XXIV Simposio de Revisiones en Cáncer

"Tratamiento médico del cáncer en el año 2022"

New targets in advanced urothelial carcinoma after platinum and immunotherapy

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ARÁN

My disclosures

- **Advisory Boards:**
  - MSD, BMS, Roche-Genentech, PYCYC, IPSEN, Novartis, Bayer, Gilead
- **Research Funding:**
  - Roche-Genentech, Astra-Zeneca
- **Travel expenses:**
  - Roche-Genentech, IPSEN, Merck-Pfizer
- **Clinical Trials:**
  - BMS, Roche-Genentech, PYCYC, EISAI, MSD, Gilead, Astellas
- **Lectures:**
  - EUSA pharma, MSD, BMS, Roche-Genentech, IPSEN, Jansen, Astellas

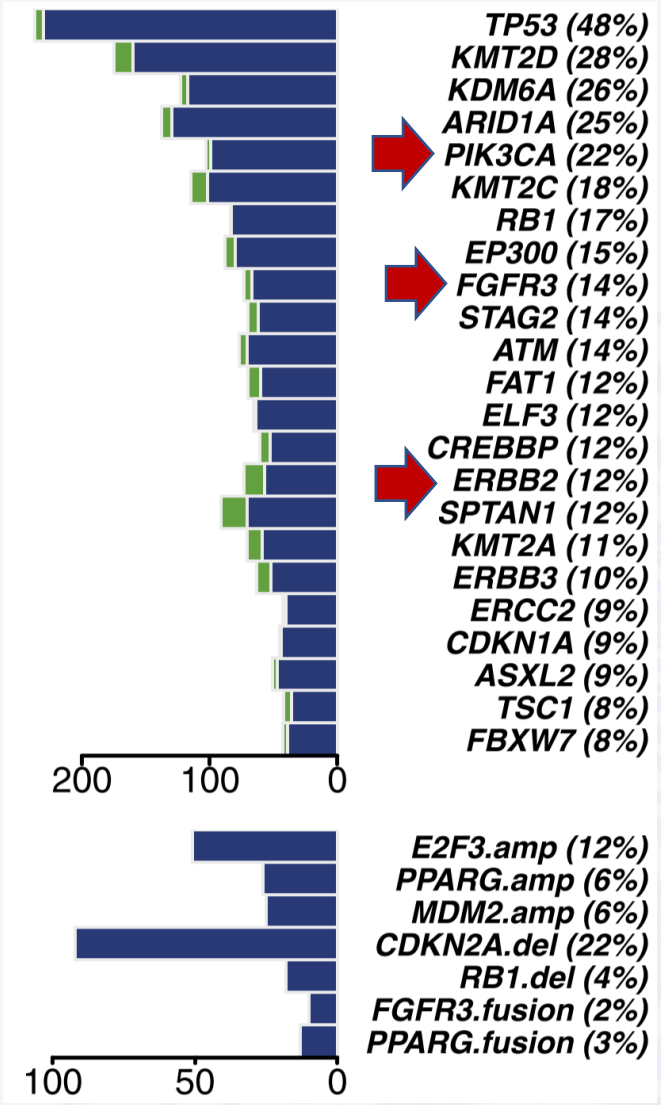
Learning objectives

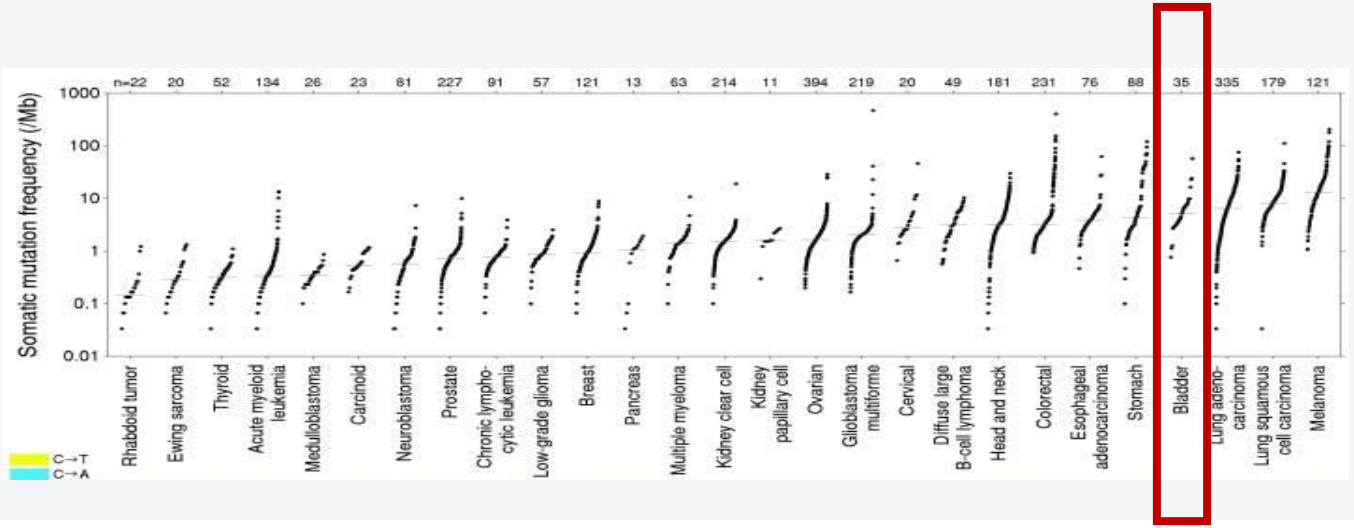
- To review new therapeutic targets in advanced urothelial cancer after progression to platinum-based chemotherapy and check point inhibition

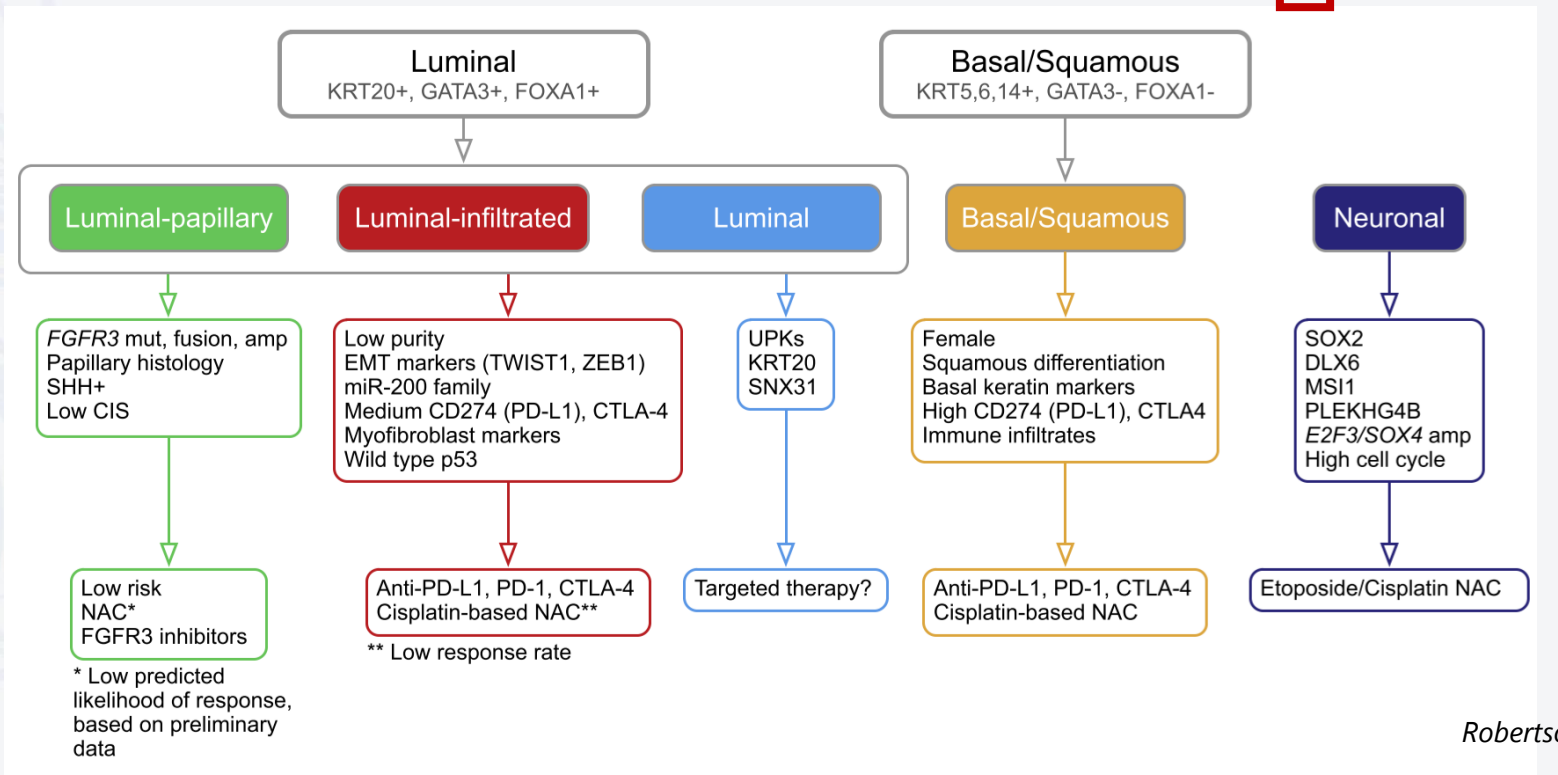
Outline

- Introduction
- Precision medicine in bladder cancer: FGFR inhibition
- Cell adhesion molecules & others as targets and new drug delivery methods: The ADCs
- Other new targets: Ephrin-B2
- Conclusions

Is mUC a good model for targeted therapy?







Robertson AG et al. Cell 2017

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Looking for new targets in mUC

- Multiple failed attempts (mainly single arm trials) in unselected population over the last decade
- Main agents tested: VEGF-targeted therapy (TKIs, mABs), EGFR/HER2 inhibitors, mTOR inhibitors
- Randomized trials are scarce and have failed (**LAMB trial**) or demonstrated little benefit (**RANGE trial**)
- Better understanding of mUC molecular behaviour has led to design novel trials, **testing targeted therapies** in **biomarker selected patients** or **uncovering new targets widely expressed** and **new ways of delivering drugs**

Petrylak, D.P., et al., Ramucirumab plus docetaxel versus placebo plus docetaxel in patients with locally advanced or metastatic urothelial carcinoma after platinum-based therapy (RANGE): a randomised, double-blind, phase 3 trial. Lancet, 2017. 390(10109): p. 2266-2277. Phase III, Double-Blind, Randomized Trial That Compared Maintenance Lapatinib Versus Placebo After First-Line Chemotherapy in Patients With Human Epidermal Growth Factor Receptor 1/2–Positive Metastatic Bladder Cancer Thomas Powles, Robert A. Huddart, Tony Elliott, et al. Journal of Clinical Oncology 2017 35:1, 48-55

Precision medicine in bladder cancer: FGFR inhibition

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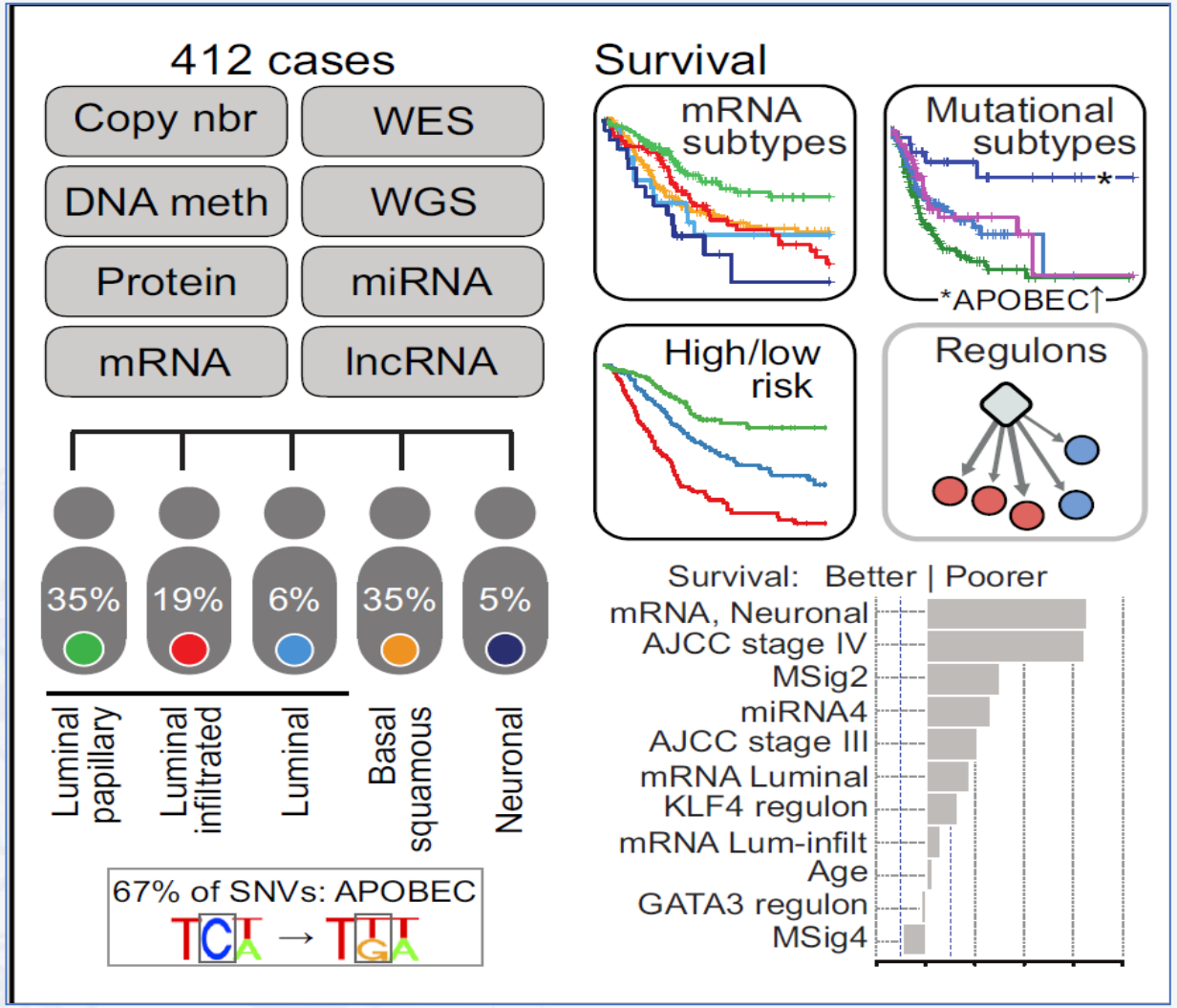
Bladder cancer should not be regarded as one disease

Cell

Comprehensive Molecular Characterization of Muscle-Invasive Bladder Cancer

Multiplatform analysis of 412 muscle invasive bladder cancer patients provides insights into mutational profiles with prognostic value and establishes a framework associating distinct tumor
subtypes with clinical options.

FGFR [specially FGFR3] appears as a commonly altered gene in MIBC [fusions, mutations, methylation, etc] representing a potential target.



Robertson et al., 2017, Cell 171, 540–556

Biomarker selected patients: FGFR as a target: First steps

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European Journal of Cancer (2014) 50, 3145–3152

Available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Clinical Trial

Phase 2 trial of dovitinib in patients with progressive *FGFR3*-mutated or *FGFR3* wild-type advanced urothelial carcinoma

Matthew I. Milowsky [a,*], Christian Dittrich [b], Ignacio Durán [c], Satinder Jagdev [d], Frederick E. Millard [e], Christopher J. Sweeney [f], Dean Bajorin [g], Linda Cerbone [h], David I. Quinn [i], Walter M. Stadler [j], Jonathan E. Rosenberg [g], Melissa Lochheed [k], Paramita Sen [k], Matthew Squires [l], Michael Shi [k], Cora N. Sternberg [h]

- 1st Generation FGFR Inhibitors did not fulfill expectations
- Neither in efficacy nor as a predictive biomarker

Best overall tumour response by *FGFR3* mutation status, as determined by investigator and central radiology review.

Clinical response	*FGFR3*^{MUT} ($n = 12$)	*FGFR3*^{WT} ($n = 31$)
Investigator review, *n* (%)		
CR	0	0
PR	0	1 (3)
SD	5 (42)	10 (32)
PD	5 (42)	12 (39)
UNK	2 (17)	8 (26)
ORR (CR + PR)	0	1 (3)
DCR[a]	3 (25)	8 (26)
95% CI for ORR	(0.0–26.5)	(0.1-16.7)
95% CI for DCR	(5.5–57.2)	(11.9-44.6)
Central radiology review, *n* (%)		
CR	0	0
PR	1 (8)	0
SD	3 (25)	12 (39)
PD	6 (50)	9 (29)
UNK	2 (17)	10 (32)
ORR (CR + PR)	1 (8)	0
DCR[a]	2 (17)	9 (29)
95% CI for ORR	(0.2–38.5)	(0.0–11.2)
95% CI for DCR	(2.1–48.4)	(14.2–48.0)

In conclusion, although generally well tolerated, dovitinib appears to have very limited single-agent activity in previously treated patients with advanced UC, regardless of *FGFR3* mutation status. Although these results do not support further investigation of single-agent dovitinib, studies evaluating more potent FGFR3 inhibitors are warranted.

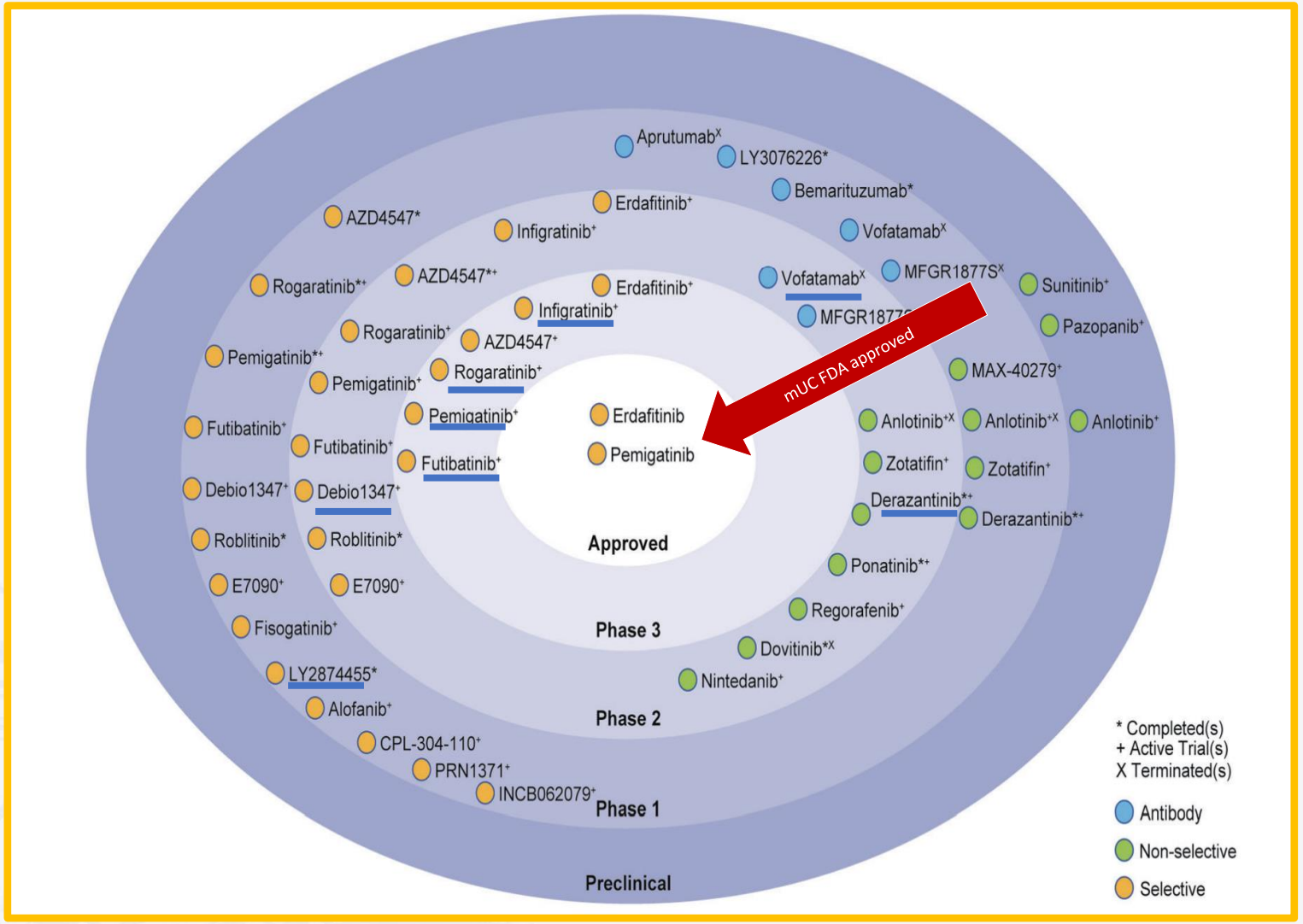
Table 3
Adverse events suspected to be related to the study drug in >10% of patients (all grades).[a]

Adverse event	All patients ($N = 44$)		
Preferred term, *n* (%)	Any grade	Grade 3	Grade 4
Any	41 (93)	25 (57)	3 (7)
Diarrhoea	29 (66)	3 (7)	0
Nausea	26 (59)	0	0
Decreased appetite	16 (36)	0	0
Vomiting	16 (36)	1 (2)	0
Fatigue	14 (32)	4 (9)	0
Asthenia	13 (30)	4 (9)	0
Rash	10 (23)	2 (5)	0
Anaemia	7 (16)	2 (5)	0
Thrombocytopenia	7 (16)	3 (7)	1 (2)
Alanine aminotransferase increased	6 (14)	1 (2)	1 (2)
Hypertension	6 (14)	0	0
Aspartate aminotransferase increased	5 (11)	1 (2)	1 (2)
Constipation	5 (11)	1 (2)	0
Dysgeusia	5 (11)	0	0

[a] Patients with multiple occurrences of an adverse event are counted only once at the highest grade.

Further Drug Development: Next Generation FGFR Inhibitors

- Multiple compounds are in different stages of development in the clinic in different tumour types
- More selective drugs
- Most of the development in later stages in focused in bladder and HCC
- TKIs, mAB, Decoy, ADCs



Krook, M.A., Reeser, J.W., Ernst, G. *et al.* Fibroblast growth factor receptors in cancer: genetic alterations, diagnostics, therapeutic targets and mechanisms of resistance. *Br J Cancer* **124,** 880–892 (2021).

ERDAFITINIB

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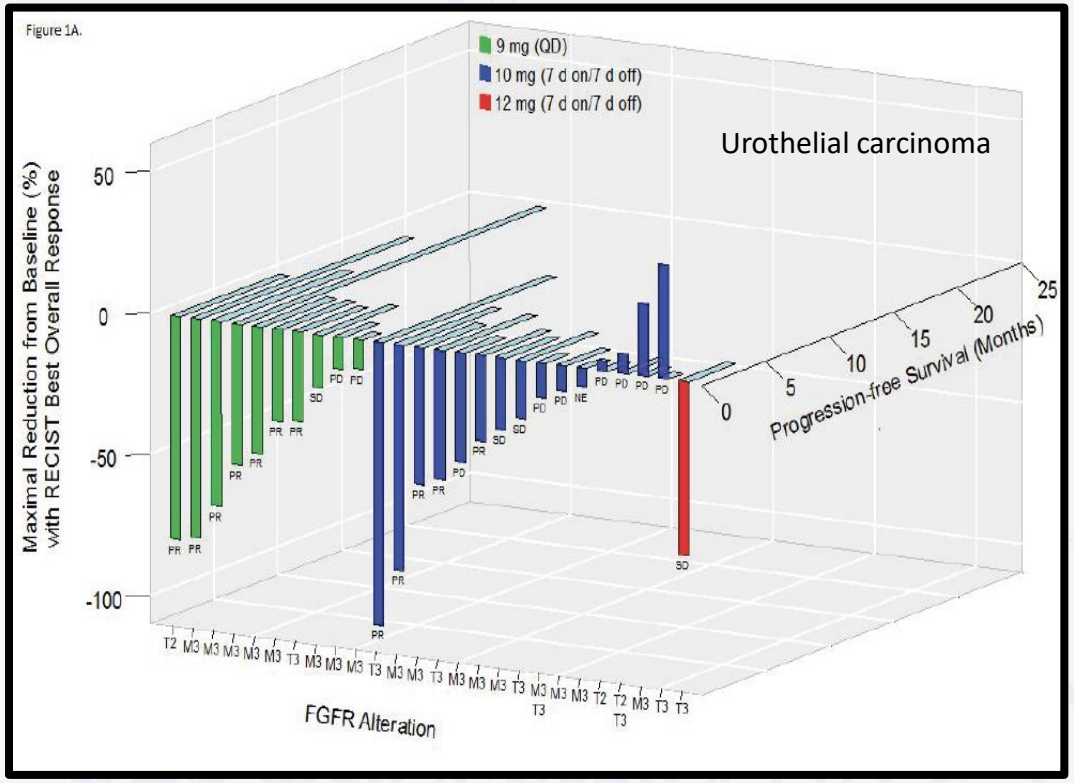
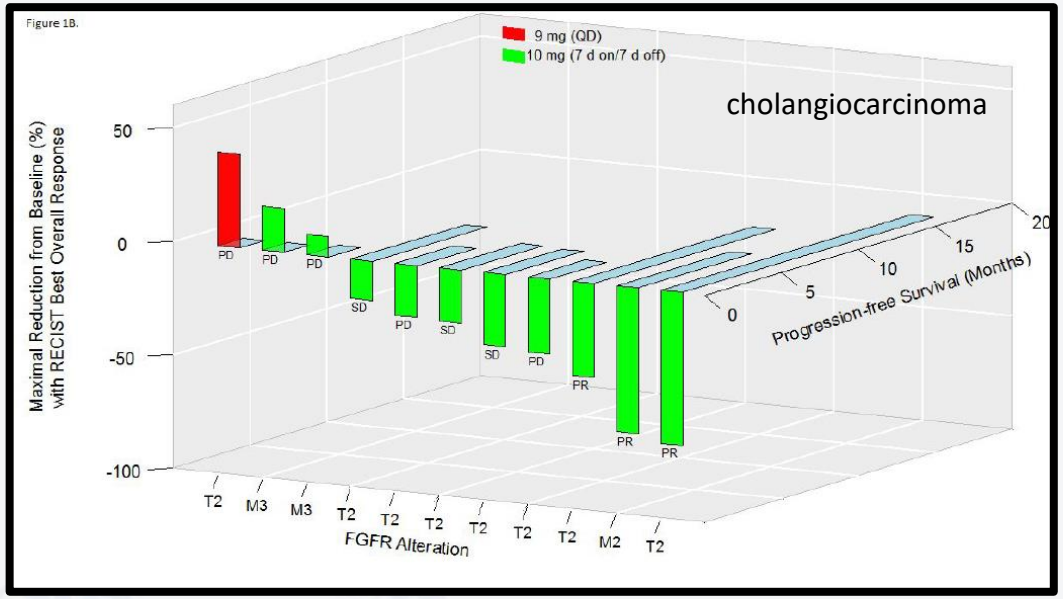
Multicenter Phase I Study of Erdafitinib (JNJ-42756493), Oral Pan-Fibroblast Growth Factor Receptor Inhibitor, in Patients with Advanced or Refractory Solid Tumors

Rastilav Bahleda, Antoine Italiano, Cinta Hierro, et al.

Clin Cancer Res Published OnlineFirst May 14, 2019.

1st signals on Phase I study



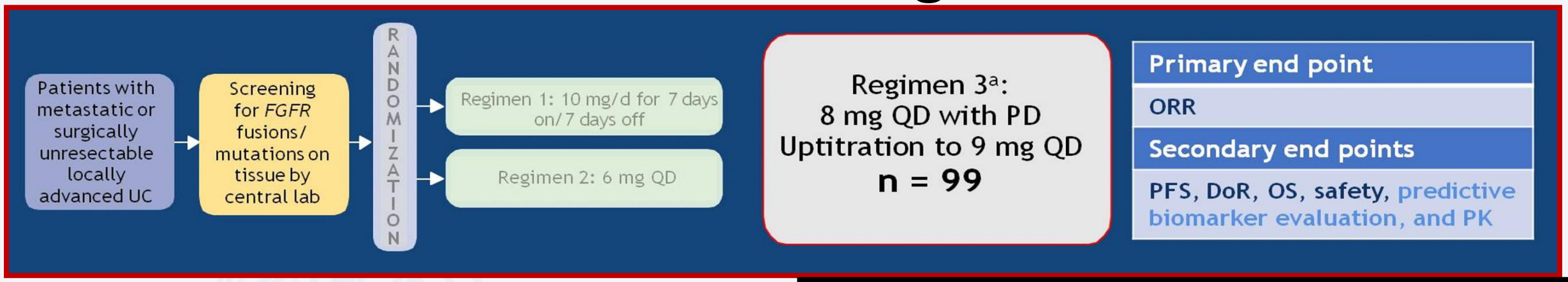


UC, Evaluable with *FGFR* Mutations or Gene Fusions	9 mg (QD) n=10	10 mg (7d on/7d off) n=15	12 mg (QD)	12 mg (7d on/7d off) n=1	Total n=26
ORR (95% CI)	7 (70%) (35%, 93%)	5 (33%) (12%, 62%)		0 NE	12 (46%) (27%, 67%)
Partial response	7 (70%)	5 (33%)		0	12 (46%)
Stable disease	1 (10%)	2 (13%)		1 (100%)	4 (15%)
Progressive disease	2 (20%)	7 (47%)		0	9 (35%)
NE/unknown	0	1 (7%)		0	1 (4%)

All patients with UC and CCA who responded to treatment with erdafitinib carried FGFR mutations or gene fusions

Erdafitinib shows tolerability and **preliminary evidence of clinical activity** in advanced solid tumors, at 2 different dosing schedules and with particularly encouraging responses in UC and CCA. [46% ORR in heavily pretreated patients]

Erdafitinib: The phase II strong signal



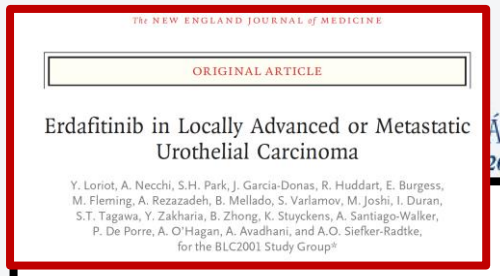
Patients

- Progression on ≥ 1 line prior systemic chemo or within 12 months of (neo)adjuvant chemo OR
- Chemo-naïve: cisplatin ineligible per protocol criteria[b]
- Prior immunotherapy was allowed

- Heavily pre-treated group of pts
- Poor prognosis group

Patients, n (%)		8 mg continuous dose (n = 99)
Age, median years (range)		68 (36-87)
ECOG performance status	0	50 (51)
	1	42 (42)
	2	7 (7)
Pre-treatment	Progressed or relapsed after chemo	87 (88)
	Chemo-naïve	12 (12)
	Prior immunotherapy	22 (22)
Number of lines of prior treatment	0	11 (11)
	1	45 (46)
	2	29 (29)
	≥ 3	14 (14)
Visceral metastases	Present	78 (79)
	Absent	21 (21)
Hemoglobin Level	≥10	84 (85)
	<10	15 (15)
Tumor location	Upper tract	23 (23)
	Lower tract	76 (77)
Creatinine clearance rate	< 60 mL/min	52 (53)
	≥ 60 mL/min	47 (47)
FGFR alterations	*FGFR2* or *FGFR3* fusion	25 (25)
	FGFR3 mutation	74 (75)

Erdafitinib activity& Safety


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Erdafitinib in Locally Advanced or Metastatic Urothelial Carcinoma

Y. Loriot, A. Necchi, S.H. Park, J. Garcia-Donas, R. Huddart, E. Burgess, M. Fleming, A. Rezazadeh, B. Mellado, S. Varlamov, M. Joshi, I. Duran, S.T. Tagawa, Y. Zakharia, B. Zhong, K. Stuyckens, A. Santiago-Walker, P. De Porre, A. O'Hagan, A. Avadhani, and A.O. Siefker-Radtke, for the BLC2001 Study Group*

ÁNCER
2022"

	Value	Rate of Response (95% CI)
		percent
Response per investigator assessment — no. of patients†		
Any objective response	40	40 (31–50)
Complete response	3	3
Partial response	37	37
Stable disease	39	39
Progressive disease	18	18
Could not be evaluated or unknown	2	2
Median time to response — mo	1.4	
Median duration of response (95% CI) — mo	5.6 (4.2–7.2)	

40% ORR

Active in visceral disease

Response according to presence or absence of visceral metastasis — no./total no.		
Present	30/78	38 (28–49)
Bone	10/21	48 (26–69)
Liver	7/20	35 (14–56)
Lung	23/57	40 (28–53)
Lymph node only	4/12	33 (7–60)
Upper tract disease‡	10/23	43 (23–64)
Lower tract disease§	30/76	39 (29–51)
Absent	10/21	48 (26–69)

Rescue after qt/io

Response according to previous treatment — no./total no.		
No chemotherapy	5/12	42
Progression or relapse after chemotherapy	35/87	40
Immunotherapy	13/22	59

Dose/Genetic matters

Response according to daily dose of erdafitinib — no./total no.		
8 mg	20/58	34 (22–47)
8 mg with dose escalation to 9 mg	20/41	49 (34–64)
Response according to genetic alteration — no./total no.		
FGFR3 mutation	36/74	49 (37–60)
FGFR2/3 fusion	4/25	16 (2–30)

- The PFS was 5.5 months, and the median duration of OS was 13.8 months.
- Treatment-related adverse events of grade 3 or higher, were reported in 46% of the patients;
- 13% of the patients discontinued treatment because of adverse events. There were NO treatment-related deaths.

Loriot Y, Necchi A, Park SH et al BLC2001 Study Group. Erdafitinib in Locally Advanced or Metastatic Urothelial Carcinoma. N Engl J Med. 2019 Jul 25;381(4):338-348.

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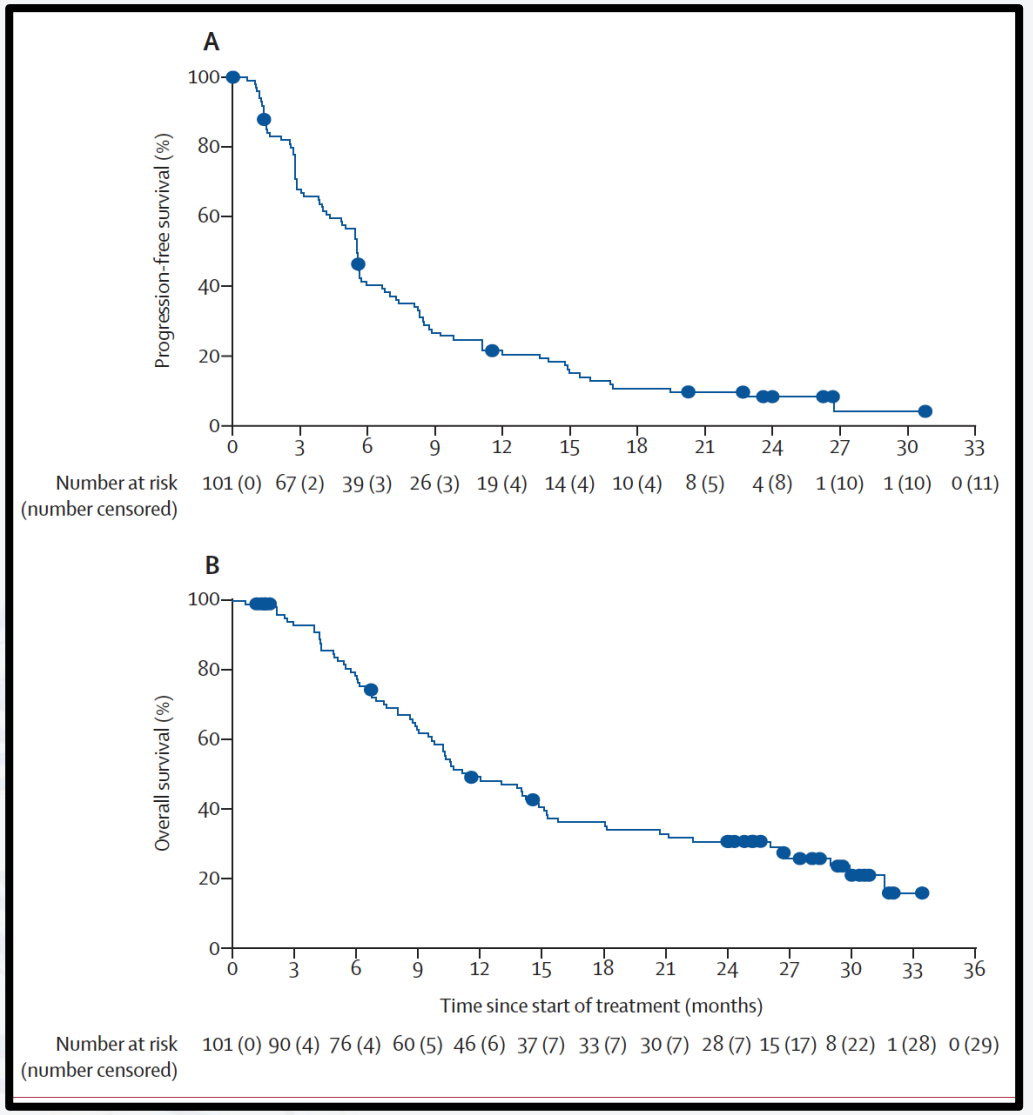
Long term follow-up

Efficacy and safety of erdafitinib in patients with locally advanced or metastatic urothelial carcinoma: long-term follow-up of a phase 2 study

*Arlene O Siefker-Radtke, Andrea Necchi, Se Hoon Park, Jesús García-Donas, Robert A Huddart, Earle F Burgess, Mark T Fleming, Arash Rezazadeh Kalebasty, Begoña Mellado, Sergei Varlamov, Monika Joshi, Ignacio Duran, Scott T Tagawa, Yousef Zakharia, Sydney Akapame, Ademi E Santiago-Walker, Manish Monga, Anne O'Hagan, Yohann Loriot, on behalf of the BLC2001 Study Group**

Findings Between May 25, 2015, and Aug 9, 2018, 2328 patients were screened, of whom 212 were enrolled and 101 were treated with the selected erdafitinib 8 mg/day UpT regimen. The data cutoff date for this analysis was Aug 9, 2019. Median efficacy follow-up was 24·0 months (IQR 22·7–26·6). The investigator-assessed objective response rate for patients treated with the selected erdafitinib regimen was 40 (40%; 95% CI 30–49) of 101 patients. The safety profile remained similar to that in the primary analysis, with no new safety signals reported with longer follow-up. Grade 3–4 treatment-emergent adverse events of any causality occurred in 72 (71%) of 101 patients. The most common grade 3–4 treatment-emergent adverse events of any cause were stomatitis (in 14 [14%] of 101 patients) and hyponatraemia (in 11 [11%]). There were no treatment-related deaths.

Interpretation With longer follow-up, treatment with the selected regimen of erdafitinib showed consistent activity and a manageable safety profile in patients with locally advanced or metastatic urothelial carcinoma and prespecified *FGFR* alterations.



Siefker-Radtke AO, Necchi A, Park SH, et al Efficacy and safety of erdafitinib in patients with locally advanced or metastatic urothelial carcinoma: long-term follow-up of a phase 2 study. Lancet Oncol. 2022 Jan 11:S1470-2045(21)00660-4

Safety

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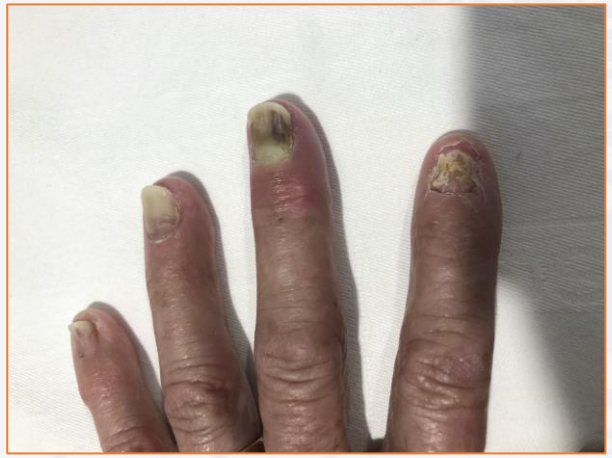
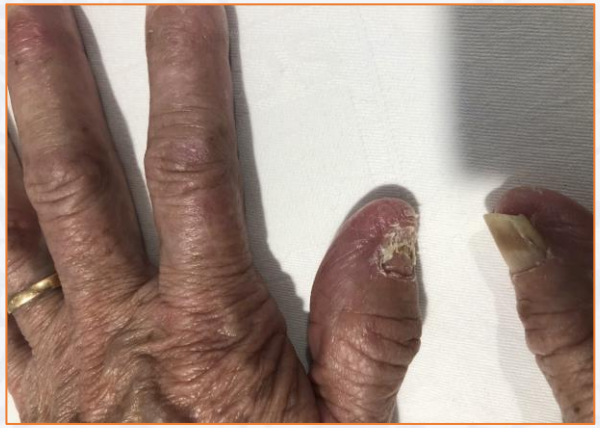
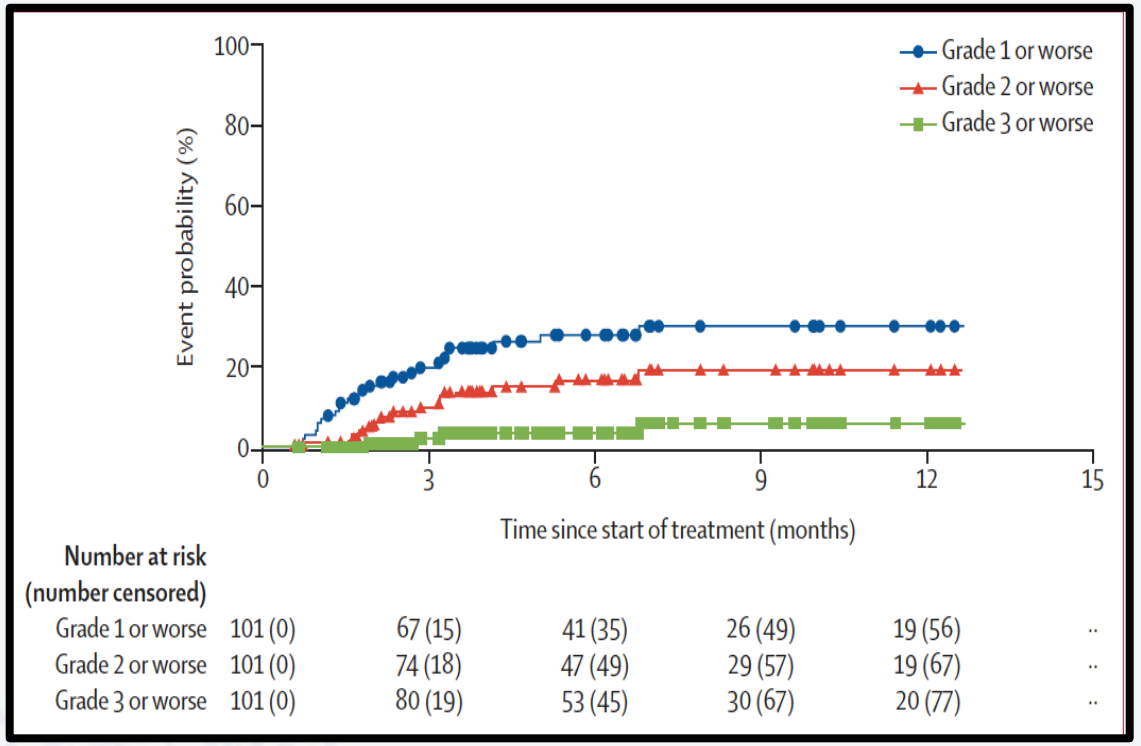
Adverse Event	Any Grade	Grade 1	Grade 2	Grade ≥3
		number of patients (percent)		
Hyperphosphatemia	76 (77)	53 (54)	21 (21)	2 (2)
Stomatitis	57 (58)	21 (21)	26 (26)	10 (10)
Diarrhea	50 (51)	31 (31)	15 (15)	4 (4)
Dry mouth	45 (46)	34 (34)	11 (11)	0
Decreased appetite	38 (38)	18 (18)	20 (20)	0
Dysgeusia	37 (37)	23 (23)	13 (13)	1 (1)
Fatigue	32 (32)	12 (12)	18 (18)	2 (2)
Dry skin	32 (32)	24 (24)	8 (8)	0
Alopecia	29 (29)	23 (23)	6 (6)	0
Constipation	28 (28)	19 (19)	8 (8)	1 (1)
Hand–foot syndrome	23 (23)	6 (6)	12 (12)	5 (5)
Anemia	20 (20)	9 (9)	7 (7)	4 (4)
Asthenia	20 (20)	2 (2)	11 (11)	7 (7)
Nausea	20 (20)	13 (13)	6 (6)	1 (1)
Dry eye	19 (19)	14 (14)	4 (4)	1 (1)
Onycholysis	18 (18)	6 (6)	10 (10)	2 (2)







Number at risk (number censored)						
Grade 1 or worse	101 (0)	67 (15)	41 (35)	26 (49)	19 (56)	..
Grade 2 or worse	101 (0)	74 (18)	47 (49)	29 (57)	19 (67)	..
Grade 3 or worse	101 (0)	80 (19)	53 (45)	30 (67)	20 (77)	..

- The proportion of patients with central serous retinopathy was 27 (27%) of 101
  - 23 [85%] of 27 events were grade 1–2
  - (63%) of 27 central serous retinopathy events had resolved
  - All ten unresolved events were grade 1–2

Loriot Y, Necchi A, Park SH et al BLC2001 Study Group. Erdafitinib in Locally Advanced or Metastatic Urothelial Carcinoma. N Engl J Med. 2019 Jul 25;381(4):338-348.
Siefker-Radtke AO, Necchi A, Park SH, et al Efficacy and safety of erdafitinib in patients with locally advanced or metastatic urothelial carcinoma: long-term follow-up of a phase 2 study. Lancet Oncol. 2022 Jan 11:S1470-2045(21)00660-4

Further development of erdafitinib in mUC & others

Phase III THOR

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

- **Primary endpoint:** OS
- **Secondary endpoints:** PFS, ORR, DoR, PROs, safety

NCT03390504.

The combination of ERDA and CET is tolerable and associated with promising antitumor activity.
ERDA 8 mg + CET 240 mg was established as RP2D.
ERDA + CET is being further explored in the ongoing randomized phase 2 portion of this study as first-line treatment for pts ineligible for cisplatin.

NORSE (NCT03473743): N = 150

- *FGFR3* mut/fus +ve
- Phase 1b/2
- 1L cis-ineligible

Erdafitinib ⟷ **Erdafitinib + cetrelimab**

Updated in ESMO 2021 [Powles T et al]

There are many other FGFR inhibitors in active development

A.O. Siefker-Radtke et al. Updated data from the NORSE trial of erdafitinib (ERDA) plus cetrelimab (CET) in patients (pts) with metastatic or locally advanced urothelial carcinoma (mUC) and specific fibroblast growth factor receptor (FGFR) alterations; ESMO 2020

Cell adhesion molecules & others as targets and new drug delivery methods: The ADCs

What about new more widely expressed target?

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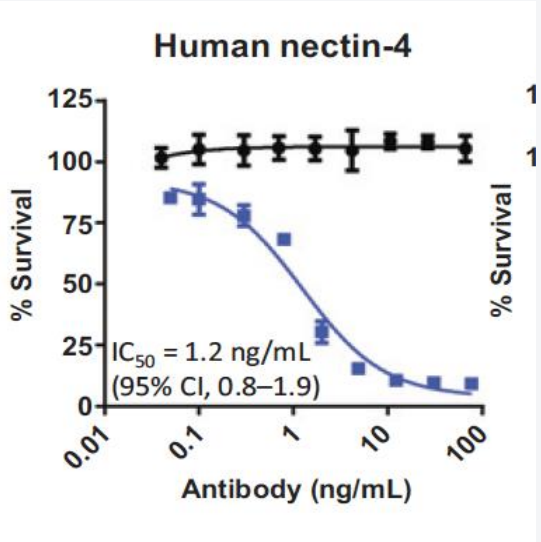
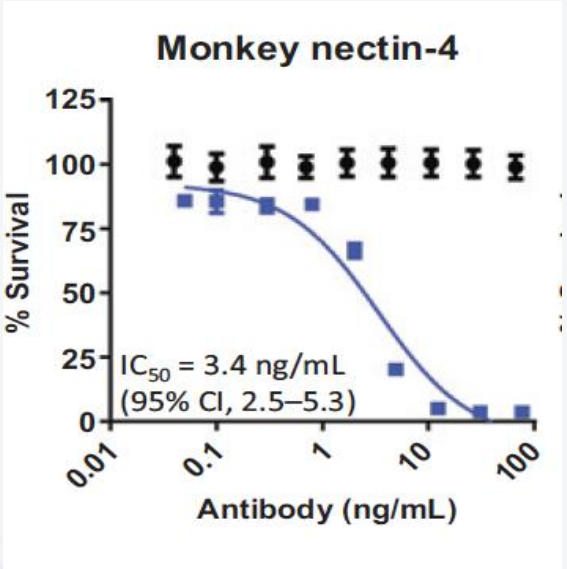
Therapeutics, Targets, and Chemical Biology
Cancer Research
Enfortumab Vedotin Antibody-Drug Conjugate Targeting Nectin-4 Is a Highly Potent Therapeutic Agent in Multiple Preclinical Cancer Models
Pia M. Challita-Eid, Daulet Satpayev, Peng Yang, Zili An, Karen Morrison, Yuriy Shostak, Arthur Raitano, Rossana Nadell, Wendy Liu, Dawn Ratay Lortie, Linnette Capo, Alla Verlinsky, Monica Leavitt, Faisal Malik, Hector Aviña, Claudia I. Guevara, Nick Dinh, Sher Karki, Banmeet S. Anand, Daniel S. Pereira, Ingrid B.J. Joseph, Fernando Doñate, Kendall Morrison, and David R. Stover

EV & NECTIN-4

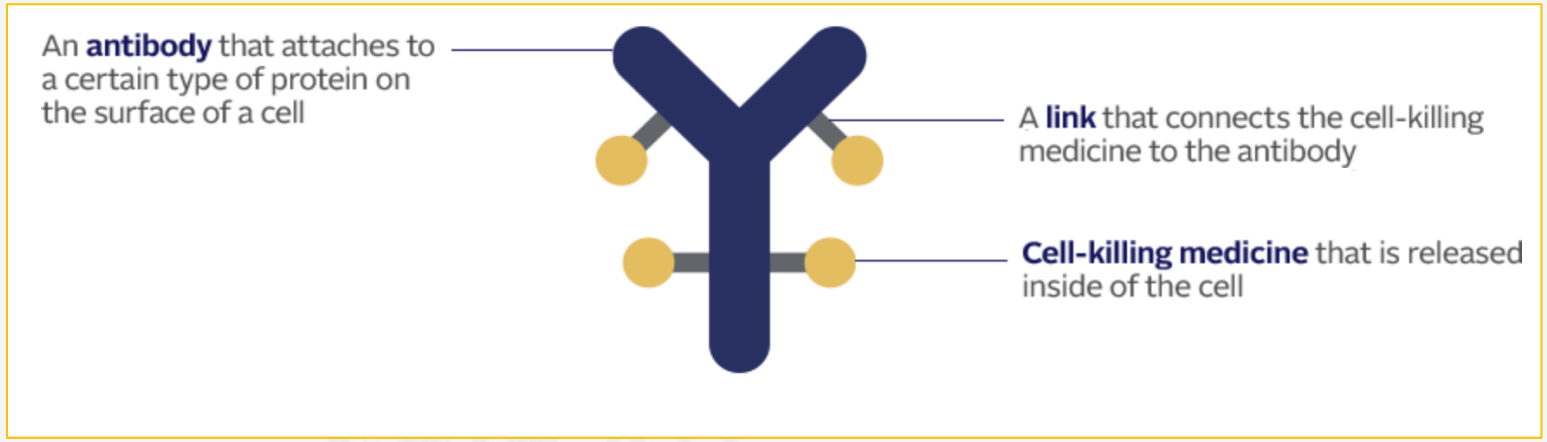
- **EV** [and antibody drug conjugate] was able to bind to cell surface–expressed **NECTIN-4** with high affinity and induced cell death in vitro in a dose-dependent manner.
- Treatment of mouse xenograft models of human **breast**, **bladder**, **pancreatic**, and **lung cancers** with EV significantly inhibited the growth and resulted in **tumour regression of breast and bladder xenografts.**
- Overall, these findings **validate nectin-4 as an attractive therapeutic target** and support further clinical development of nectin-4–targeting ADCs



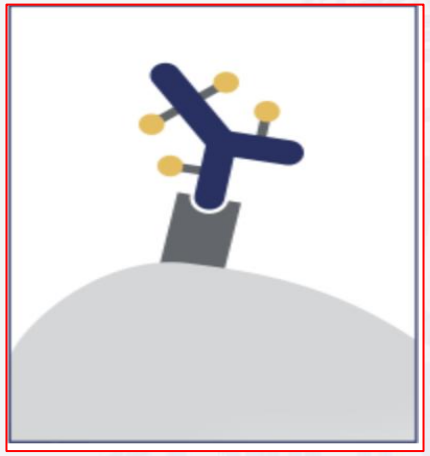


Chalita-Eid PM et al. Cancer Res; 76(10); 3003–13. 2016

Antibody Drug Conjugates (ADCs)



Antibody–drug conjugates (ADC) are an emerging class of targeted therapeutic agents with the ability to deliver a **highly cytotoxic payload** to tumour sites by utilizing the **exquisite specificity of a mAb** as a **delivery vehicle**



ADC **binds to tumor target cell surface antigens**

The binding triggers a receptor mediated **internalization**

The internalized ADCs **release cytotoxic payloads** inside the tumor cell and leads to cell death

Mullard A. Maturing antibody-drug conjugate pipeline hits 30. Nat Rev Drug Discov 2013;12:329–32 Schema modified from https://www.padcev.com/about-padcev

What makes every ADC different: Target, payload and linkage

ADC	Targeted Ag	Payload	Linkage
Enfortumab Vedotin [1,2]	Nectin-4	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

MMAE: Monomethyl Auristatin E

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

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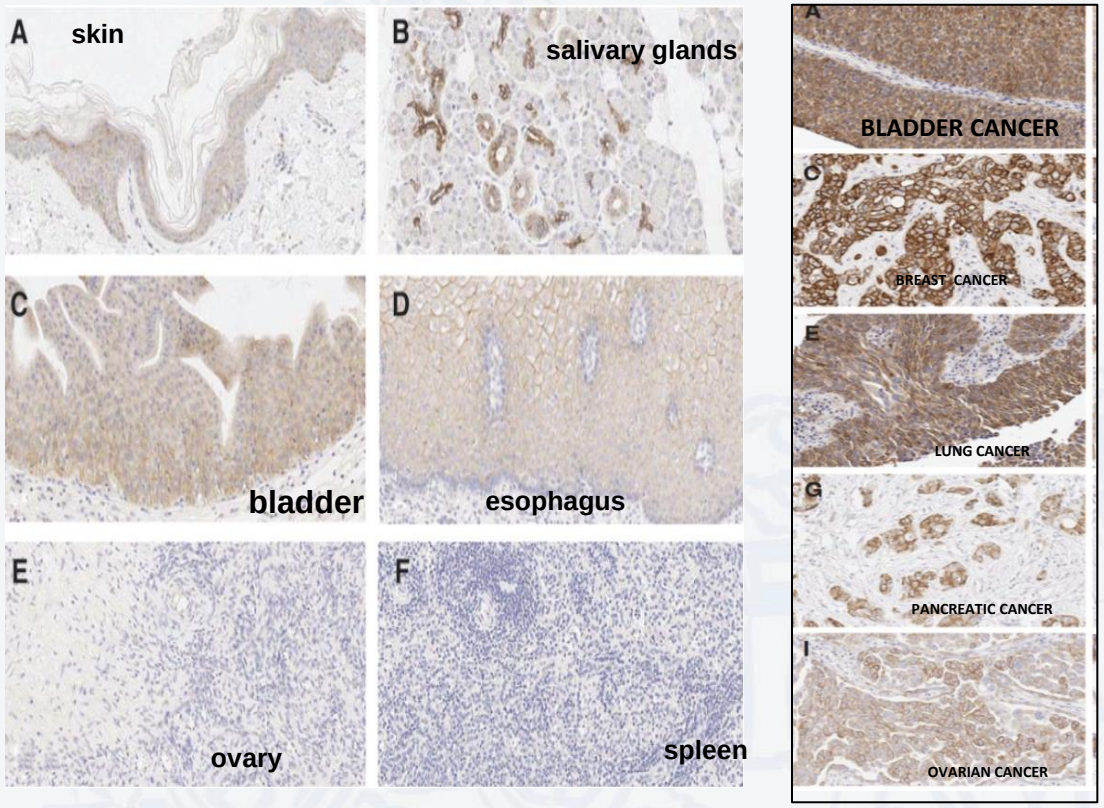
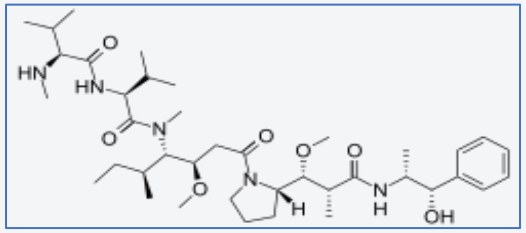
What makes every ADC different: The case of Enfortumab Vedotin

TARGETED ANTIGEN



Nectin-4 expression in human normal tissues and cancer patient specimens

PAYLOAD



Monomethyl auristatin E is an antimitotic agent which inhibits cell division by blocking the polymerisation of tubulin

It is derived from peptides occurring in marine shell-less mollusc [Dolabella Auricularia] named dolastatins which showed potent activity in preclinical studies, against a range of hematological malignancies and solid tumors.

Chalita-Eid PM et al. Cancer Res; 76(10); 3003–13. 2016

Phase I dose escalation/expansion cohort: **EV-101**

EV-101: A Phase I Study of Single-Agent Enfortumab Vedotin in Patients With Nectin-4–Positive Solid Tumors, Including Metastatic Urothelial Carcinoma

Jonathan Rosenberg, MD[1]; Srikala S. Sridhar, MD[2]; Jingsong Zhang, MD, PhD[3]; David Smith, MD[4]; Dean Ruether, MD[5]; Thomas W. Flaig, MD[6]; Joaquina Baranda, MD[7]; Joshua Lang, MD[8]; Elizabeth R. Plimack, MD[9]; Randeep Sangha, MD[10]; Elisabeth I. Heath, MD[11]; Jamie Merchan, MD[12]; David I. Quinn, MBBS, PhD[13]; Sandy Srinivas, MD[14]; Matthew Milowsky, MD[15]; Chunzhang Wu, PhD[16]; Elaina M. Gartner, MD[17]; Peiying Zuo, PhD[16]; Amal Melhem-Bertrandt, MD[16]; and Daniel P. Petrylak, MD[18]

Characteristic	mUC, No. (%)
No. of patients	155
Median age, years (range)	67 (24-86)
Prior therapy	
Platinum-based chemotherapy	149 (96)
Cisplatin	117 (75)
Carboplatin	61 (39)
Anti–PD-(L)1[a]	112 (72)
Taxanes	54 (35)
Prior lines of therapy in metastatic setting	152 (98)
≥ 3	45 (29)
Site of metastasis at baseline	
Visceral	120 (77)
Lung	79 (51)
Liver	60 (39)
Lymph node only	12 (8)

- Patients with **Nectin-4–expressing solid tumors** who progressed on ≥ **1 prior chemotherapy** regimen and/or CPI.
- Patients received **escalating doses** of EV up to **1.25 mg/kg** on **days 1, 8, and 15 of every 28-day cycle.**
- PRIMARY OBJECTIVES were the determination of **safety/tolerability**, **recommended phase II dose** and **pharmacokinetic profile** of EV.
- A SECONDARY OBJECTIVE was to evaluate EV **antitumor activity.**

- **Rash, periph. neuropathy**, **fatigue & alopecia**, the most common TRAEs.
- The **confirmed ORR** was **43% & DOR** was 7.4 months (at 1.25 mg/Kg)
- **Median OS** was **12.3 months**, and the OS rate at 1 year was **51.8%**.
- Similar benefit regardless of age and prior anti–PD-(L)1 treatment, liver metastases, or GU upper-tract disease

Rosenberg JE et al. J Clin Oncol 38:1041-1049.

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Phase 2 Trial: EV-201

Pivotal Trial of Enfortumab Vedotin in Urothelial Carcinoma After Platinum and Anti-Programmed Death 1/Programmed Death Ligand 1 Therapy

Jonathan E. Rosenberg, MD[1,2]; Peter H. O'Donnell, MD[3]; Arjun V. Balar, MD[4]; Bradley A. McGregor, MD[5]; Elisabeth I. Heath, MD[6]; Evan Y. Yu, MD[7,8]; Matthew D. Galsky, MD[9]; Noah M. Hahn, MD[10]; Elaina M. Gartner, MD[11]; Juan M. Pinelli, PA-C, MMSc[11]; Shang-Ying Liang, PhD[11]; Amal Melhem-Bertrandt, MD[12]; and Daniel P. Petrylak, MD[13]

- **Phase II, single-arm study** of EV **1.25mg/kg** (IV on **days 1, 8, and 15** of **every 28-day** cycle) in **mUC** previously treated with **platinum chemotherapy** and **anti–PD-1/L1 therapy.**
- The **primary end point** was **OBJECTIVE RESPONSE RATE** by **blinded independent central review**.
- Key **secondary end points** were **DURATION OF RESPONSE**, **PROGRESSION-FREE SURVIVAL**, **OVERALL SURVIVAL**, **SAFETY**, and **TOLERABILITY**.

Current extent of disease	
Metastatic	125 (100)
Metastasis sites	
Lymph nodes only	13 (10)
Visceral disease‡	112 (90)
Bone	51 (41)
Liver	50 (40)
Lung	53 (42)

Best response to PD-1/L1–containing therapy	
Responder	25 (20)
Nonresponder	100 (80)

No. of prior systemic therapies in locally advanced or metastatic setting§	
Median	3
Min, max	1, 6
≥ 3	63 (50)

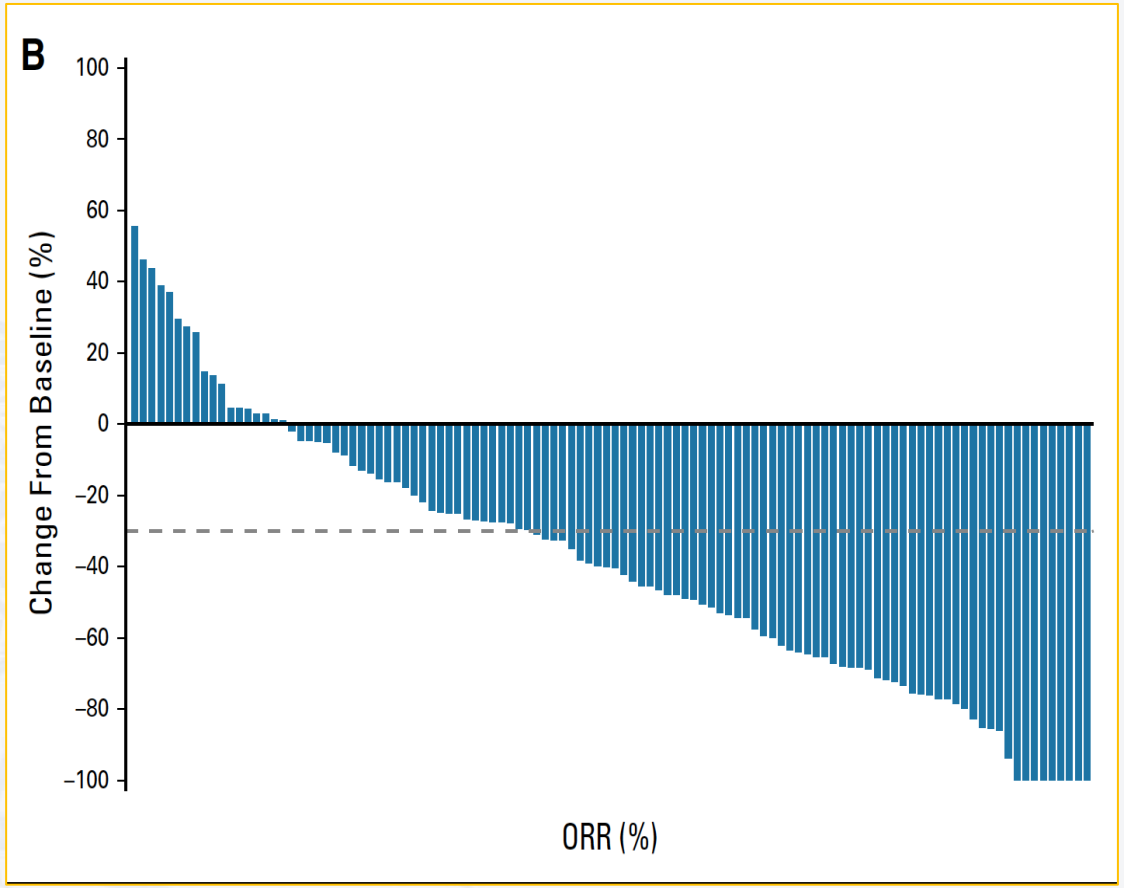
- **Enfortumab vedotin** was administered to **125 patients** with metastatic urothelial carcinoma.
- Median follow-up was 10.2 months (range, 0.5 to 16.5 months).

Rosenberg JE et al. J Clin Oncol 37:2592-2600. 2019

Phase 2-EV-201: Activity

Confirmed objective response rate was **44%** (95% CI, 35.1% to 53.2%), including **12% complete responses**
[highly consistent with phase I data]

Response	Patients (N = 125)
Objective response rate	55 (44)
95% CI*	35.1 to 53.2
Best overall response†	
Complete response	15 (12)
Partial response	40 (32)
Stable disease	35 (28)
Progressive disease	23 (18)
Not evaluable‡	12 (10)



Rosenberg JE et al. J Clin Oncol 37:2592-2600. 2019

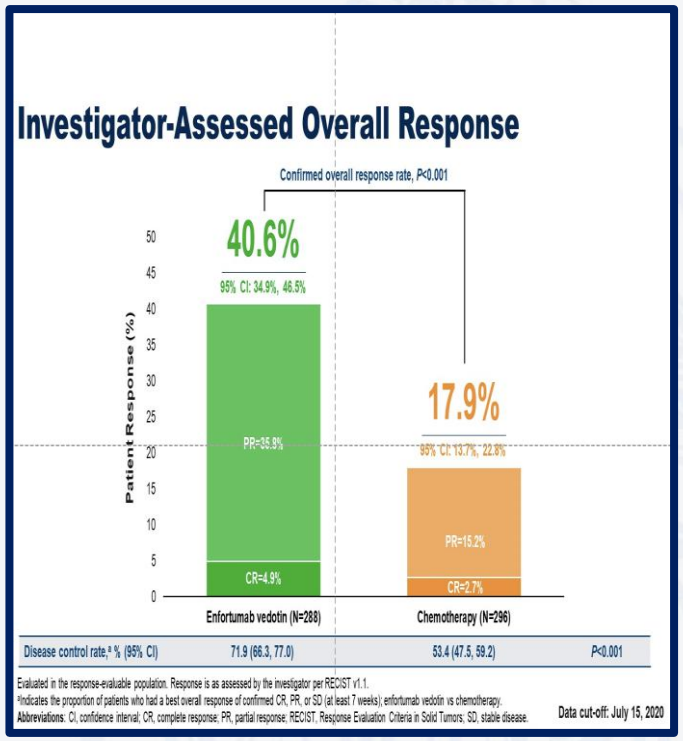
The randomized control trial

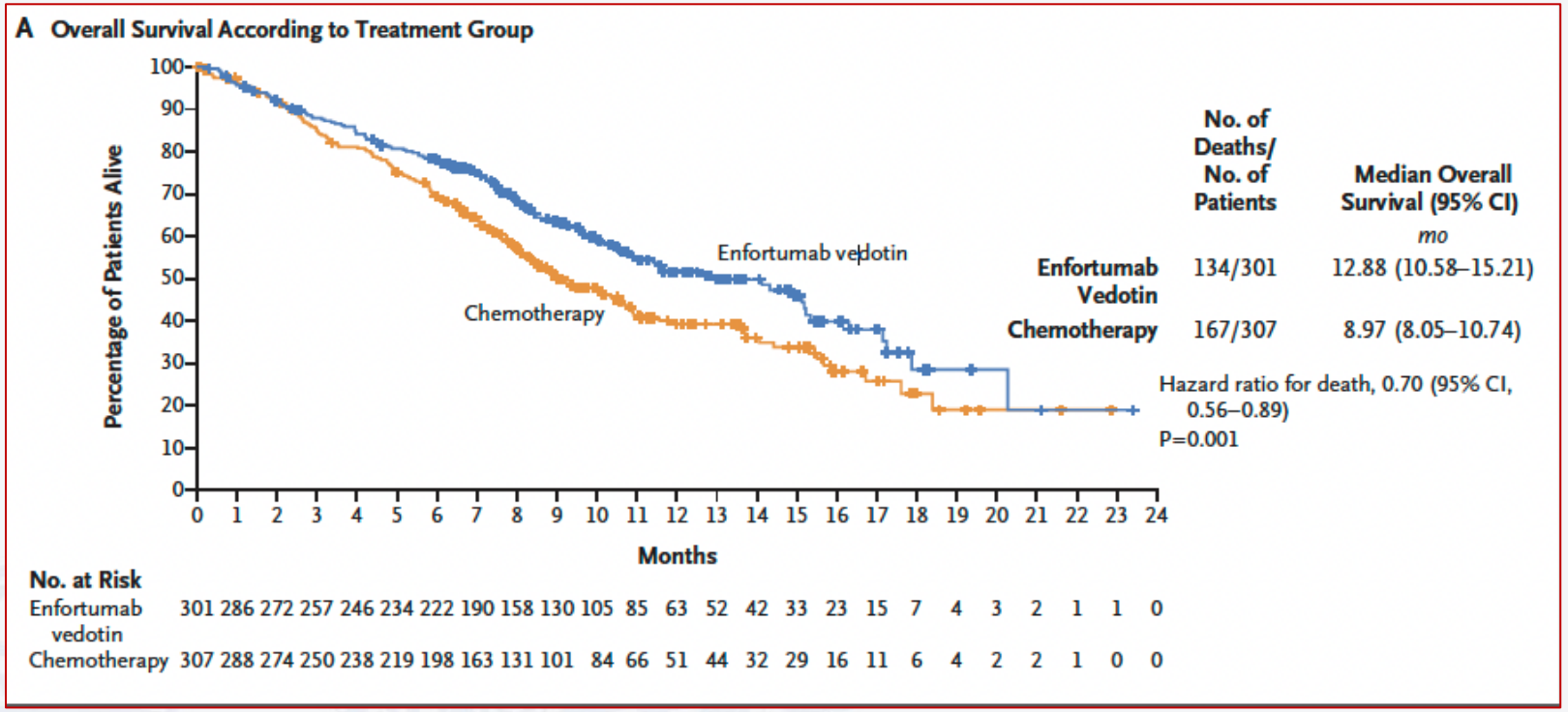
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Enfortumab Vedotin in Previously Treated Advanced Urothelial Carcinoma

Thomas Powles, M.D., Jonathan E. Rosenberg, M.D., Guru P. Sonpavde, M.D., Yohann Loriot, M.D., Ph.D., Ignacio Durán, M.D., Ph.D., Jae-Lyun Lee, M.D., Ph.D., Nobuaki Matsubara, M.D., Christof Vulsteke, M.D., Ph.D., Daniel Castellano, M.D., Chunzhang Wu, Ph.D., Mary Campbell, M.D., Maria Matsangou, M.B., Ch.B., M.D., and Daniel P. Petrylak, M.D.





EV significantly prolonged OS and improved ORR compared with standard chemotherapy in patients with mUC who had previously received platinum-based chemotherapy and a PD-1 or PD-L1 inhibitor

Thomas Powles, Jonathan E. Rosenberg, Guru P. Sonpavde et al NEJM 2021

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Randomized setting after Platinum-CPI: Safety

Treatment-Related Adverse Events

Adverse Event	Enfortumab Vedotin N=296		Chemotherapy N=291	
	All Grade	Grade ≥3	All Grade	Grade ≥3
Any adverse event	**94%**	**51%**	**92%**	**50%**
Alopecia	45%	0	36%	0
Peripheral sensory neuropathy	34%	3%	21%	2%
Pruritus	32%	1%	4%	0
Fatigue	31%	6%	23%	4%
Decreased appetite	31%	3%	23%	2%
Diarrhea	24%	3%	16%	2%
Dysgeusia	24%	0	7%	0
Nausea	23%	1%	22%	1%
Rash maculopapular	16%	7%	2%	0
Anemia	12%	3%	20%	8%
Neutrophil count decreased	10%	6%	17%	13%
Neutropenia	7%	5%	8%	6%
White blood cell decreased	5%	1%	11%	7%
Febrile neutropenia	1%	1%	5%	5%
Serious adverse events[a]	23%	-	23%	-
Leading to treatment withdrawal	14%	-	11%	-

TRAEs leading to death, excluding disease progression, occurred in 7 patients (2.4%) treated with EV and 3 (1.0%) treated with chemotherapy.

Evaluated in the safety population; displaying adverse events (AEs) occurring in ≥20% or grade ≥3 AEs occurring in ≥5% of patients in either treatment group. Dashes indicate 'not applicable.'
Treatment-related AEs are events with a reasonable possibility of relationship to treatment (investigator-assessed) or missing relationship and are not time-adjusted.
This slide contains updated data in the chemotherapy arm to adjust for compounded rounding.
[a]AEs that were deemed "serious" in the view of the investigator or sponsor and based upon predefined criteria.
Abbreviations: AE, adverse event; EV, enfortumab vedotin; TRAEs, treatment-related adverse events.

Data cut-off: July 15, 2020

PRESENTED AT: Genitourinary Cancers Symposium

PRESENTED BY: Thomas Powles
#GU21

Adverse Events of Special Interest

Treatment-Related Adverse Event	Enfortumab Vedotin N=296		Chemotherapy N=291	
	All Grade	Grade ≥3	All Grade	Grade ≥3
Skin Reactions[a]	**47%**	**15%**	**16%**	**1%**
Rash	44%	15%	10%	0[c]
Severe cutaneous adverse reactions[b]	20%	5%	8%	1%
Peripheral neuropathy	**46%**	**5%**	**31%**	**2%**
Sensory events	44%	4%	30%	2%
Motor events	7%	2%	2%	0
Hyperglycemia	**6%**	**4%**	**0[c]**	**0**

The majority of TRAEs of special interest were mild-to-moderate in severity.

Evaluated in the safety population; displaying selected TRAEs of special interest to EV. Differences between AE rates in current and prior slide may be due to preferred term groupings.
TRAE are events with a reasonable possibility of relationship to study treatment as assessed by the investigator or missing relationship.
[a]Encompasses rash and severe cutaneous adverse reactions.
[b]Severe cutaneous adverse reactions included the following (by Preferred Term): stomatitis, drug eruption, conjunctivitis, blister, dermatitis bullous, skin exfoliation, erythema multiforme, exfoliative rash, fixed eruption, mouth ulceration, pemphigus, and toxic skin eruption.
[c]One patient had the TRAE that is listed.
Abbreviations: EV, enfortumab vedotin; TRAE, treatment-related adverse event.

Data cut-off: July 15, 2020

PRESENTED AT: Genitourinary Cancers Symposium
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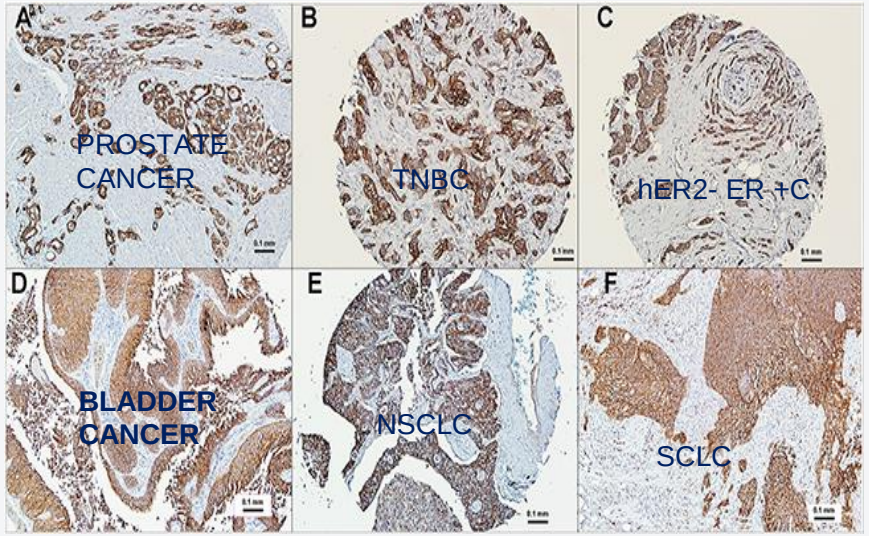
Presented By Thomas Powles at 2021 Genitourinary Cancers Symposium

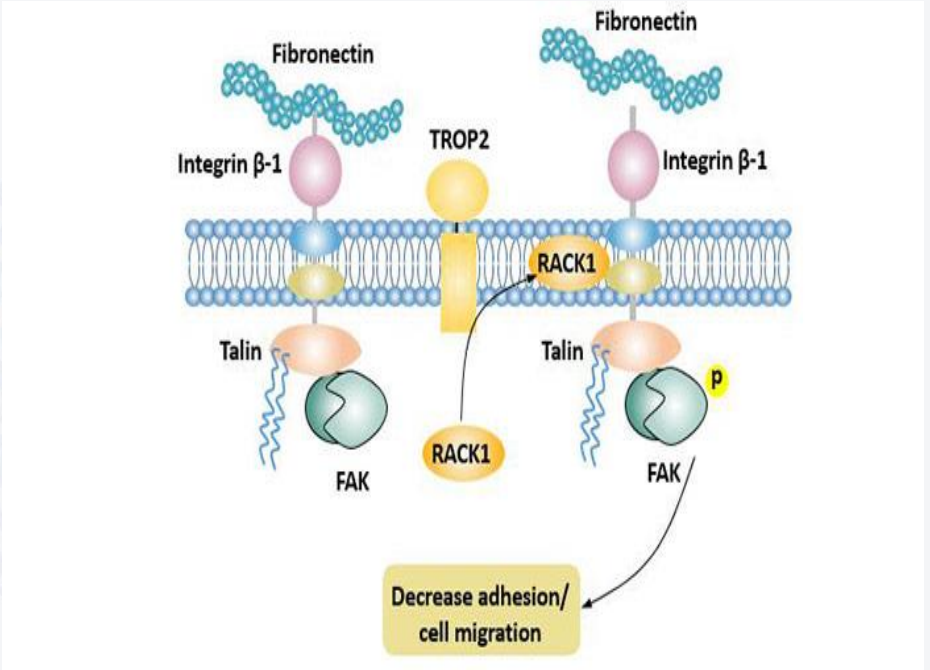
THE TUMOR ANTIGEN: TROP-2

- TROP-2 is the **trophoblast cell-surface antigen**

- it is linked to **cell migration** and **anchorage-independent growth**, with **high expression** in **human epithelial cancers**

- **Trop-2** protein is known to be **expressed** in normal urothelium and in **<u>83% of urothelial carcinomas</u>** with **<u>higher expression in invasive UC</u>** and with **<u>correlation with stage</u>**





Goldenberg DM et al Oncotarget, 2018, Vol. 9, (No. 48) ; Stepan LP et al; J Histochem Cytochem 2011; 59:701-10.

TropHY- Urotelial Program

- The **TropHY-U-01** Study includes three cohorts

SG

- **COHORT 1 [3rd line]**
  - Patients after one line of **chemo** and **CPI**
- **COHORT 2 [2nd line after CPI]**
  - Patients **not eligible for platinum** and who received a **CPI**

SG+ CPI

- **COHORT 3 [2ND line after chemo]**
  - Patients **who progress after chemo** but never received CPI

Other developments in different stages of UC to be started soon

original reports

TROPHY-U-01: A Phase II Open-Label Study of Sacituzumab Govitecan in Patients With Metastatic Urothelial Carcinoma Progressing After Platinum-Based Chemotherapy and Checkpoint Inhibitors

Scott T. Tagawa, MD, MS[1]; Arjun V. Balar, MD[2]; Daniel P. Petrylak, MD[3]; Arash Rezazadeh Kalebasty, MD[4]; Yohann Loriot, MD, PhD[5]; Aude Fléchon, MD, PhD[6]; Rohit K. Jain, MD[7]; Neeraj Agarwal, MD[8]; Manojkumar Bupathi, MD, MS[9]; Philippe Barthelemy, MD, PhD[10]; Philippe Beuzeboc, MD, PhD[11]; Phillip Palmbos, MD, PhD[12]; Christos E. Kyriakopoulos, MD[13]; Damien Pouessel, MD, PhD[14]; Cora N. Sternberg, MD[1]; Quan Hong, MD[15]; Trishna Goswami, MD[15]; Loretta M. Itri, MD[15]; and Petros Grivas, MD, PhD[16]

FDA APPROVED

Key Objective

Patients with advanced or metastatic urothelial cancer (mUC) have limited treatment options after progression on platinum or checkpoint inhibitors (CPI). The TROPHY-U-01 study evaluated sacituzumab govitecan (SG), a trophoblast cell surface antigen 2–directed antibody-drug conjugate, in patients with locally advanced or unresectable or mUC who had progressed after prior platinum and CPI.

Knowledge Generated

Of 113 patients who received SG, central review confirmed an objective response rate (ORR) of 27% with six complete responses and 25 partial responses, confirming results from the prior phase I/II study demonstrating that SG is generally well tolerated and has significant anticancer activity in heavily pretreated patients with mUC who had progressed on platinum and CPI.

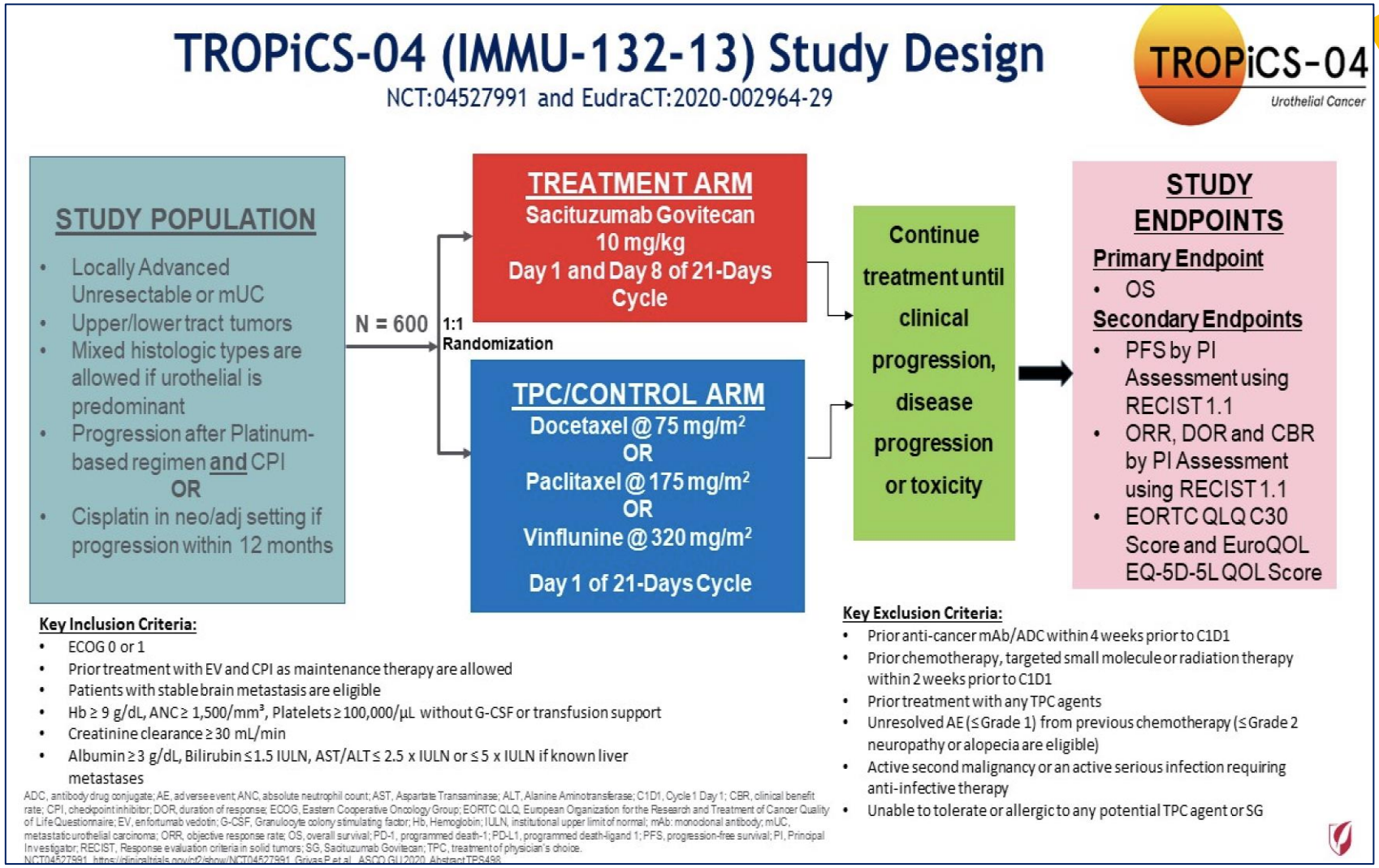
Relevance

The ORR of 27%, median duration of response of 7.2 months, and median overall survival of 10.9 months compare favorably with single-agent chemotherapy in this population, where ORR is approximately 10% and overall survival is 7 to 8 months.

Tagawa ST, Balar AV, Petrylak DP, et al TROPHY-U-01: A Phase II Open-Label Study of Sacituzumab Govitecan in Patients With Metastatic Urothelial Carcinoma Progressing After Platinum-Based Chemotherapy and Checkpoint Inhibitors. J Clin Oncol. 2021 Aug 1;39(22):2474-2485.

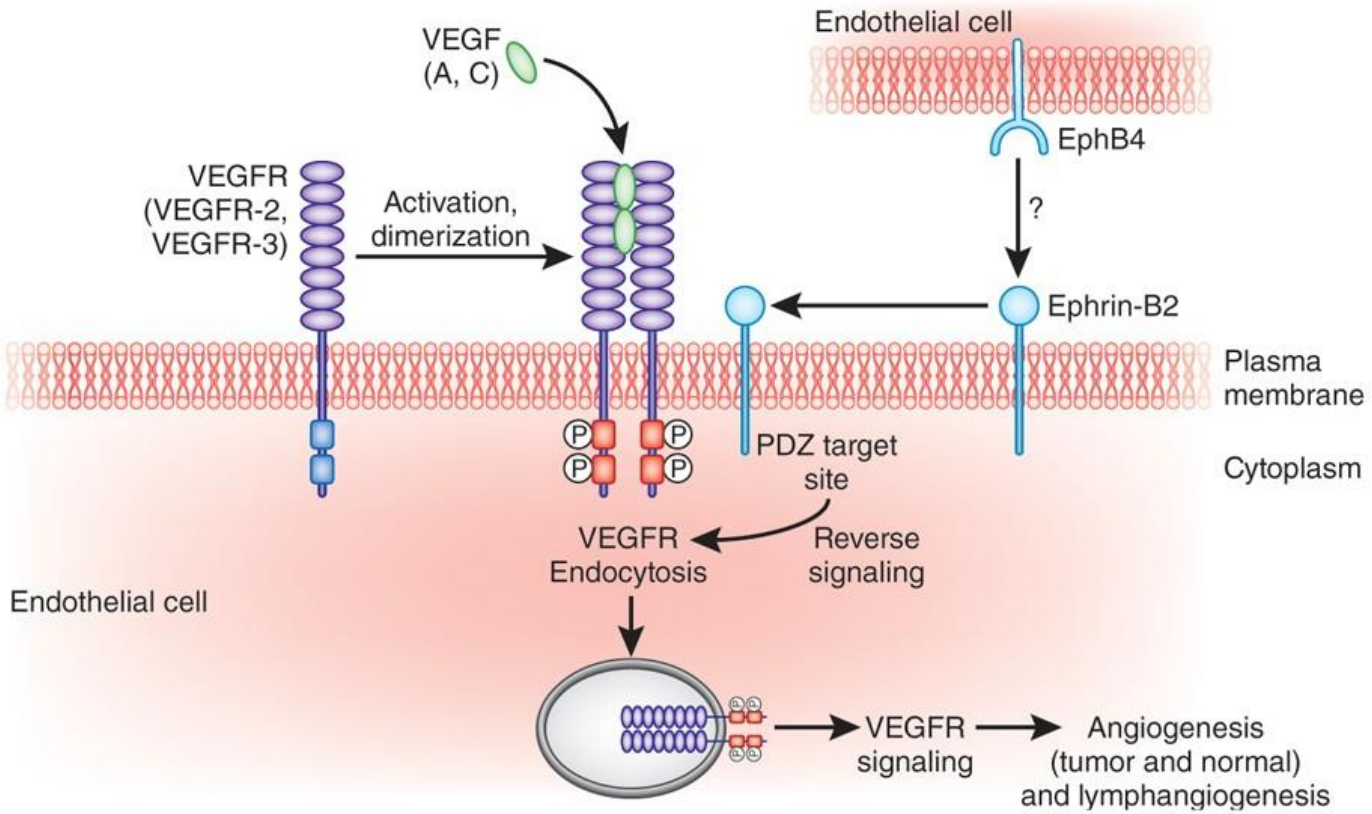
TROPICS-04 & Further development

ONGOING



Also SG is being tested in other settings either as single agent or in combinations

Coming up soon: New targets Ephrin-B2



Nature Medicine volume 16, pages752–754 (2010); Sadegh et al, Oral presentation at ESMO 2021. Abstract 651O

Current treatment scenario

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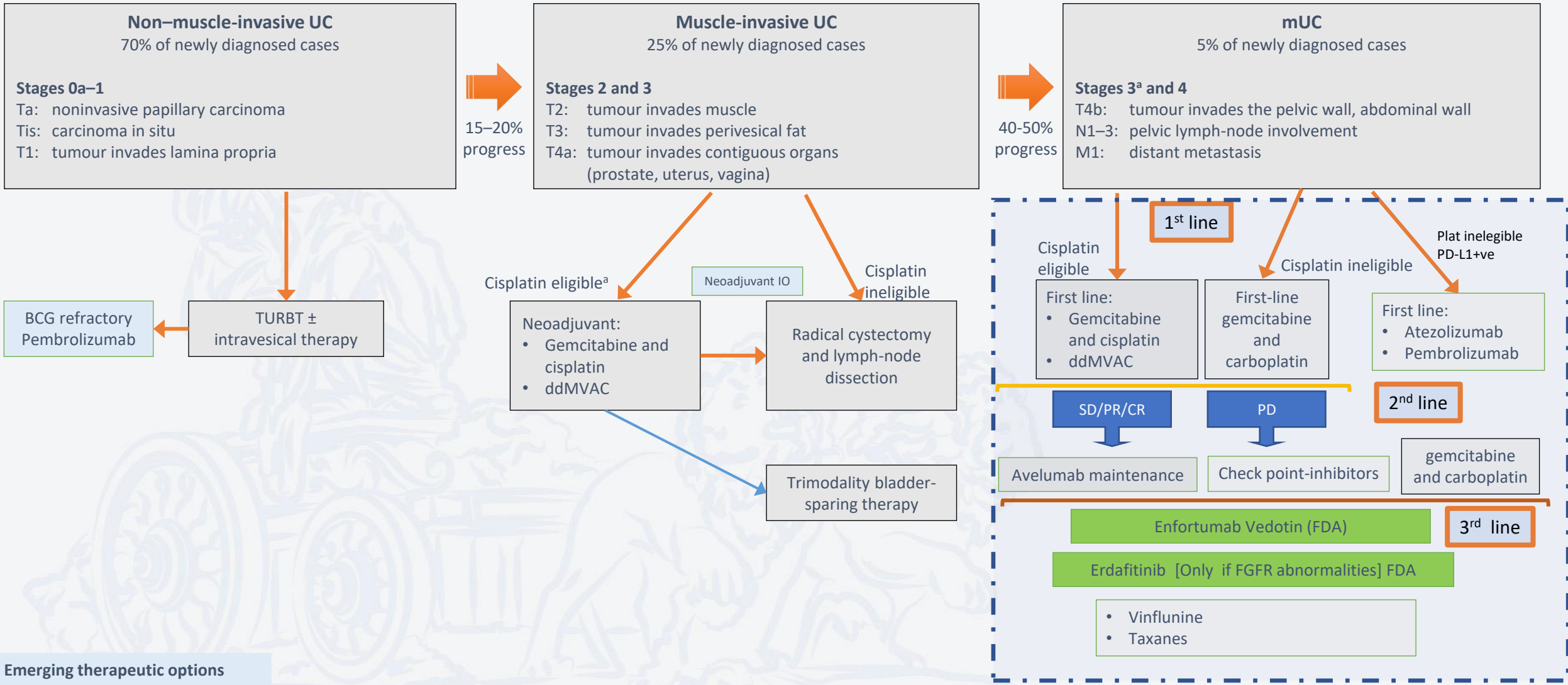

Emerging therapeutic options

FGFR, fibroblast growth factor receptor.

Figure adapted from: Apolo A. Oral presentation at ASCO 2018. de Wit R, et al. Poster presentation at ASCO 2019; abstract 4530. Szabados B, et al. Poster presented at EAU 2019. Abstract 1121. Sternberg CN, et al. Eur Urol 2019; doi: 10.1016/j.eururo.2019.03.015.

Summary

- Bladder cancer therapeutics is evolving in parallel to a **better knowledge of the molecular biology** of this disease

- **New treatment targets** after platinum-based chemotherapy and CPIs include **genetic aberrations in FGFR** and **specific widely expressed targets to facilitate drug delivery**

- Both **FGFR inhibitors** and **ADCs** represent currently the standard of care in mUC patients upon progression to platinum-based chemotherapy and CPIs

- **Efficacy**, **level of evidence** and **safety profile** need to be taken into account when making treatment decisions in this setting

Gracias