Advances in bladder cancer and renal cell cancer therapy

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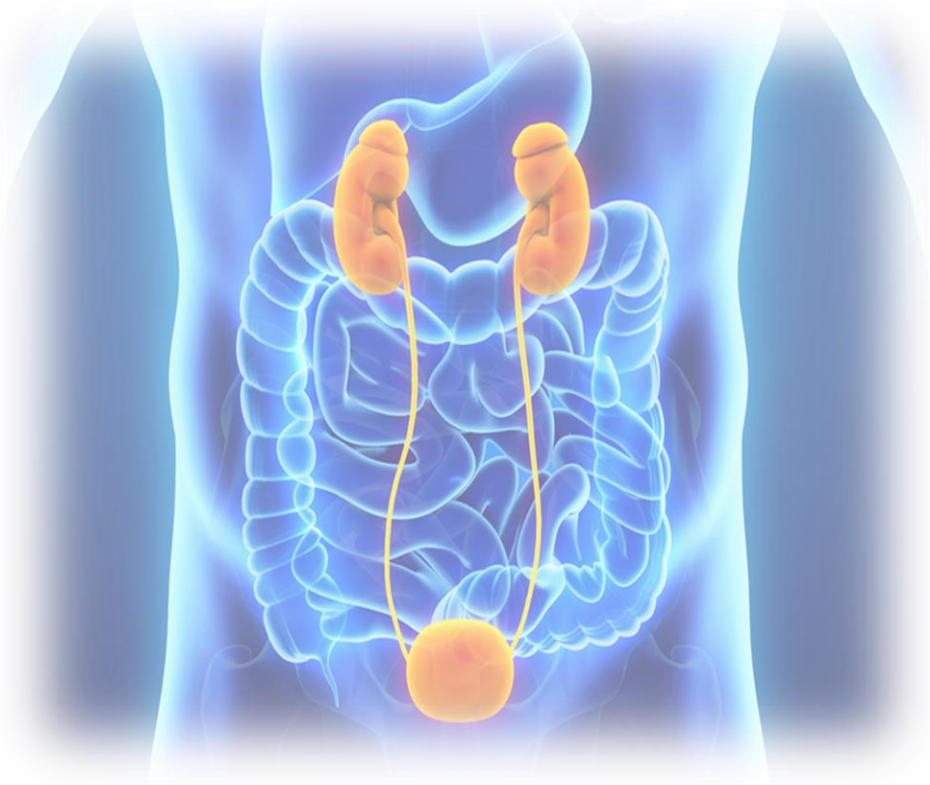
Disclosure

- Travel support : Ipsen, Recordati.

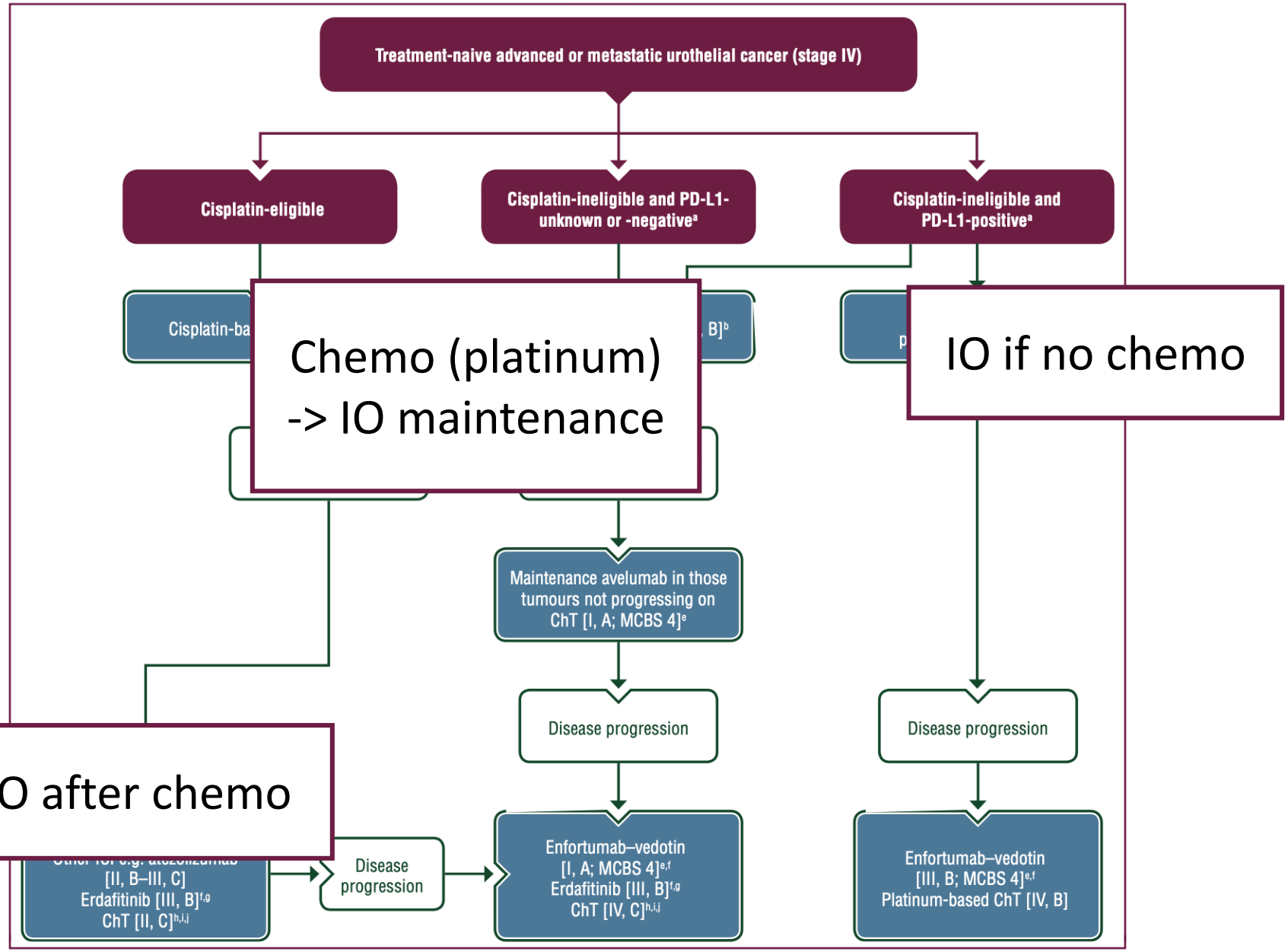
Outline

- Muscle-Invasive Bladder Cancer (MIBC)
  - Metastatic
    - ADC
    - FGFRi
    - PARPi
  - Non metastatic
    - Adjuvant
    - Neo Adjuvant

- Clear cell Renal Cell Carcinoma (ccRCC)
  - Metastatic
    - Triplet
    - HIF inhibitors
  - Non metastatic
    - Adjuvant
    - Neo Adjuvant

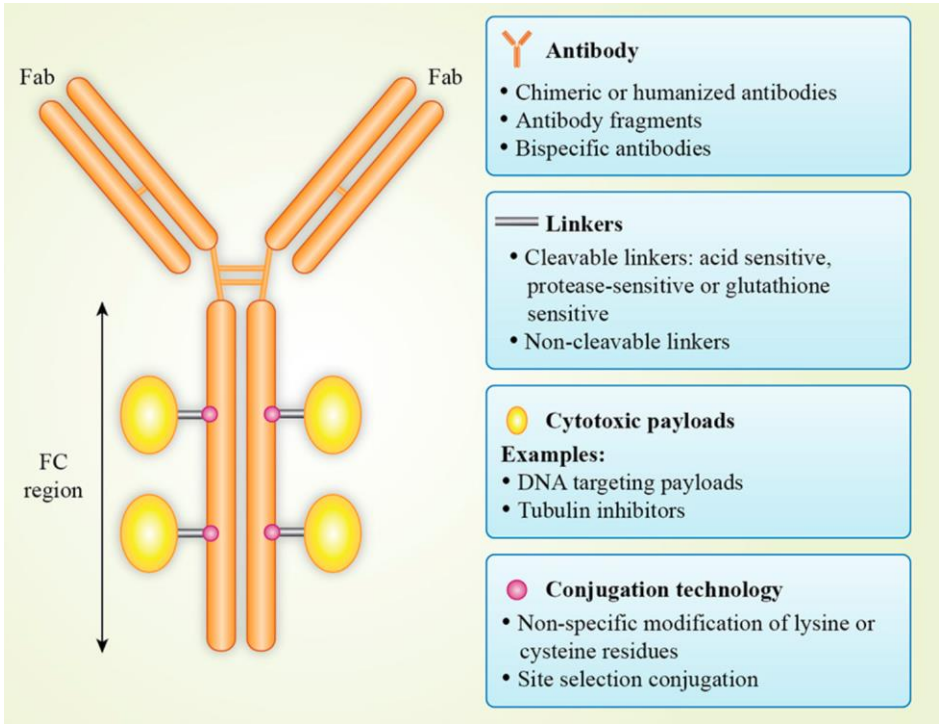


Metastatic
Muscle-Invasive Bladder Cancer

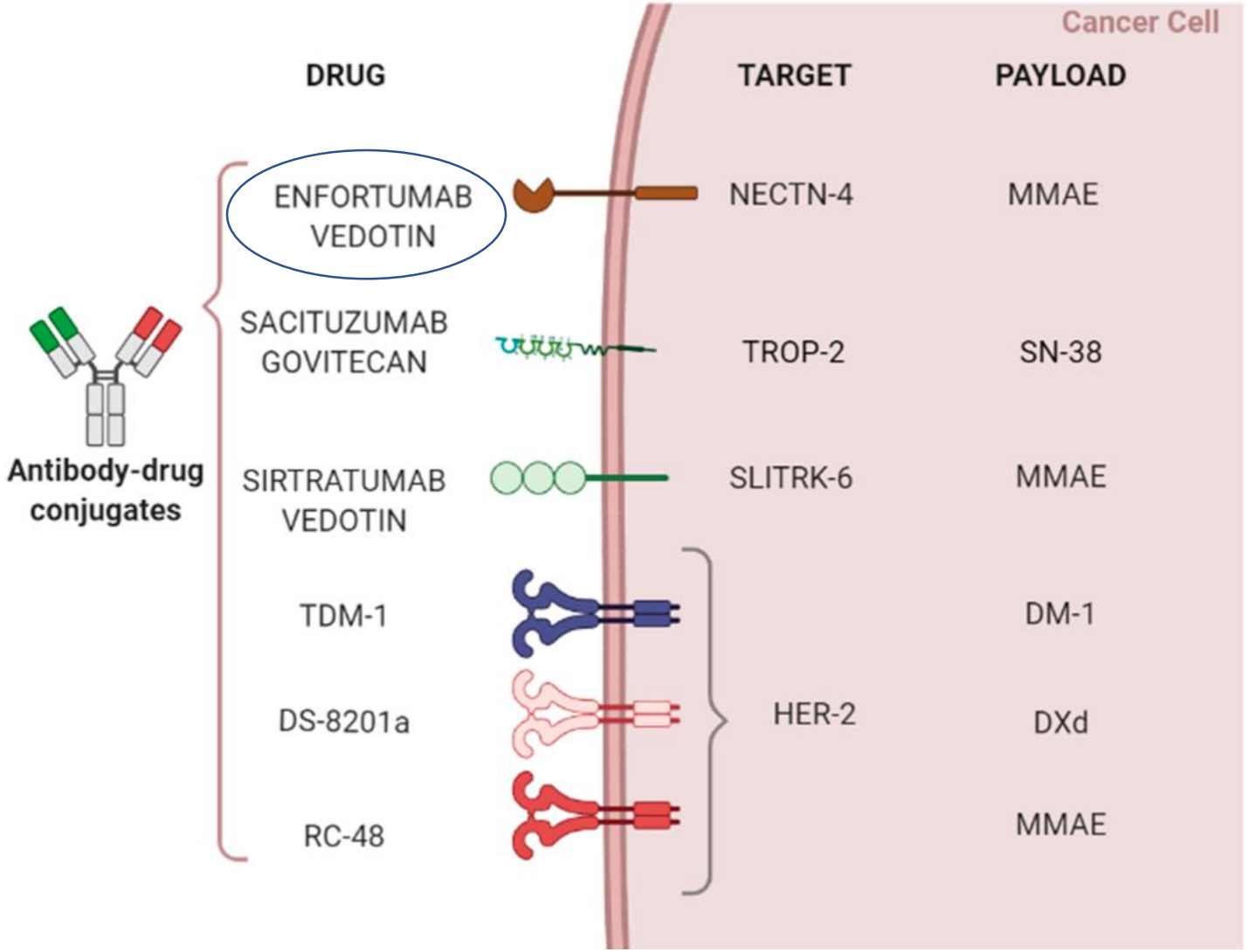


Powles et al., Annals of Oncology, 2022

Antibody-Drug Conjugates



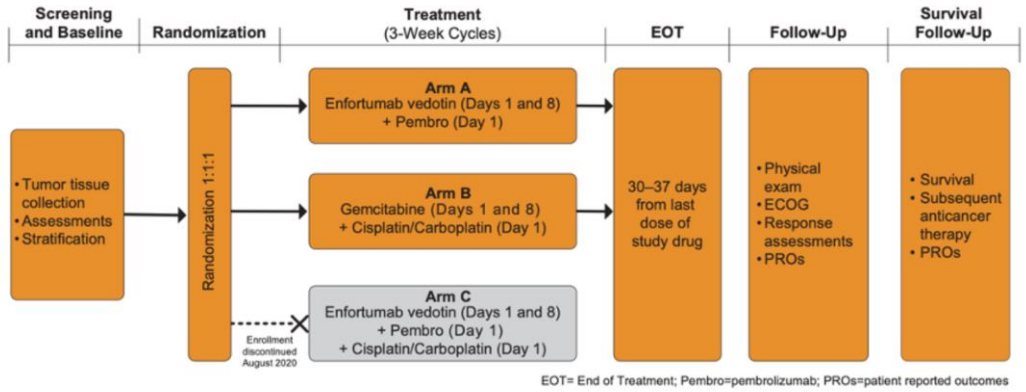
Delivering cytotoxic payloads by specific antibody targeting antigen expressed on cancer cells membrane.



Hafeez U., Molecules, 2020
Ungaro A., Cells, 2022

Enfortumab Vedotin

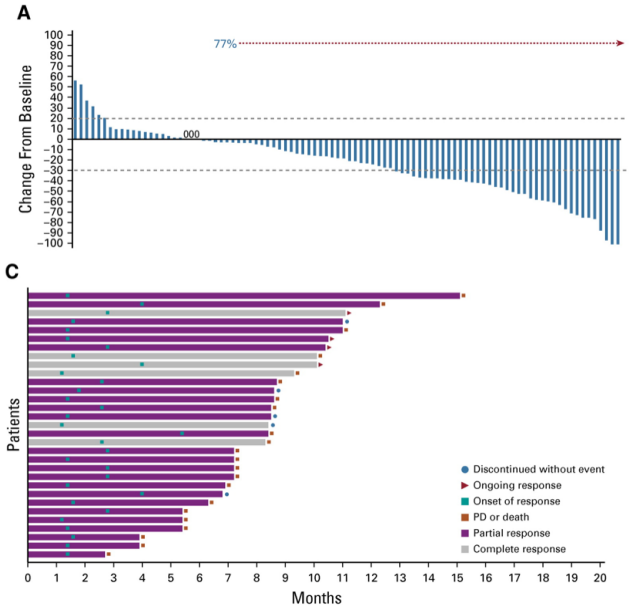
EMA approved

Phase III	EV 301 – EV vs Chemo (Docetaxel, Paclitaxel, Vinflunine) After platinum-based regimen and ICI	⇒ ORR 40,6% vs 17,9% ⇒ PFS 5,5m vs 3,7m ⇒ OS 12,9m vs 8,9m	≥ 3L
Phase II	EV 201 cohort 2 – EV monotherapy After ICI, cisplatin ineligible patients	⇒ ORR 52% (CR : 22%) ⇒ mPFS 5,8m ⇒ mOS 14,7m	2L
Phase Ib/II	EV 103 – EV + pembrolizumab vs EV 1L, cisplatin ineligible patients	⇒ ORR 64% vs 45% ⇒ CR : 10% vs 4%	1L Cisplatin ineligible
Phase III		**EV-302** Enrollment : ON Platinum-eligible patients	1L platinum eligible

Powles et al., NEJM, 2021
Vasant Balar A., GU Cancers Symposium, 2021
Rosenberg, ESMO 2022

Other ADCs

Sacituzumab Govitecan

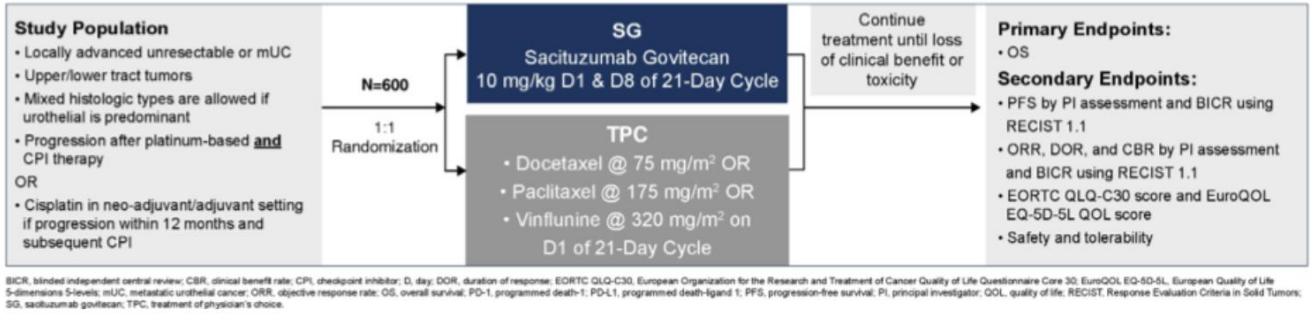


TROPHY-U-01

Phase II
ORR 27,4%
mPFS 5,4m

FDA approved

TROPiCS-04

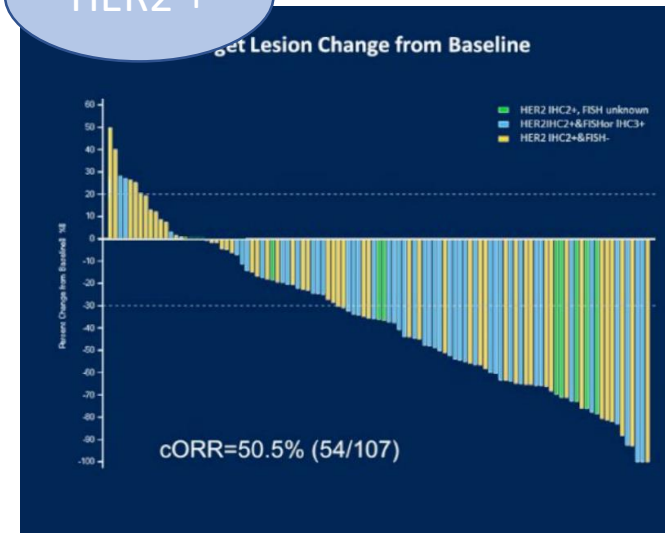


BICR, blinded independent central review; CBR, clinical benefit rate; CPI, checkpoint inhibitor; D, day; DOR, duration of response; EORTC QLQ-C30, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EuroQOL EQ-5D-5L, European Quality of Life 5-dimensions 5-levels; mUC, metastatic urothelial cancer; ORR, objective response rate; OS, overall survival; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PI, principal investigator; QOL, quality of life; RECIST, Response Evaluation Criteria in Solid Tumors; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

Disitamab Vedotin

RC48-C005 and RC48-C009

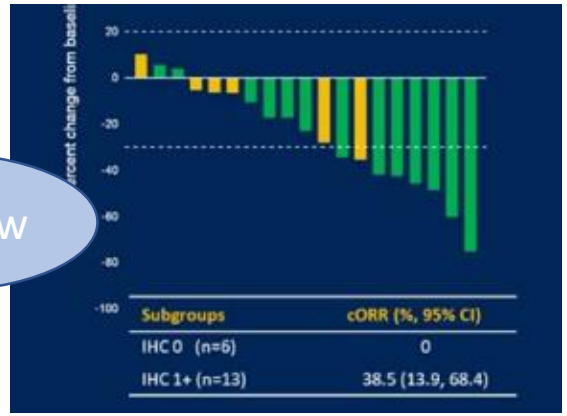
HER2 +



Subgroup Analysis for cORR

Subgroups	cORR (%, 95% CI)
HER2 status	
IHC2+FISH+ or IHC3+ (n=45)	62.2% (46.5%, 76.2%)
IHC2+FISH- (n=53)	39.6% (26.5%, 54.0%)
metastasis site	
Visceral Metastasis (n=97)	51.5% (41.2%, 61.8%)
Metastasis to Liver (n=48)	52.1% (37.2%, 66.7%)
Prior therapies	
Post PD1/PDL1 Treatments (n=27)	55.6% (35.3%, 74.5%)
Post 1 line of Chemotherapy (n=38)	50.0% (33.4%, 66.6%)
Post ≥2 Lines of Chemotherapy (n=69)	50.7% (38.4%, 63.0%)

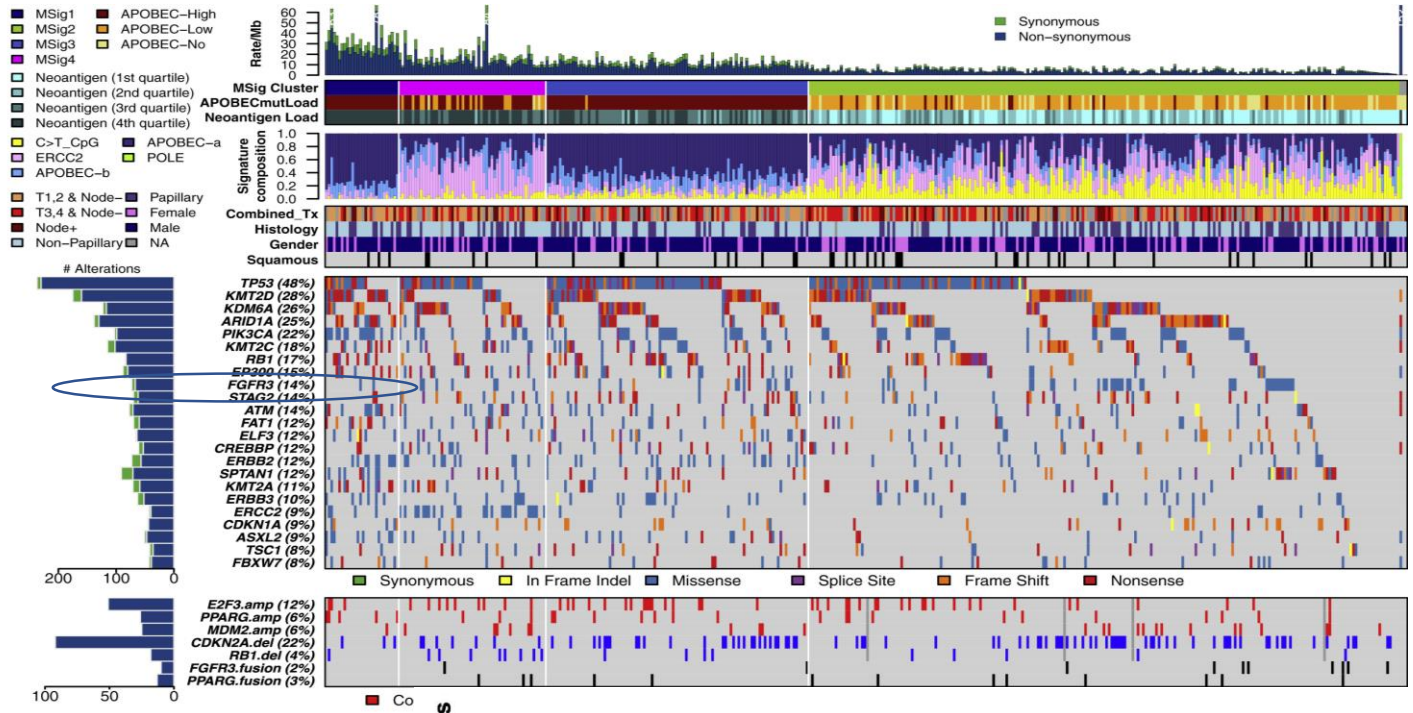
HER2 low



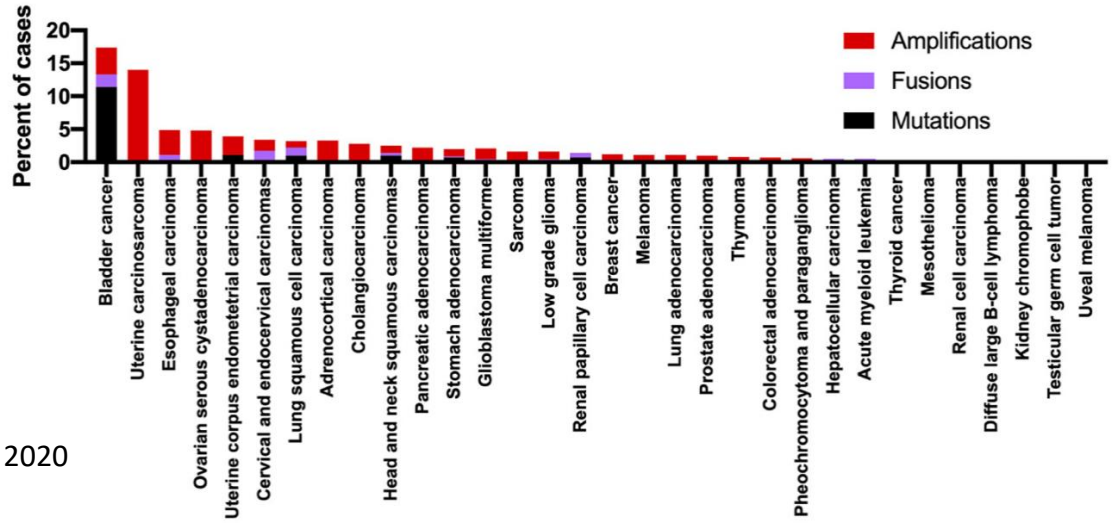
Subgroups	cORR (%, 95% CI)
IHC 0 (n=6)	0
IHC 1+ (n=13)	38.5 (13.9, 68.4)

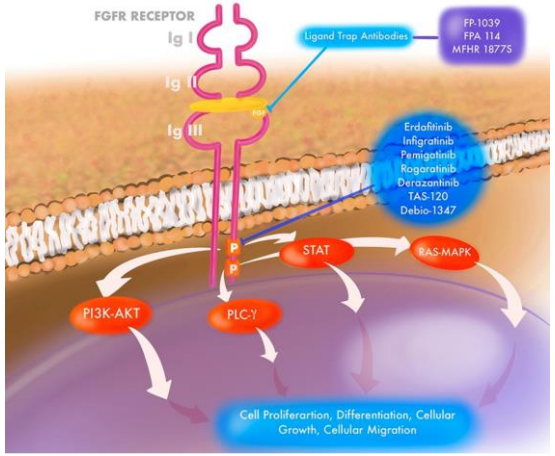
Tagawa et al., JCO, 2021
Sheng X., ASCO, 2022

FGFR inhibitor



FGFR3 Alterations

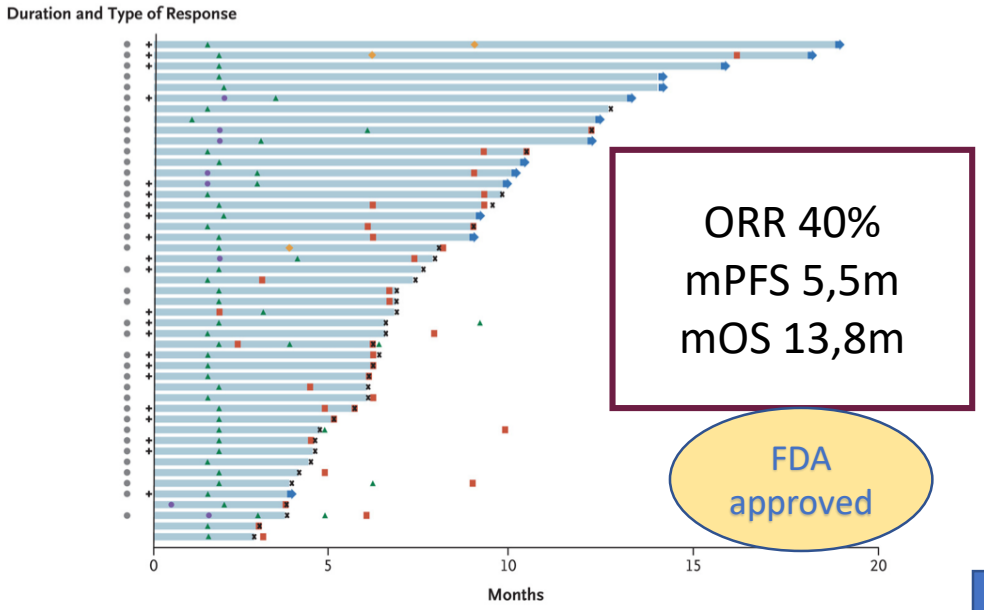




- Erdafitinib
- Infigratinib
- Pemigatinib
- Rogaratinib
- Derazantinib
- TAS-120
- Debio 1347
- Vofatamab

Robertson et al., Cell, 2017
Kacew et al., Front. Immunol., 2020
Garje, The Oncologist, 2020

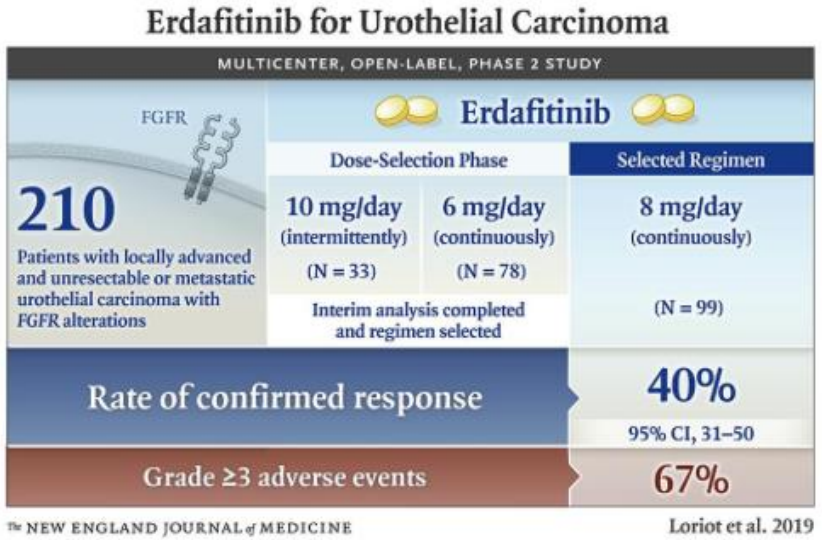
Erdafitinib



Loriot et al., NEJM, 2019

ORR 40%
mPFS 5,5m
mOS 13,8m

FDA approved



After chemotherapy ± immunotherapy
FGFR 3 mutation or FGFR2/3 fusion

THOR trial

Adults with surgically unresectable or metastatic UC; meet molecular eligibility criteria for *FGFR* alteration status per FGFRi Clinical Trial Assay; ECOG PS 0-2 (N = 631)

Cohort 1
Prior anti–PD-(L)1, ≤2 prior lines of systemic tx

- **Erdafitinib** starting at 8 mg/day PO QD in 21-d cycles
- **Investigator's choice of treatment***

Cohort 2
No prior anti–PD-(L)1, 1 prior line of systemic tx

- **Erdafitinib** starting at 8 mg/day PO QD in 21-d cycles
- **Pembrolizumab** 200 mg IV Q3W

Until PD, intolerable toxicity, consent withdrawal, or investigator decision

*Vinflunine 320 mg/m^2 IV or docetaxel 75 mg/m^2 IV Q3W.

Perspectives for FGFR inhibitors

FORT-2

- Rogaratinib + Atezolizumab
- High FGFR 1/3 mRNA expression levels
- Ongoing, not recruiting

NCT04601857

- Futibatinib (TAS-120) + Pembrolizumab
- FGFR3 mutation or FGFR1-4 fusion/rearrangement (cohort A) or other FGFR/non-FGFR aberrations (cohort B)

NCT05614739

- LOXO-435 +/- Pembrolizumab
- FGFR3 alterations

FGFRi + IO

NCT04963153

- Erdafitinib + EV
- FGFR2/3 genes alteration
- After platinum-based chemotherapy and ICI

FGFRi + EV

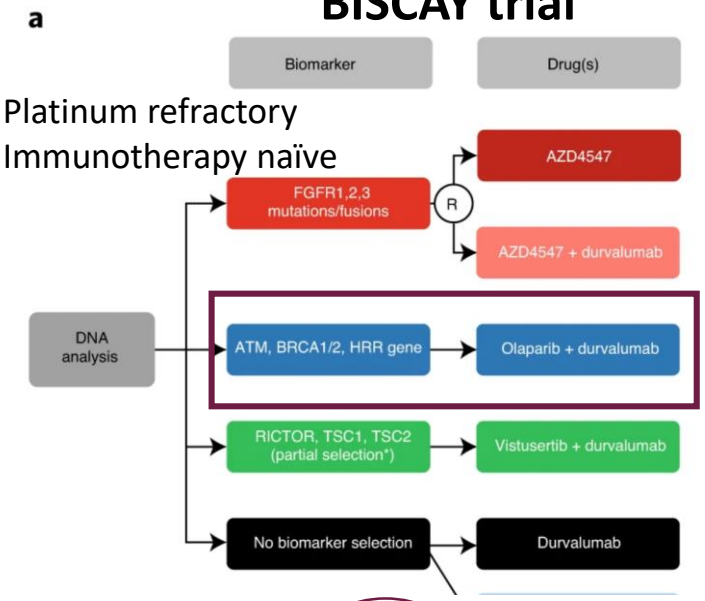
NCT05030077

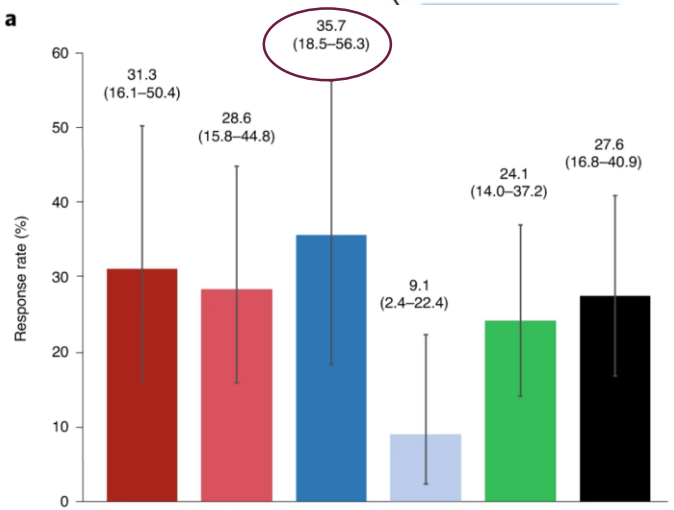
- Anlotinib + Platinum/gemcitabine
- 1L mUC

FGFRi + ChT

PARP inhibitor

BISCAY trial

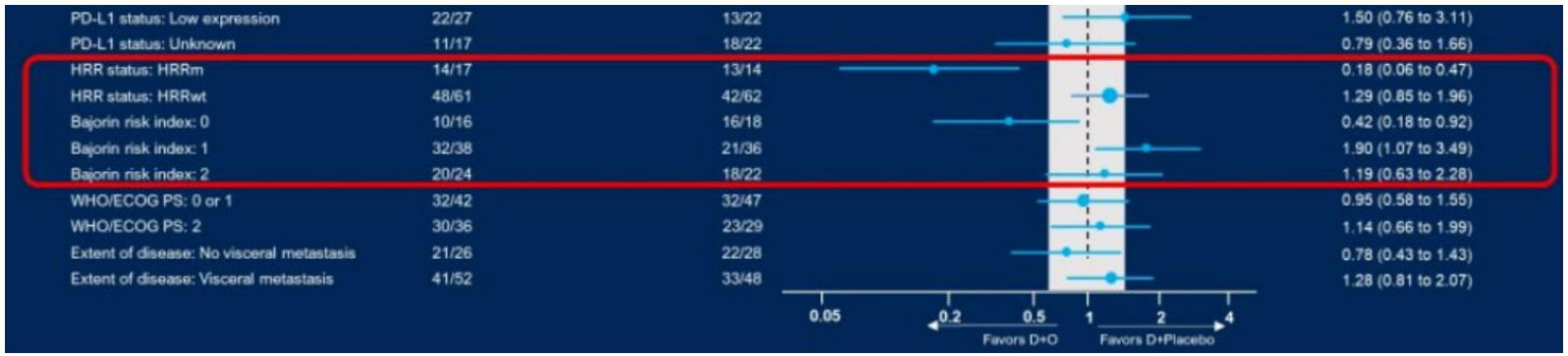




	AZD4547	AZD4547 + durvalumab	Olaparib + durvalumab selected	Olaparib + durvalumab unselected	Vistusertib + durvalumab	Durvalumab
Number of patients	16	21	14	22	29	29

BAYOU trial

- 1L, platinum ineligible patients
- **No benefit** of durvalumab combined with olaparib versus durvalumab + placebo in ITT population
- **Positive signal** in HRRm subgroup

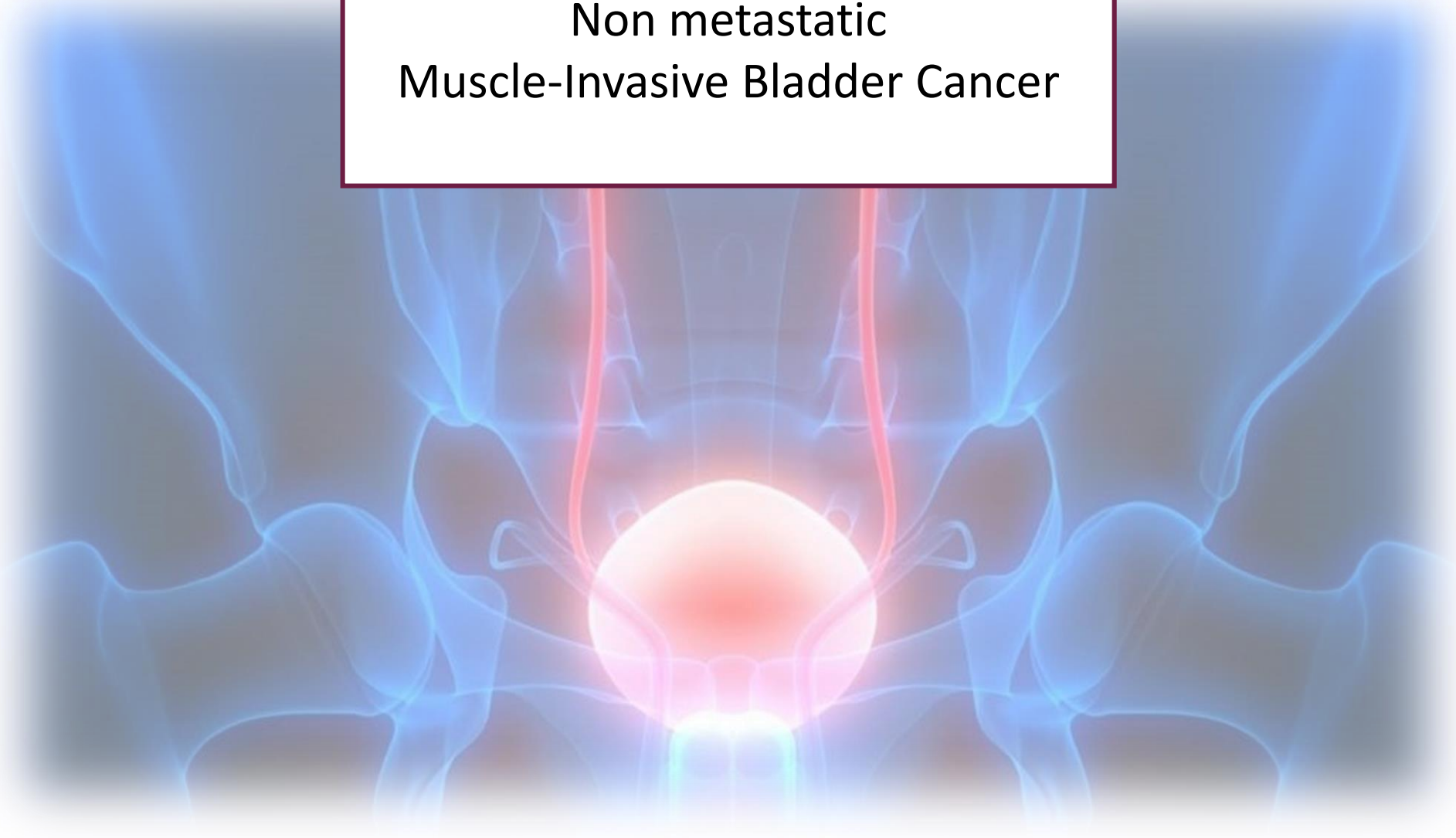


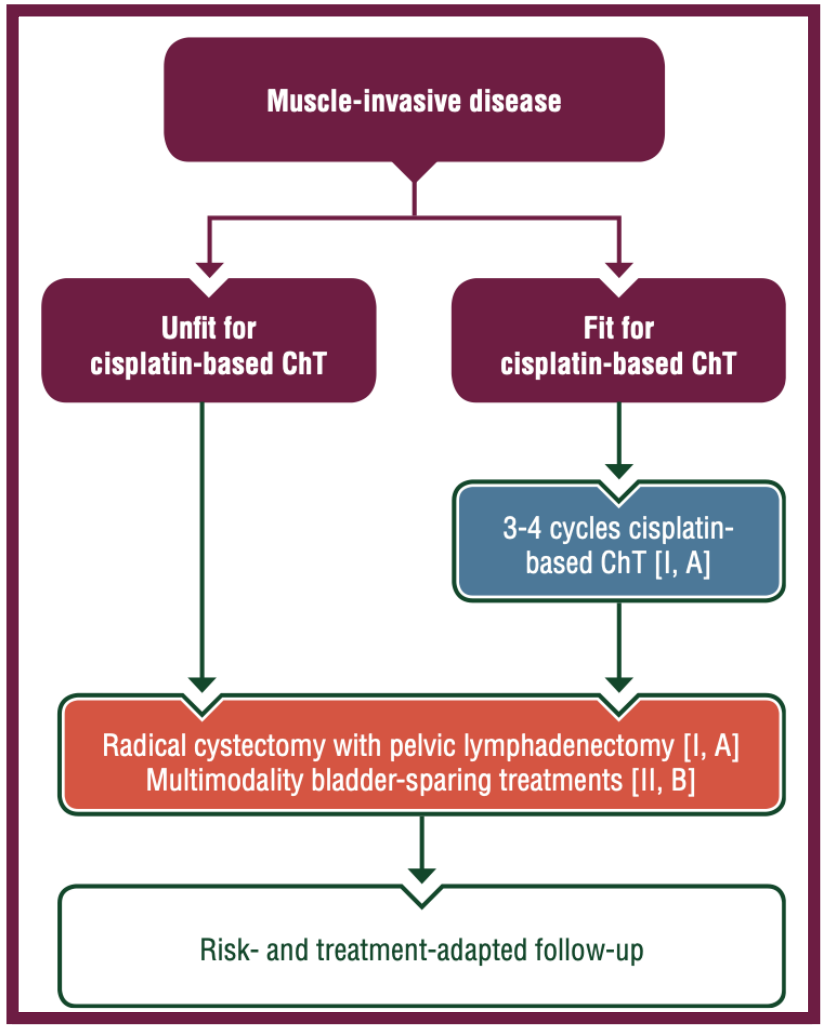
ATLANTIS trial

- DNA Repair Deficiency or > 10% LOH
- Rucaparib in maintenance after platinum-based chemotherapy response
- **Benefit** in PFS (35 weeks vs 15 weeks)

Powles et al., Nature, 2021
Rosenberg J E, ASCO, 2022
Crabb S., ASCO, 2022

Non metastatic
Muscle-Invasive Bladder Cancer





Powles et al., Annals of Oncology, 2022

Adjuvant Immunotherapy

High risk of relapse

Trial	IO	Patients	Population	DFS	OS
IMvigor010	Atezolizumab 1y	809	ypT2-4a or ypN+ pT3-4a or pN+	✗	✗
Checkmate 274	Nivolumab 1y	709	ypT2-4a or ypN+ pT3-4a or pN+	ITT ✓ PD-L1+ ✓	⏳
AMBASSADOR	Pembrolizumab 1y	739	ypT2-4a or ypN+ pT3-4a or pN+	⏳	⏳

FDA

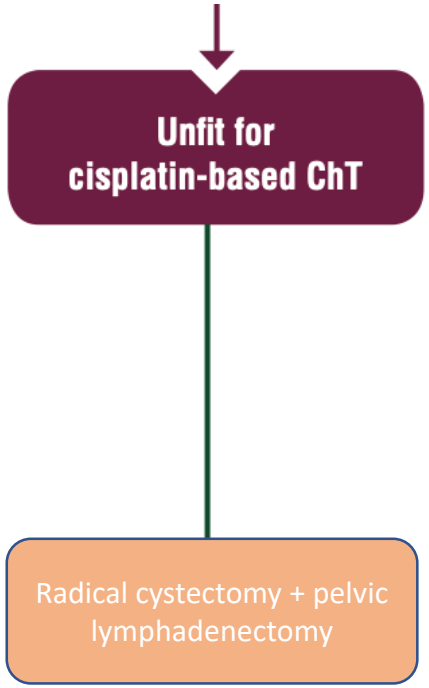
Nivolumab – ITT : HR 0,70

Nivolumab – PD-L1+ : HR 0,55

EMA

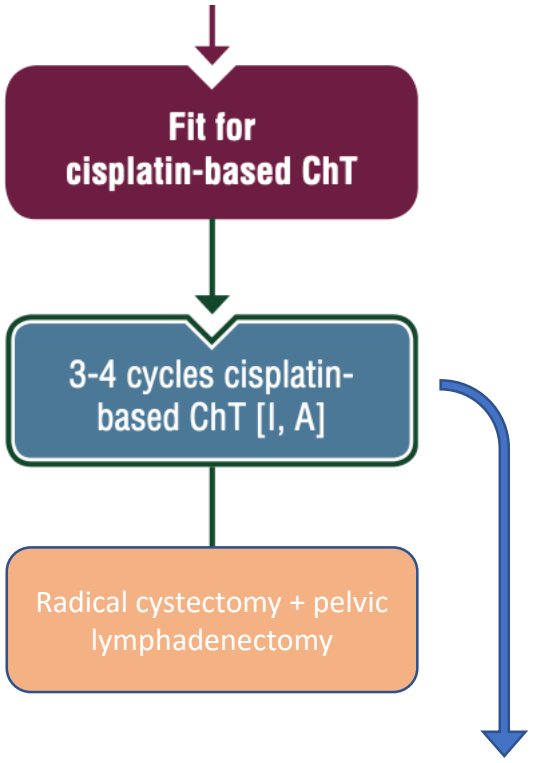
Belmunt et al., The Lancet Oncology, 2021
Bajorin et al., NEJM, 2021
Apolo et al., GU Cancers Symposium, 2019

Neo Adjuvant Immunotherapy



Cisplatin **ineligible** patients					
Trial	**Phase**	**Patients**	**Population**	**Treatment**	**pCR**
CPI					
ABACUS	II	88	T2-T4N0	Atezolizumab x2	31%
NABUCCO	Ib	24	T3-4 N0 or T1-4 N1-3	Nivolumab + Ipilimumab x2	46%
AURA	II	28	T2-T4 N0-+	Avelumab	36%
Chemo + CPI					
HCRN GU14-188 (2)	II	37	T2-4 N0	G + Pembrolizumab -3-5x	45,2%
AURA	II	28	T2-T4 N0-+	Taxol + gem + Avelumab	18%
CPI + RT					
RACE IT	II	31	T3-T4 N0-+	Nivolumab x4 + RT	38,7%
CPI + other					
NEODURVARIB	II	28	T2-T4 N0	Durvalumab + olaparib	44,5%

Neo Adjuvant Immunotherapy



VESPER trial - pCR :
ddMVAC 42%
Cis-Gem 36%

Pfister et al., European Urology, 2021

Cisplatin **eligible** patients					
Trial	**Phase**	**Patients**	**Population**	**Treatment**	**pCR**
CPI					
PURE-01	II	155	T2-T4 N0	Pembrolizumab x3	39%
DUTRENEO	II	61	T2-T4 N0-1	Durvalumab + Tremelimumab x3	34,8%
Chemo + CPI					
HCRN GU14-188 (1)	Ib/II	43	T2-T4 N0	CG + Pembrolizumab	44%
LOCC 1520	II	39	T2-4 N0-x	CG + Pembrolizumab (split cisplatin)	36%
BLASST-1	II	41	T2-T4a N0-1	CG + Nivo	49%
AURA	II	26 26	T2-T4 N0-+	CG + Avelumab ddMVAC + Avelumab	54% 61%
SAKK 06/17	II	53	T2-T4 N0-1	CG + Durvalumab	34%

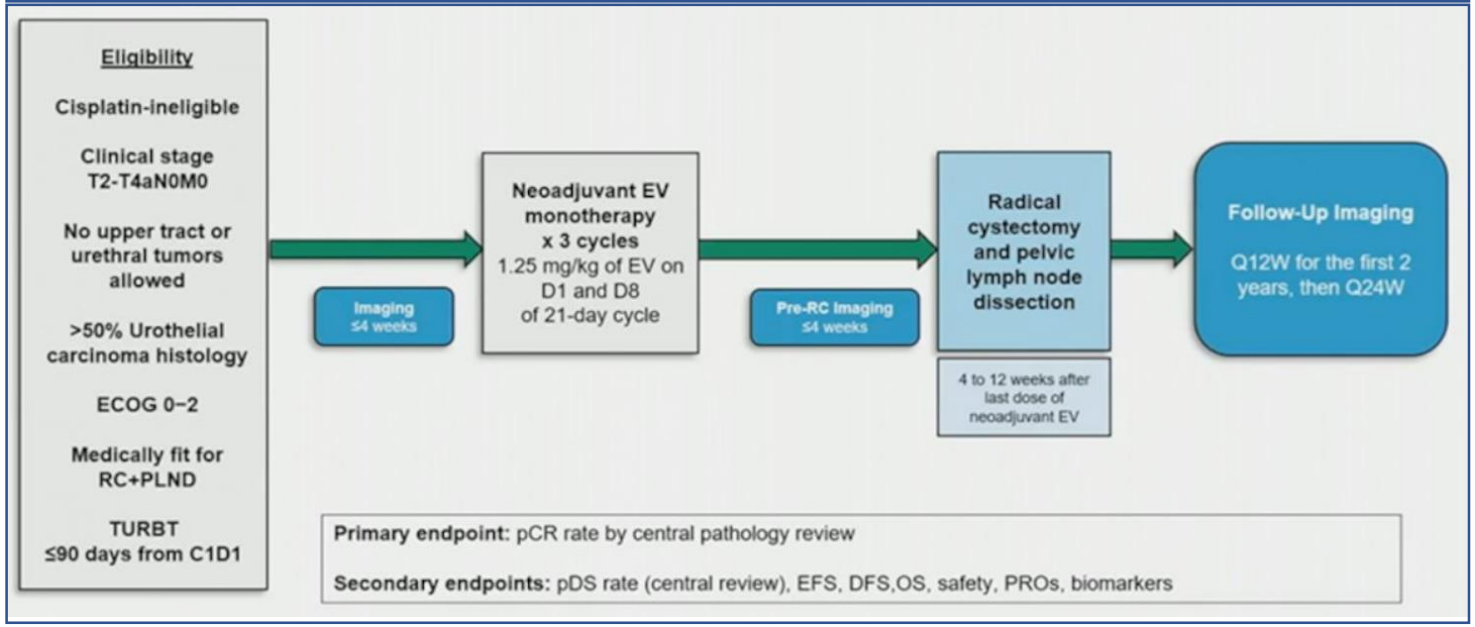
PERSPECTIVES

Peri-operative immunotherapy

- **NIAGARA** Durvalumab + GC => RC => Durvalumab – Phase III
- **KEYNOTE-866** Pembrolizumab + GC => Pembrolizumab – Phase III
- **ENERGIZE** Nivolumab + GC => RC => Nivolumab – Phase III

Neo Adjuvant Antibody-Drug Conjugate

EV-103 Cohort H– Phase I/IIb – Neo-Adj EV - Cisplatin ineligible patients



Primary endpoint :

⇒ pCR (ypT0N0) : 36,4%

Key secondary endpoints :

⇒ pDS (ypT0,Tis,Ta,T1,N0) : 50%

⇒ Safety

⇒ Promising anti-tumoral activity in cisplatin ineligible patients

⇒ No delay to undergo surgery

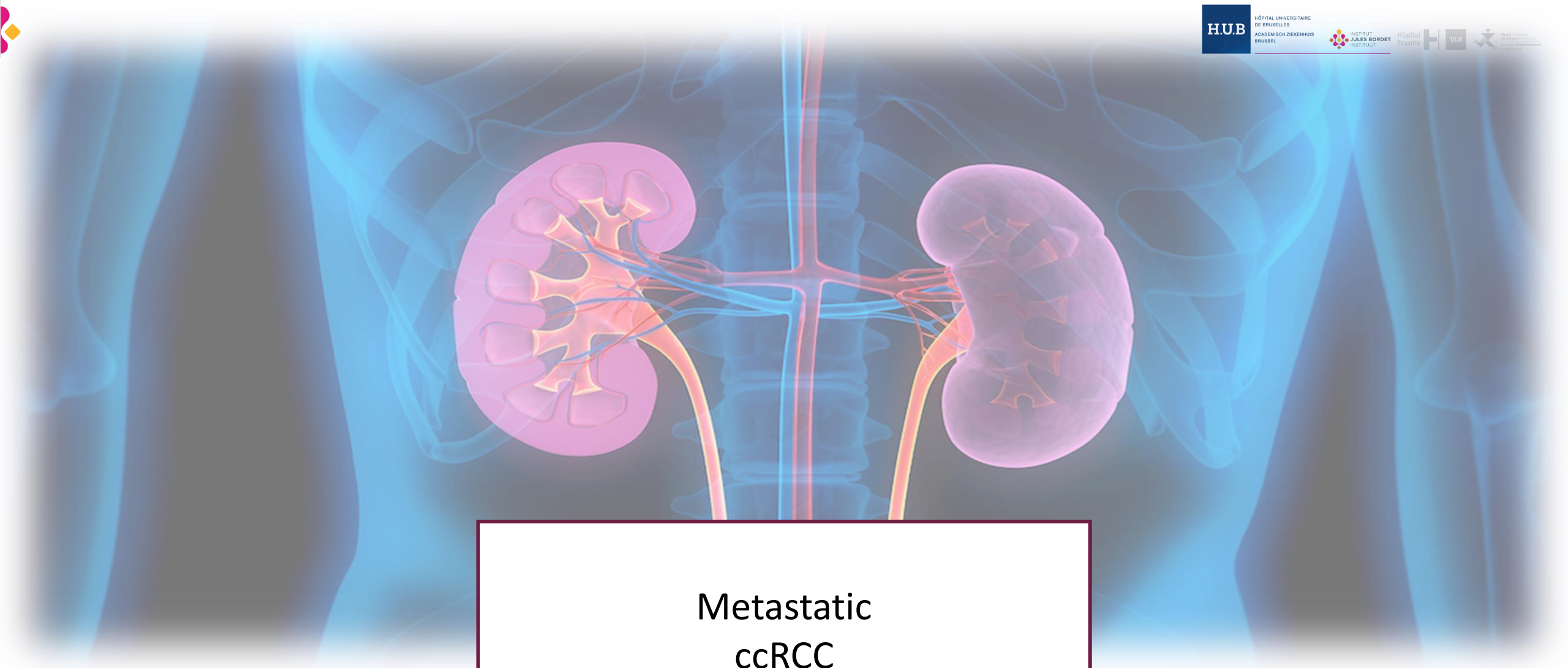
⇒ AE consistent with previous safety profile of EV

PERSPECTIVES

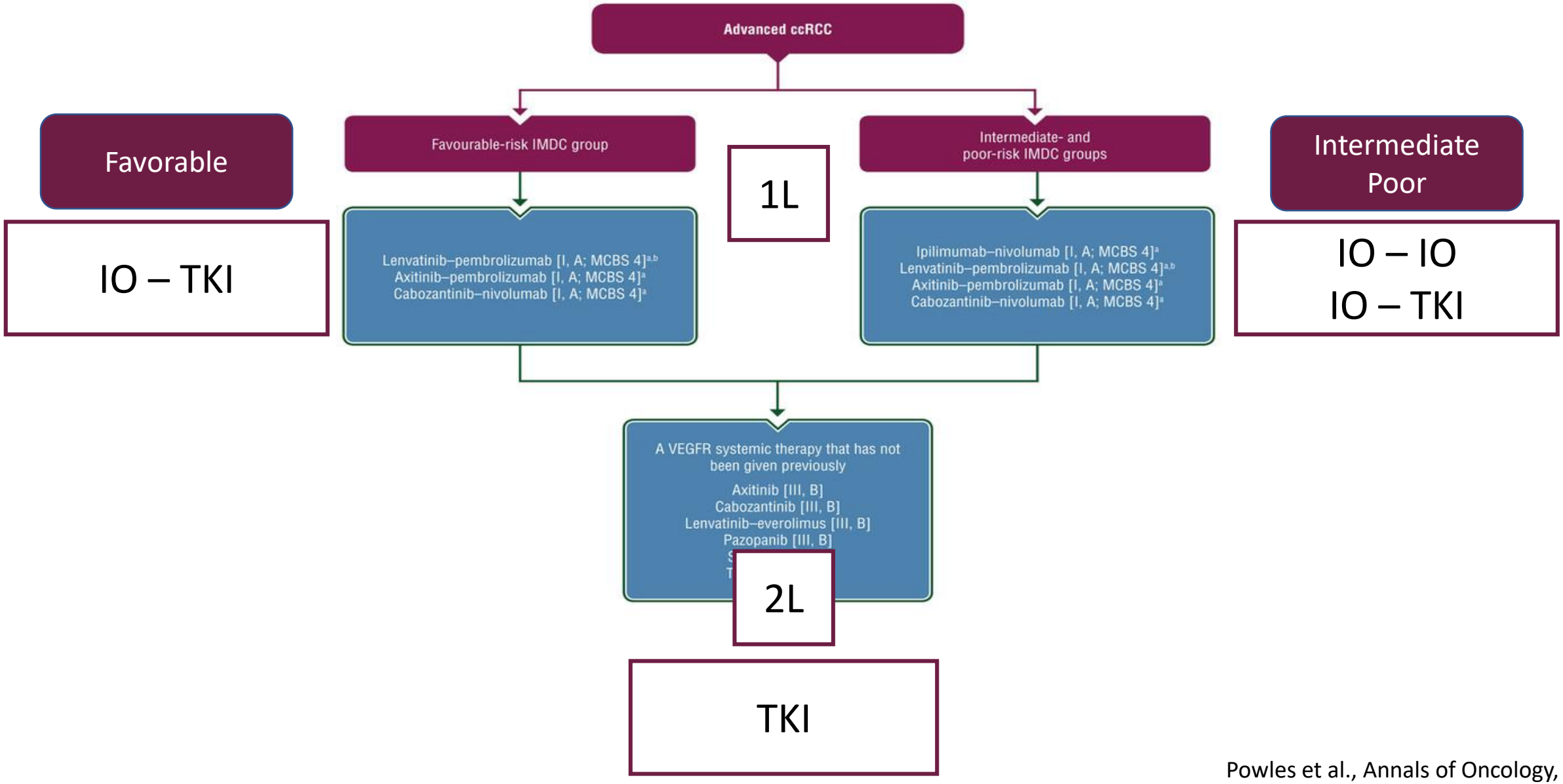
Novel drugs development

- **Anti-PD-1** Toripalimab + CG
- **IL-2** Bempegaldesleukin + Nivolumab
- **Oral IDO-1 inhibitor** Linrodostat mesylate
- **Anti-BTN3A** ICT01 ± pembrolizumab
- **Anti-CD137** Urelumab + Nivolumab

Petrylak, ASCO 2022

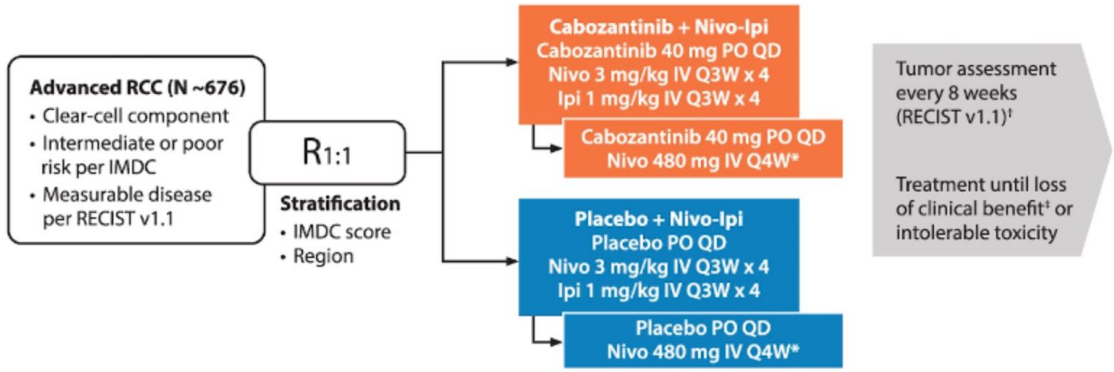


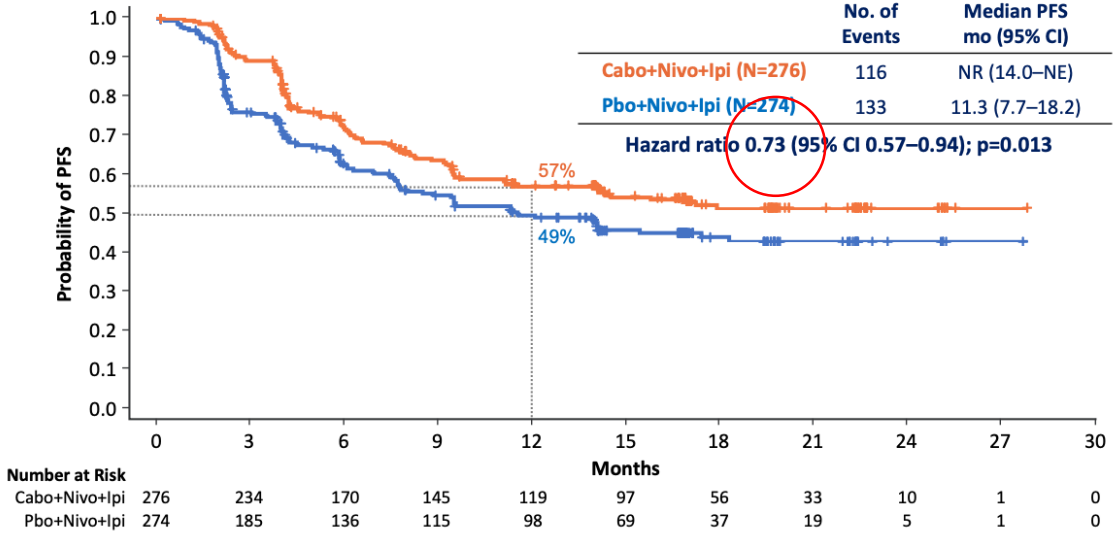
Metastatic ccRCC



Powles et al., Annals of Oncology, 2021

COSMIC-313 : TRIPLET (IO + IO + TKI)





Tumor Response (PITT Population)

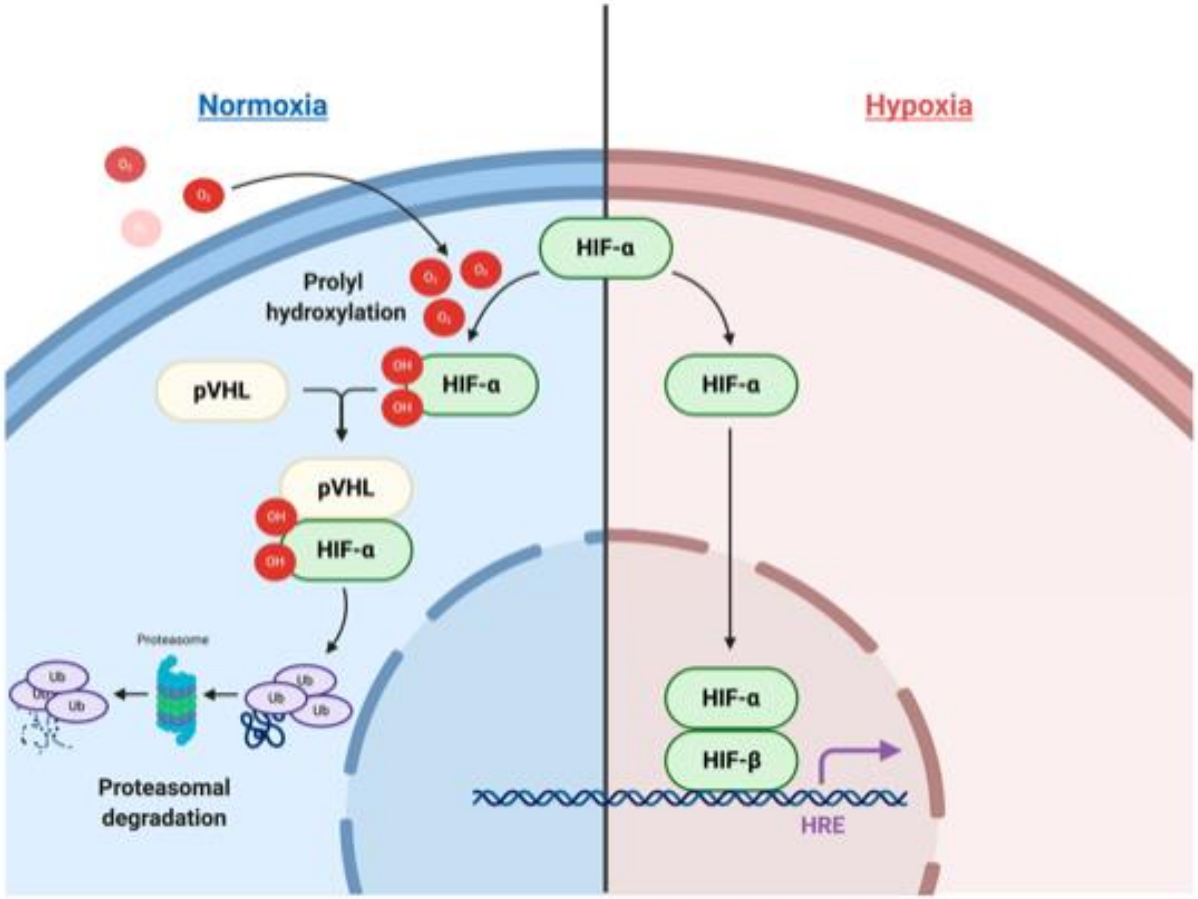
	Cabo+Nivo+Ipi (N=276)	Pbo+Nivo+Ipi (N=274)
Objective response rate (95% CI), %	43 (37.2–49.2)	36 (30.1–41.8)
Best overall response, n (%)		
Complete response	7 (3)	9 (3)
Partial response	112 (41)	89 (32)
Stable disease	119 (43)	100 (36)
Progressive disease	23 (8)	55 (20)
Not evaluable	15 (5)	21 (8)
Disease control rate, %	86	72
Median time to objective response (range), mo	2.4 (1.5–17.1)	2.3 (1.9–16.8)
Median duration of response (95% CI), mo	NR (20.2–NE)	NR (NE–NE)

Tumor response per RECIST v1.1 by BIRC
Disease control rate = complete response + partial response + stable disease

	Cabo+Nivo+Ipi (N=426)		Pbo+Nivo+Ipi (N=424)	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4
Treatment-related adverse events				
Any event,* %	99	73	91	41
Alanine aminotransferase increased	46	26	17	6
Aspartate aminotransferase increased	44	20	16	5
Diarrhea	41	4	18	3
Palmar-plantar erythrodysesthesia	28	3	4	0
Hypothyroidism	24	<1	15	0
Hypertension	23	8	5	2
Fatigue	22	2	21	1
Lipase increased	22	9	13	6
Amylase increased	20	5	12	2
Rash	20	2	20	1
Pruritus	20	0	26	<1

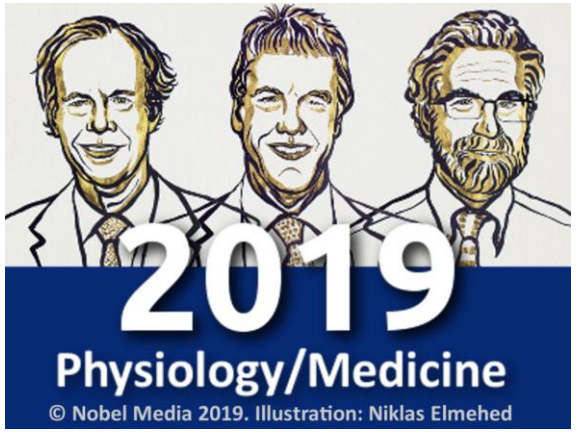
Choueri T., ESMO, 2022

HIF pathway



HIF = Hypoxia-Inducible Factor

pVHL = Von Hippel Lindau protein



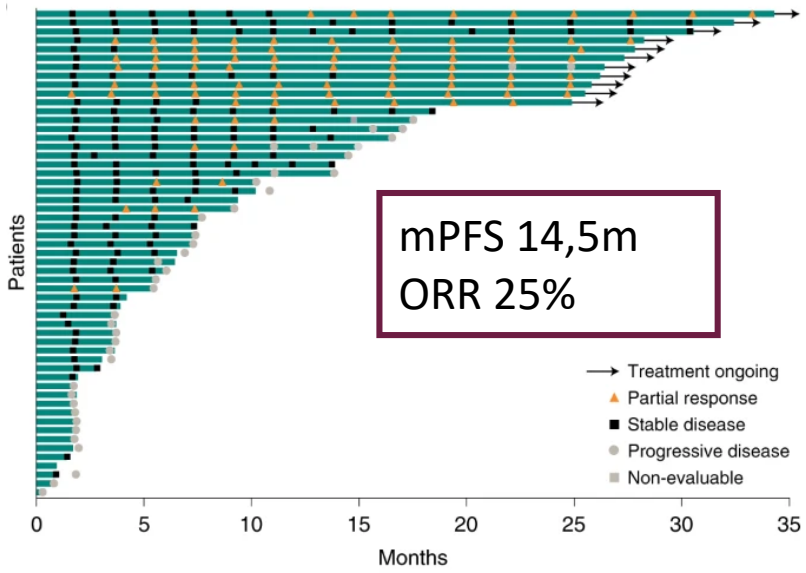
- HIF dimers are imported into nucleus to promote transcription
- pVHL induces HIF degradation
- The majority of sporadic ccRCCs have somatic loss of both VHL alleles

- Belzutifan
- ARO-HIF2
- NKT2152
- XL-092

Vito et al., Cells, 2020

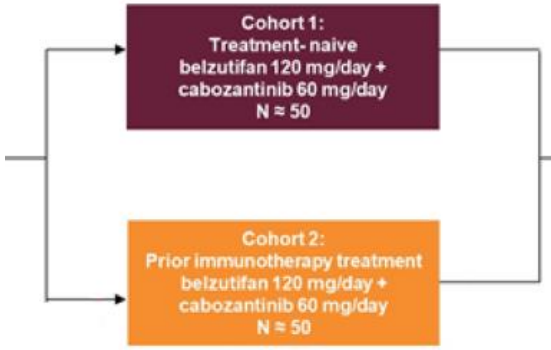
Belzutifan - Inhibitor of HIF-2α

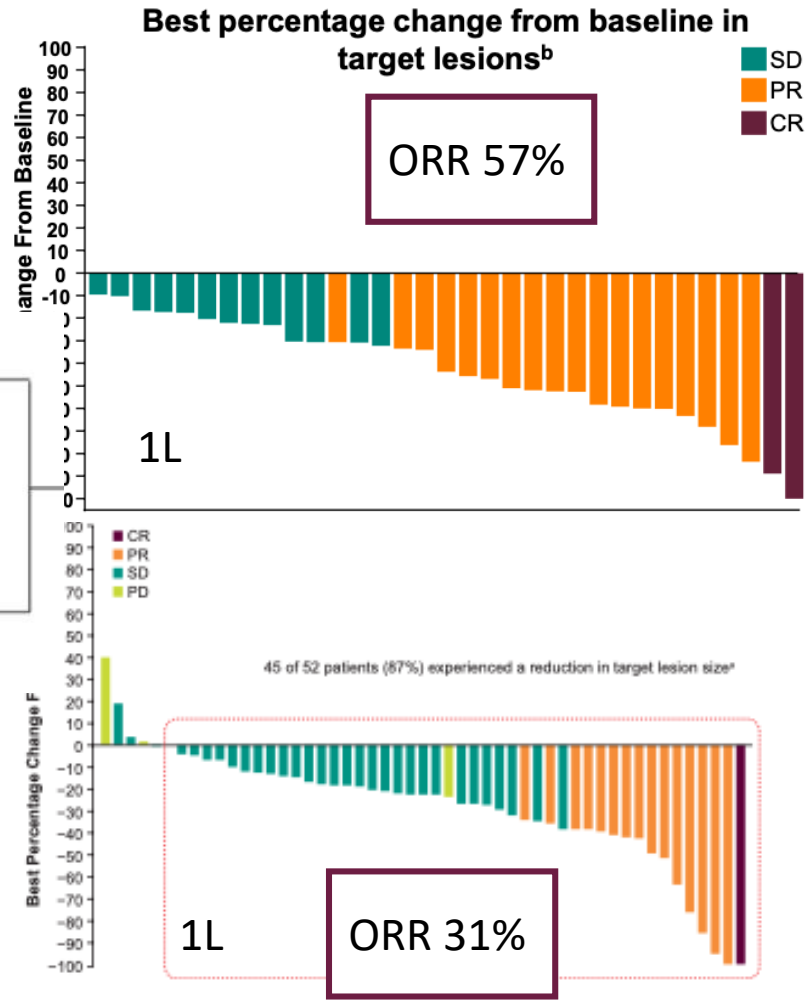
LITESPARK-001 - Phase I - Belzutifan



mPFS 14,5m
ORR 25%

LITESPARK-003 – Phase II – Belzutifan + Cabozantinib





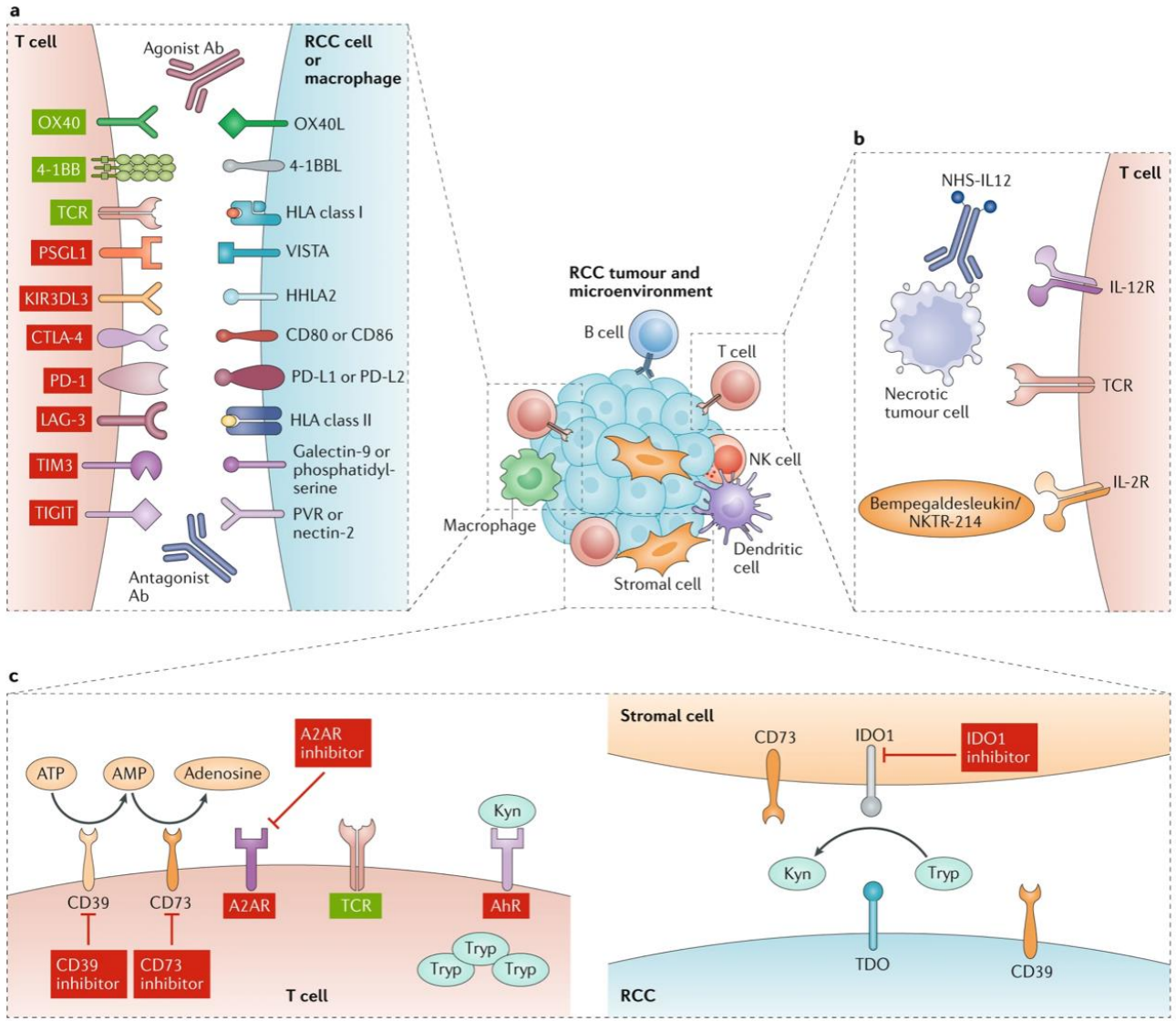
Phase III

- MK-6482-005 – Belzutifan vs Everolimus – 3/4L
- MK-6482-005 – Belzutifan + Lenvatinib vs Cabozantinib – 2L
- MK-6482-012 – Belzutifan + Pembro + Lenva vs Quavonlimab + P + L vs P + L – 1L

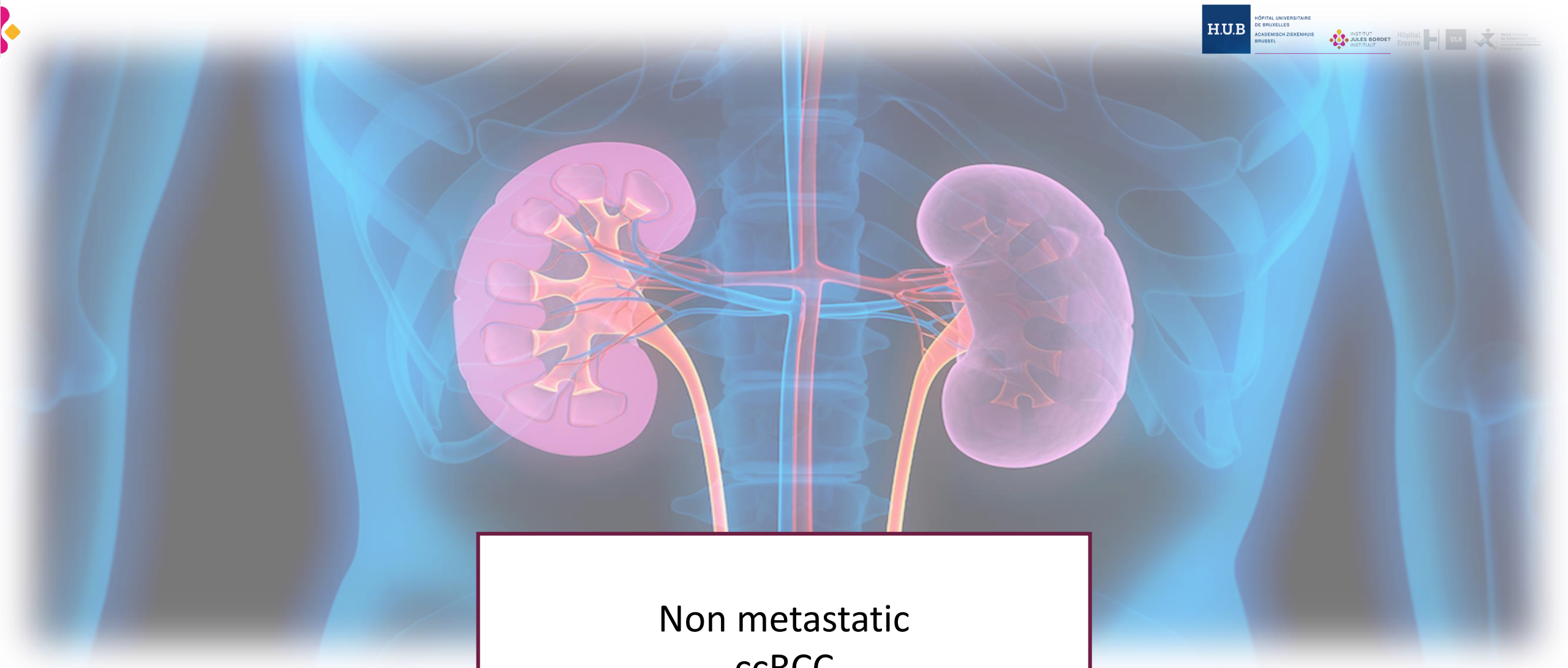
Choueri et al., Nature Medicine, 2021

Immunomodulator – Targeting the RCC immune microenvironment

- **ICI** Botensilimab + Balstilimab
- **Anti LAG-3** Relatilmab
- **IDO-1 inhibitor** Linrodostat
- **Anti-IL-27** SRF-388
- **A2AR inhibitor** Ciforadenant
- **Anti-CD70 CART** ALLO-316



Braun et al, Nat Rev Clin Oncol, 2021



Non metastatic ccRCC

Adjuvant therapy

Intermediate-High Risk
- pT2, grade 4 or sarcomatoïd, N0,M0
- pT3, any grade, N0, M0

High Risk
- pT4 any grade N0 M0
- Any pT, any grade, N+, M0

M1 NED
- NED after resection of oligometastatique

TKI

Trial	Patients	OS
ASSURE	1943	✗
S-TRAC	615	✗
PROTECT	1538	✗
ATLAS	724	⧗
EVEREST	1545	⧗

Immunotherapy

Trial	Patients	Treatment	DFS	OS
IMmotion 010	778	Atezolizumab	✗	⧗
KEYNOTE-564	994	Pembrolizumab	✓ EMA approved	⧗
CHECKMATE 914	816	Nivolumab + ipi	✗	⧗
PROSPER	819	Nivolumab (NA + A)	✗	⧗
RAMPART	…	Durvalumab (+/-treme)	Recruiting	Recruiting

PERSPECTIVES

Phase III Belzutifan + Pembrolizumab (LITESPARK-022)

Neo adjuvant Axitinib + Avelumab (NeoAvAx)

Take Home Messages

- MIBC
  - New strategies and combinations are promising – ADC, FGFRi, PARPi
- ccRCC
  - HIF-2alpha inhibitor –Belzutifan– is currently being tested in phase III trials with encouraging results
- Translational research may help patient selection and biomarker-driven strategies

Thank you for your attention

GU onco-team at Jules Bordet Institute - HUB