Urothelial cancer:
Bladder-preserving strategies followed by systemic relapse
Clinical Case Discussion

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SECHENOV UNIVERSITY

BARCELONA 2019 ESMO congress

Disclosure

Personal financial interests

- Advisory board and speaker:
  Astellas; AstraZeneca; Bayer; Bristol-Myers Squibb; Cepheid; Ferring; Ipsen; Janssen; Lilly; MSD; Olympus; Pfizer; Roche; Richard Wolf; Sanochemia; Sanofi
- Advisory board: Urogen
- Patent:
  Method to determine prognosis after therapy for prostate cancer;
  Methods to determine prognosis after therapy for bladder cancer;
  Prognostic methods for patients with prostatic disease;
  Soluble Fas urinary marker for the detection of bladder transitional cell carcinoma

Non-financial interests

- Professor and Chairman, Department of Urology; Comprehensive Cancer Center; Medical University Vienna, Vienna, Austria
- Adjunct Professor; Weill Medical College of Cornell University, New York, NY, USA
- Adjunct Professor; UT Southwestern, Dallas, TX, USA
- Adjunct Professor; Charles University, Prague, CZ Republic
- Adjunct Professor; I.M. Sechenov First Moscow State Medical University, Moscow, Russia
- Bladder Cancer Research Consortium
- The Bladder Cancer Detection Group
- The Upper Tract Urothelial Carcinoma Collaboration
- Movember Foundation

Discussion points

- ✓ Treatment of non-metastatic muscle invasive Bca
- ✓ Neo-adjuvant chemotherapy
- ✓ 1st line therapy for metastatic BCa
- ✓ 2nd line therapy for metastatic BCa
- ✓ Novel therapies for metastatic BCa

BCa, bladder cancer

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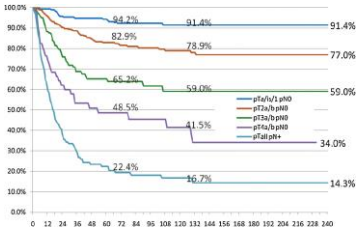
BCa, bladder cancer

Treatment of MIBC

clinical practice guidelines

Bladder cancer: ESMO Practice Guidelines for diagnosis, treatment and follow-up†

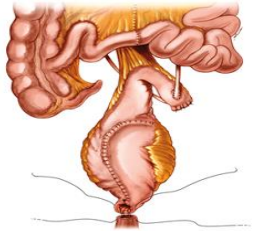
Guidelines on Muscle-invasive and Metastatic Bladder Cancer



- **Radical cystectomy & extended lymphadenectomy (standard)**
  - extended LAE has potentially shown to be beneficial (III, A)
    may be curative in few node & micro-metastasis

Hautmann et al.
Eur Urol 2012

Recommendations	Strength rating
Offer RC in T2-T4a, N0M0, and high-risk non-MIBC.	Strong
Perform a lymph node dissection as an integral part of cystectomy.	Strong



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LAE, lymphadenectomy; MIBC, muscle-invasive bladder cancer

Rational for bladder preservation

Radical cystectomy is morbid

→ 4% perioperative mortality — Bochner et al. Eur Urol 2015

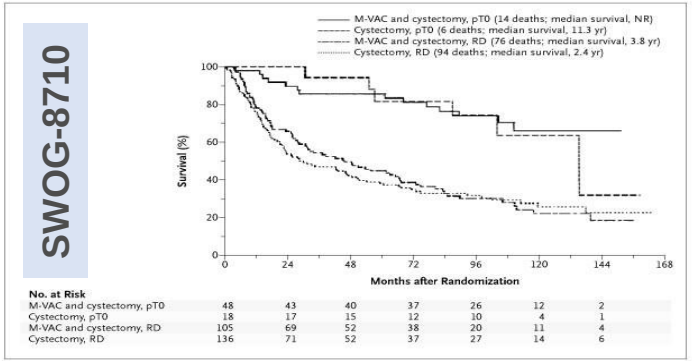
→ 66% morbidity — Shabsigh et al. Eur Urol 2009

→ 25% readmission / ~6% go to an ICU! — Hu et al. Cancer 2014

<u>pT0 rate</u> <u>with over 85% alive @ 5 years</u>

→ 15% pT0 at RC

→ 38% after NAC



Grossman et al. N Engl J Med 2003

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Radiotherapy with or without Chemotherapy in Muscle-Invasive Bladder Cancer

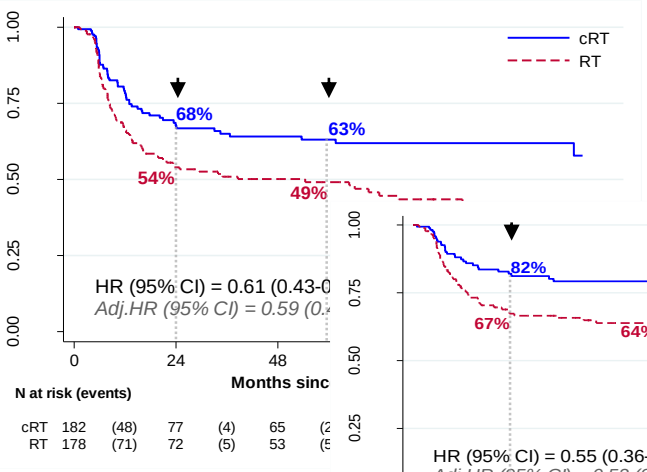
James et al. N Engl J Med. 2012

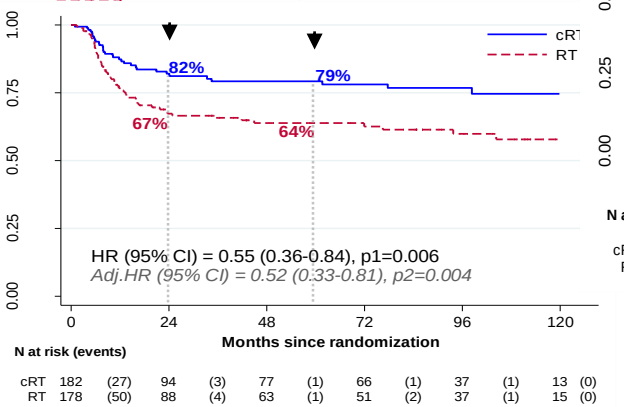
Snapshot of data: July 2016

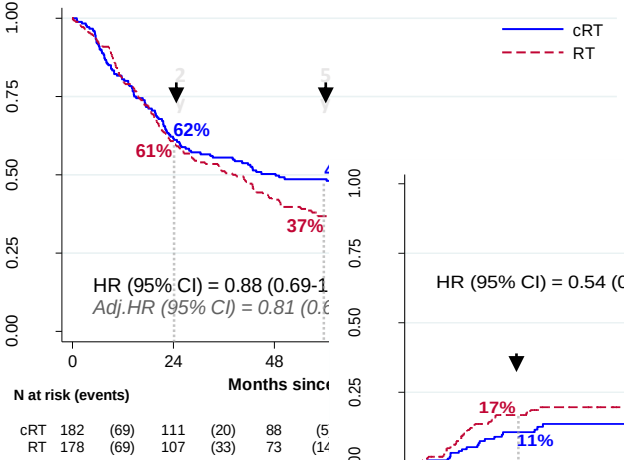
- Randomized phase 3 trial
- Median follow-up of 117.1 months

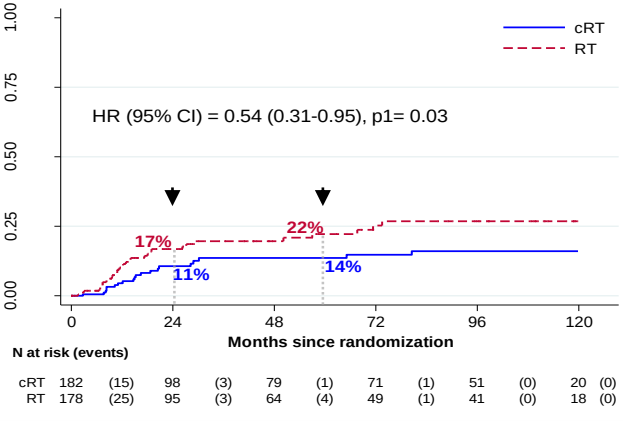
<u>Chemotherapy + radiotherapy</u>

- 39% reduction loco-regional recurrence
- 45% reduction invasive recurrence
- 12% reduction all-cause mortality
- 46% reduction need for salvage RC









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TMT bladder preservation trials

Trial, Phase	Stage	No	Radiation (Gy)	Concomitant chemotx	Adjuvant chemotx	Complete Response	Bladder intact survival	5-yr OS
BC2001, III	T2–T4a	360	55 to 64	5FU and Mitomycin				48%
RTOG 02–33, Randomized II	T2–4a	93	40.3 + 24	Paclitaxel/Cis 5FU/Cisplatin	Gemcitabine /Cis/Pac x 4	72% Pac 62% 5FU	67% Pac 71% 5FU	71% Pac 75% 5FU
RTOG 99-06, I/II	T2–T4a	80	40.3 + 24	Cis + Paclitaxel	GC x 4	81%	47%	56%
RTOG 97-06, I/II	T2–T4a	46	40.8 + 24	Cis	MCV x 3	74%	47% (3 yr)	61% (3 yr)
RTOG 95-06, I/II	T2–T4a	34	24 + 40	Cis + 5-FU		67%	66% (3 yr)	83% (3 yr)
RTOG 89-03, III	T2–T4a	123	39.6 + 25.2	Cis		75%	44% (4 yr)	62% (4 yr)
RTOG 85-12, II	T2–T4	42	40 + 24	Cis		66%		52%
Range	**T2-T4**	**34-360**	**~60-65**	**-**	**-**	**62-81%**	**44-71%**	**52-83%**

Premo et al. Urol Clin North Am 2015

TMT, trimodal therapy

Treatment of MIBC

clinical practice guidelines

Bladder cancer: ESMO Practice Guidelines for diagnosis, treatment and follow-up†

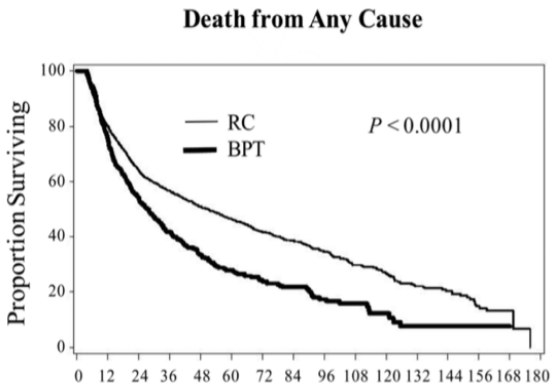
Guidelines on Muscle-invasive and Metastatic Bladder Cancer

- **External beam radiotherapy <u>may be considered as curative option</u>** as part of a **<u>multimodality bladder-preservation approach</u> (III)**
  - in patients unfit for surgery also or palliation (bleeding, pain)

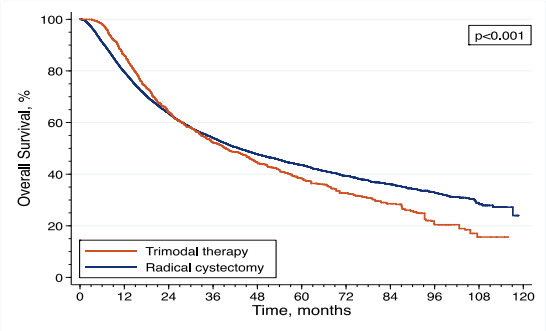
Recommendation	Strength rating
Do not offer radiotherapy alone as primary therapy for localised bladder cancer.	Strong
Offer MMT as an alternative to selected, well-informed and compliant patients, especially for whom cystectomy is not an option.	Strong

MIBC, muscle-invasive bladder cancer, MMT, multimodality treatment

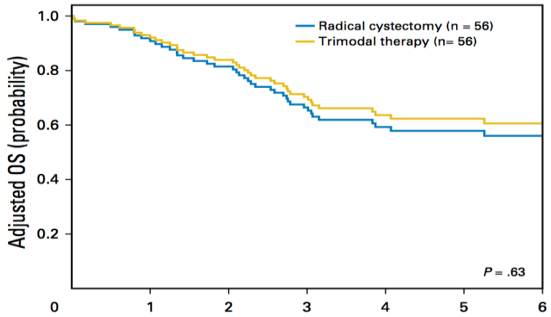
Comparative Effectiveness



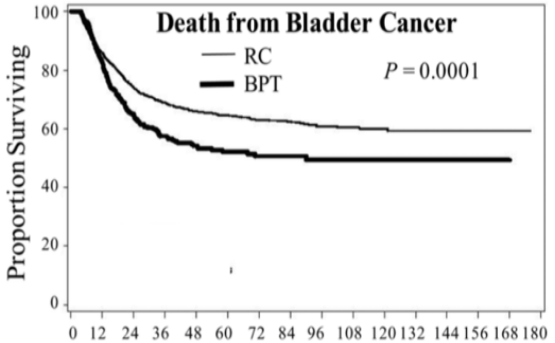
RC (n= 1426) vs BPT (n= 417)



RC (n= 1426) vs TMT (n= 11 586)

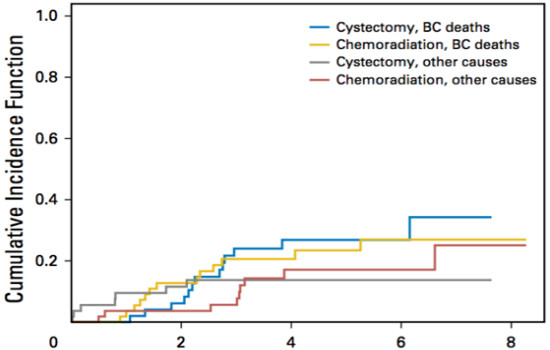


RC (n= 56) vs TMT (n= 56)



HR=1.37,
95%CI =1.2-1.6; *P*<0.001

Adverse treatment effect of TMT vs. RC decreased with age (*P*=0.004).



Bekelman et al. Value Health 2013

Seisen et al. Eur Urol 2017

Kulkarni et al. J Clin Oncol 2017

The optimal candidate for TMT!

Preferred or Ideal	Less than Ideal	Relative Contraindications	Absolute Contraindications
• T2 • No hydronephrosis • No CIS • Visibly complete TURBT • Unifocal tumor • Good bladder function and capacity	• T3a • Incomplete TURBT • Multifocal tumor • Poor bladder function or capacity	• T3b–T4a • Diffuse CIS • Lymph node positive disease	• T4b • Tumor-Related Hydronephrosis • Prior pelvic radiation therapy • Not a candidate for chemotherapy • Prostatic stromal invasion

TMT, trimodal therapy; TURBT, transurethral resection of bladder tumour; CIS, carcinoma in-situ

Premo et al. Urol Clin North Am 2015

Discussion points

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- ✓ **Neo-adjuvant chemotherapy**
- ✓ 1st line therapy for metastatic BCa
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Neadjuvant CTx

➢ **Platinum-based NAC before RC or definitive RT (I, A)**

<u>Rationale</u>

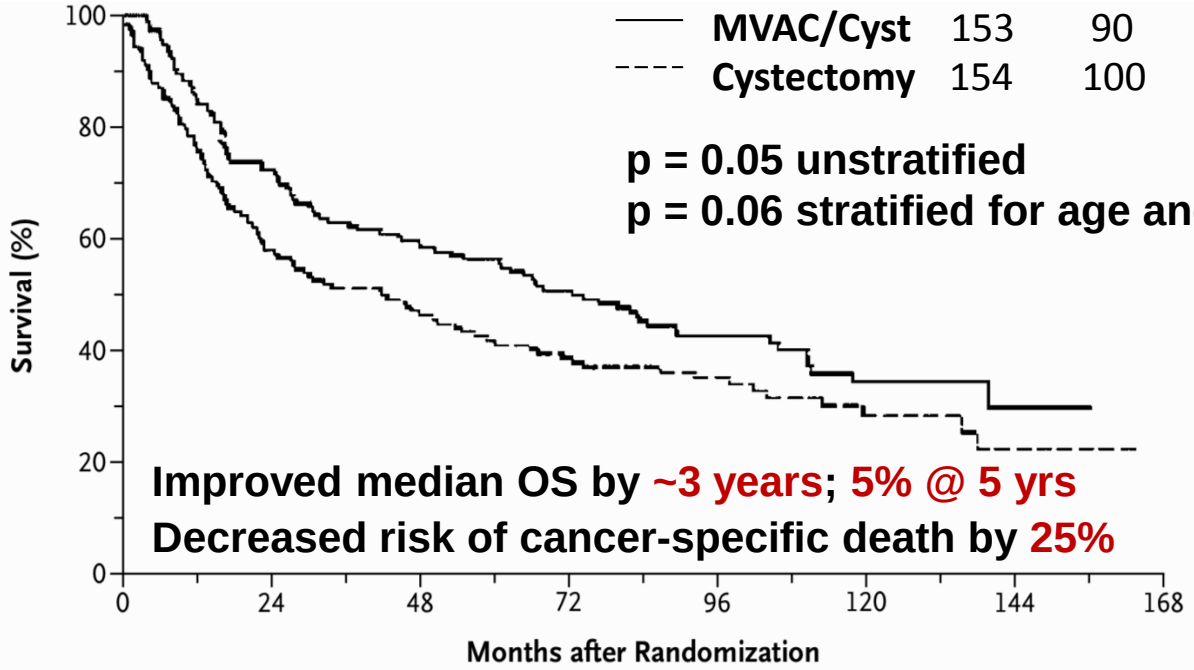
- Deaths generally not local events → as a result of metastatic disease
- Local interventions will not deal with micrometastases
- Best when pelvic blood supply is intact
- *In vivo* chemo-sensitivity trial
- Chemotherapy can cure some patients with metastatic BCa

Series	ChemoRx	No Pts	Primary Rx	Survival Benefit
Shearer	MTX	376	RT/RC	No
Wallace	Cisplatin	225	RT	No
Martinez-Pin	Cisplatin	121	RC	No
Nordic-2	MTX-cisplatin	317	RC	No
Vitale	Cis/FU/RT	104	RC	No
Shipley	CMV	121	Cisplatin-RT	No
Pellegrini	MVEC	171	RC	No
Malmstrom	**Doxorubicin/Cis**	**325**	**RT/RC**	**T3,T4**
Hall	**CMV**	**975**	**RT/RC/both**	**Yes**
Grossman	**MVAC**	**317**	**RC**	**Yes**

SWOG-8710

	At Risk	Deaths	Median in Months
MVAC/Cyst	153	90	77
Cystectomy	154	100	46

p = 0.05 unstratified
p = 0.06 stratified for age and stage



Improved median OS by ~3 years; 5% @ 5 yrs
Decreased risk of cancer-specific death by 25%

No. at Risk							
M-VAC and cystectomy	153	112	92	75	46	23	6
Cystectomy alone	154	88	67	50	37	18	7

Grossman et al. NEJM 2003

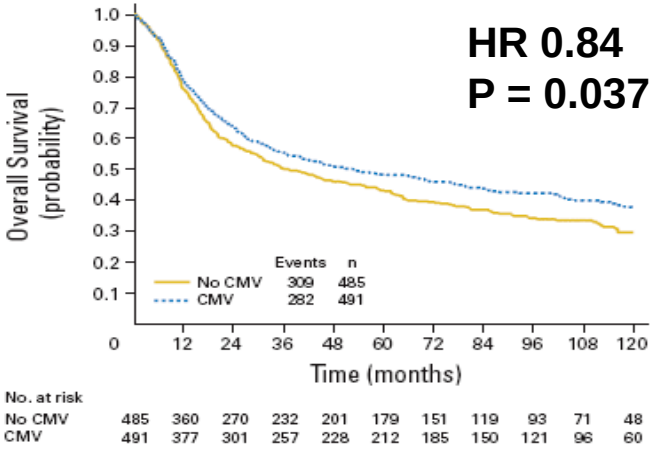
CMV for MIBC - BA06 30894 Trial

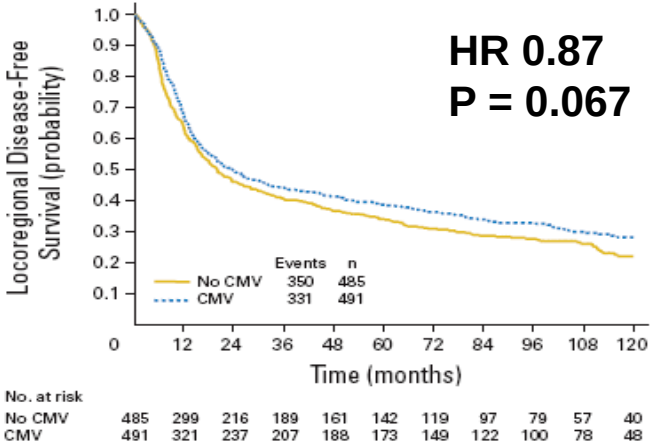
- Long-term results, median F-U is 8.0 years
- N = 976
- Randomized to 3 cycles of CMV
- Cystectomy and/or RT

→ pT0: 33% for CMV vs 12% in surgery alone

→ 6% absolute survival improvement @ 10 years

→ 16% reduction in the risk of death





Int Collaboration of Trialists, J Clin Oncol, 2011

Discussion points

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- ✓ **1st line therapy for metastatic BCa**
- ✓ 2nd line therapy for metastatic BCa
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Clinical considerations are currently the drivers of our treatment decisions in metastatic urothelial cancer

Patient/clinical characteristics

- Age
- Treatment history
- **Performance status**
- Comorbidities
  - **Renal function**
  - **Cardiac dysfunction/failure**
  - Peripheral vascular disease
- General health status (e.g. **haemoglobin**)

Tumour/disease characteristics

- Disease or treatment-related comorbidities
  - Renal function
  - Peripheral neuropathies
- Symptomatic disease or disease burden
- Presence of **visceral metastases**

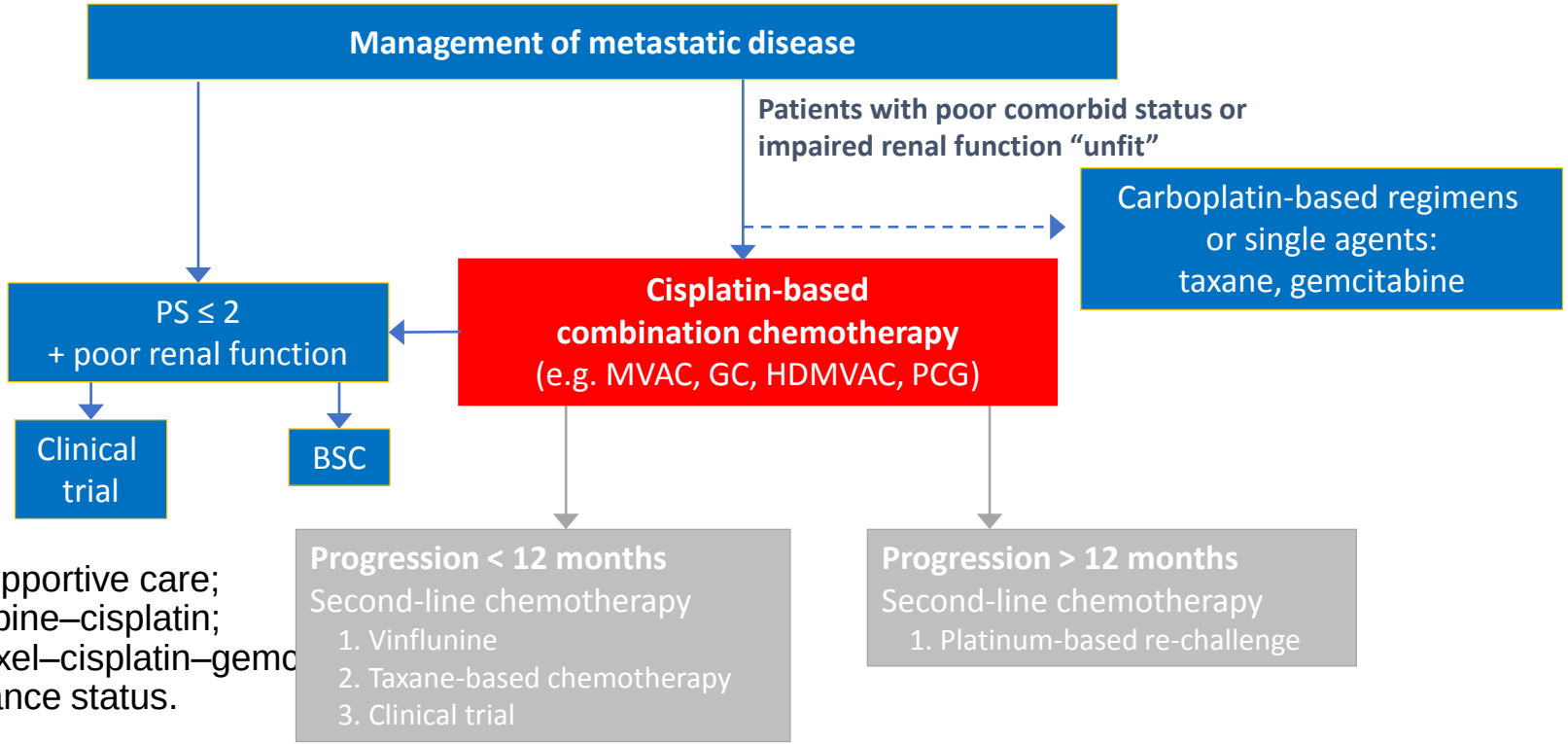
NCCN, National Cancer Care Network.

Treatment/logistical factors

- Eligibility for a clinical trial
- Tolerability of proposed therapy and symptom management
- Site of administration and proposed schedule
- Need for supportive agents to minimise dose delays and dose reductions
- Patient preference

Adapted from NCCN Guidelines bladder cancer. Version 4.2019. Available from: www.nccn.org/professionals/physician_gls/pdf/bladder.pdf. Accessed September 2019.

Options in the management of metastatic UC before 2016?



BSC, best supportive care;
GC, gemcitabine–cisplatin;
PCG, paclitaxel–cisplatin–gemc
PS, performance status.

Bellmunt et al. Ann Oncol 2014.

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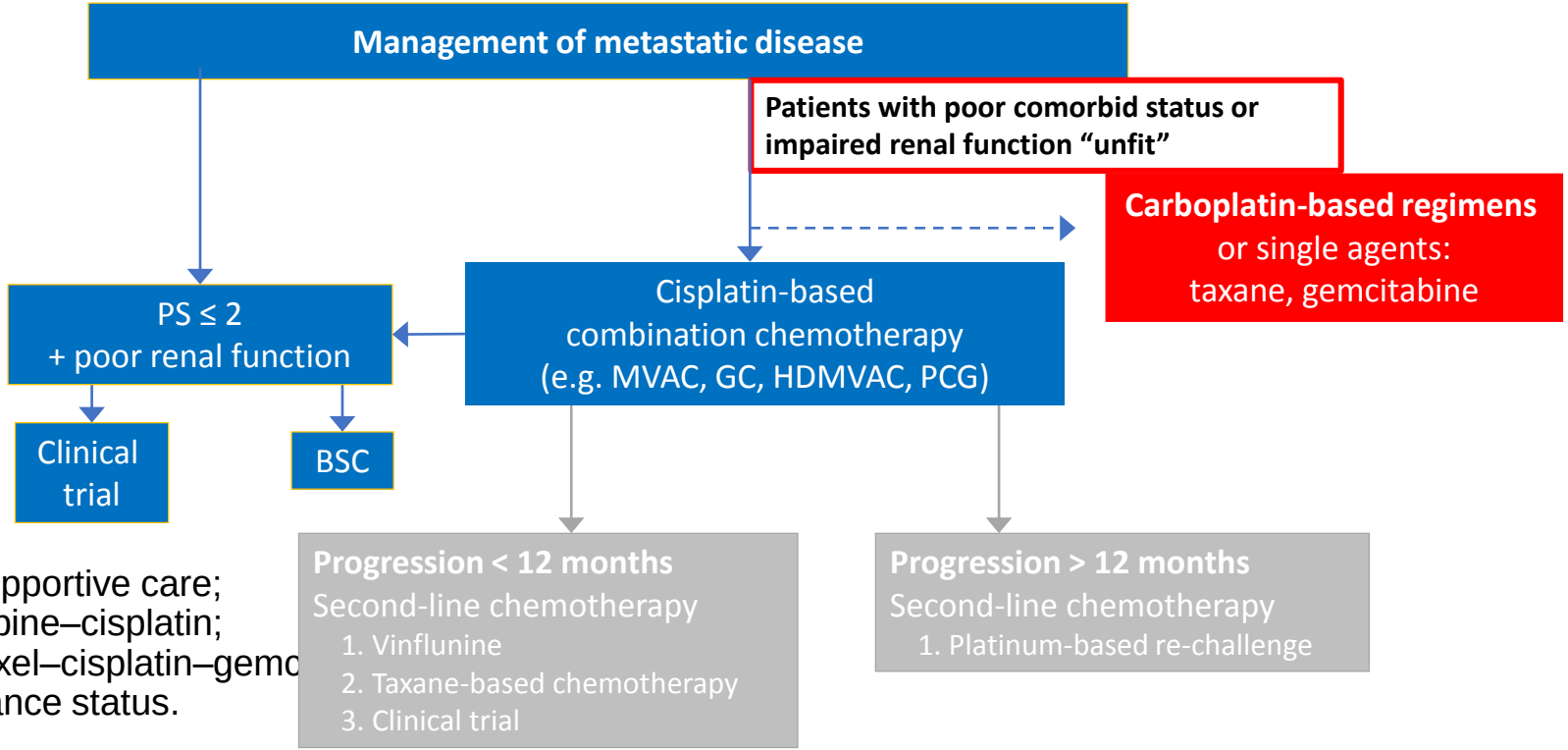

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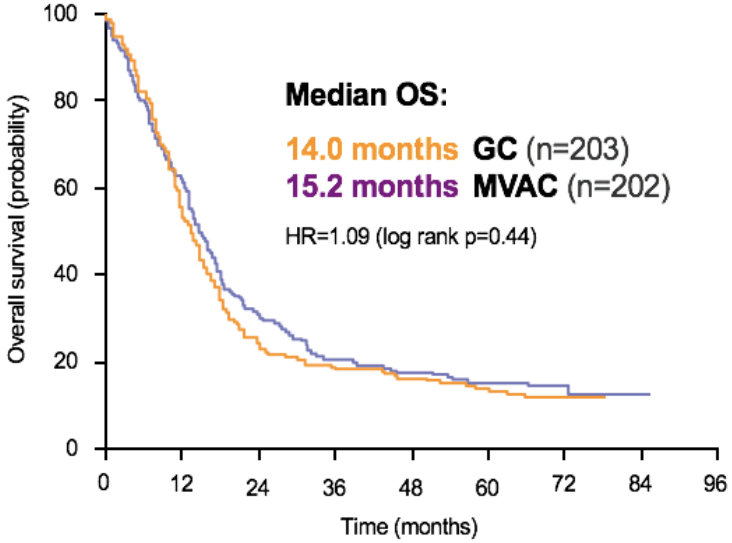
Bellmunt et al. Ann Oncol 2014.

1st line platinum-based CTx

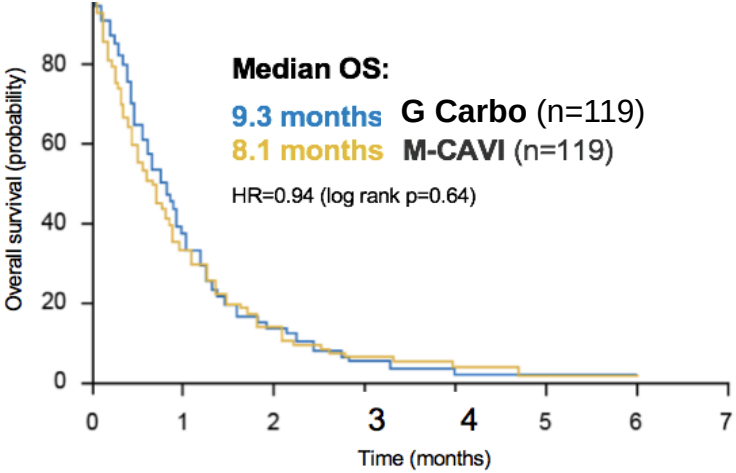
- **Cisplatin-based chemotherapy**
  - ORR 50-60%
  - 1yr OS 60%

von der Maase et al. J Clin Oncol 2005

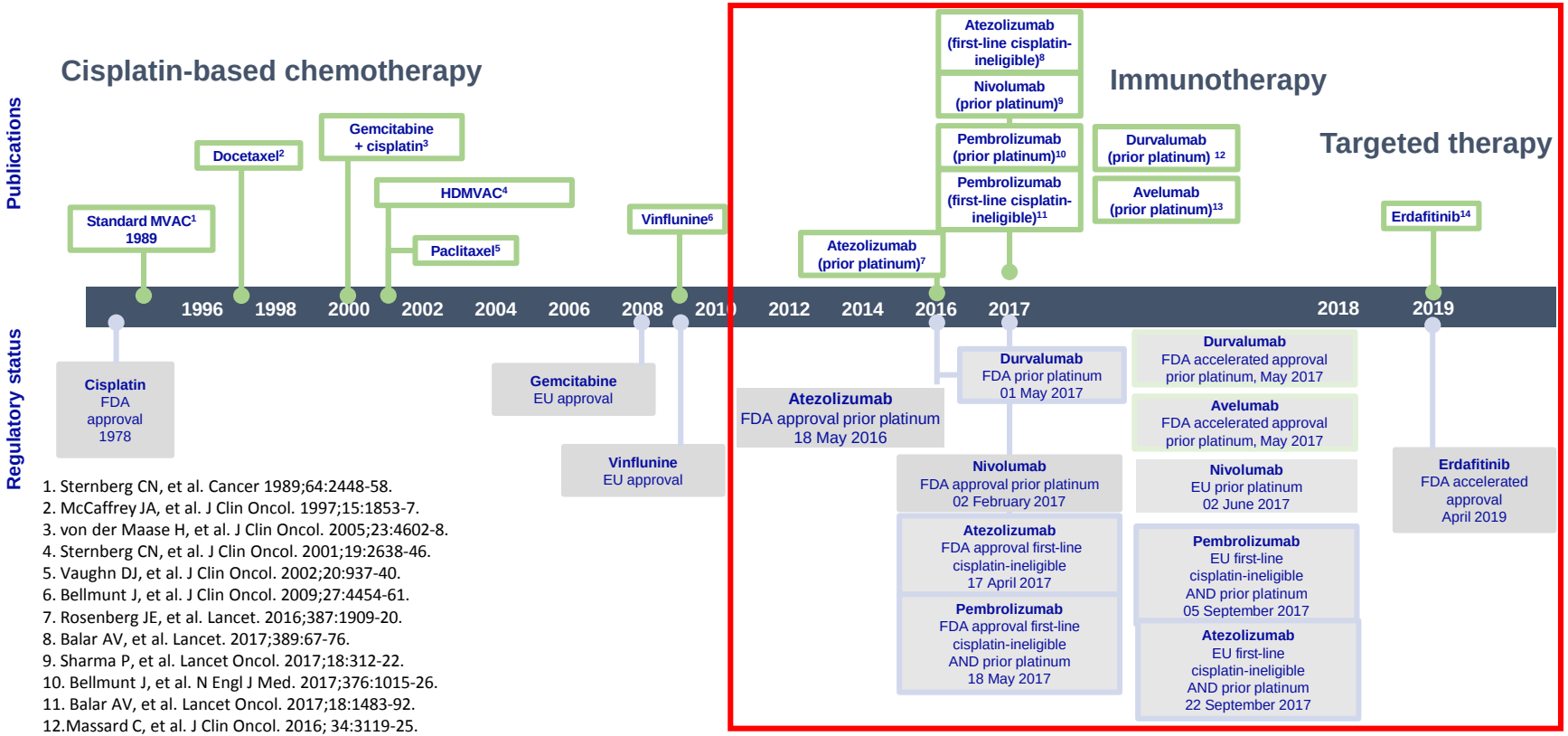


- **Carboplatin-based chemotherapy**
  - ORR 36%
  - 1yr OS 37%

de Santis et al. J Clin Oncol 2011



Evolution of systemic therapy for urothelial cancer



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.
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10. Bellmunt J, et al. N Engl J Med. 2017;376:1015-26.
11. Balar AV, et al. Lancet Oncol. 2017;18:1483-92.
12.Massard C, et al. J Clin Oncol. 2016; 34:3119-25.
13. Apolo A, et al. J Clin Oncol. 2017;35:2117-24.
14. Loriot Y, et al. N Engl J Med. 2019;381:338-48.

EU, European Union; FDA, US Food and Drug Administration;
(HD)MVAC, (high-dose) methotrexate–vinblastine–doxorubicin–cisplatin.

Immune-checkpoint inhibitors in the front-line in the cisplatin-ineligible setting

These are different studies and there is no comparative intent.

	Atezolizumab[1]	Pembrolizumab[2]
Phase	Phase II (IMvigor210 Cohort 1)	Phase II (KEYNOTE-052)
Number of patients	119	370
Dosing	1,200 mg every 3 weeks	200 mg every 3 weeks
ORR	23% (9% CR)	24% (5% CR)
Duration of response	70% ongoing at 17.2 months	78% ongoing at ≥ 6 months
Median OS	15.9 months	11.5 months[3]
Median PFS	2.7 months	2 months
Gr 3/4 treatment-related AEs	16%	16%

AE, adverse event; CR, complete response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

[1]Balar et al. Lancet 2017
[2]Balar et al. Lancet Oncol. 2017

PD-L1 expression

- Preliminary data from KEYNOTE-361 and IMvigor130 show reduced survival with pembrolizumab and atezolizumab compared with chemotherapy in patients with locally advanced or metastatic urothelial cancer who have not received prior therapy and whose tumours have low expressions of PD-L1.

→1 June 2018: the CHMP issued an update to the pembrolizumab and atezolizumab labels for first-line treatment of urothelial cancer in cisplatin-ineligible patients

Pembrolizumab as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy **and whose tumours express PD-L1 with a combined positive score ≥ 10**

Atezolizumab as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma who are considered cisplatin-ineligible **and whose tumours have a PD-L1 expression ≥ 5%**

CHMP, Committee for Medicinal Products for Human Use.

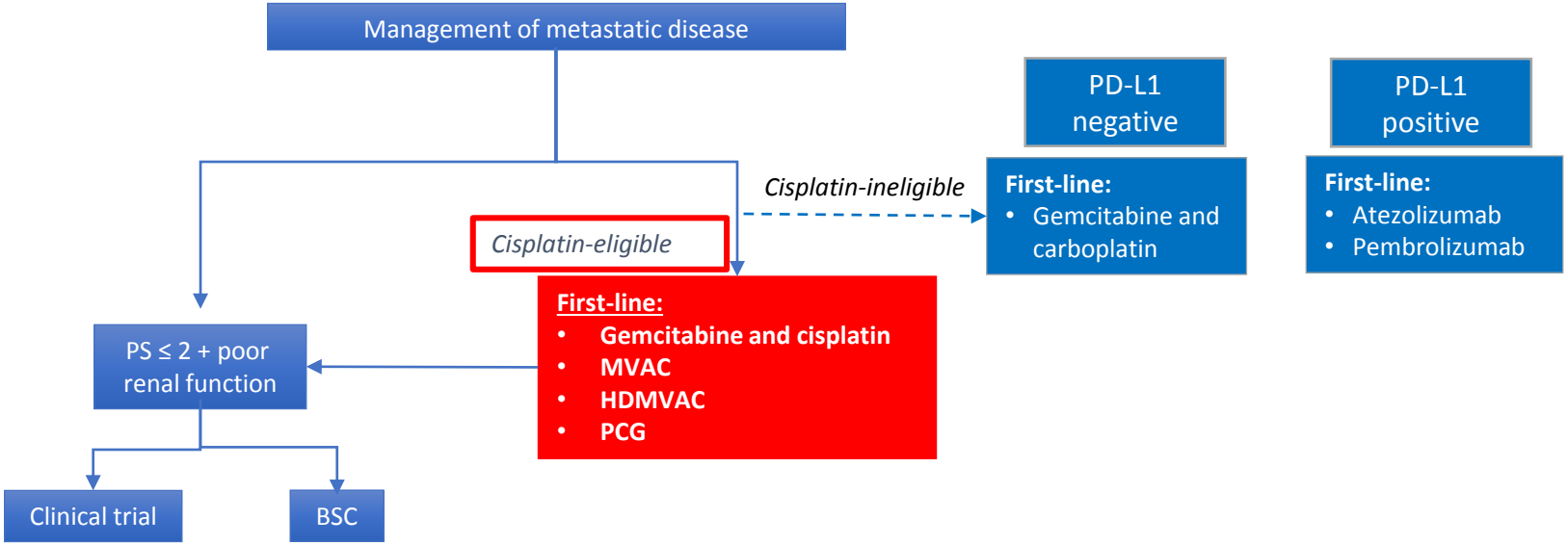
EMA press release 1 June 2018. EMA restricts use of Keytruda and Tecentriq in bladder cancer. Available from: www.ema.europa.eu/en/news/ema-restricts-use-keytruda-tecentriq-bladder-cancer. Accessed September 2019.

Immune-checkpoint inhibitors in the front-line in the cisplatin-ineligible setting

Pembrolizumab or **atezolizumab** is a reasonable therapeutic choice for front-line patients with PD-L1-positive advanced UC who are not eligible for cisplatin-based chemotherapy [III, B]

Update to Bellmunt J, et al. Ann Oncol 2014;25 (Suppl 3):iii40–iii48.
Available from: www.esmo.org/Guidelines/Genitourinary-Cancers/Bladder-Cancer/eUpdate-Bladder-Cancer-Treatment-Recommendations. Last updated August 2019. Accessed September 2019.

What are the current options in the management of mUC in clinical practice? Updated ESMO Guidelines



HDMVAC, high dose MVAC; PCG, paclitaxel cisplatin gemcitabine.

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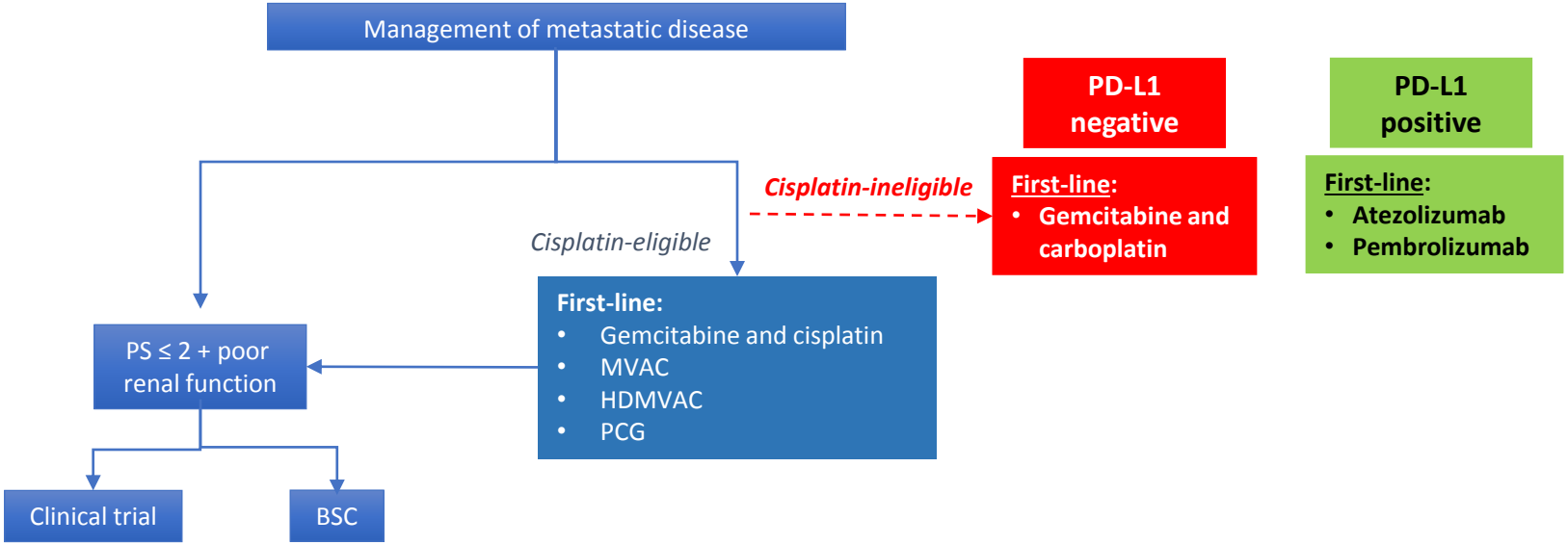

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2nd line post-platinum single agent studies

Author	Agent	Patients	RR (%)	PFS (months)	OS (months)
Witte[1]	Ifosfamide	56	20	2	5
McCaffrey[2]	Docetaxel	30	13	4	9
Lorusso[3]	Gemcitabine	31	23	4	5
Vaughn[4]	Paclitaxel	31	10	2	7
Sweeney[5]	Pemetrexed	47	28	3	10
Wulfing[11]	Lapatinib	39	2	2	4
Gallagher[12]	Sunitinib	77	5	2	7
Ko[13]	Nab-paclitaxel	48	28	6	11
Quinn[14]	Eribulin	150	34	4	9.5

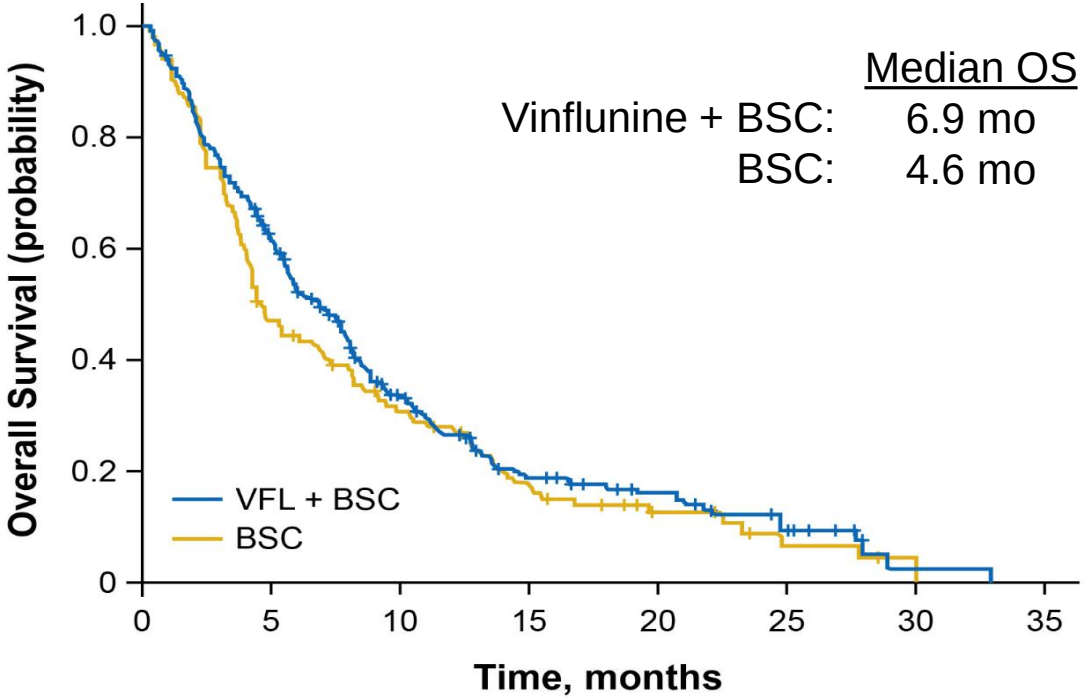
Response Rate = 12%

Progression-free survival = 3 months

Overall survival = 7 months

[1]JCO 1997;15(1):589-93 / [2]JCO 1997;15(5):1853-7 / [3]Eur J Can 1998;34(8)1208-12 / [4]JCO 2002;20(4):937-40 / [5]JCO 2006;24(21):3451-7 / [6]Invest New Drugs 2007;25(3):265-70 / [7]The Oncologist 2015;20(5):508-15 / [8]Cancer 2007;110(4):759-63 / [9]JCO 2009;27(27):4454-61 / [10]Cancer 2009;115(18):4090-5 / [11]Cancer 2009;115(13):2881-90 / [12]JCO 2010;28(8)1373-79 / [13]Lancet Oncol 2013;14(8):769-76.

2nd line Vinflunine



	Median OS
Vinflunine + BSC:	6.9 mo
BSC:	4.6 mo

Bellmunt J et al. Ann Oncol 2013

2nd line immune-checkpoint inhibition

These are different studies and there is no comparative intent

	Atezolizumab	Nivolumab	Pembrolizumab	Avelumab	Durvalumab
Phase	Phase III randomized vs chemotherapy	Phase II single-arm	Phase III randomized vs chemotherapy	Phase Ib	Phase I/II
Number of patients	931	265	542	249 (161 patients, ≥ 6 months of f/u)	191
Dosing	1,200 mg every 3 weeks	3 mg/kg every 2 weeks	200 mg every 3 weeks	10 mg/kg every 2 weeks	10 mg/kg every 2 weeks
ORR	13.4%	19.6%	21.1%	17%	17.8%
Duration of response	63% of responses ongoing at median f/u of 21.7 months	77% of responses ongoing at median f/u of 7 months	72% of responses ongoing at median f/u of 14.1 months	96% of responses ongoing at f/u of 7 months	50% of responses lasting ≥6 months
Median OS	8.6 months	8.7 months	10.3 months	6.5 months	18.2 months
Median PFS	2.1 months	2.0 months	2.1 months	1.5 months	1.5 months
Rate of Grade 3/4 treatment-related AEs	20%	18%	15%	8%	6.8%

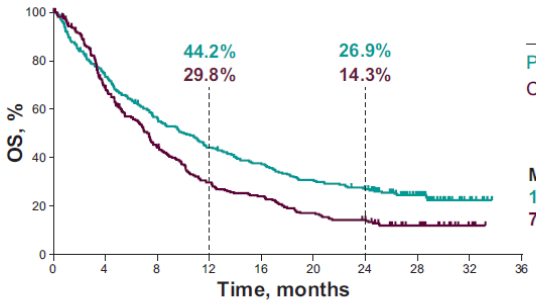
f/u, follow-up.

Slide courtesy of Grivas

1. Powles et al. Lancet. 2018; 2. Sharma et al. Lancet Oncol. 2017; 3. Bellmunt et al. N Engl J Med. 2017; 4. Patel et al. Lancet Oncol. 2018; 5. Powles et al. JAMA Oncol. 2017.

Post-platinum pembrolizumab KN 045 – updated data

OS in all patients

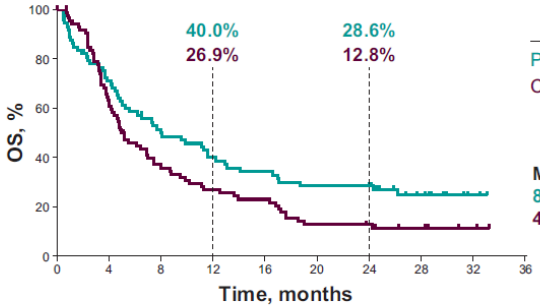


	Events, n	HR (95% CI)[a]	P[b]
Pembro	200	0.70	0.00015
Chemo	219	(0.57-0.85)	

Median (95% CI):
10.1 months (8.0-12.3 months)
7.3 months (6.1-8.1 months)

No. at risk										
Pembrolizumab	270	195	148	116	98	80	67	33	7	0
Chemotherapy	272	173	109	73	59	42	34	18	4	0

OS in patients with PD-L1 CPS ≥10



	Events, n	HR (95% CI)[a]	P[b]
Pembro	53	0.55	0.00122
Chemo	72	(0.37-0.81)	

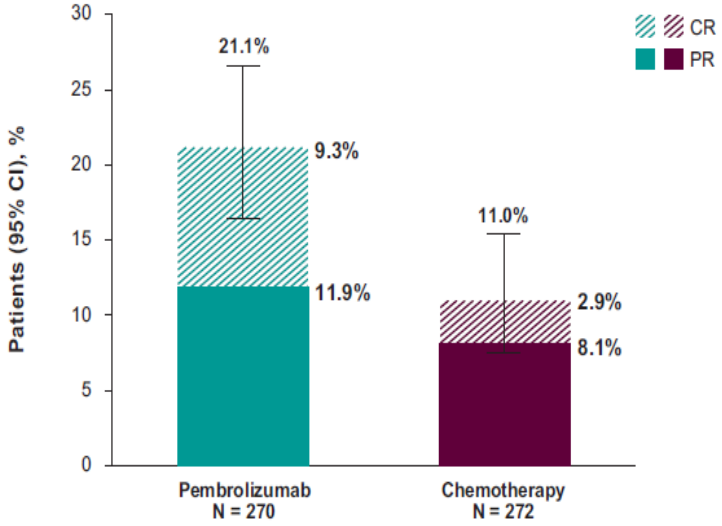
Median (95% CI):
8.0 months (5.0-12.3 months)
4.9 months (4.0-7.4 months

No. at risk										
Pembrolizumab	74	51	35	28	24	20	20	9	2	0
Chemotherapy	90	52	28	21	18	10	9	6	2	0

Adapted from: Fradet Y et al. ASCO 2018.

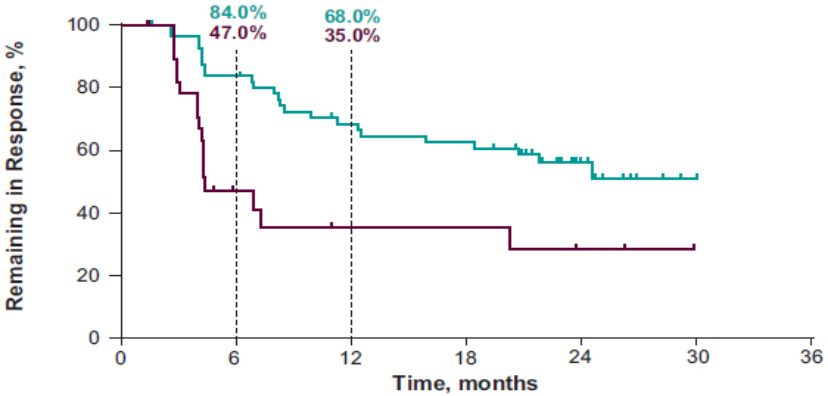
KEYNOTE-045: ORR & DOR in the total population

ORR



Duration of CR or PR

	Time to Response, median (range), mo	Duration of Response, median (range), mo
Pembro	2.1 (1.4-6.3)	NR (1.6+ to 30.0+)
Chemo	2.1 (1.7-4.9)	4.4 (1.4+ to 29.9+)



No. at risk							
Pembrolizumab	57	46	35	32	13	1	0
Chemotherapy	30	8	5	5	2	0	0

CI, confidence interval; CR, complete response; NR, not reached; ORR, objective response rate; PR, partial response.

Adapted from: Fradet Y et al. ASCO 2018.

Immune-checkpoint inhibitors in the second-line treatment of metastatic urothelial cancer

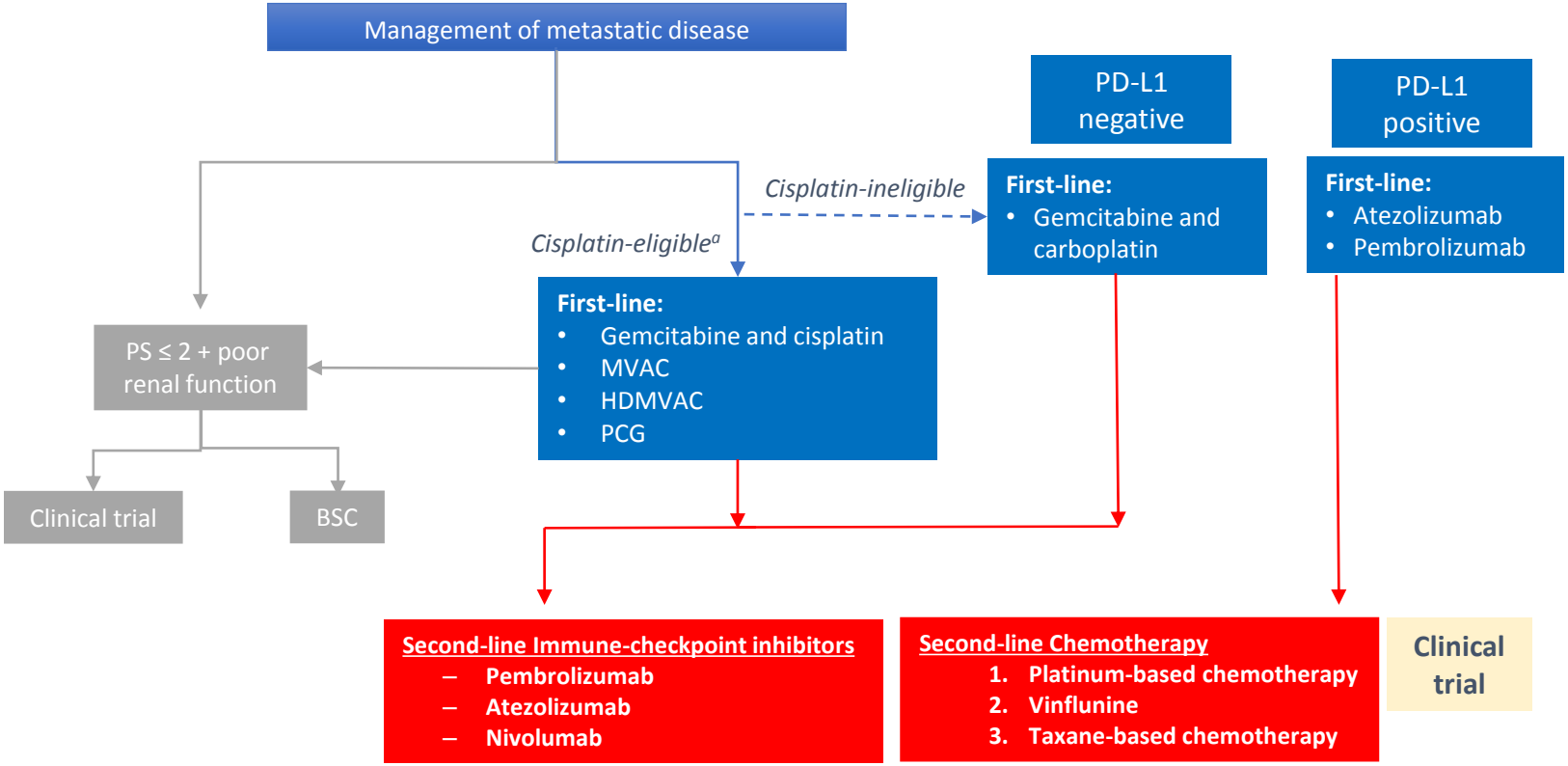
Pembrolizumab should be considered in patients with platinum-refractory urothelial cancer, as it improves OS [I, A]

The therapeutic use of **other immune-checkpoint inhibitors** that are EMA-approved **can be considered**, supported with lower level evidence: atezolizumab [II, B]; nivolumab [III, B]

EMA, European Medicines Agency.

Update to Bellmunt J, et al. Ann Oncol 2014;25 (Suppl 3):iii40–iii48.
Available from: www.esmo.org/Guidelines/Genitourinary-Cancers/Bladder-Cancer/eUpdate-Bladder-Cancer-Treatment-Recommendations.
Last updated August 2019. Accessed September 2019.

What are the current options in the management of mUC in clinical practice? Updated ESMO Guidelines



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Update to Bellmunt J, et al. Ann Oncol 2014;25 (Suppl 3):iii40–iii48.
Available from: www.esmo.org/Guidelines/Genitourinary-Cancers/Bladder-Cancer/eUpdate-Bladder-Cancer-Treatment-Recommendations.
Last updated August 2019. Accessed September 2019.

Discussion points

- ✓ Treatment of non-metastatic muscle invasive Bca
- ✓ Neo-adjuvant chemotherapy
- ✓ 1st line therapy for metastatic BCa
- ✓ 2nd line therapy for metastatic BCa
- ✓ **Novel therapies for metastatic BCa**

How should we select patients?

Biomarkers to identify patients more likely to respond

- **Criteria for therapy based on molecular characteristics**
  - → Patients most likely to respond
  - → Faster and more conclusive answers

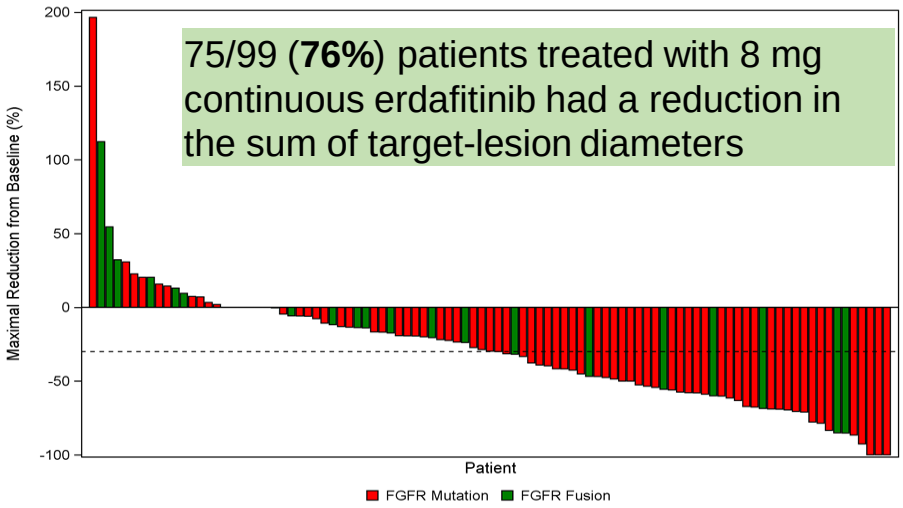
OLD MODEL: large populations

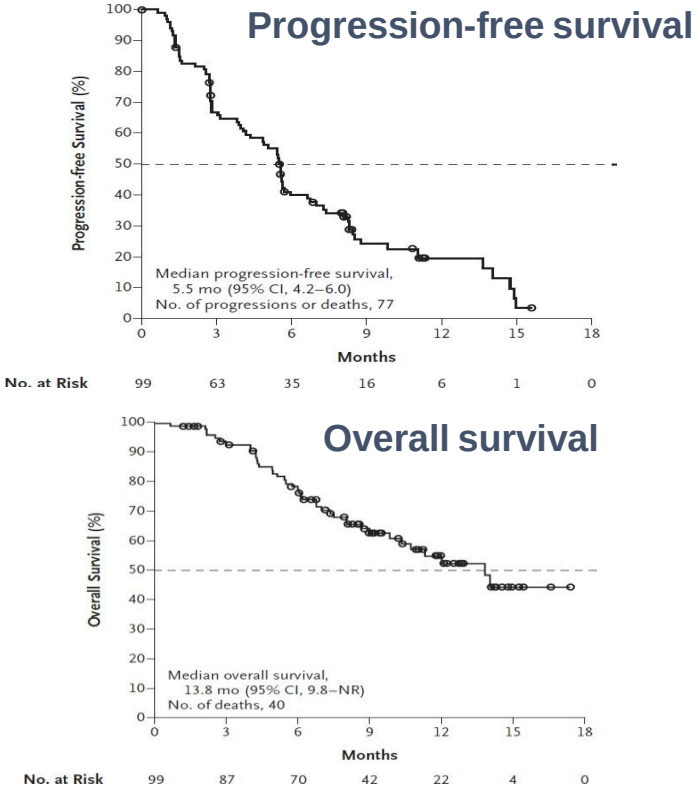
→ **Low efficacy with unnecessary side effects**

NEW MODEL: small populations with relevant molecular defects

→ All patients have the potential to respond

Erdafitinib FDA-approved for platinum-treated urothelial cancer with selected FGFR2/3 alterations





CI, confidence interval; Mo, months; No., number; NR, not reached

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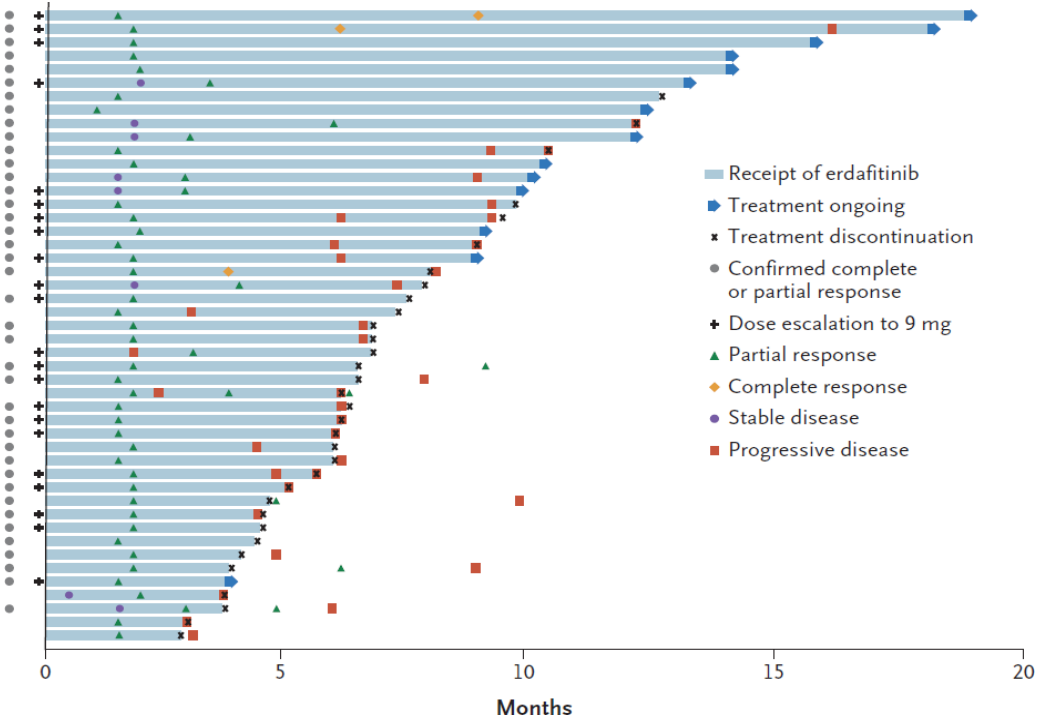
Loriot et al. N Engl J Med. 2019

Siefker-Radtke et al. ASCO 2018; abstract 4503.

Erdafitinib FDA-approved for platinum-treated urothelial cancer with selected FGFR2/3 alterations



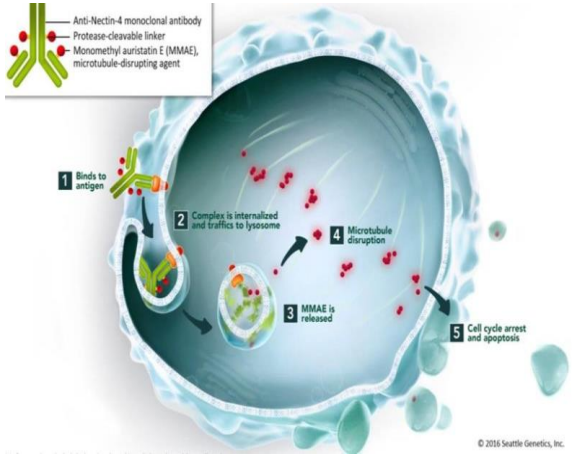
Median DOR 5.6 months
(95% CI: 4.2–7.2)

DOR, duration of response

~ 30% of these responses maintained for > 12 months

Loriot et al. N Engl J Med. 2019

Enfortumab vedotin targets nectin 4-expressing urothelial carcinoma



Results from EV-201[1]

ORR

44%

mPFS

5.8 months

mOS

11.7 months

These are different studies and there is no comparative intent.

	KEYNOTE-045 phase 3 trial[1]		EV-101[3]
	Pembrolizumab	Paclitaxel/docetaxel/ vinflunine	Enfortumab vedotin
ORR, %	21.1[2]	11.0[2]	43
mPFS, months	2.1	3.3	5.4
mOS, months	10.1	7.2	12.9
DOR, months	29.7	4.4	7.4

mOS, median overall survival;
mPFS, median progression-free survival;
ORR, objective response rate.

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1.Necchi et al. Abstract ESMO 2019; abstract 919P
2.Fradet et al. Annals of Oncology. 2019.
3. Rosenberg et al. ASCO GU 2019; abstract 377.

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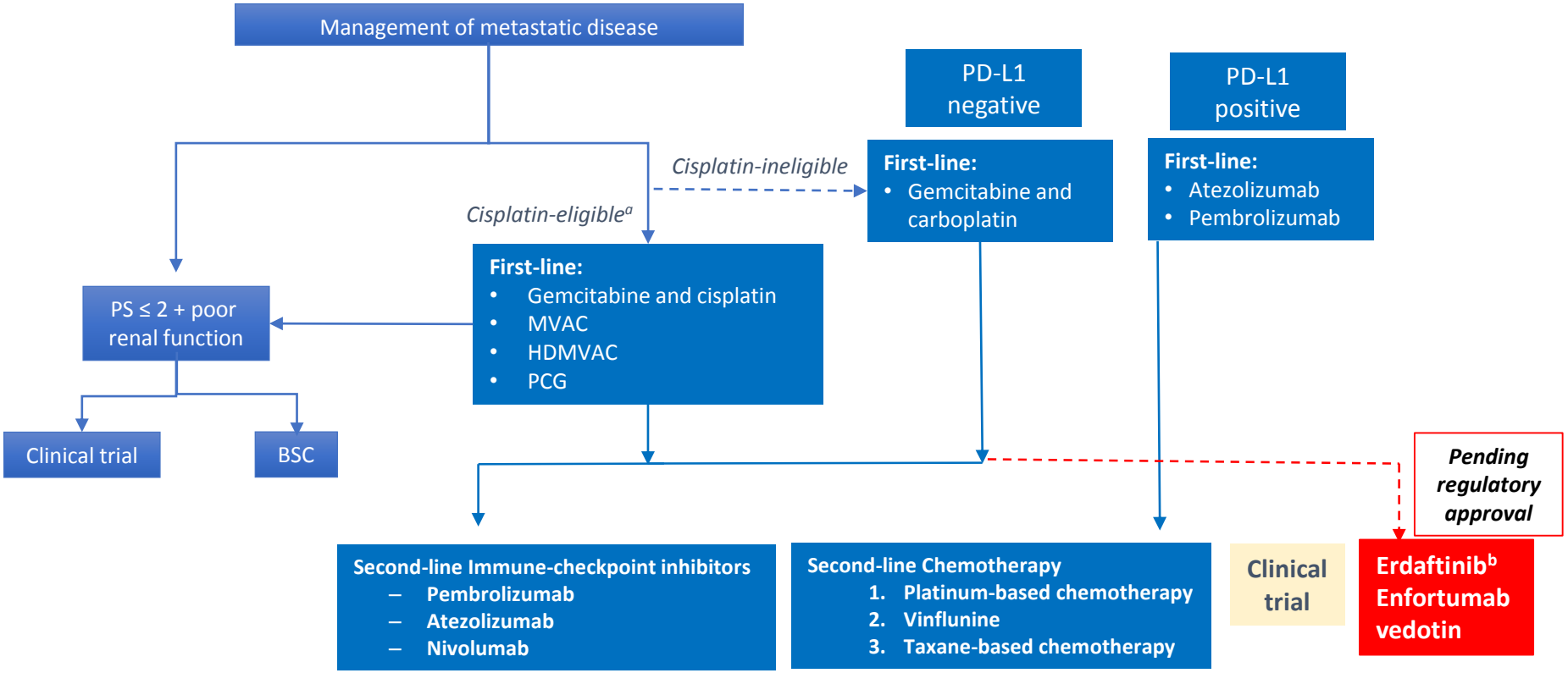

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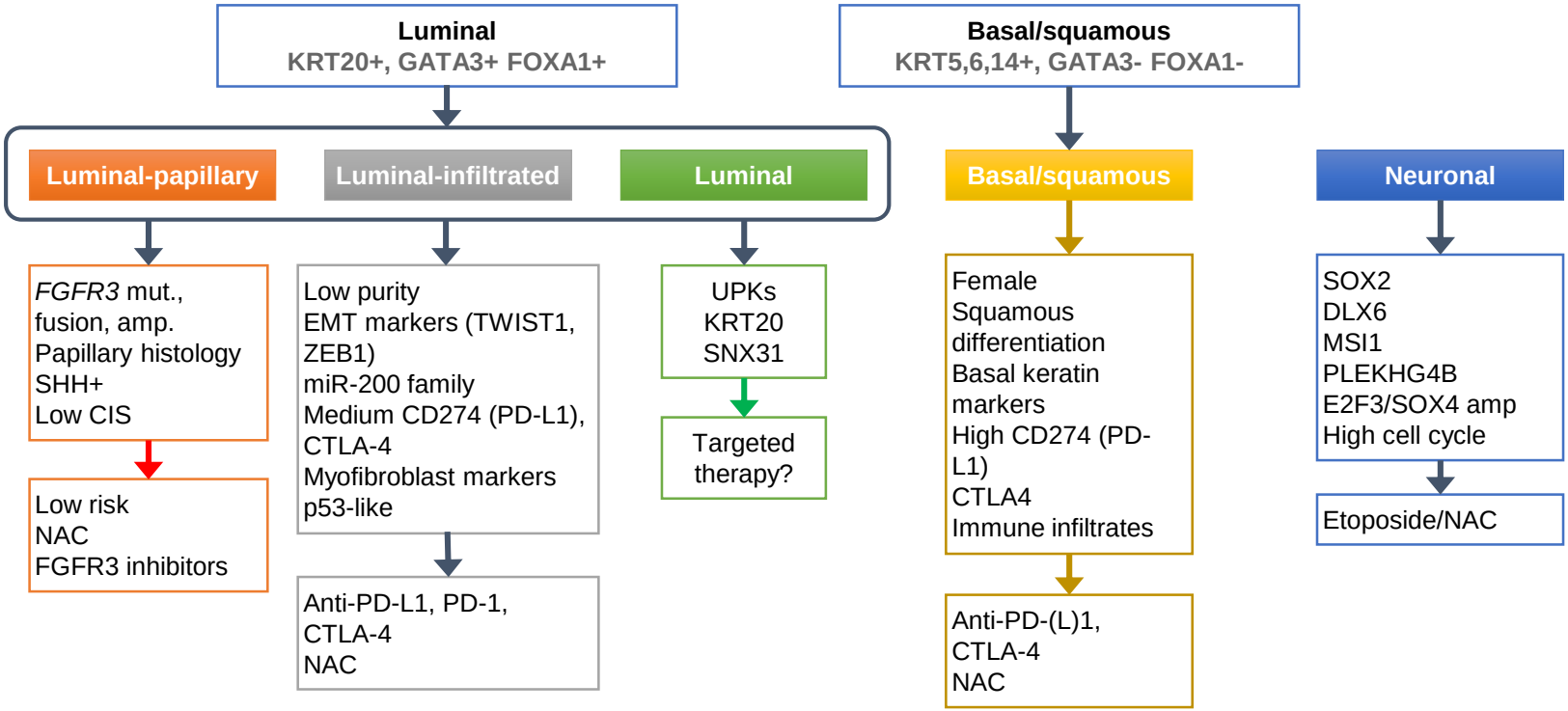
Available from: www.esmo.org/Guidelines/Genitourinary-Cancers/Bladder-Cancer/eUpdate-Bladder-Cancer-Treatment-Recommendations.
Last updated August 2019. Accessed September 2019.

Comprehensive molecular characterization of MIBC



amp, ampification; MIBC, MIBC, muscle-invasive bladder cancer
PD-(L)1, programmed death (ligand)-1; SHH, sonic hedgehog

Robertson et al. Cell. 2017

Thank you