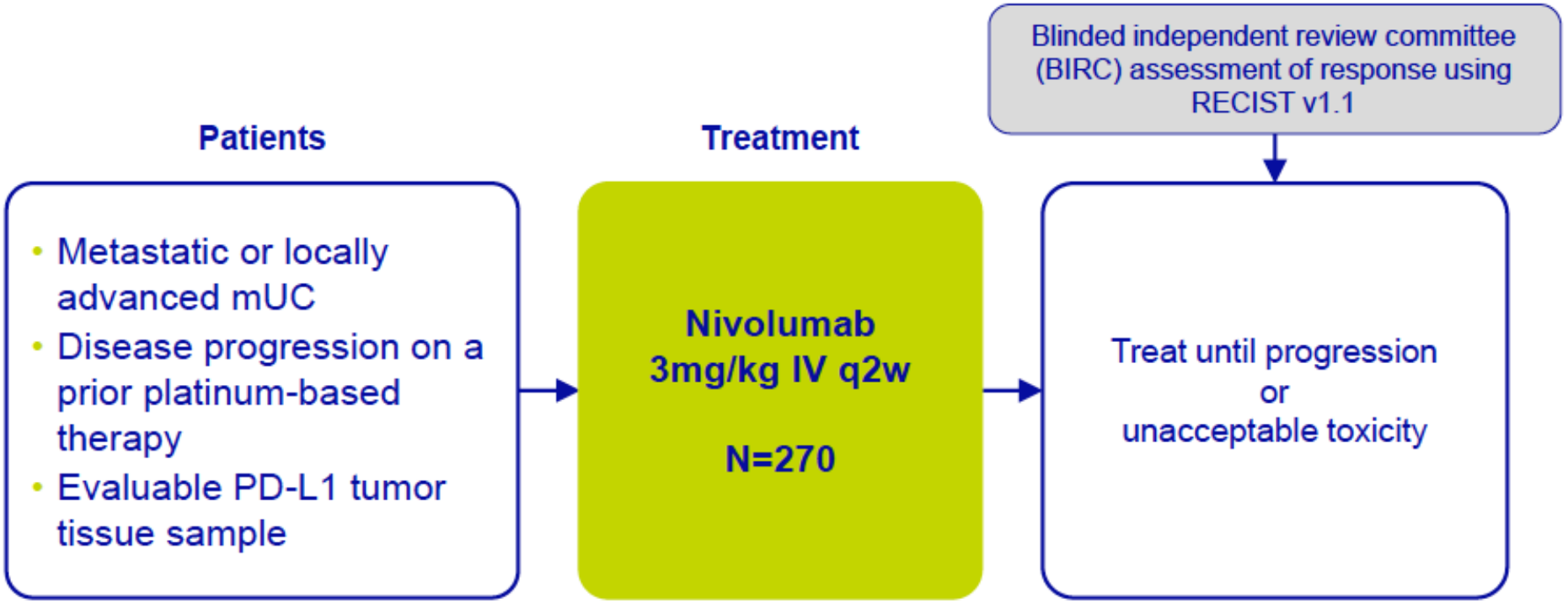
CPS, combined positive score (defined as percentage of PD-L1+ tumour cells (TC) and infiltrating immune cells (IC) relative to the total number of TC. High PD-L1 expression was defined as CPS ≥10%

Data cut-off date: September 7, 2016

Bellmunt J et al. N Engl J Med 2017 Mar 16;376(11):1015-1026

CheckMate275 study design

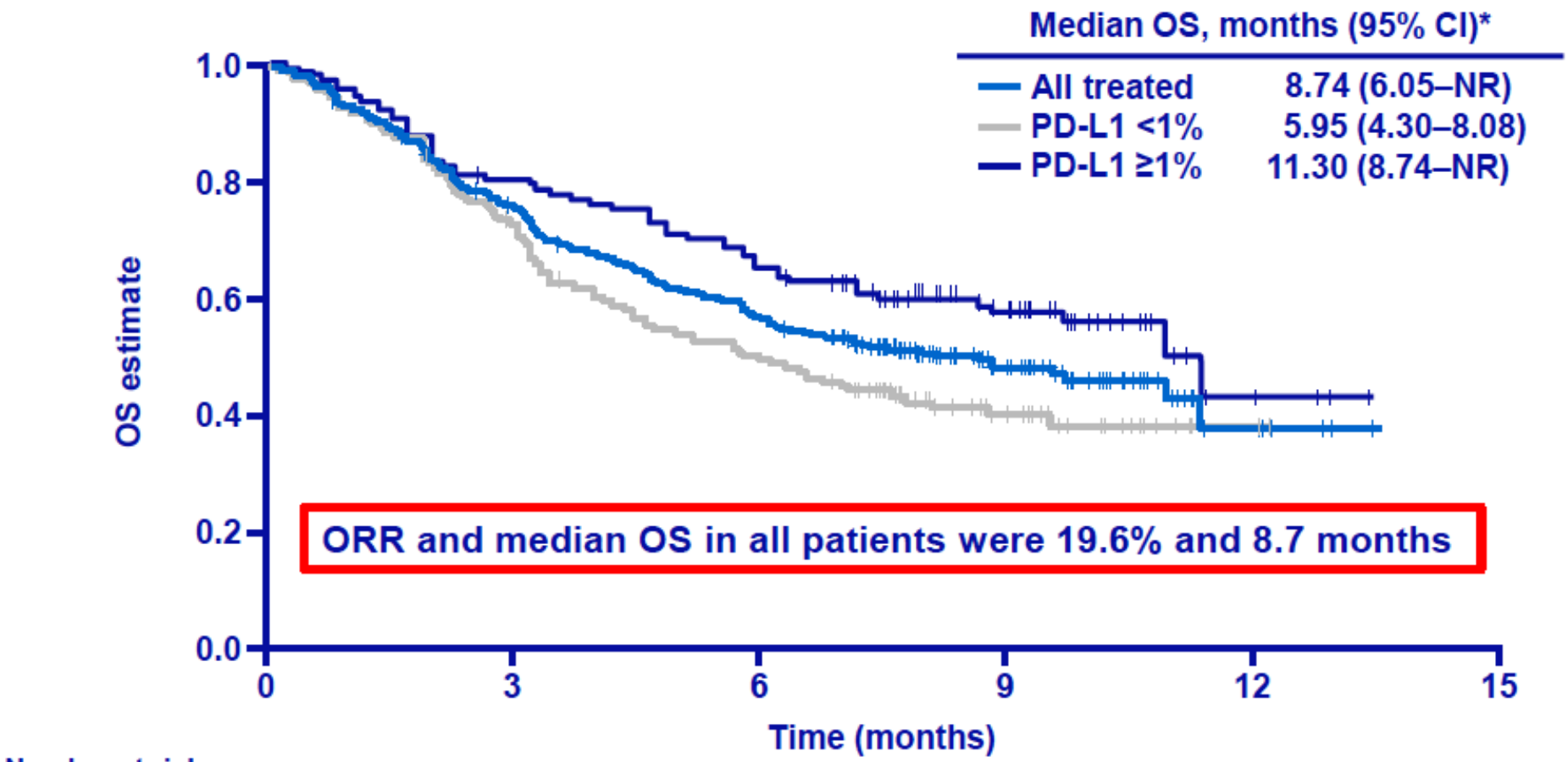
Open-label, single-arm, phase II study



- **Primary endpoint:** ORR based on blinded independent review committee (BIRC) (RECIST v1.1) evaluation in all patients and in patients with tumour PD-L1 expression ≥1% and ≥5%

NCT02387996
Sharma P et al. Lancet Oncol 2017 Mar;18(3):312-322.

CheckMate275 overall survival



*Similar results were seen using the 5% PD-L1 tumour expression cut-off

Sharma P et al. Lancet Oncol 2017; Lancet Oncol 2017 Mar;18(3):312-322

Durvalumab and avelumab in prior platinum urothelial cancer: summary of antitumour activity

Durvalumab[1]

	N=103
Confirmed ORR, % (95% CI)	20.4 (13.1, 29.5)
CR, %	3.9

Median duration of follow-up, 8.4 months
PD-L1-high expression defined as ≥25% of tumour cells (TCs) or immune cells (ICs) staining for PD-L1; PD-L1-low/negative expression defined as <25% of both TCs and ICs staining for PD-L1

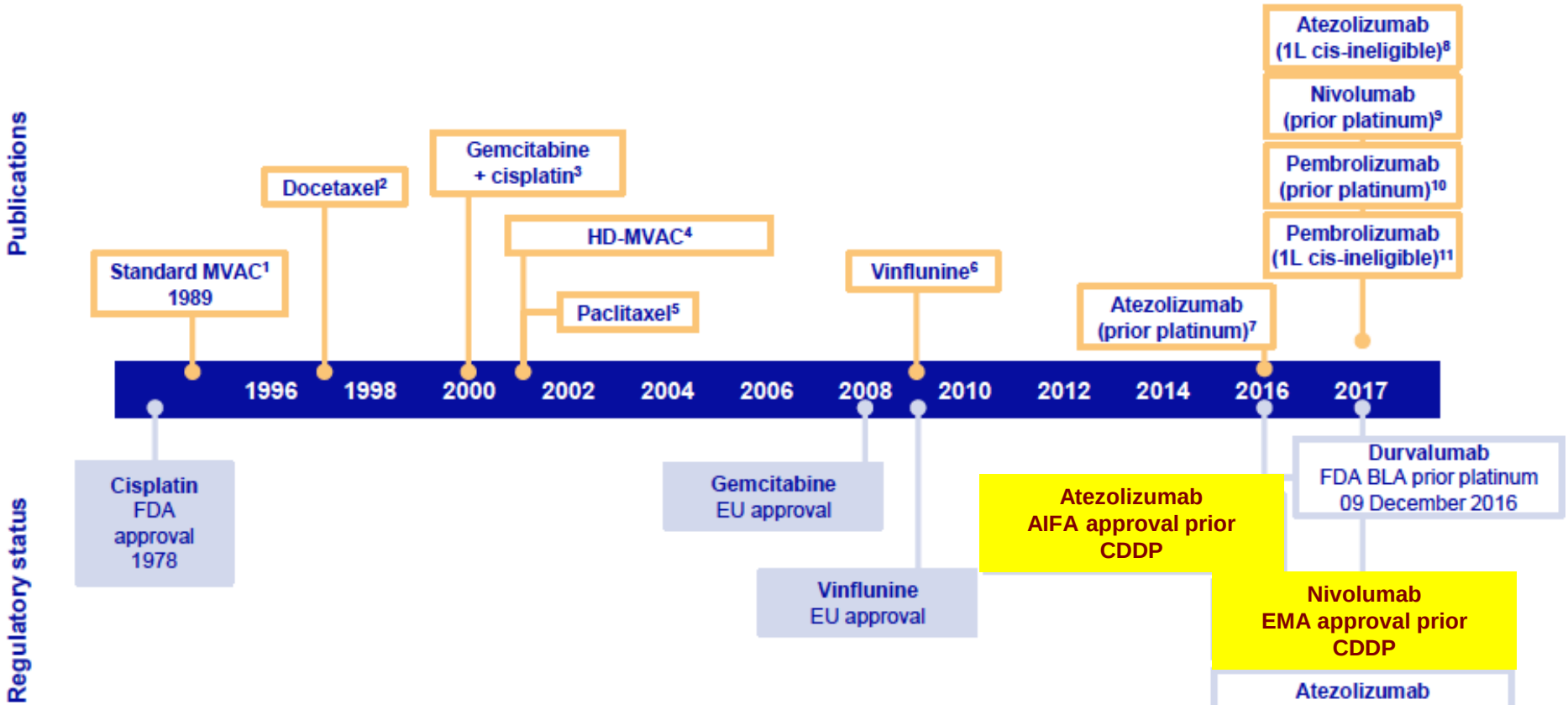
Avelumab[2]

	N=153
Confirmed ORR, % (95% CI)	17.6 (12.0, 24.6)
CR, %	5.9

Clinical cut-off, 19 March 2016. Median duration of follow-up, 7.3 months

1. Powles T et al. J Clin Oncol 2017;35(Suppl 6S):Abstract 286
2. Patel et al. J Clin Oncol 2017;35(Suppl 6S):Abstract 330

Evolution of systemic therapy for urothelial cancer



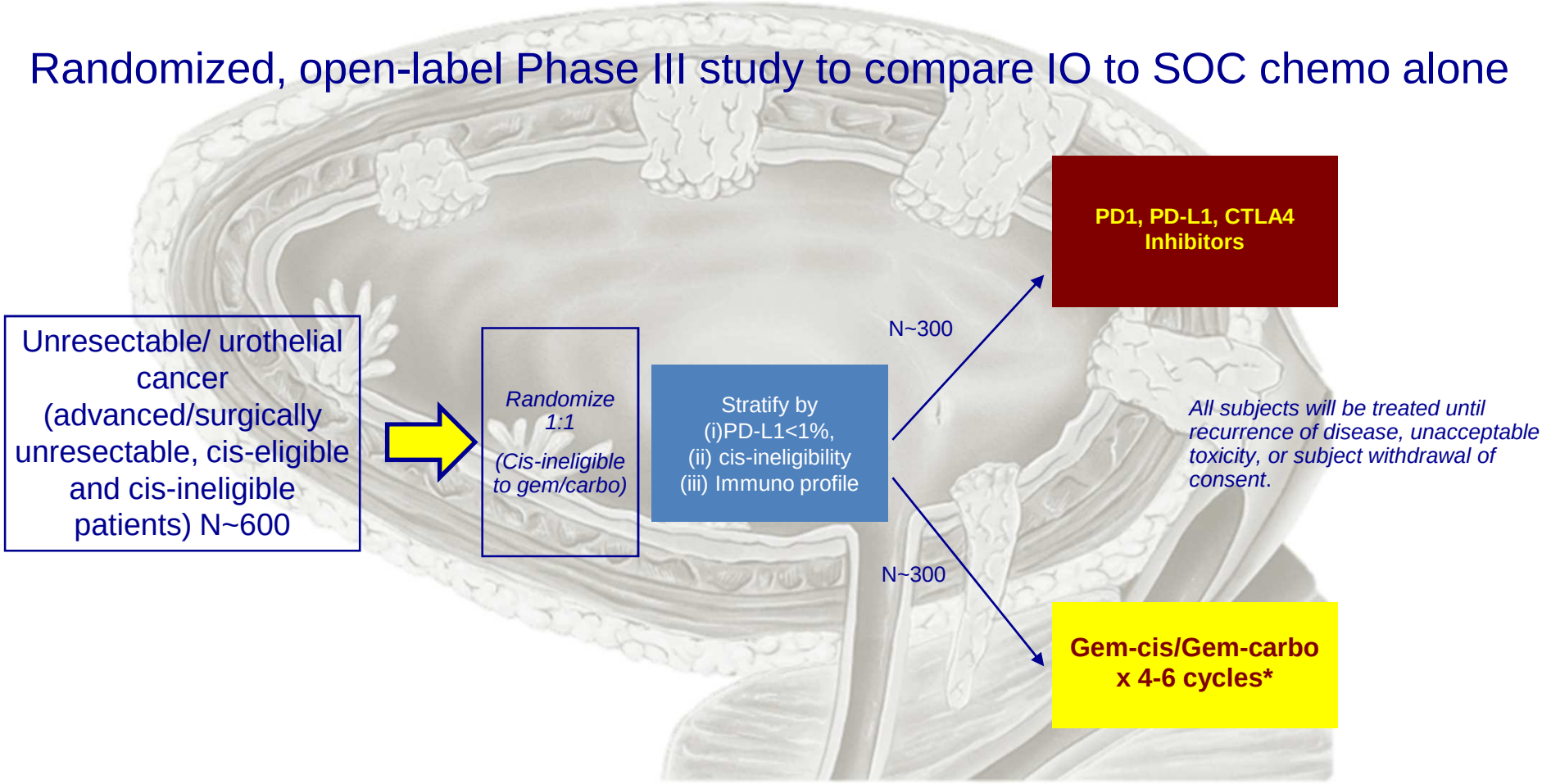
BLA, Biologics License Application

http://www.accessdata.fda.gaov/scripts/cder/drugsatfda/index.cfm; http://www.ema.europa.eu/ema/

1. Sternberg CN et al. Cancer 1989;64:2448–58; 2. McCaffrey JA et al. J Clin Oncol 1997;15:1853–7
3. von der Maase H. et al. J Clin Oncol 2005;23:4602–8; 4. Sternberg CN. et al. J Clin Oncol 2001;19:2638–46
5. Vaughn DJ et al. J Clin Oncol 2002;20:937-40; 6. Bellmunt J et al. J Clin Oncol 2009;27:4454–61
7. Rosenberg JE et al. Lancet 2016;387:1909–20; 8. Balar AV et al. Lancet 2017;389:67–76
9. Sharma P et al. Lancet Oncol 2017; doi: 10.1016/S1470-2045(17)30065-7
10. Bellmunt J et al. N Engl J Med 2017; doi: 10.1056/NEJMoa1613683
11. Balar AV et al. J Clin Oncol 2017;35(suppl 6S):Abstract 284

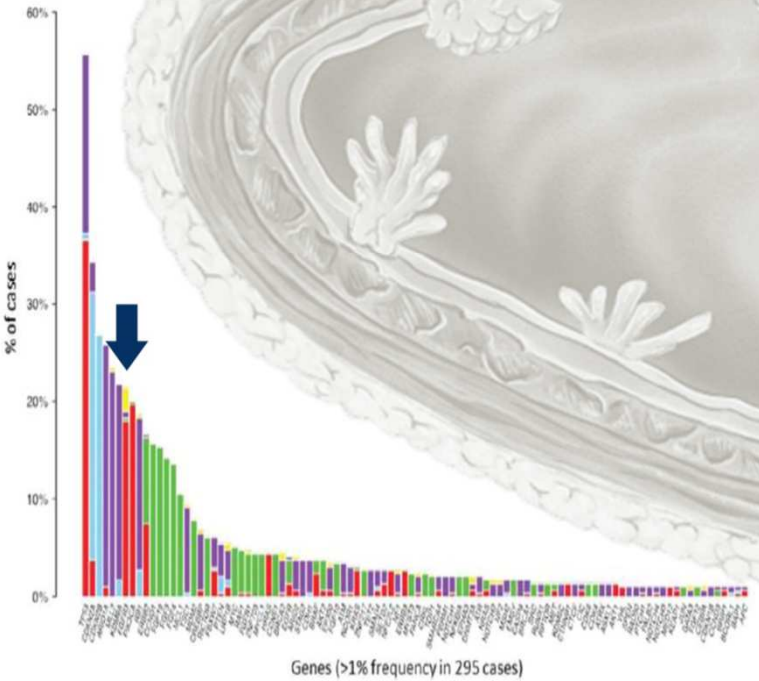
First-line Bladder Cancer trial

Randomized, open-label Phase III study to compare IO to SOC chemo alone



- Primary endpoint: co-primary OS and PFS
- Treated subjects will be evaluated for recurrence every 8 wks +/- 1 for 48 wks, followed by 12 wks thereafter

FGFR inhibition in bladder cancer



Comprehensive genomic profiling of 295 cases of clinically advanced urothelial carcinoma of the urinary bladder reveals a high frequency of clinically relevant genomic alterations. Ross JS, Cancer. 2015

≥ 2 line Bladder Cancer

Molecular Profiling

Stratify by
(i)PD-L1<1%,
(ii) cis-ineligibility
(iii) Immuno profile

FGFR Inhibitors

PD1, PD-L1, CTLA4 Inhibitors

Conclusion

- Mortality rate and treatment options for bladder cancer (BC) have not changed substantially in the last 30 years[1]
- Although the majority of pts are diagnosed with early-stage disease, there is a high probability of recurrence[2]
- Pts are generally older with co-morbidities, and up to 50% may not be eligible for first-line cisplatin-based chemo[3]
- PD1 pathway inhibition represents a significant advance in the treatment of mUC with favorable rates of response, survival and toxicity
- EMA approved Atezolizumab, Nivolumab for treatment of pts who have progressed following platinum-based therapy. PD-L1 IHC testing (SP142) had been approved as a complementary diagnostic.

1. Abdollah, et al. 2013; 2. Babjuk, et al. 2011; 3. Stenzl, et al. 2011; 4. Plimack E, ASCO 2016