Postgraduate Medical Oncology April 2021

Treatment of metastatic Bladder Cancer

EORTC
European Organisation for Research and Treatment of Cancer
The future of cancer therapy

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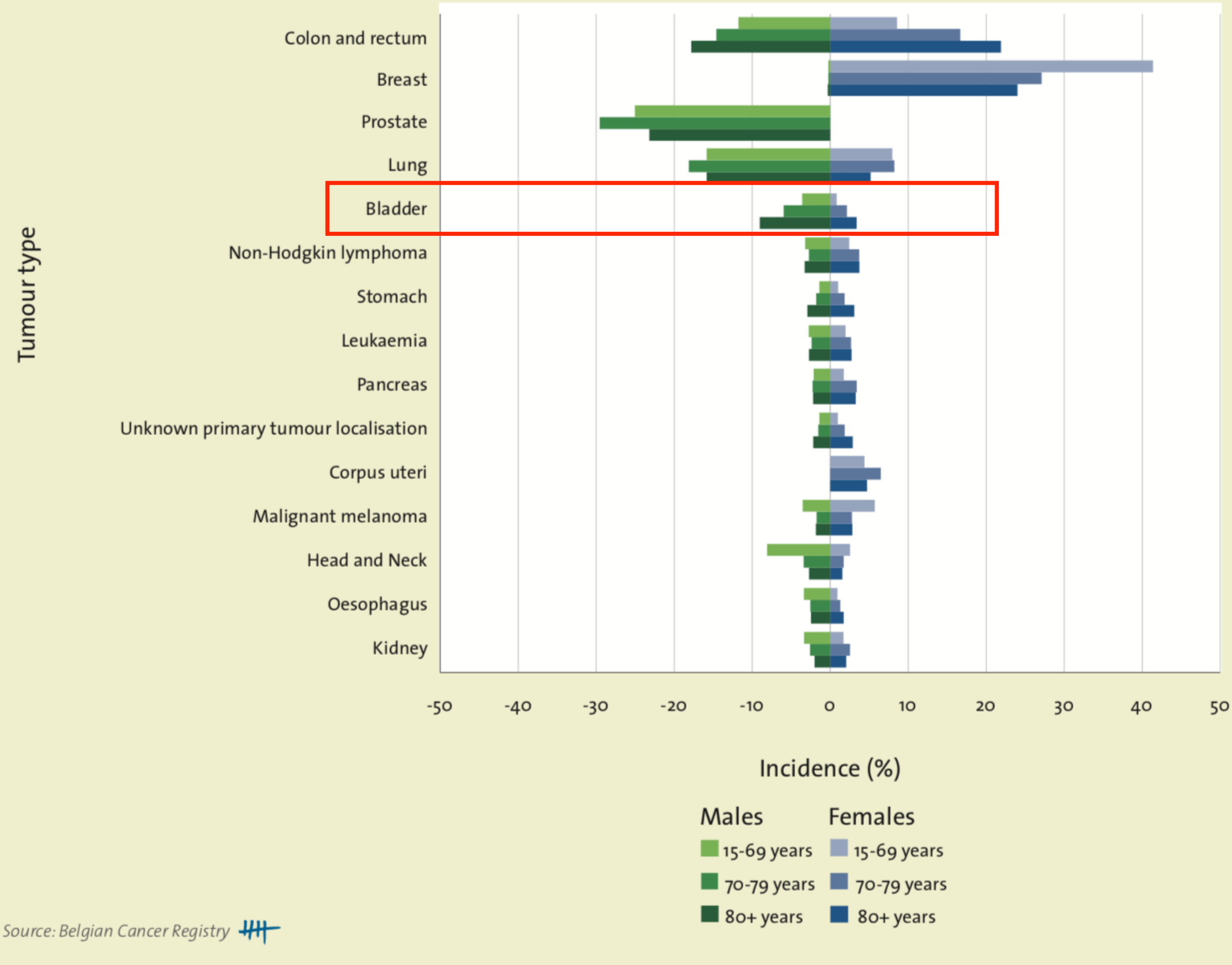
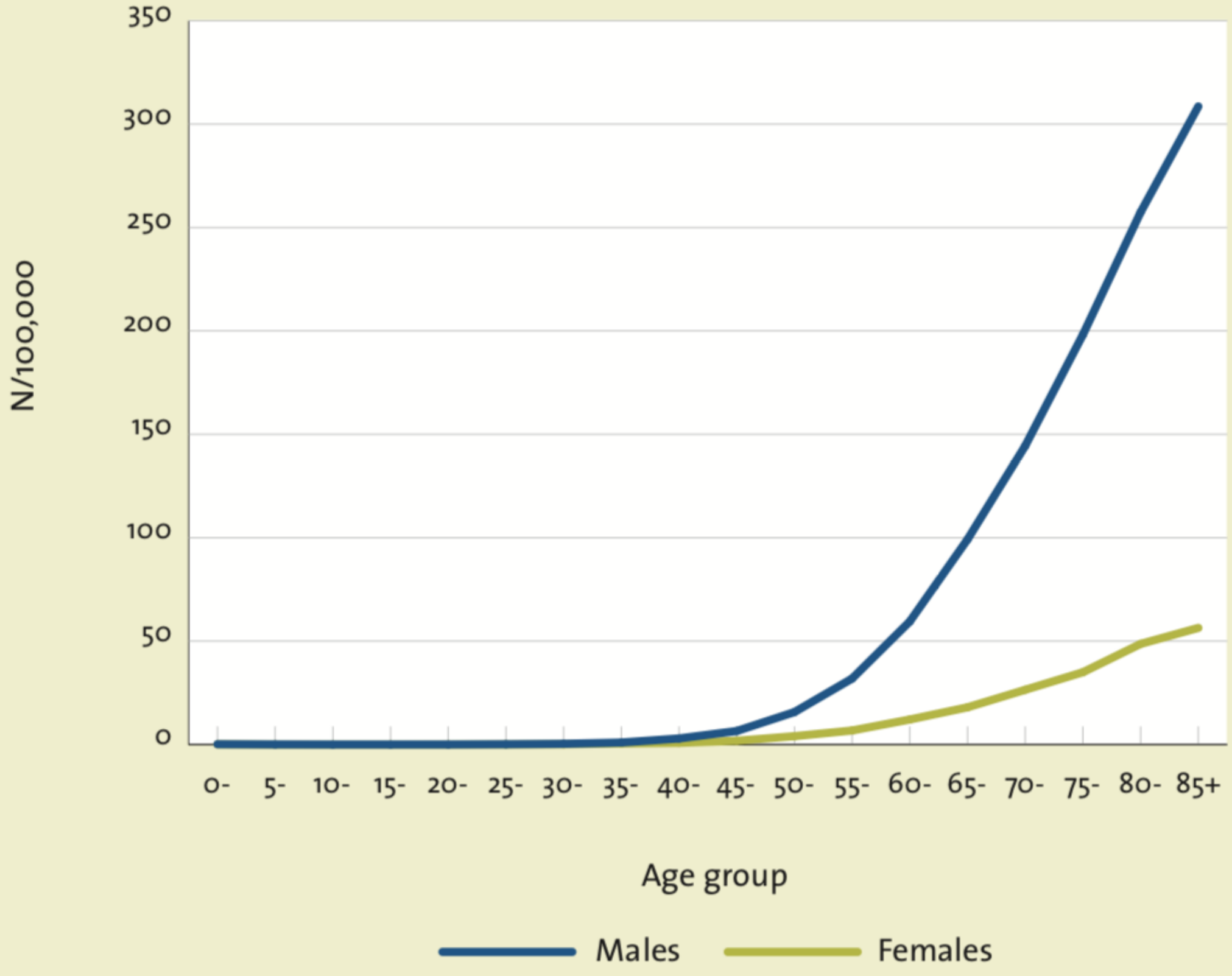
Figure 4 The 15 most frequent tumours in the age group 80+ years in Belgium, by sex and age group (2004-2016)



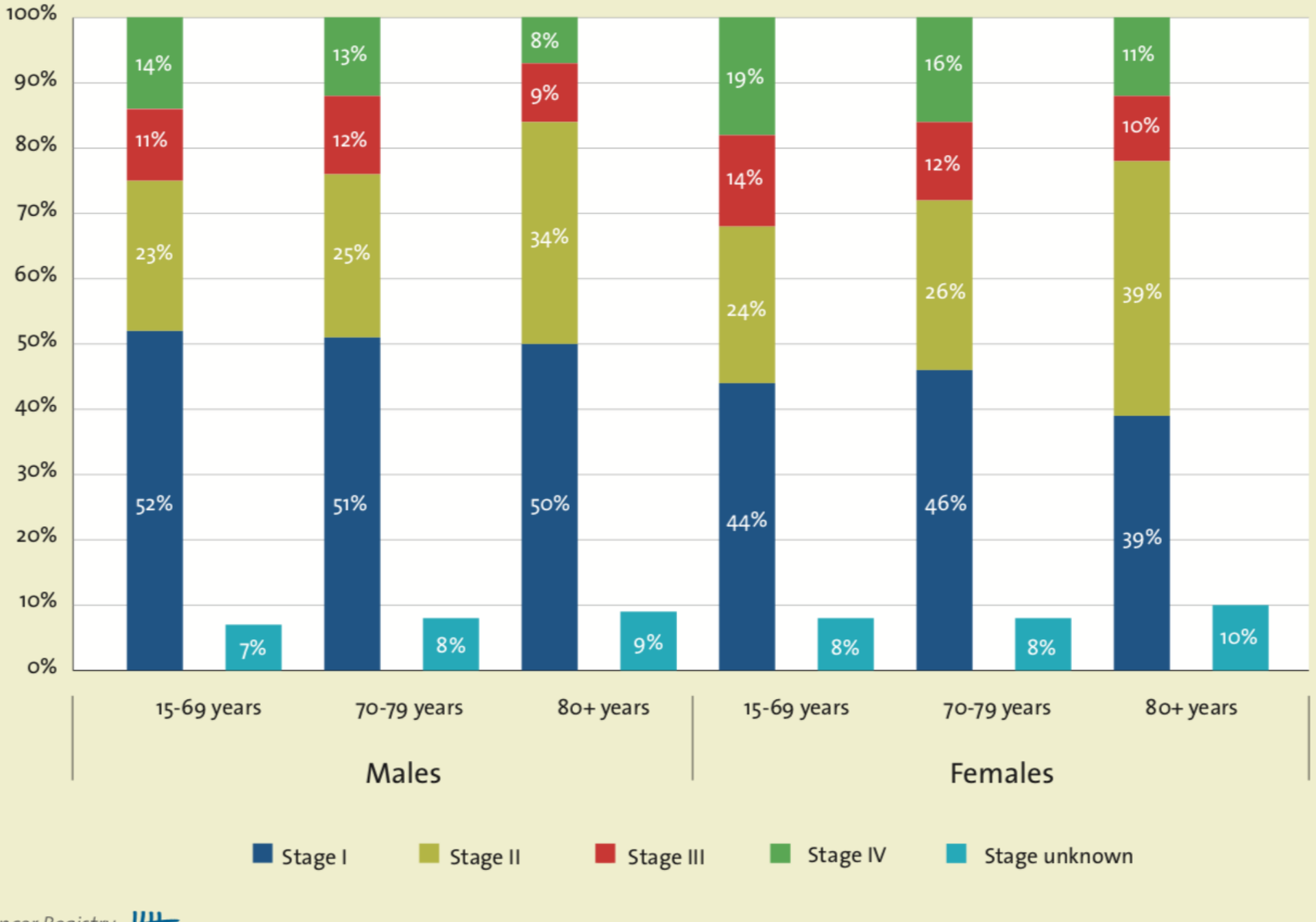
Source: Belgian Cancer Registry

Figure 1 Bladder cancer: Age-specific incidence rates (N/100,000) by sex, Belgium 2004-2016



Source: Belgian Cancer Registry

Figure 4 Bladder cancer: Stage distribution by age group and sex, Belgium 2010-2016



Source: Belgian Cancer Registry

Survival metastatic UC

- Bajorin Risk Score:
  - KPS < 80%
  - M+ (visceral or bone)

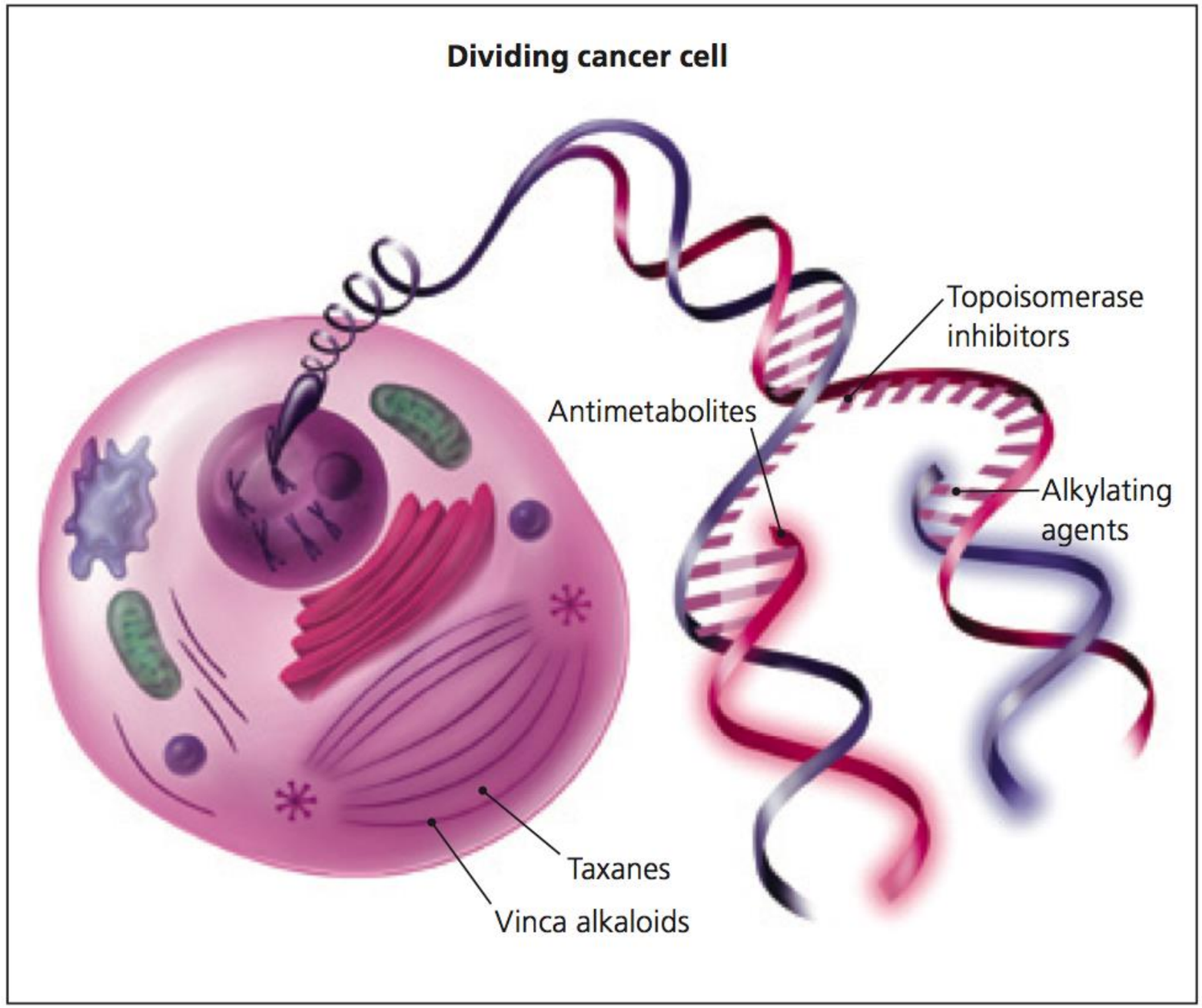
# Risk Factors	mOS (months)
0	33
1	19
2	9

- No treatment: mOS 6 months

mUC - Outline

- Chemotherapy
- Immunotherapy
- Optimal Treatment sequence of metastatic disease
- ADC
- FGF-R inhibitors
- Trials/future

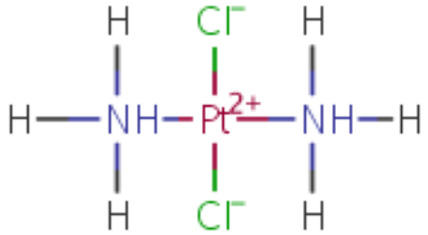
Chemotherapy basics

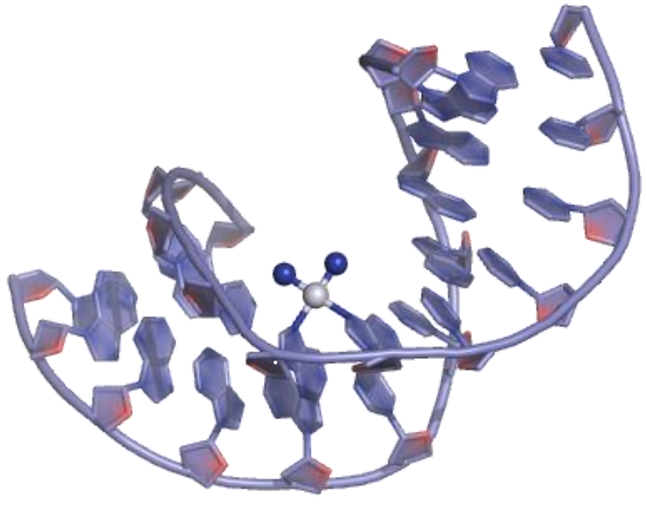


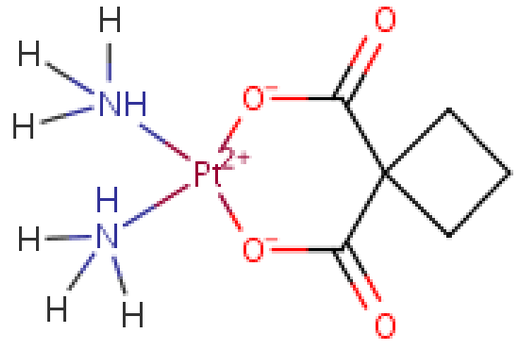
Gerber, AM Fam Physician 2008;77:311

CIS-Pt vs Carbo-Pt

- cis-diammine-dichloroPt
- Solid tumors, radiosensitizer
- Increased toxicity
  - nephrotoxicity
  - neurotoxicity
  - ototoxicity
  - Nausea/vomiting







- cis-diammine (cyclobutanedicarboxylato)Pt
- Solid tumors
- Faster renal clearance, less nephrotoxic, less nausea/vomiting
- Trombopenia

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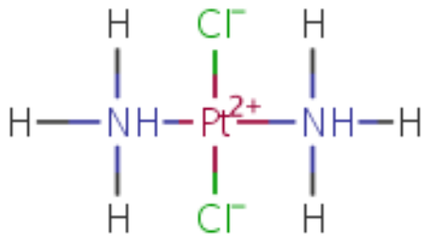
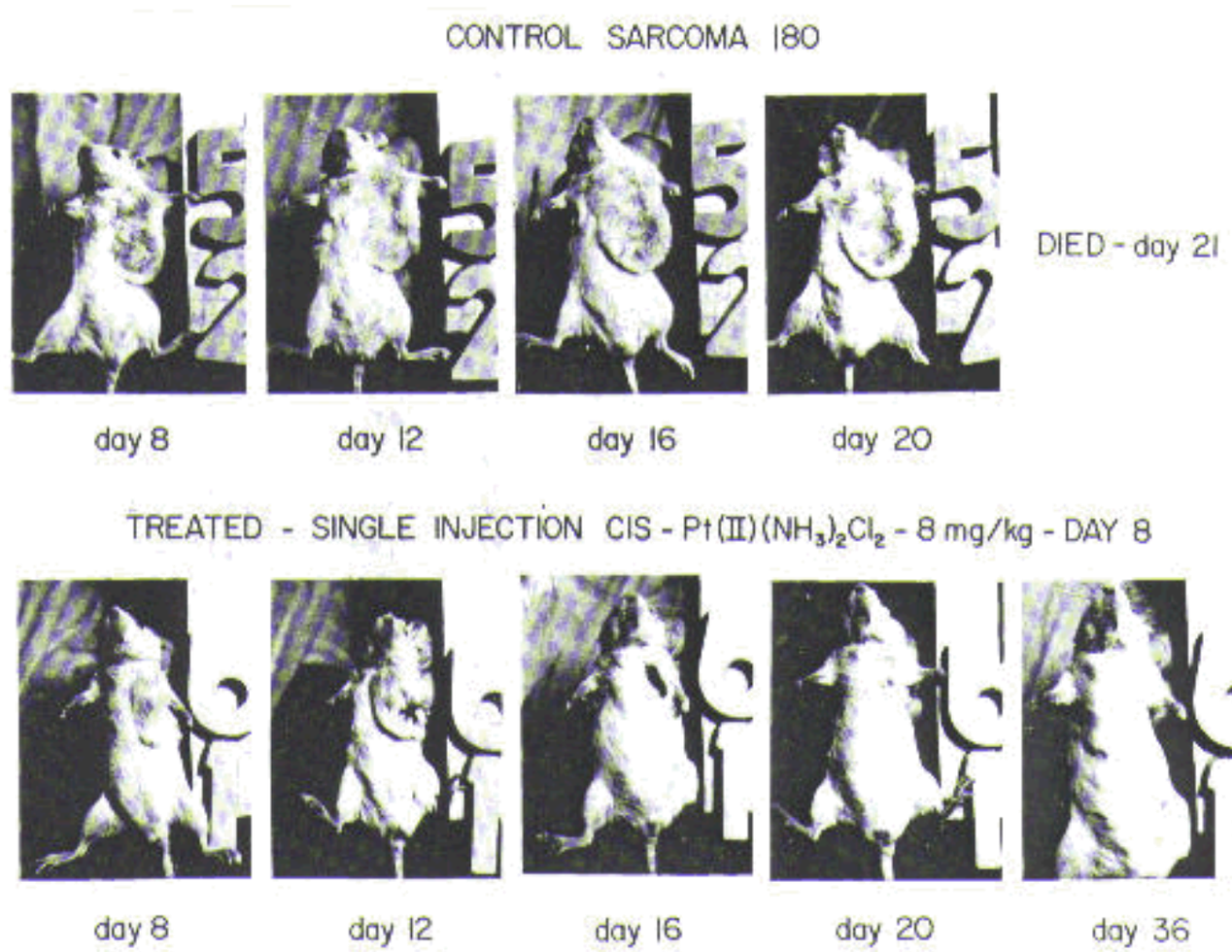
CIS-Pt vs Carbo-Pt





Rosenberg, B., VanCamp, L., Trosko, J. E., Mansour, V. H. *Nature,*1969, 222, pp. 385-386.

Metastatic bladder cancer

Table 1. Trials comparing the efficacy of M-VAC versus cisplatin-based chemotherapy

Study	Regimen	*n*	Response rate (%)	PFS (months)	OS (months)	*P*-value (OS)
Loehler10	M-VAC	126	39	Not reported	12.5	<0.001
	Cisplatin	150	12	Not reported	8.2	
Logothetis9	M-VAC	65	65	Not reported	12.6	<0.001
	Cisplatin, cyclophosphamide, adriamycin	55	46	Not reported	10	
Von der Masse11	M-VAC	202	46	7.4	14.8	0.75
	GC	203	49	7.4	13.8	

Phase II

Metastatic bladder cancer

MVAC > CisPt mono [1]

M-VAC : greater toxicity, especially leukopenia, mucositis, granulocytopenic fever, and drug-related mortality.
ORR : 39% v 12%
PFS : 10.0 v 4.3 months
OS : 12.5 v 8.2 months

GC = MVAC [2]

Less toxicity with GC
OS HR 1.04; 0.82 to 1.32; P = .75),
PFS HR 1.05; 0.85 to 1.30
RR GC 49%; MVAC 46%

GC > Carbo/Gem [3]

Higher ORR and CR for GC
Less toxicity with Carbo/Gem
Survival data?

[1] Loehrer et al., Journal of Clinical Oncology 1992 10:7, 1066-1073
[2] Von de Maase et al., Journal of Clinical Oncology 2000 18:17,3068-77
[3] Galsky et al. , *Annals of Oncology 2012*, 23:2, 406–410

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Metastatic bladder cancer

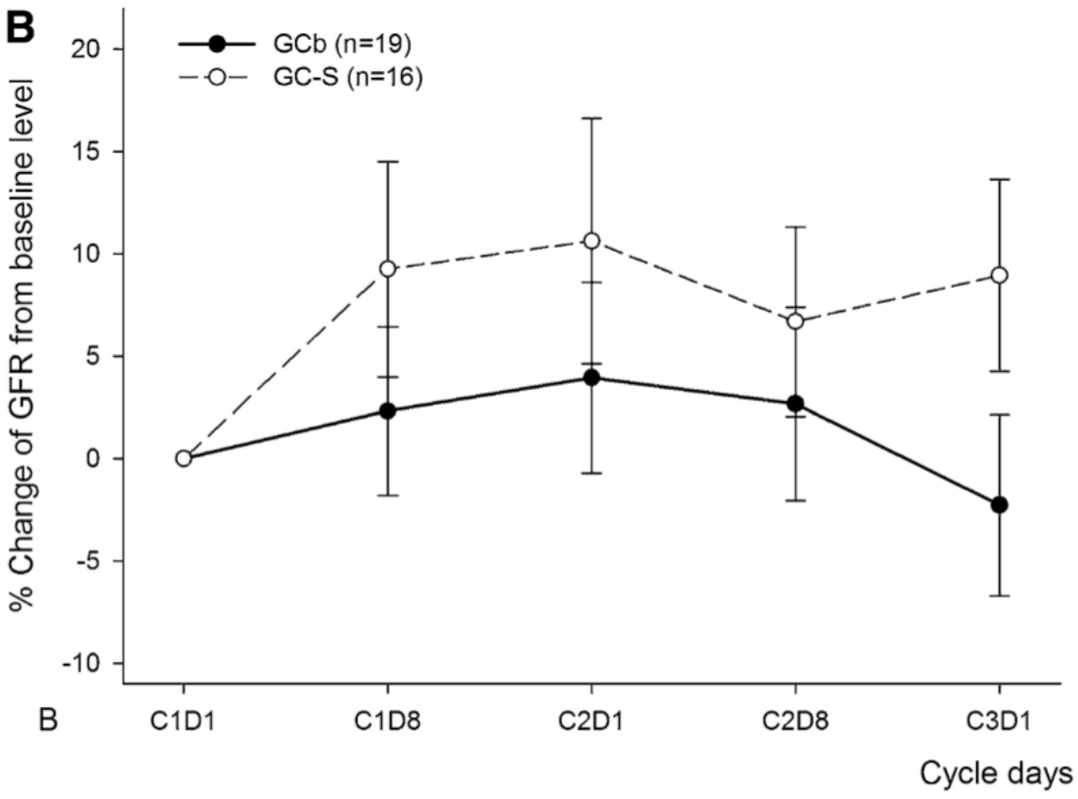
Table 2. Trials evaluating carboplatin-based options for cisplatin-ineligible patients

Author	Regimen	Regimen including dose and schedule	*n*	Response rate (%)	PFS (months)	OS (months)	Toxicity (Grades III and IV)
Xu17	Carboplatin-Gemcitabine	Gemcitabine 1200 mg/m^2 on days 1 and 8 and carboplatin AUC = 5 on day 1 every 21 days	54	54	Not reported	14.4	Neutropenia 36.6%; anemia 26.8%; thrombocytopenia 24.4%
Bamias18	Gem-Carbo biweekly	Carboplatin, AUC = 2.5; Gemcitabine 1,250 mg/m^2 biweekly	34	24	4.4	9.8	3 cases of grade 3 toxicity (9%)

Split dose Gem-Cis

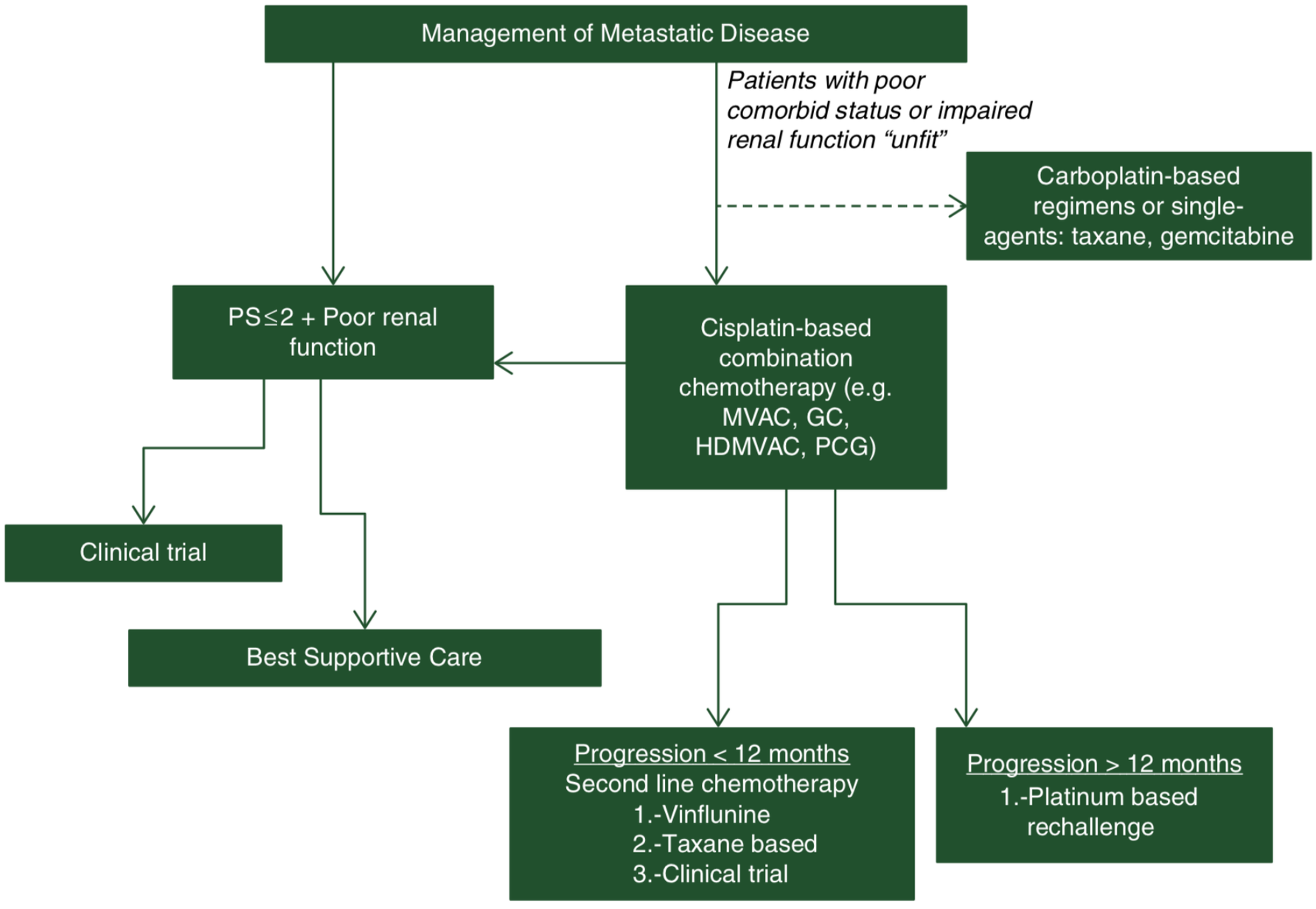
- D1 + D8: CisPt 35 mg/m2 + Gemcitabine 1000 mg/m2
- vs D1: Carbo AUC 4.5 + Gemcitabine 1000 mg/m2 and D8: Gemcitabine 1000mg/m2

	CIS/Gem split	Carbo/Gem
CR	1	0
PR	12	6
SD	3	5
PD	3	8



Kim et al. Cancer Chemother Pharmacol (2015) 76:141–153

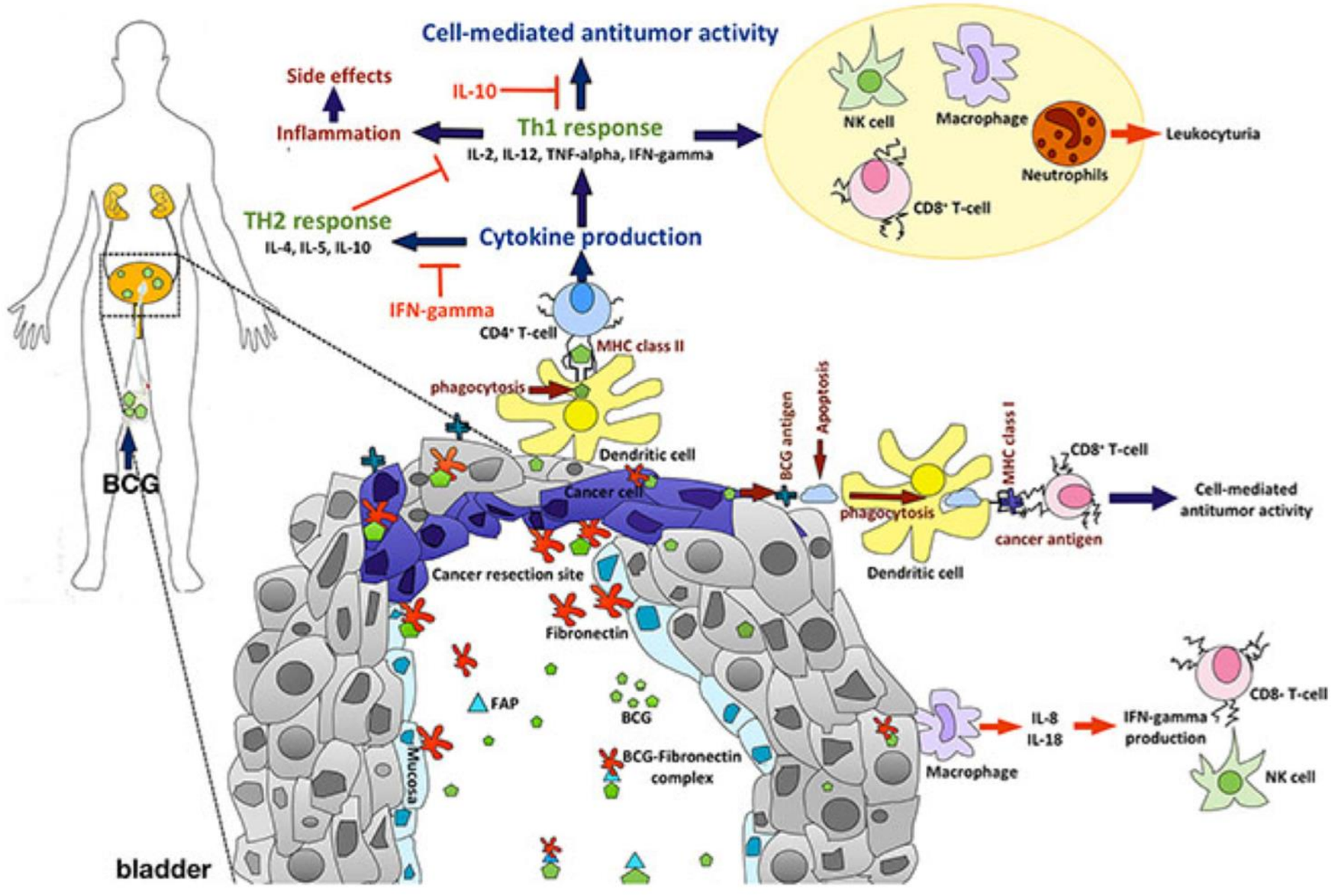
Metastatic bladder cancer



ESMO guidelines 2014

Checkpoint inhibition in Metastatic Bladder Cancer

Bladder cancer is an immune responsive disease



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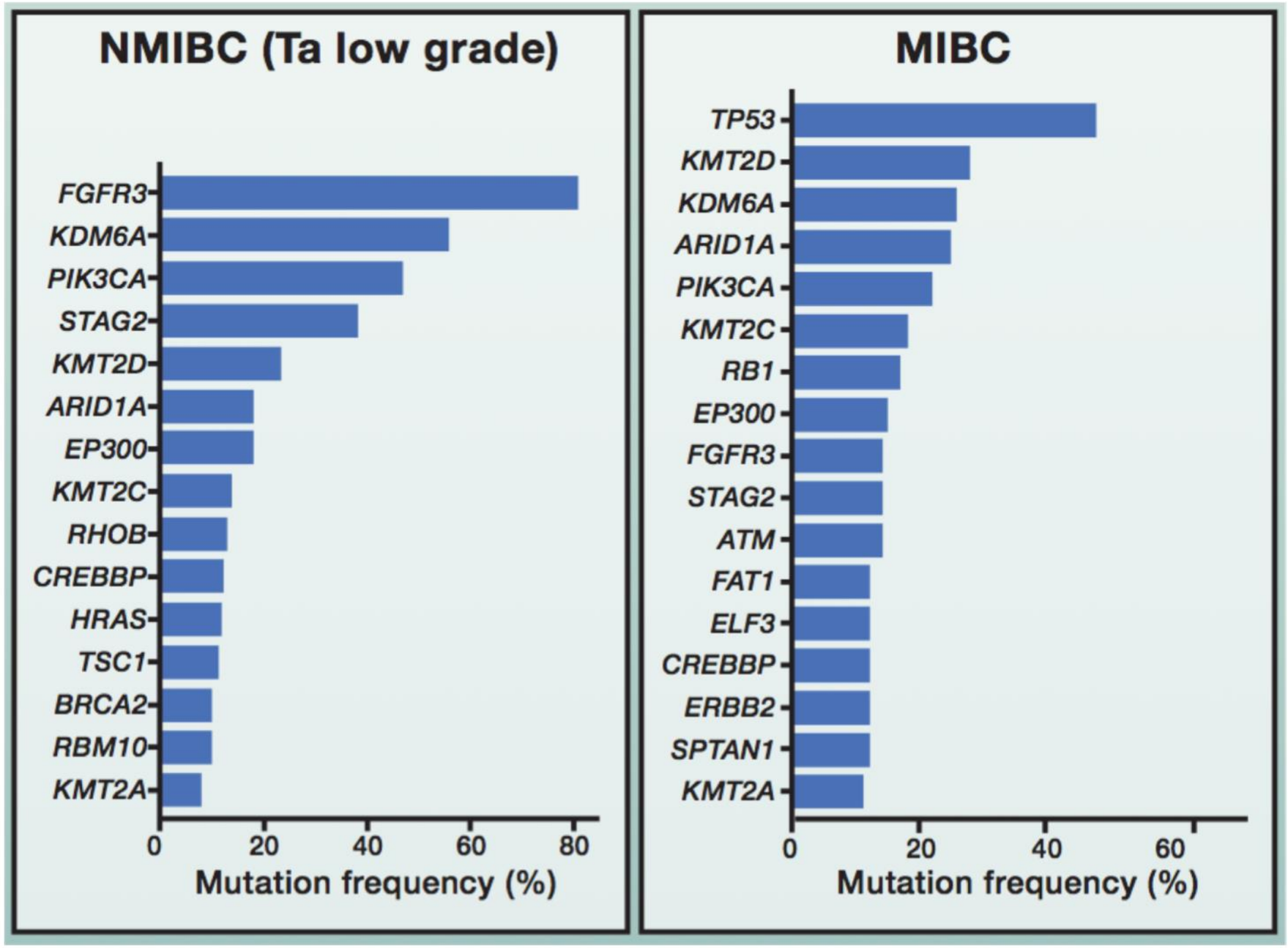
Bladder cancer is an immune responsive disease



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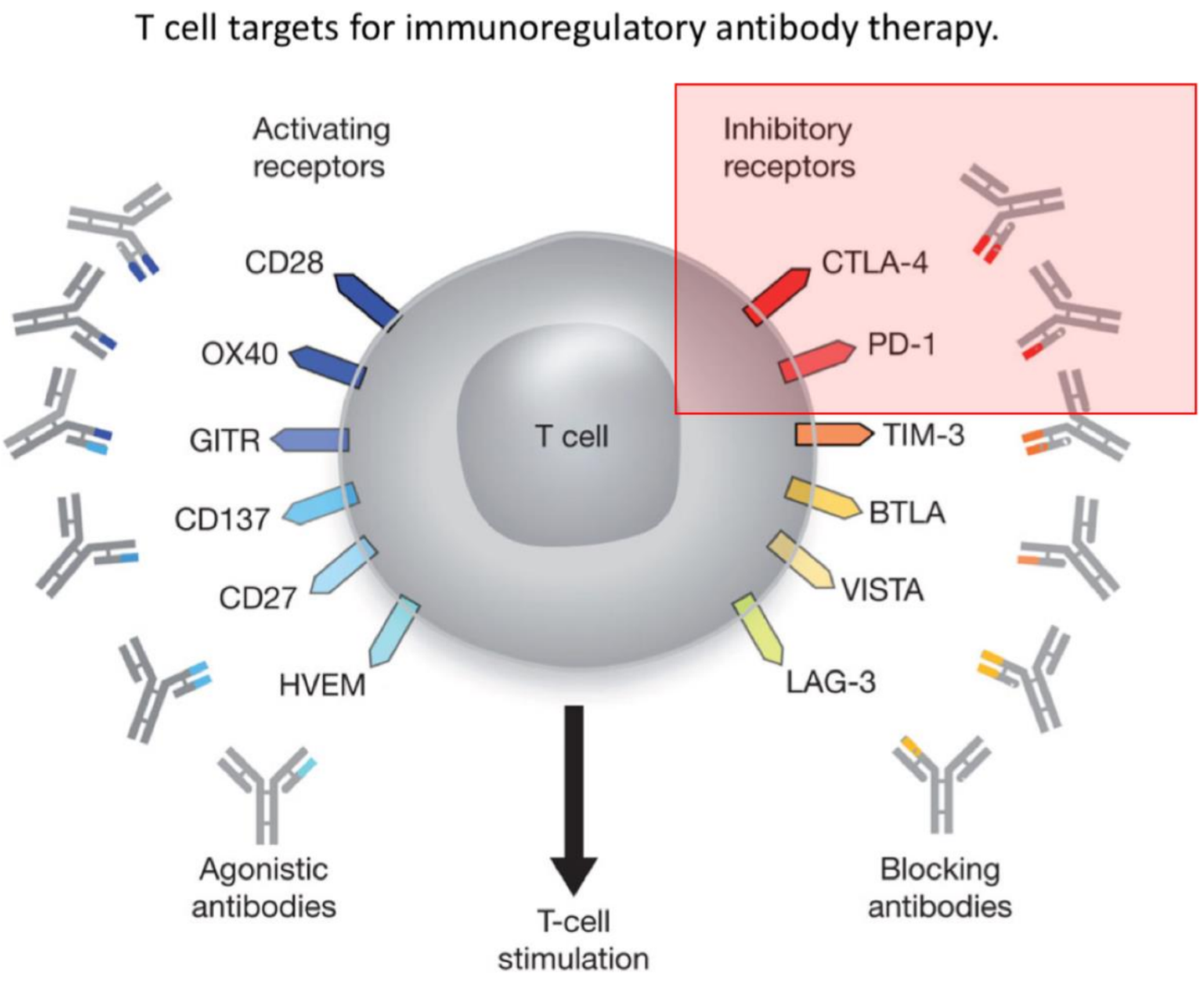
High mutational load from early stage. Hurst et al. Cancer Cell *34*, August 13, 2018

Checkpoint inhibition is effective in bladder cancer



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I Mellman *et al. Nature* **480**, 480-489 (2011) doi:10.1038/nature10673

nature

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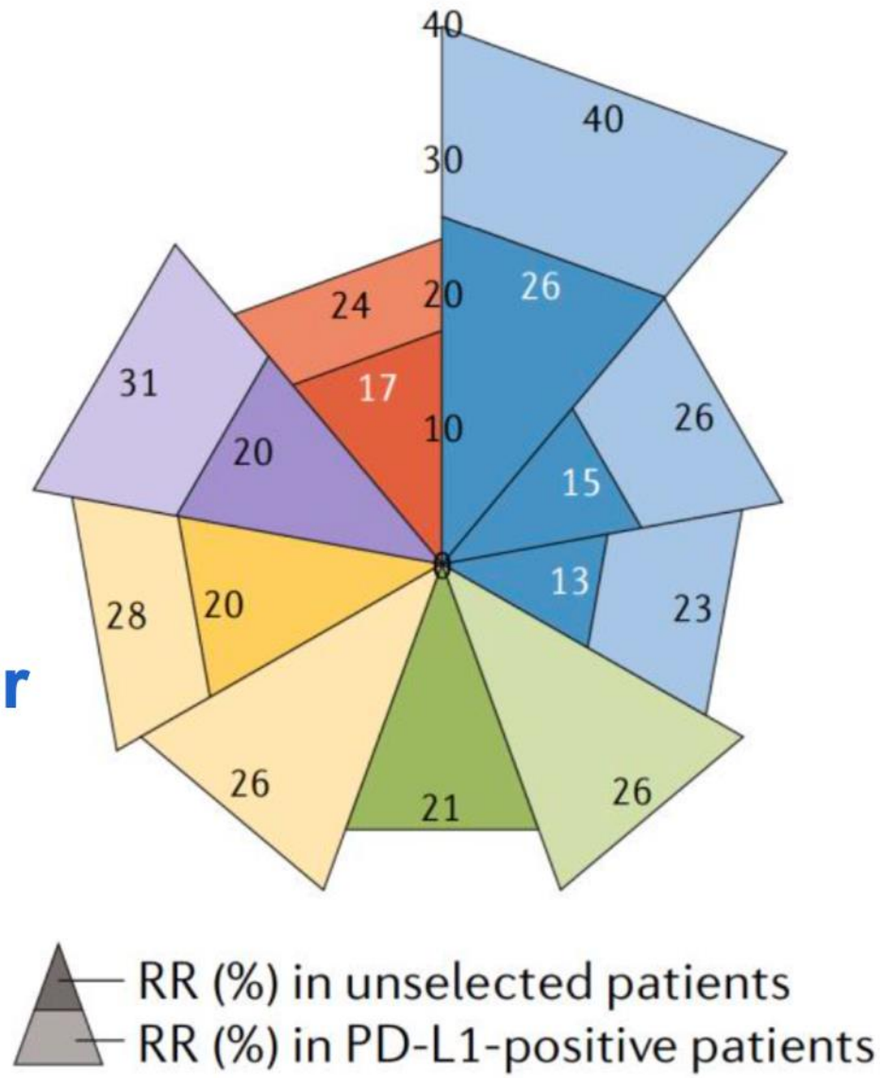
Checkpoint inhibition is effective in bladder cancer



unselected	13-26%
PD-L1+	23-40%

Powles et al. Nat Rev Urol (2018)

Immunotherapy (IO)	Atezolizumab	Nivolumab	Pembrolizumab	Durvalumab	Avelumab

What is the best sequence in mUCC?

4-6 lines
Platinum

CPI

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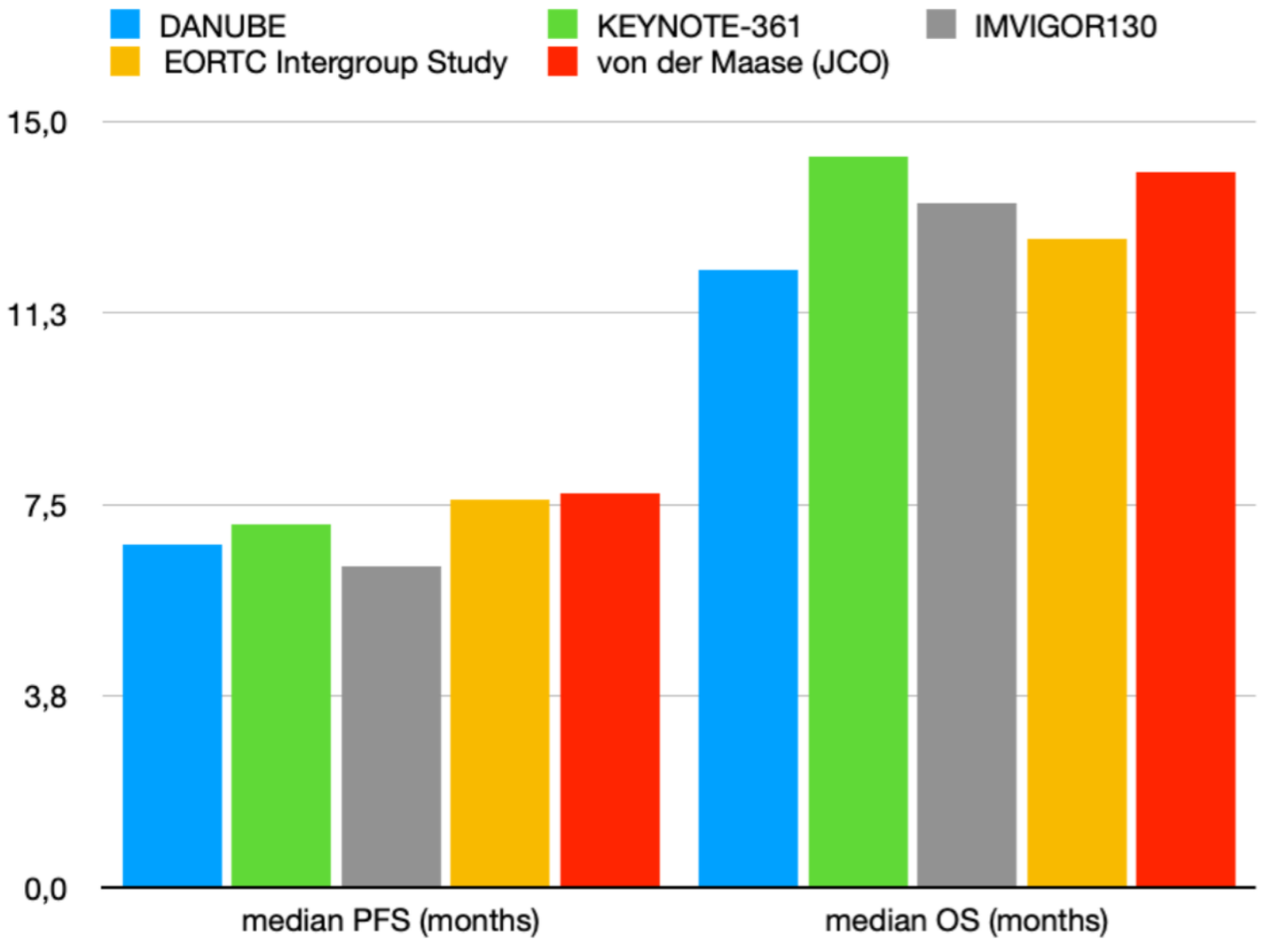

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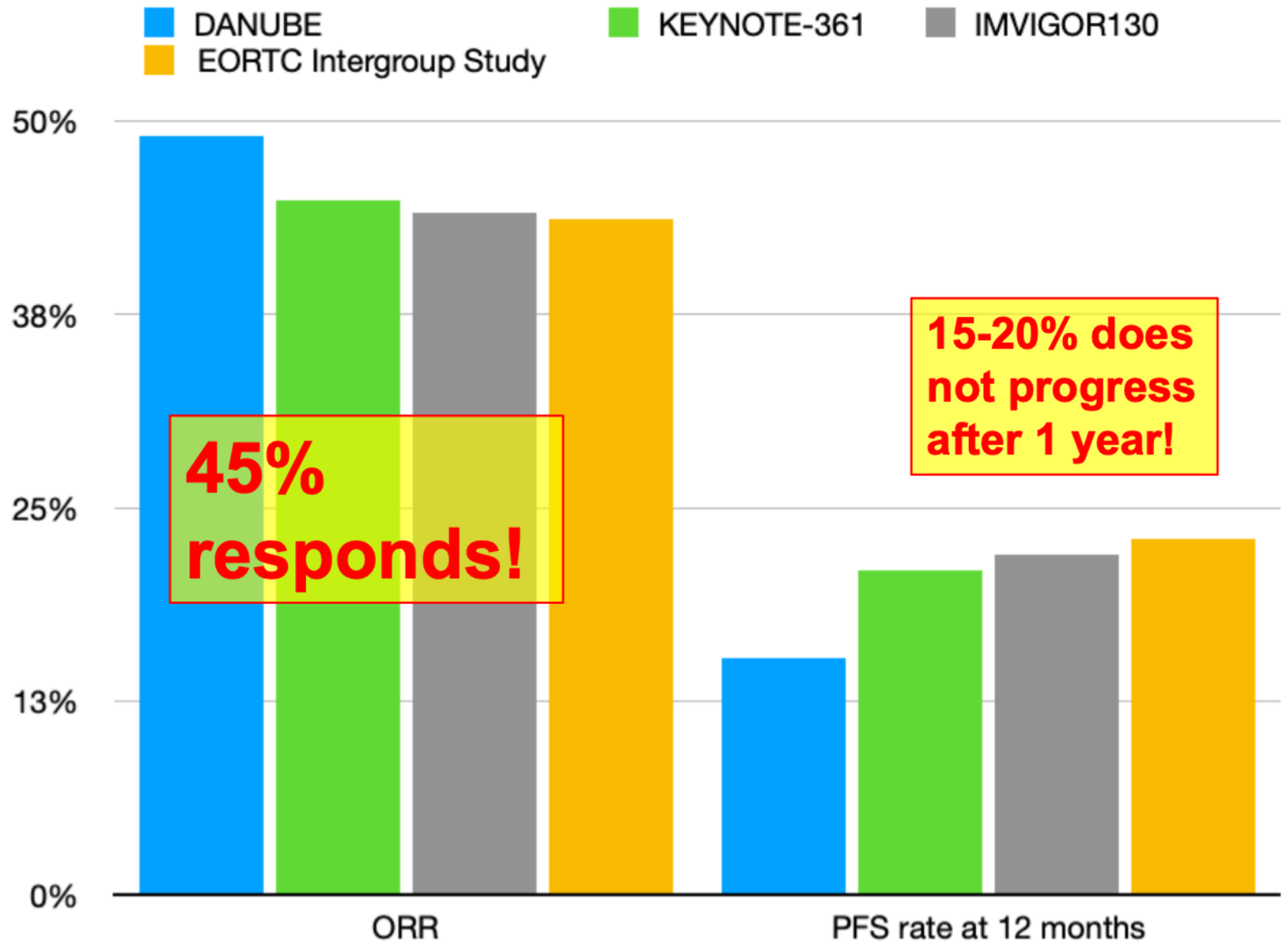
What is the best sequence in mUCC?

4-6 lines Platinum



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What is the best sequence in mUCC?

Combination

4-6 lines Platinum

+

CPI

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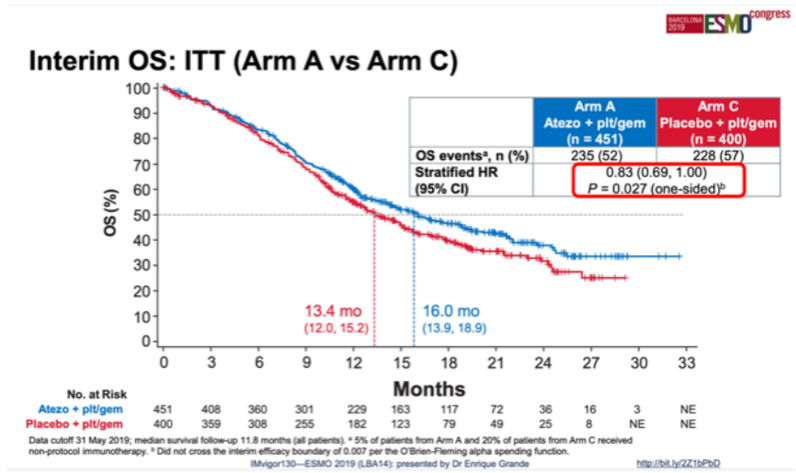
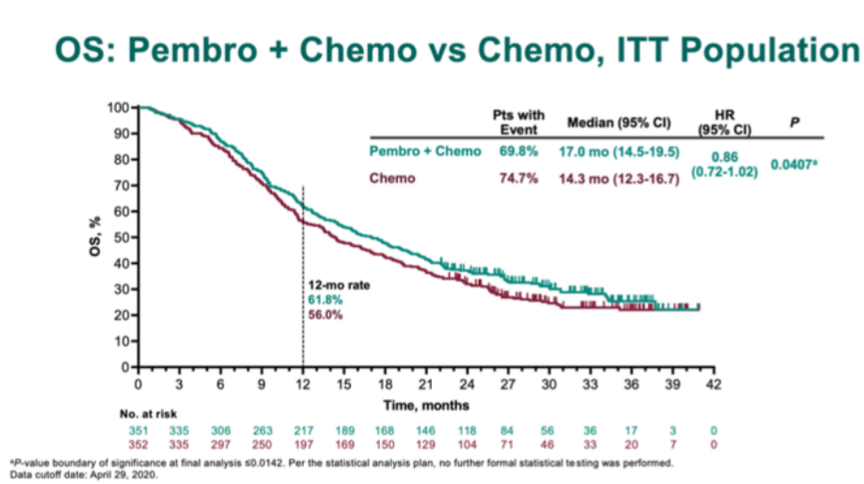
Imvigor 130



Keynote 361



No survival benefit!

+ Danube (IO+IO)

What is the best sequence in mUCC?

Combination

4-6 lines Platinum

+

CPI

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LAST CHANCE !

- CHECKMATE 901: Nivo+Ipi vs Nivo+Pt/Gem vs Pt/Gem
- NILE: Durva+ Pt/Gem vs Durva+Treme+Pt/Gem vs Pt/Gem
- IMVigor 130 : mature data @ ESMO 2021

What is the best sequence in mUCC?

Sequential

4-6 lines Platinum

PD →

CPI

Pembrolizumab, Nivolumab, Atezolizumab, Durvalumab, Avelumab

6-7 months PFS

+

10-12 months OS

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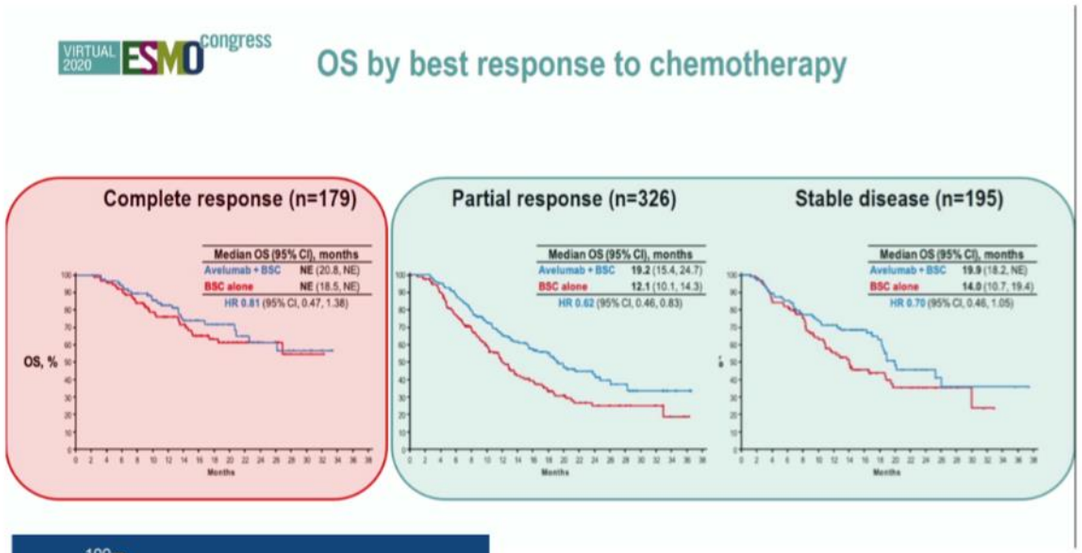
10 months Keynote 45 (pembrolizumab)
11.1 months Imvigor211 (atezolizumab)

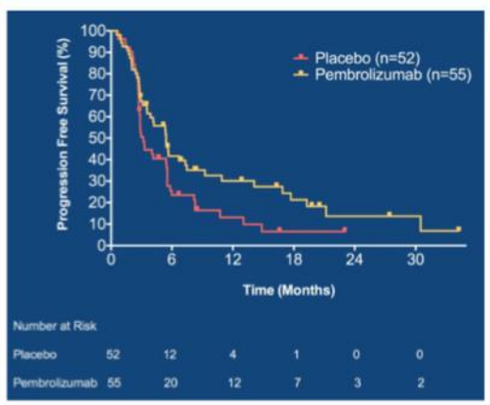
What is the best sequence in mUCC?

Maintenance

4-6 lines Platinum → CPI

SD or PR/CR





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21.4 months Javelin 100 (avelumab)
22 months HCRN GU14 – 182 (pembrolizumab)

What is the best strategy in first line treatment of mUCC?

- Concomittant therapy is not superior to monotherapy
- First line cisplatin/carboplatin + gemcitabine has a high response rate (45%), good responders (15-20%) have a long response (>1 year)
- IO
  - Sequential therapy at progression (2nd line) : good results with long treatment free period for a subset of patients (maybe CR ?)
  - Maintenance therapy in Pt-responding patients has good results, but not an option for non-responders and overtreatment of a subset of patients is unavoidable
  - Only a subset of PD-L1 high expression patients, benefit from IO in first line.
- In cisplatin ineligible patients, carboplatin/gemcitabine first line is a good choice (or a trial!)

2nd line after Pt based 1st line

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2L mUC Key Data Comparison (IO agents)

	Checkmate 032[1,2]	Checkmate-275[3,4]	NCT02261220[5]	Study 1108[6]	IMvigor 210[7]	IMvigor 211[8]		KEYNOTE-045[9]		JAVELIN ST[10]
	Nivo 1mg/kg + Ipi 3mg/kg* (n=92)	Nivolumab (n=270)*	Durva + Treme (n=168)*	Durva (n=182)*	Atezo (n=310)*	Atezo (n=467)	Chemo (n=464)	Pembro (n=272)	Chemo (n=270)	Avelumab (n=226)*
Phase/Pt pop	Ph 1/2 2L adv/mUC	Ph 2 2L mUC	Ph 1b 2L adv/mUC	Ph 1/2 2L adv/mUC	Ph 2 2L adv/mUC	Ph 3 2L adv/mUC		Ph 3 2L mUC		Ph 1 2L mUC
1 EP	ORR, DOR	ORR	SAEs, Eff by PD-L1 (<25%)	SAEs, ORR	ORR	OS		OS, PFS		ORR, DLT
mPFS (mos, ITT)	**4.9**	**1.94**	**1.9**	**1.5**	**--**	**2.1**	**4.0**	**2.1**	**3.3**	**1.5**
ORR (%)	**38.0**	**20.4**	**20.8**	**17.8**	**16.0**	**13.4**	**13.4**	**21.1**	**11.0**	**16.1**
CR (%)	**7**	**6.3**	**--**	**3.7**	**6**	**3**	**3**	**7.0**	**3.3**	**5.0**
ORR in PD-L1+ (cut-off)	**58.1(≥1%)**	**25.8 (≥1%)**	**29.4 (≥25%)**	**27.4 (≥25%)**	**19 (≥1%)**	**23 (≥5%)**	**21.6 (≥5%)**	**20.3 (≥10%)**	**6.7 (≥10%)**	**23.8 (≥5%)**
ORR in PD-L1- (cut-off)	**23.8 (<1%)**	**15.8 (<1%)**	**15.1 (<25%)**	**5.1 (<25%)**	**9 (<1%)**	**--**	**--**	**--**	**--**	**11.5 (<5%)**
mDOR (all-comers)	22.9	17.74	NR	NR	NR	21.7	7.4	NR	4.4	20.1
mOS (mos)	**15.3**	**8.57**	**9.5**	**18.2**	**7.9**	**8.6**	**8.4**	**10.3**	**7.3**	**7.7**
mOS (PD-L1+)	**24.1**	**11.86**	**18.9**	**20.0**	**11.9**	**11.1**	**10.6**	**8.0**	**4.9**	**8.4**
Grade 3–4 TRAEs (%)	39	17.8†	28.6	6.8	18	Any grade: 69	Any grade: 89	15.0	49.4	10.8
Discontinuation (%)	11	3.0†	--	3.3	3.2	6	15	5.6	11	7.2
PD-L1 status evaluation	TC	TC†	TC or IC	TC or IC	IC	IC		CPS: TC + IC relative to total TC		TC

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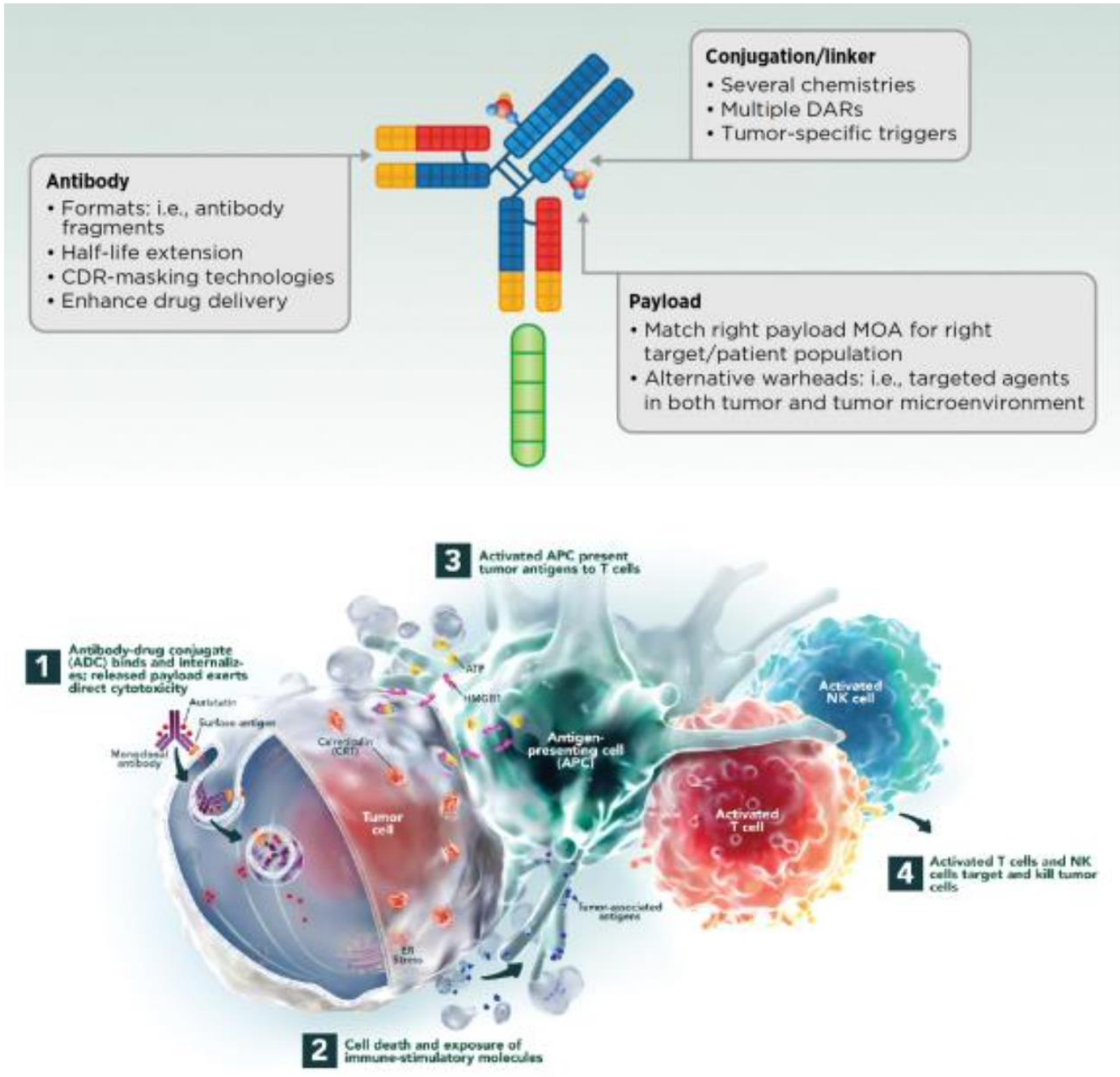
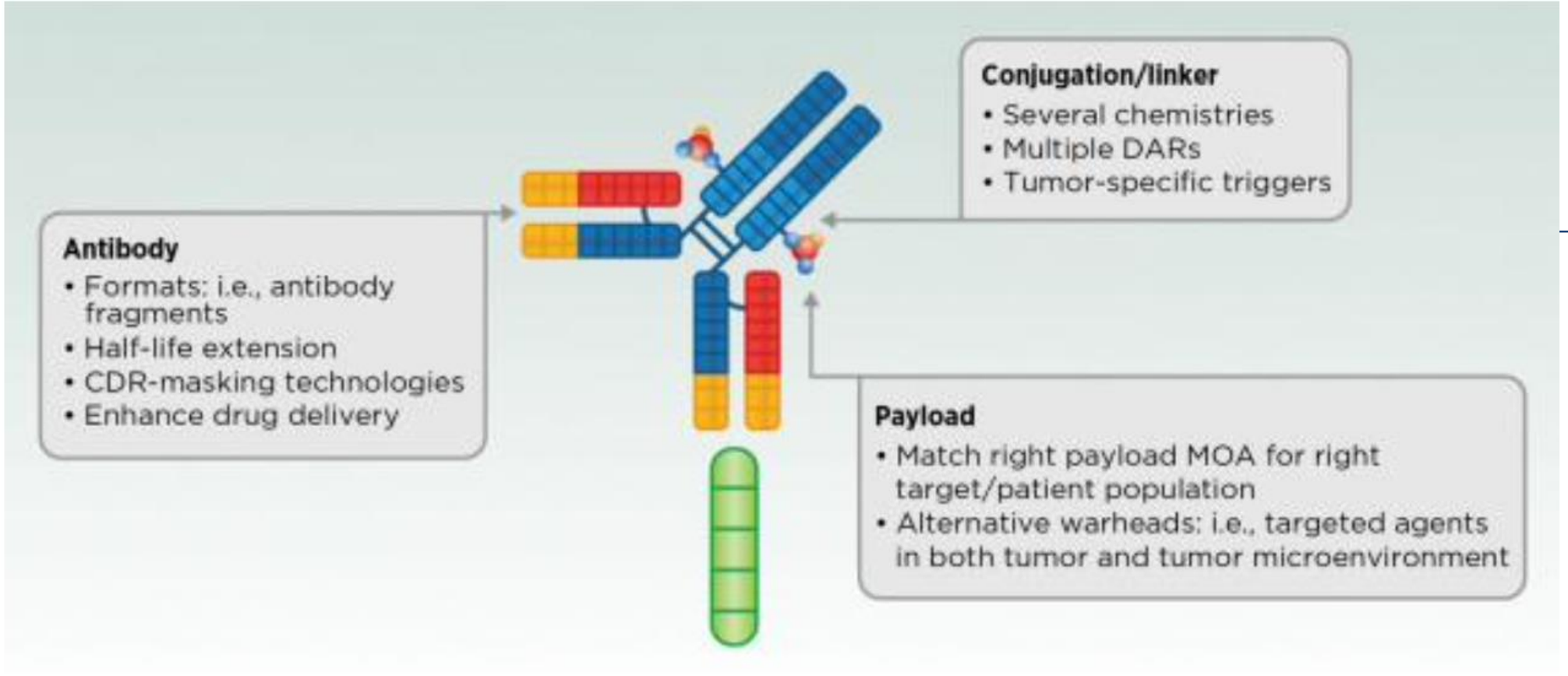
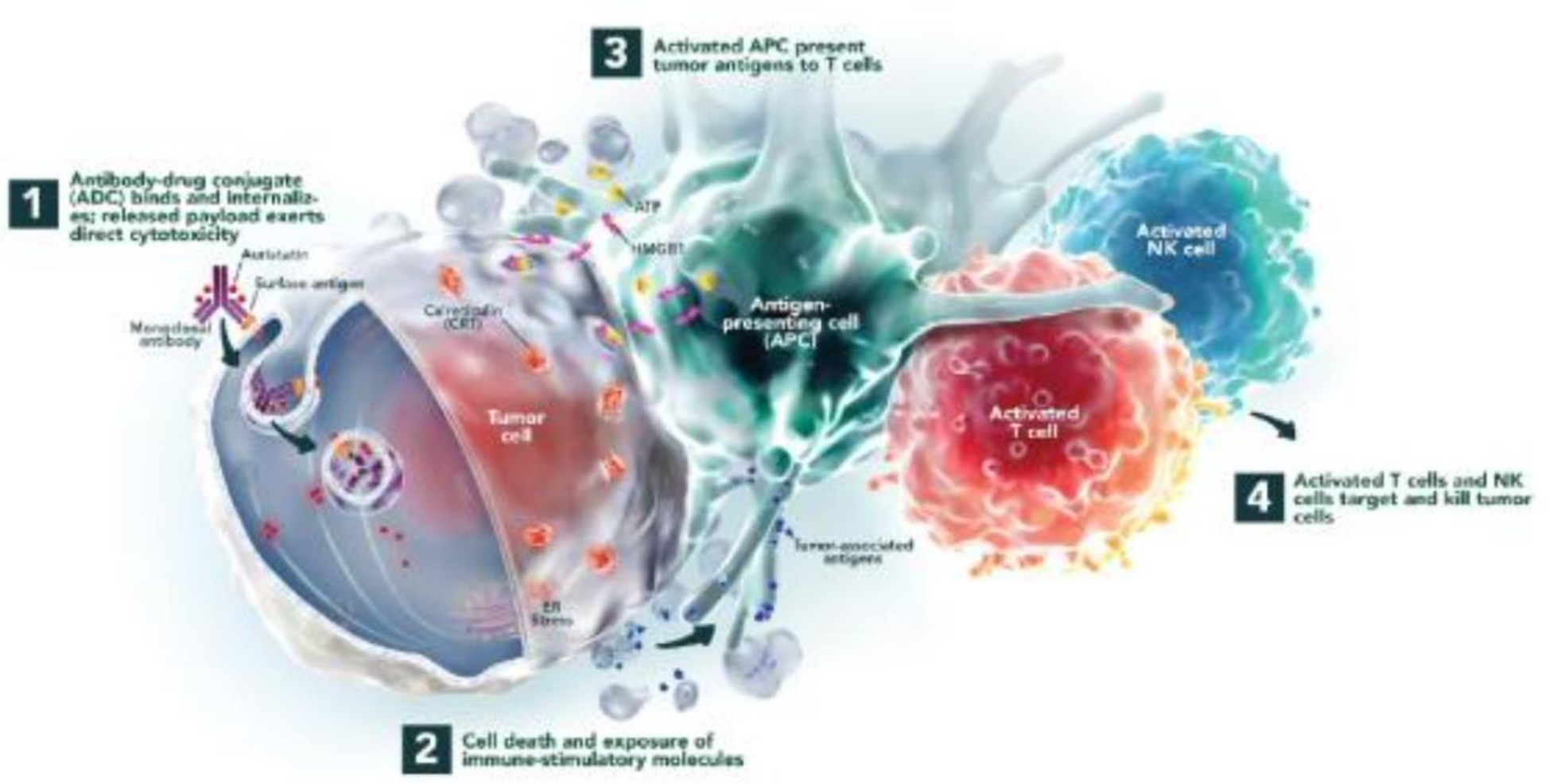
2nd line after IO maintenance /3d line




Antibody
• Formats: i.e., antibody fragments
• Half-life extension
• CDR-masking technologies
• Enhance drug delivery
Conjugation/linker
• Several chemistries
• Multiple DARs
• Tumor-specific triggers
Payload
• Match right payload MOA for right target/patient population
• Alternative warheads: i.e., targeted agents in both tumor and tumor microenvironment


1 Antibody-drug conjugate (ADC) binds and internalizes; released payload exerts direct cytotoxicity
Auristatin
Surface antigen
Monoclonal antibody
Calreticulin (CRT)
Tumor cell
ER Stress
ATP
HMGB1
2 Cell death and exposure of immune-stimulatory molecules
3 Activated APC present tumor antigens to T cells
Antigen-presenting cell (APC)
Tumor-associated antigens
Activated T cell
Activated NK cell
4 Activated T cells and NK cells target and kill tumor cells

EV-301: global, open-label phase III trial

- Advanced of metastatic UCa
- Radiographic progression or relapse during or after PD-1/PD-L1 treatment for advanced UCa
- Prior platinum-containing regimen for advanced UCa
- ECOG PS 0-1

R*

EV (N=301)
1.25 mg/kg on d1, 8 and 15 of each 28d cycle

Preselected chemotx (N=307)
DOC or paclitaxel or vinflunine on d1 of each 21d cycle

Primary endpoint
- OS

Secondary endpoints
- PFS (RECIST v1.1)
- DCR
- ORR (RECIST v1.1)
- Safety

*stratification factors: ECOG PS, geographic region, liver mets

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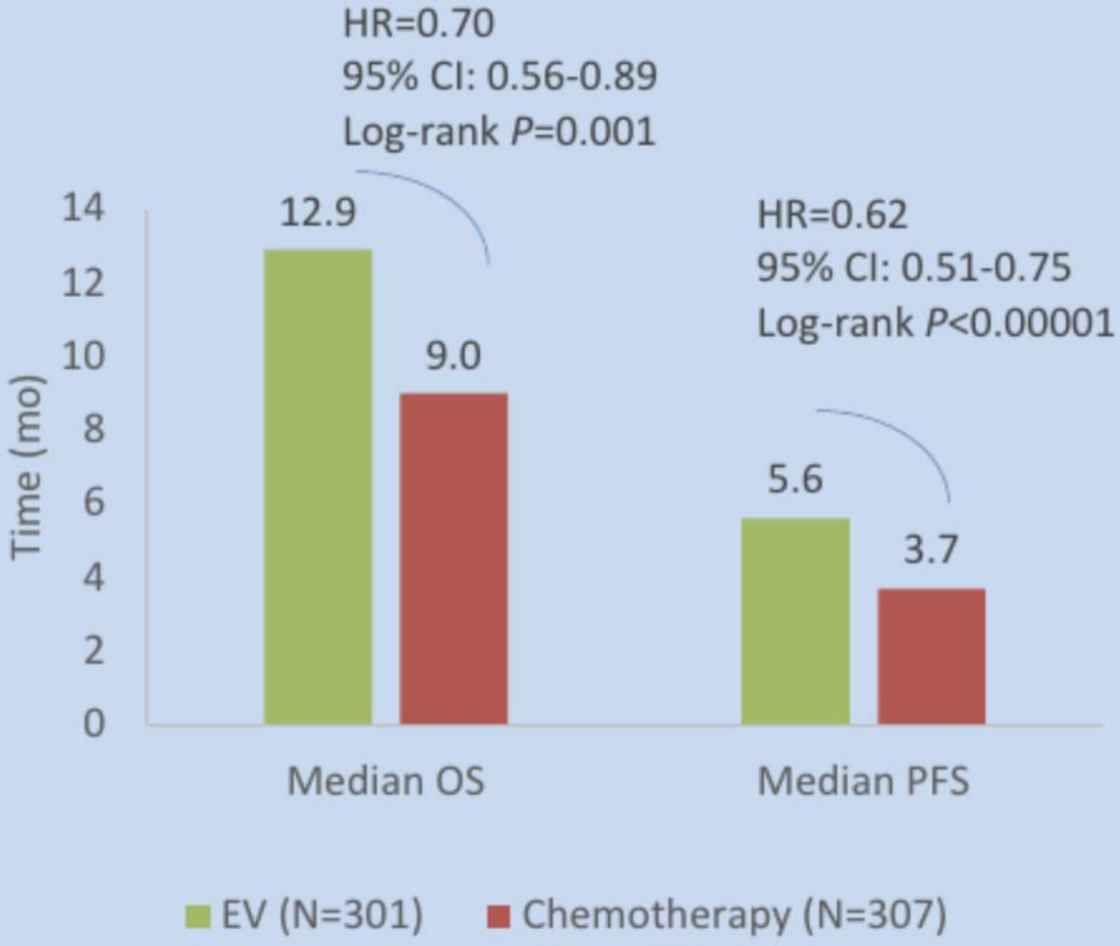
Efficacy

Survival



Response (investigator assessed)

	EV (N=288)	Chemotherapy (N=296)
ORR (%)*	41	18
CR (%)	5	3
DCR (%)*	72	53

*$P<0.001$

T Powles, ASCO GU 2021

Safety

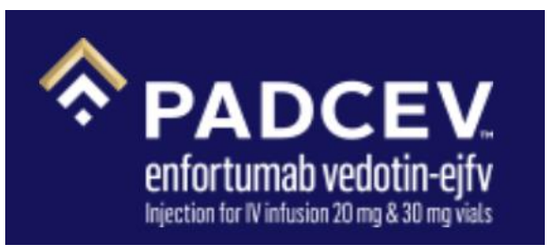
	EV (N=296)	Chemotherapy (N=291)
Median tx exposure (mo)	5.0	3.5
Grade ≥3 AE (%)	51	50
AE leading to tx withdrawal (%)	14	11

AEs of special interest*

TRAE grade ≥3 (%)	EV (N=296)	Chemotx (N=291)
Skin reactions	15	1
Rash	15	0
Severe cutaneous adverse reaction	5	1
Peripheral neuropathy	5	2
Sensory	4	2
Motor	2	0
Hyperglycaemia	4	0

*Mainly mild-to-moderate in severity

Coming soon 3d line



MARKETS SGEN $147.23 UNCH

Seagen : EMA Accepts MAA Of Enfortumab Vedotin For Urothelial Cancer Treatment

CONTRIBUTOR

RTTNews.com — RTTNews

PUBLISHED

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Other ADCs

ADC	Targeted Ag	Payload	Linkage
Enfortumab Vedotin [1,2]	Nectin-4	Monomethyl Auristatin E (MMAE)	Protease cleavable linker
Tisotumab Vedotin [3]	Tissue factor (thromboplastin)	MMAE	Protease cleavable linker
ASG-15ME [4]	SLITRK6	MMAE	Protease cleavable linker
Sacituzumab Govitecan [5]	Trop-2	SN-38	Hydrolysable cleavable linker
RC-48 [6]	Her-2	MMAE	Cathepsin cleavable linker

TROPiCS-04

1.-JE Rosenberg : TPS4590 Journal of Clinical Oncology 36, no. 15_suppl .2018; 2.-Petrylak D et al. Journal of Clinical Oncology 37, no. 18_suppl (June 20 2019) 4505-45 ; 3. De Bono JS, et al. Lancet Oncol. 2019 Mar;20(3):383-393. 4. D. Petrylak: Annals of Oncology (2016) 27 (6): 266-295 ; 5.- Scott Tagawa at 2019 ASCO GU: *Journal of Clinical Oncology* 37, no. 7_suppl (March 1 2019) 354-354.; 6. Sheng X et al. Journal of Clinical Oncology 37, no. 15_suppl (May 20 2019) 4509-4509

3d line - FGF-R inhibition

- 20% FGF-R activating mutation
- overexpression in 10% of cases, rearrangement in 20%, and activating mutations in 70%

Drug	Target	Inhibition Type	Ongoing Trials
Infigratinib BGJ 398	FGFR 1-3	Reversible	Phase III
Rogaratinib BAY 116387	FGFR 1-3	Reversible	Phase III
Erdafitinib JNJ42756493	FGFR 1-4	Reversible	Phase III
Pemigatinib INCB053828	FGFR 1-3	Reversible	Phase III
TAS-120	FGFR 1-4	Covalent	Phase II
Derazantinib ARQ 087	FGFR 1-4	Reversible	Phase II
LY2874455	FGFR 1-4	Reversible	Phase I
AZD4547	FGFR 1-3	Reversible	Phase II
Debio 1347	FGFR 1-3	Reversible	Phase II
BLU- 554	FGFR 4	Irreversible	Phase I ext
B-701	FGFR3	mAB	Phase II

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The NEW ENGLAND JOURNAL of MEDICINE

Erdafitinib for Urothelial Carcinoma

MULTICENTER, OPEN-LABEL, PHASE 2 STUDY

210

Patients with locally advanced and unresectable or metastatic urothelial carcinoma with *FGFR* alterations

Erdafitinib

Dose-Selection Phase

10 mg/day (intermittently) (N = 33)

6 mg/day (continuously) (N = 78)

Interim analysis completed and regimen selected

Selected Regimen

8 mg/day (continuously) (N = 99)

Rate of confirmed response

40%

95% CI, 31–50

Grade ≥3 adverse events

67%

Y. Loriot et al. 10.1056/NEJMoa1817323

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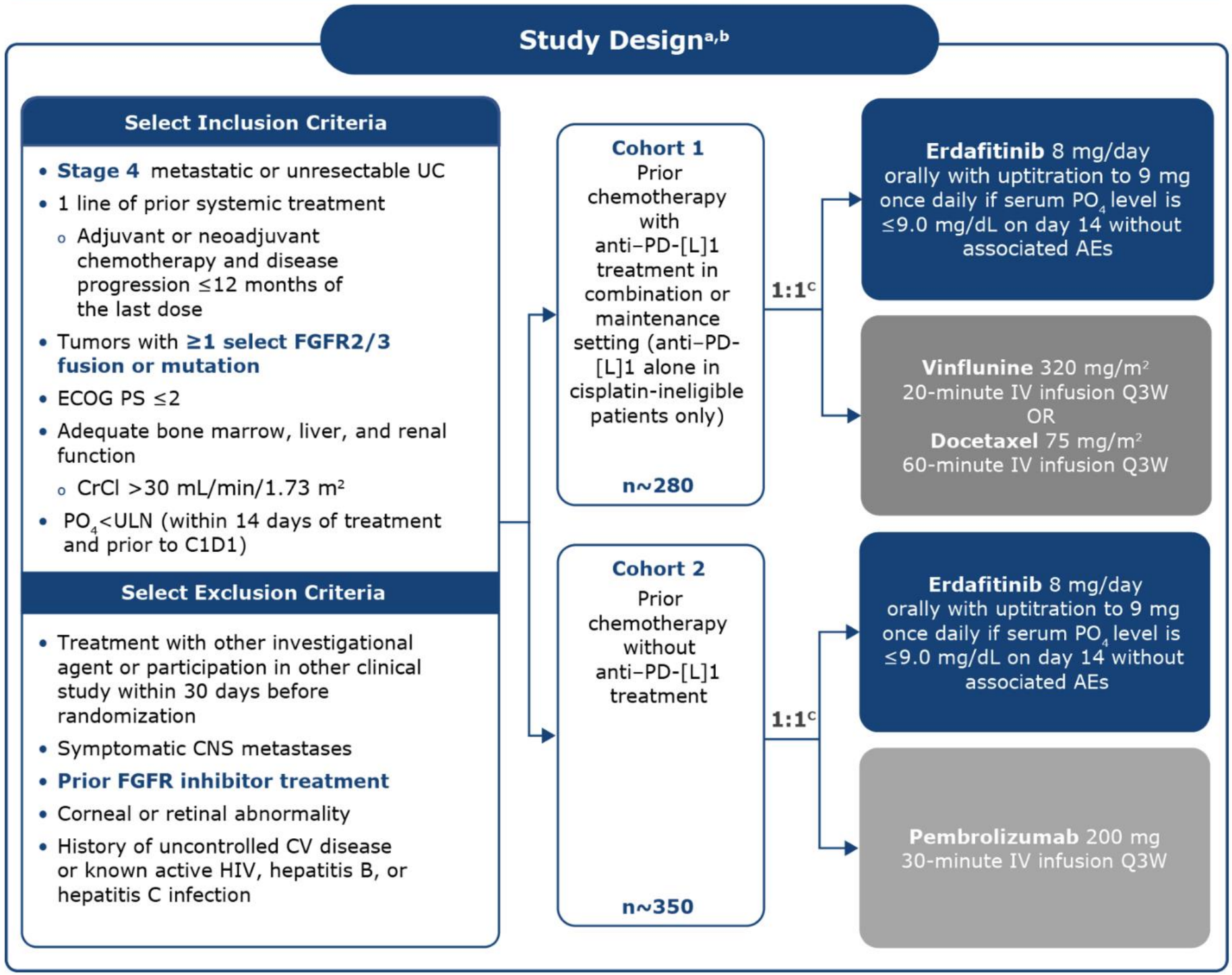
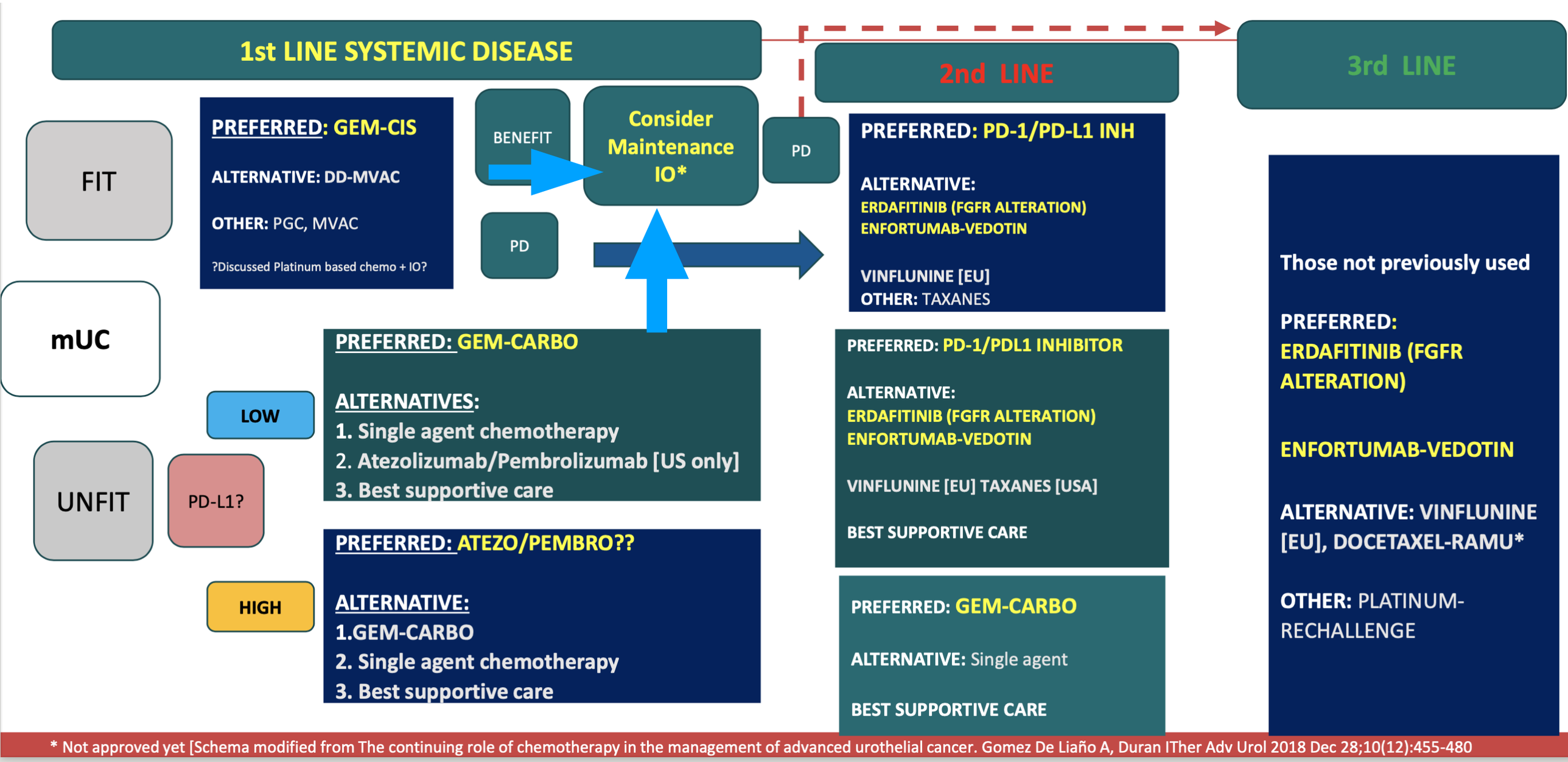
THOR study (pre-treated mUCC)



Summary



* Not approved yet [Schema modified from The continuing role of chemotherapy in the management of advanced urothelial cancer. Gomez De Liaño A, Duran IThere Adv Urol 2018 Dec 28;10(12):455-480

Future?

- Combos! ADC + IO / FGF-R I + IO / IO + TKI

Take home messages

- Cisplatin combination is standard in first line metastatic bladder cancer
- Checkpoint ini
- Checkpoint inhibitor is standard in second line (pembrolizumab only phase III positive trial)

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UNIVERSITEIT GENT

DE MAESENEER DAAN
Consulent Uro-Oncologie
Medische Oncologie

Universitair Ziekenhuis Gent
C. Heymanslaan 10 | B 9000 Gent
T +32 (0)9 332 21 11
E info@uzgent.be

www.uzgent.be
Volg ons op

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