LE PATOLOGIE ONCOLOGICHE DELL'UROTELIO: RIDEFINIRE IL PERCORSO CLINICO CONSIDERANDO LA CENTRALITA' DEL PAZIENTE

23 Novembre, 2018 Hotel Michelangelo P.za Luigi di Savoia, 6 Milano

Oltre l'immunoterapia: nuovi bersagli terapeutici

Dr Roberto Iacovelli

Gemelli

Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Università Cattolica del Sacro Cuore

Agenda

- The angiogenesis
- New conjugates antibodies
- The FGFR

The end of angiogenesis-era in UCs

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

mUCs previously treated with platinum

R

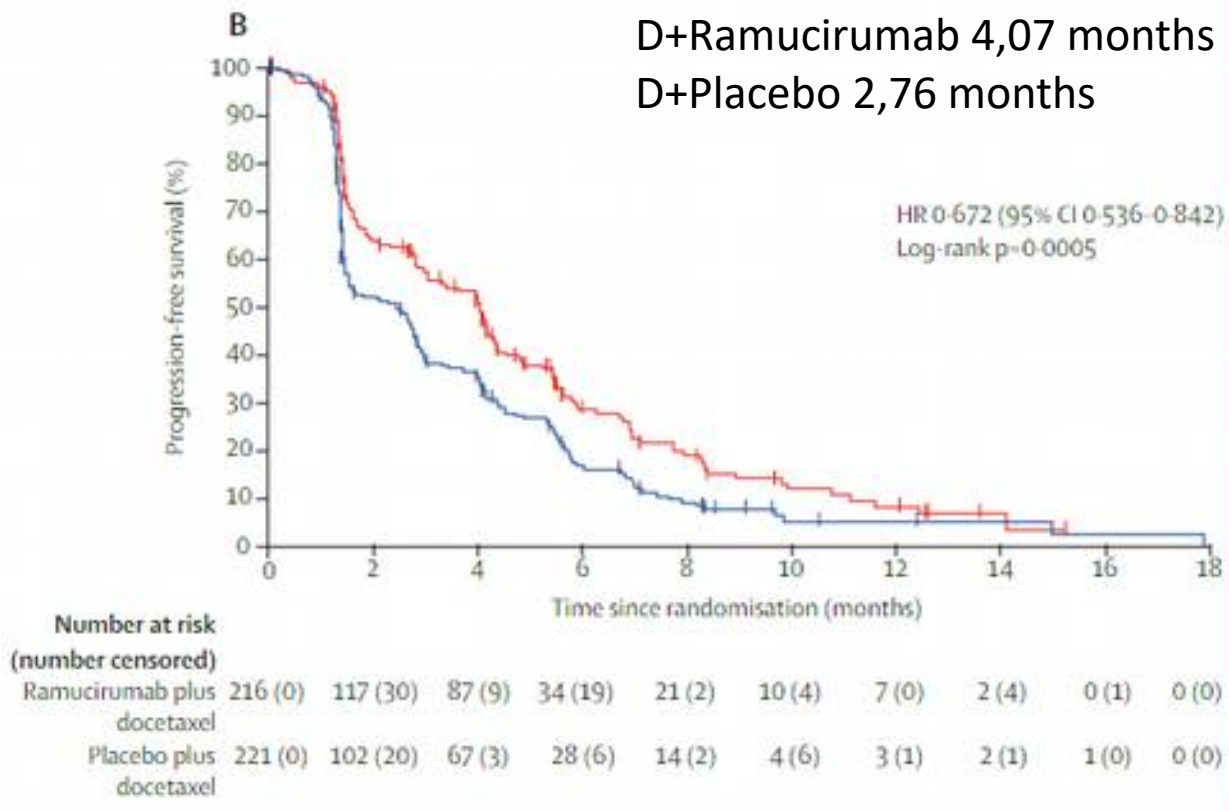
N°=524

Docetaxel + Ramucirumab

Docetaxel + Placebo

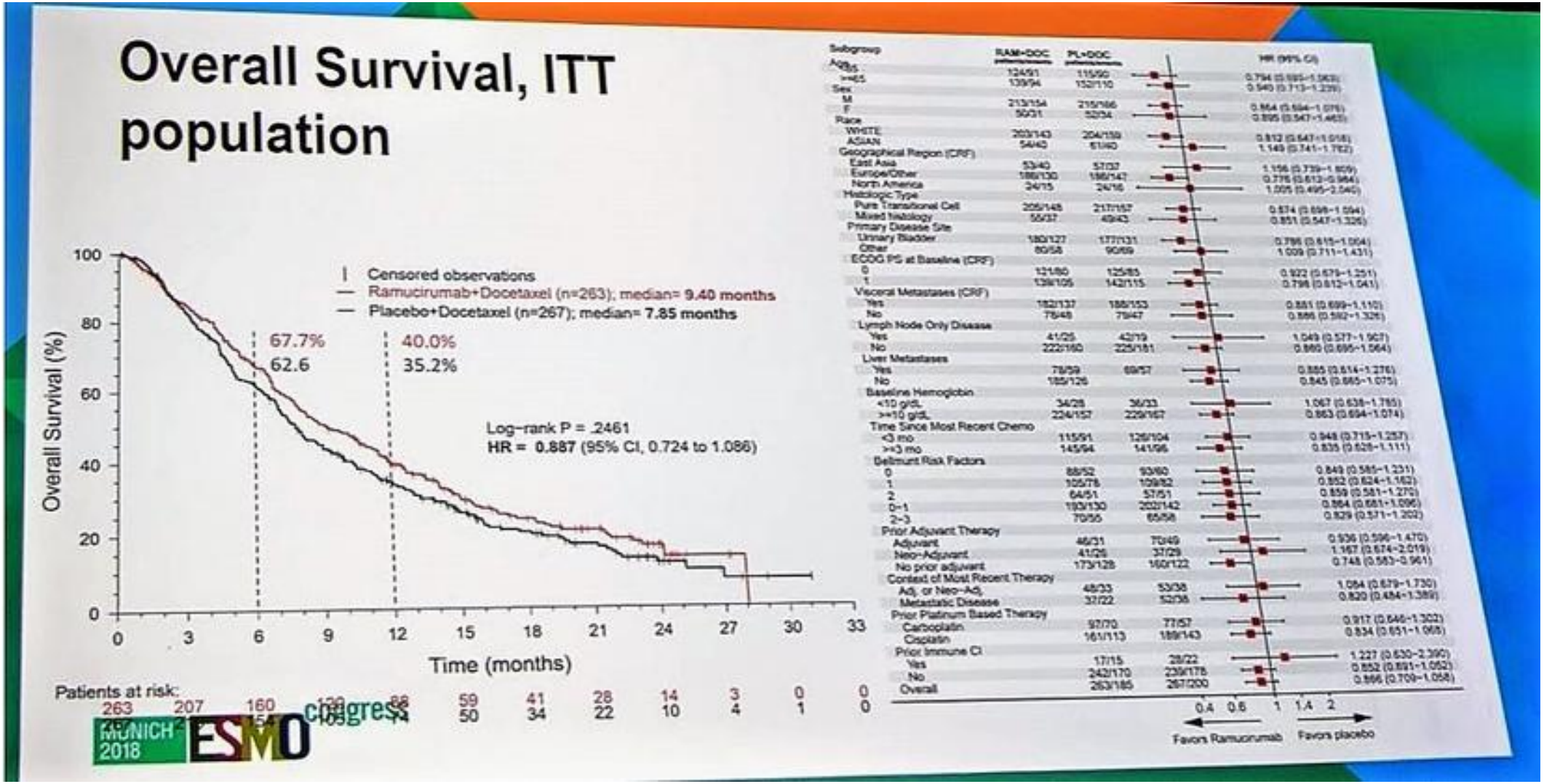
Primary endpoint: PFS
Secondary endpoints: OS, ORR, safety

Median PFS:
D+Ramucirumab 4,07 months
D+Placebo 2,76 months



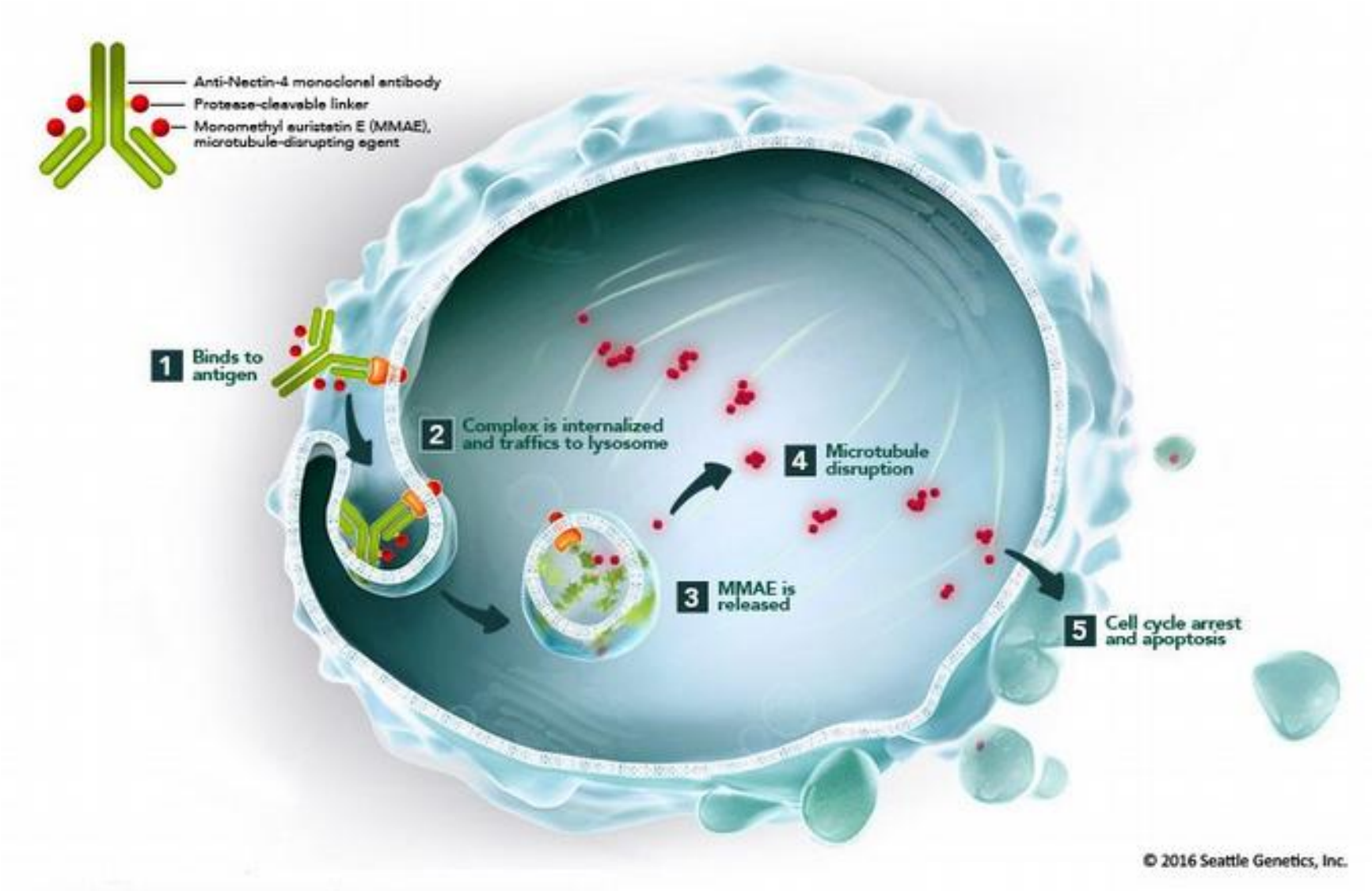
Petrylak DP, et al. Lancet. 2017;390:2266-2277.

The end of angiogenesis-era in UCs



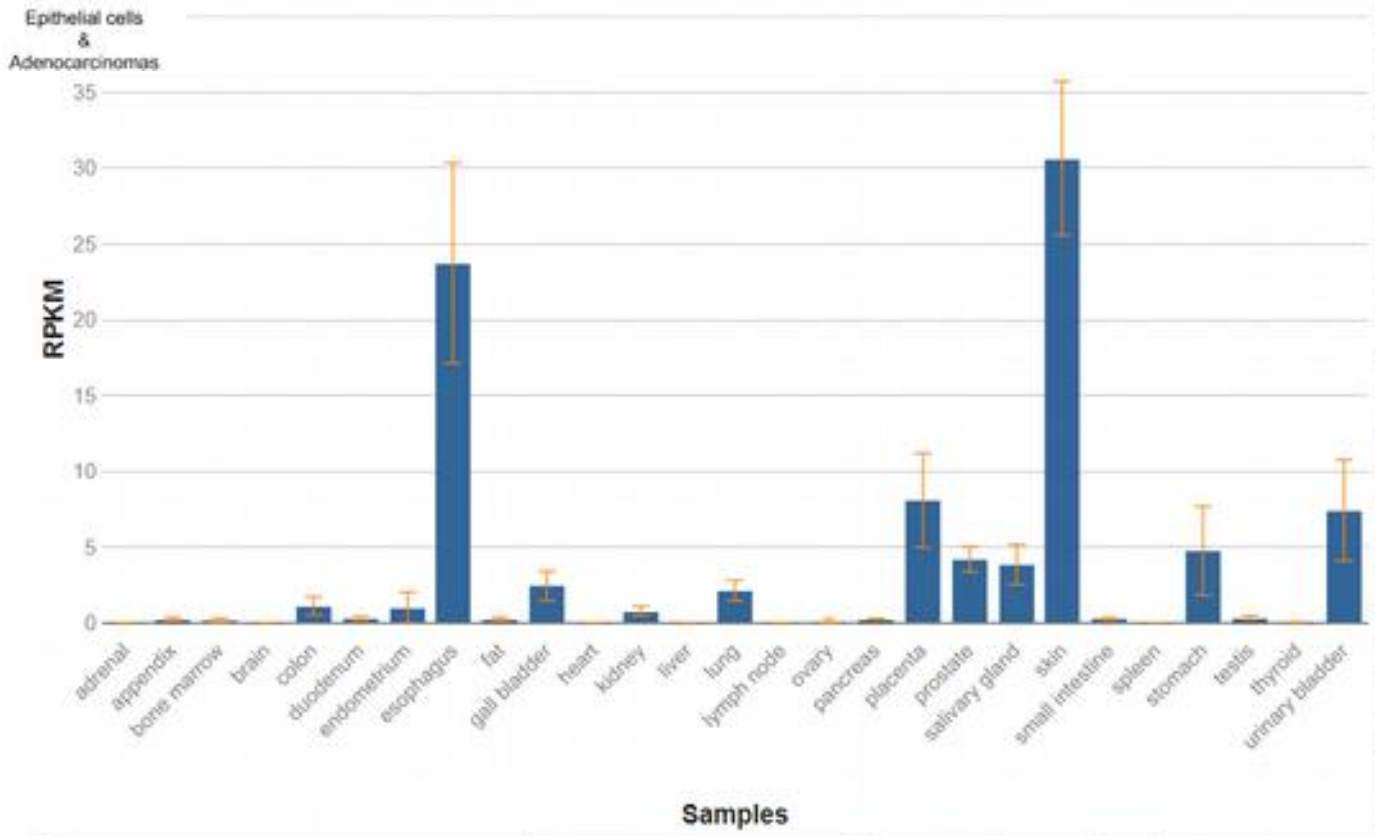
Petrylak DP, et al. Presented at ESMO 218, abst 865PD.

Conjugated Antibody: Enfortumab Vedotin

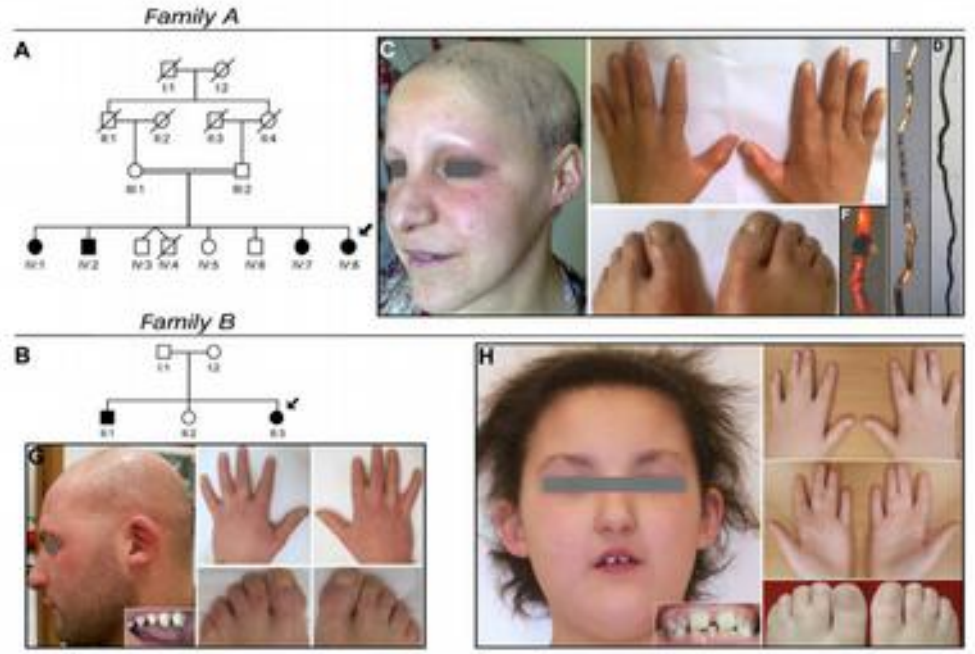


Nectin-4

The encoded protein contains two immunoglobulin-like (Ig-like) C2-type domains and one Ig-like V-type domain. It is involved in cell adhesion through trans-homophilic and -heterophilic interactions. It is a single-pass type I membrane protein.



Mutations in this gene are the cause of ectodermal dysplasia-syndactyly syndrome type 1, an autosomal recessive disorder.

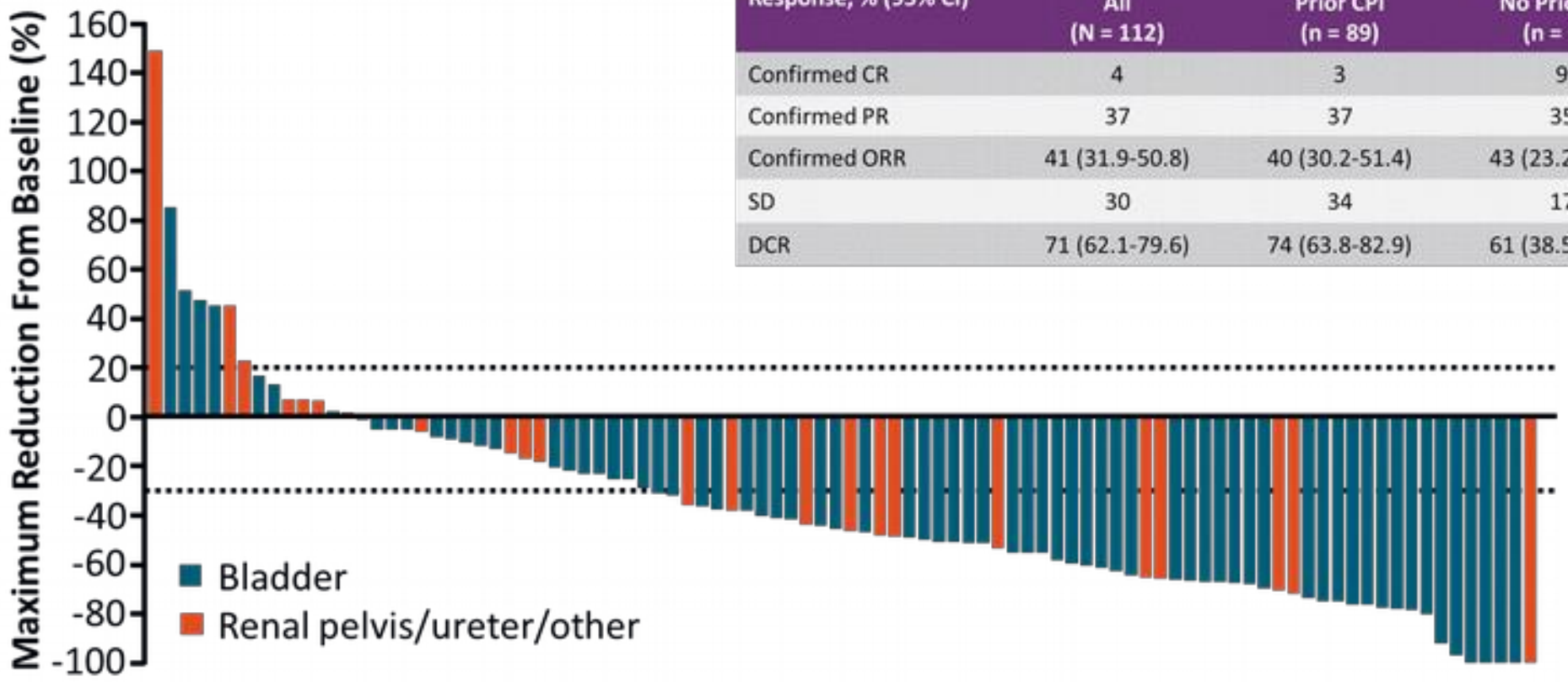


https://www.ncbi.nlm.nih.gov/gene/81607
Brancati F, et al. Am. J. Hum. Genet. 87: 265-273, 2010.

Conigated Antibody: Enfortumab Vedotin

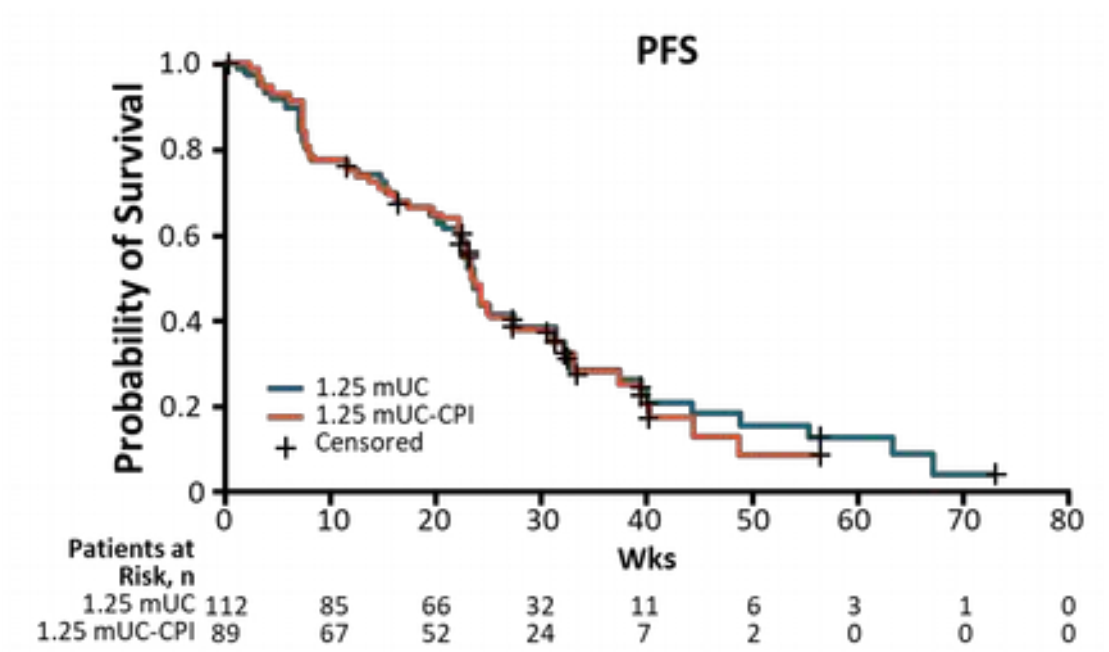
Change in Tumor Burden From Baseline in All Patients (N = 112)

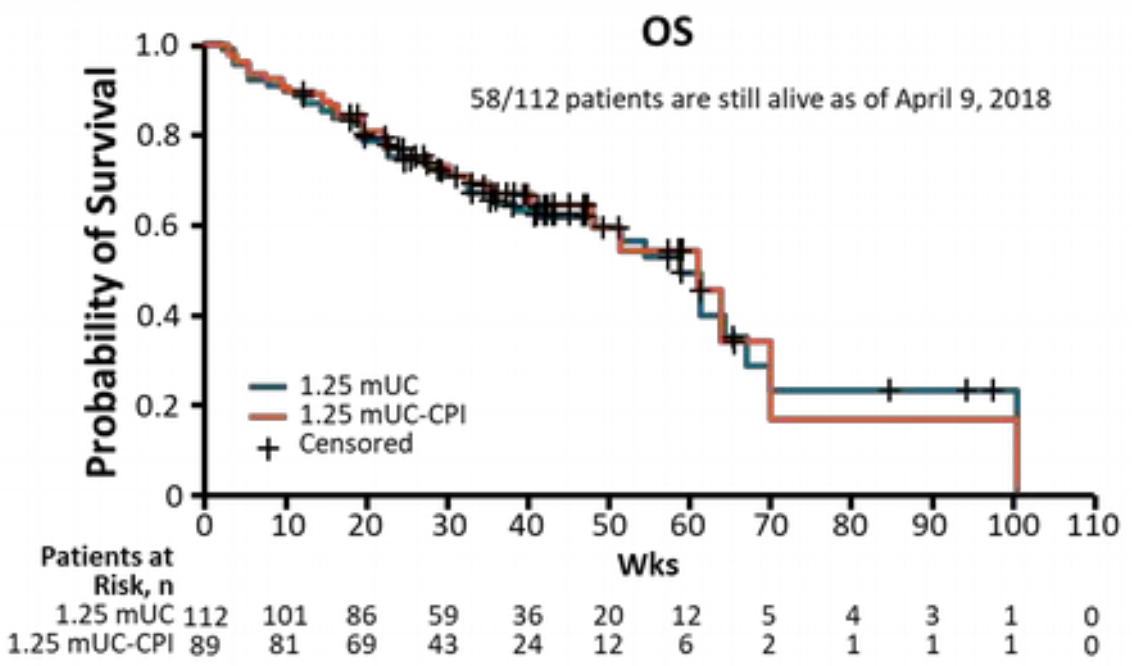
Response, % (95% CI)	EV 1.25 mg/kg			
	All (N = 112)	Prior CPI (n = 89)	No Prior CPI (n = 23)	Liver Metastases (n = 33)
Confirmed CR	4	3	9	0
Confirmed PR	37	37	35	39
Confirmed ORR	41 (31.9-50.8)	40 (30.2-51.4)	43 (23.2-65.5)	39 (22.9-57.9)
SD	30	34	17	21
DCR	71 (62.1-79.6)	74 (63.8-82.9)	61 (38.5-80.3)	61 (42.1-77.1)



Rosenberg JE, et al. ASCO 2018. Abstract 4504.

Conigated Antibody: Enfortumab Vedotin



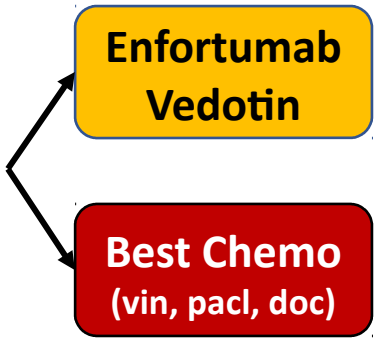


Survival Endpoint	EV 1.25 mg/kg	
	All (N = 112)	Prior CPI (n = 89)
Median PFS, mos (95% CI)	5.4 (5.1-6.2)	5.4 (5.1-6.2)
OS ▪ Median, mos (95% CI) ▪ Estimated 6-mo rate, % ▪ Estimated 12-mo rate, %	 13.6 (11.0-15.4) 74.4 56.3	 14.0 (11.0-16.1) 75.6 54.2

Rosenberg JE, et al. ASCO 2018. Abstract 4504.

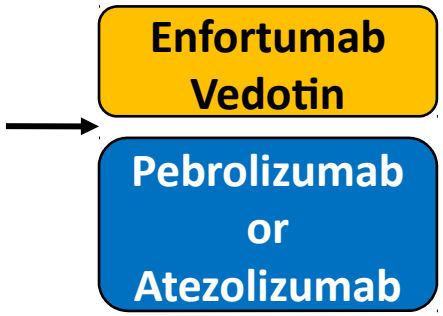
Ongoing Trials

Adv/metast. disease, Previous cisplatin and CPI.



Phase: III
Primary endpoint: OS
Patients: 550

Adv/metast. disease, Previous Tx



Phase: Ib
Primary endpoint: Safety
Patients: 85

Adv/metast. disease, Previous cisplatin and CPI.

Phase: II
Primary endpoint: ORR
Patients: 100 (Cohort 1)

Adv/metast. disease, Prev CPI, platinum-naïve and cisplatin-ineligible

Phase: II
Primary endpoint: ORR
Patients: 100 (Cohort 2)

Clinicaltrial.gov

The inhibition of the FGFR

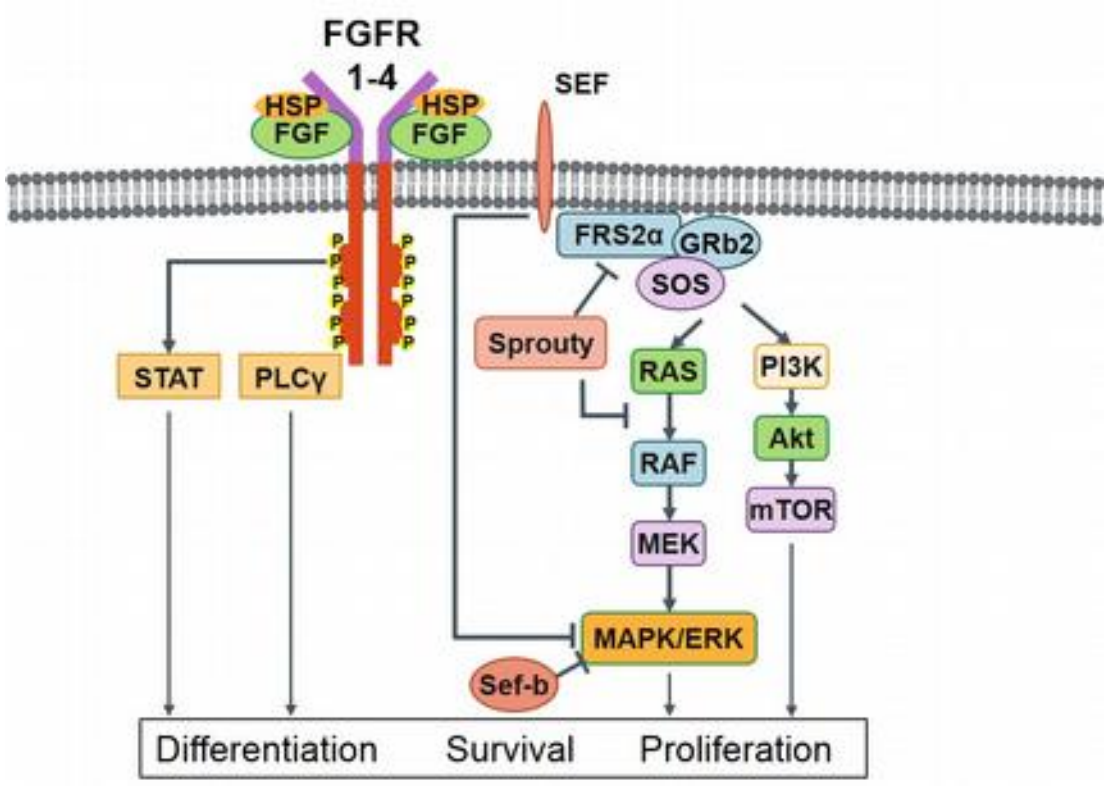
4 distinct receptors in the FGFR family

Serve as receptors for 22 proteins that comprise the FGF family and control growth, differentiation, survival, angiogenesis, and invasion

Driver events in various malignancies include

- Point mutations
- Gene fusions
- Gene amplification
- Protein overexpression

Driver events may play a role in acquired resistance to other targeted therapies



Slide credit: clinicaloptions.com

The inhibition of the FGFR

Gene	Molecular Alterations	Cancer Type
FGFR1	Amplification	Squamous NSCLC (20%) Breast cancer (10%) Ovarian cancer (~ 5%) Bladder cancer (3%) Others: oral SCC, esophageal SCC
	Mutations	Melanoma (rare) Glioblastoma Pilocytic astrocytoma (5% to 8%)
	Translocations	8p11 myeloproliferative syndrome Chronic myeloid leukemia (rare)

Gene	Molecular Alterations	Cancer Type
FGFR2	Amplification	Gastric cancer (5% to 10%) Breast cancer (4% of TNBC)
	Mutations	Endometrial cancer (12%) Squamous NSCLC (3%) Melanoma (loss of function?)
	Germline SNP	Second intron SNP: BC susceptibility
FGFR3	Amplification	Bladder cancer Salivary adenoid cystic cancer
	Mutations	Bladder cancer (50% to 60% NMIBC) Cervical cancer (5%) Myeloma (5%) Spermatocytic seminoma (7%)
	Translocations	Myeloma (15% to 20%)
FGFR4	Amplification/ mutations	Rhabdomyosarcoma (7% to 8%)
	Germline SNP	Coding SNP; poor prognosis

Chae YK, et al. Oncotarget. 2017;8:16052-16074.

The inhibition of the FGFR

"Multi" TKIs often hit FGFR, but at a lower potency than primary targets

- Dovitinib (TKI258)
- Cediranib (AZD 2171)
- Brivanib (BMS-58266)
- Nintedanib (BIBF-1120)

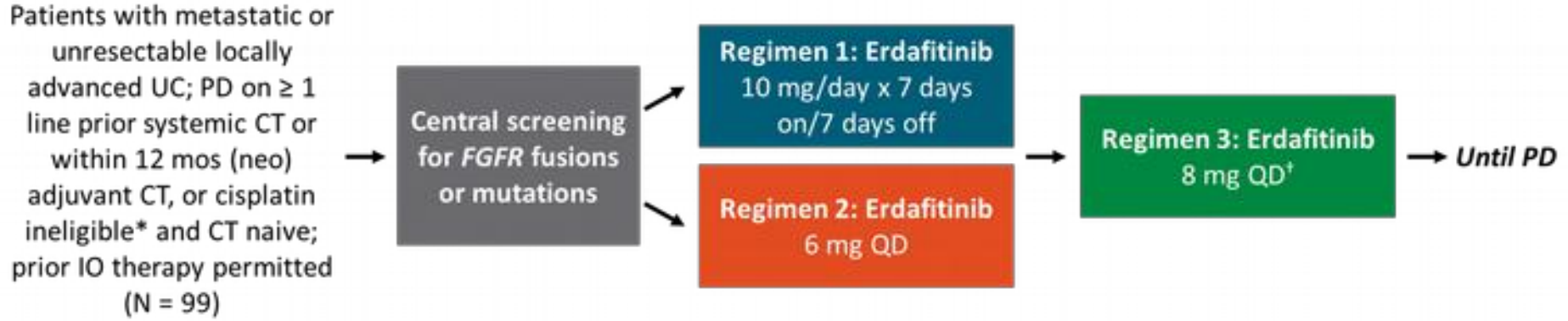
Numerous selective FGFR TKIs are in development

- AZD4547
- BAY 1163877 (rogaratinib)
- BGJ398 (infigratinib)
- JNJ-42756493 (erdafitinib)
- LY2874455
- PRN1371

The inhibition of the FGFR

BLC2001: Study Design

- International, open-label phase II trial



*Defined as peripheral neuropathy or impaired renal function. †Titration up to 9 mg QD if target not reached for serum phosphate (≥ 5.5 mg/dL) by Day 14 and no TRAEs.

- Primary endpoint: ORR
  - Study has 85% power with 1-sided α = 0.025 to test primary hypothesis that ORR > 25% in Regimen 3
- Secondary endpoints: PFS, OS, safety, DoR, PK, predictive biomarker evaluation

Siefker-Radtke AO, et al. ASCO 2018. Abstract 4503. Siefker-Radtke AO, et al. ASCO 2016. Abstract TPS4575. ClinicalTrials.gov. NCT02365597.

Slide credit: clinicaloptions.com

The inhibition of the FGFR

BLC2001: Antitumor Activity

Response,*† n (%)	Patients (N = 99)
ORR	40 (40.4)
▪ CR	3 (3.0)
▪ PR	37 (37.4)
SD	39 (39.4)
PD	18 (18.2)
Median TTR, mos	1.4
Median DoR, mos	5.6

*Investigator-assessed response confirmed with second scan ≥ 6 wks after first observation of response. †Response unknown, n = 2.

- Tumor shrinkage observed in 76% of evaluable patients receiving erdafitinib 8 mg QD
- Reponses were durable

Response, %	Patient Subgroups				
	CT Naive (n = 12)	PD/Relapse After CT (n = 87)	Visceral Mets (n = 78)	No Visceral Mets (n = 21)	Prior IO (n = 22)
ORR to erdafitinib	41.7	40.2	38.5	47.6	59.0
ORR to prior IO	--	--	--	--	5

Siefker-Radtke AO, et al. ASCO 2018. Abstract 4503.

Slide credit: clinicaloptions.com

BLC2001: Most Common TRAEs

TRAEs in > 20% of Patients, n (%)	Erdafitinib 8 mg QD (N = 99)	
	Any Grade	Grade 3
Hyperphosphatemia	72 (73)	2 (2)
Stomatitis	54 (55)	9 (9)
Dry mouth	43 (43)	0
Diarrhea	37 (37)	4 (4)
Dysgeusia	35 (35)	1 (1)
Dry skin	32 (32)	0
Alopecia	27 (27)	0
Decreased appetite	25 (25)	0
Hand–foot syndrome	22 (22)	5 (5)
Fatigue	21 (21)	2 (2)

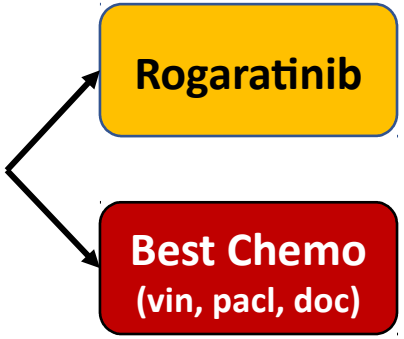
- Most TRAEs were grade 1/2
  - No grade 4/5 TRAEs observed
- Serious TRAEs observed in 9 patients (9%)
  - No serious TRAE observed in ≥ 1 patient

Siefker-Radtke AO, et al. ASCO 2018. Abstract 4503.

Slide credit: clinicaloptions.com

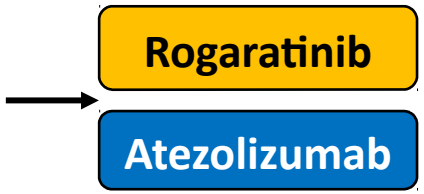
Ongoing Trials

Adv/metast. disease, Previous cisplatin, FGFR mut/ampl



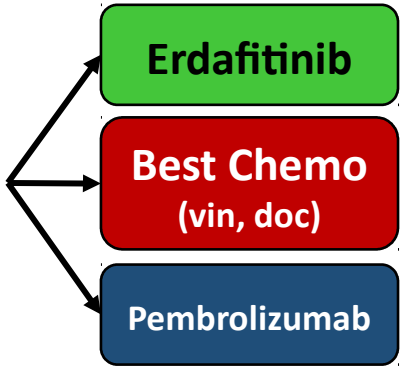
Phase: II/III
Primary endpoint: OS
Patients: 400

Adv/metast. disease, Previous cisplatin, FGFR mut/ampl



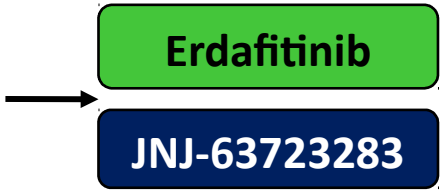
Phase: I/II
Primary endpoint: PFS, safety
Patients: 190

Adv/metast. disease, Previous cisplatin, FGFR mut/ampl



Phase: III
Primary endpoint: OS
Patients: 631

Adv/metast. disease, Previous cisplatin, FGFR mut/ampl



Phase: I/II
Primary endpoint: Safety, ORR
Patients: 102

Clinicaltrial.gov