The dilemma in the first line setting and beyond

Advanced Urothelial Cancers

Philippe Barthélémy
Institut de CANcérologie Strasbourg Europe
ICANS.eu

DISCLOSURES

- **Advisory board, Consulting**
  - ROCHE, PFIZER, MSD, BMS, IPSEN, SANOFI, JANSSEN CILAG, NOVARTIS, EUSAPharma

- **Honoraria**
  - EISAI, ASTELLAS

OUTLINE

- *Recommandations*
  - *1st line - 2nd line*
- **2019 reported data**
  - **1st line setting : IMvigor 130**
  - **2nd line setting and beyond**
- **Future**
  - **Combinations**

ALGORITHM FOR 1ST AND 2ND LINE CHEMOTHERAPY IN ADVANCED UC UNTIL RECENTLY

First line setting

Population	CISPLATIN eligible	CISPLATIN ineligible
Chemotherapy regimen	**Gemcitabine-Cisplatin MVAC-HD**	**Gemcitabine-Carboplatin**
ORR	50-60%	36%
OS, median, months	**15 months**	**9 months**
OS, 1 year	60%	37%

Second line setting

Platinum resistant/refractory
Docetaxel/Paclitaxel Vinflunine
12%
7 months
26%

ESMO Guidelines Bellmunt et al 2014

ESMO GUIDELINES FOR TARGETED AND IMMUNE THERAPY

	First line cisplatin ineligible, PD-L1 postive	Platinum refractory	Platinum and ICIs refractory
Pembrolizumab	IIIB	IA	
Atezolizumab	IIIB	IIB	
Nivolumab		IIIB	
Avelumab		IIIC*	
Durvalumab		IIIC*	
Enfortumab vedotin			IIIB*
Erdafitinib		IIIB*	IIIB*

*Not EMA approved as of 18th Aug 2019.
UC: urothelial cancer; ICIs: Immune checkpoint inhibitors; ADC: antibody drug conjugate; FGFR: fibroblast growth factor receptor;
Numbers represent levels of evidence according to ESMO guidelines.

- Thomas Powles
- Begona Perez-Valderrama
- Maria De Santis
- Robert Huddart
- Yohann Loriot
- Andrea Necchi
- Alain Ravaud
- Eva Comperat
- Michiel Van Der Heijden
- Joaquim Bellmunt

ePublished 22 August 2019

EMA AND FDA APPROVAL IN THE FIRST LINE SETTING

	First line cisplatin ineligible, PD-L1 positive	Platinum refractory	Platinum and ICIs refractory
Pembrolizumab	IIIB	IA	
Atezolizumab	IIIB	IIB	
Nivolumab		IIIB	
Avelumab		IIIC*	
Durvalumab		IIIC*	
Enfortumab vedotin			IIIB*
Erdafitinib		IIIB*	IIIB*

*Not EMA approved as of 18th Aug 2019.
UC: urothelial cancer; ICIs: Immune checkpoint inhibitors; ADC: antibody drug conjugate; FGFR: fibroblast growth factor receptor;
Numbers represent levels of evidence according to ESMO guidelines.

Phase II data

	IMvigor110 atezolizumab	Keynote-052 pembrolizumab
Number	119	370
PS 2	20%	42%
Visceral mets	65%	85%
RR	23%	24%
PFS	2.1 months	2.3 months
OS	15.9 months (10.4- NE)	11.5 months 10.0-13.3)

J Bellmunt et al NEJM 2017 ; T Powles et al Lancet 2018 Feb 24

T Powles ESMO 2019

PHASE III TRIALS ASSESSING IO IN 1ST LINE SETTING

NCT
- First-l… …ed/metastatic
- ECOG

Co-primary … safety

→ R →
- Atezolizumab
- Platinum-based chemotherapy + atezolizumab
- Cisplatin + gemcitabine OR carboplatin + gemcitabine

NCT0251… (DANUBE):[2] **N=1,005**
- First-line unresectable stage IV
- Eligible/ineligible for cisplatin-based chemotherapy

Co-primary endpoints: PFS and OS

→ R →
- Durvalumab
- Durvalumab + tremelimumab
- Cisplatin + gemcitabine OR carboplatin + gemcitabine

NCT02853305 (KEYNOTE-361):[3] **N=990**
- First-line unresectable or metastatic
- ECOG PS ≤2

Co-primary endpoints: PFS and OS

→ R →
- Pembrolizumab + cisplatin/gemcitabine OR Pembrolizumab + carboplatin/gemcitabine
- Pembrolizumab
- Cisplatin + gemcitabine OR carboplatin + gemcitabine

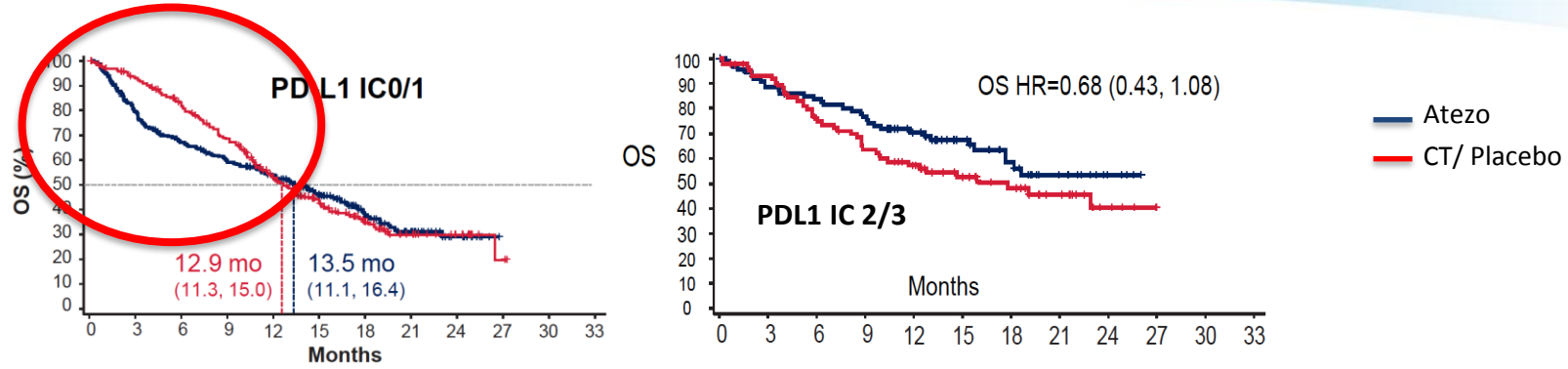
NCT03036098 (CheckMate-901):[4] **N=897**
- First-line unresectable or metastatic
- ECOG PS ≤1

Co-primary endpoints: PFS and OS

→ R →
- Nivolumab + ipilimumab
- Nivolumab + cisplatin + gemcitabine
- Cisplatin + gemcitabine OR carboplatin + gemcitabine

- ECOG PS, Eastern Cooperative Oncology Group performance status; OS, overall survival; PD-1, programmed death-1; PD-L1, programmed death ligand-1; PFS, progression-free survival.
- 1. NCT02807636. Available at: http://www.clinicaltrials.gov (accessed November 2017); 2. NCT02516241. Available at: http://www.clinicaltrials.gov (accessed November 2017); 3. NCT02853305. Available at: http://www.clinicaltrials.gov (accessed November 2017); 4. NCT03036098. Available at: http://www.clinicaltrials.gov (accessed November 2017).

DOES THE MONOTHERAPY ARM CHANGE CLINICAL PRACTICE ?



Ineligible for Cisplatin based therapy	PD-L1 +ve*	IO or Gemcitabine/Carboplatin
	PD-L1 –ve	Gemcitabine/Carboplatin

EMA restriction : Reduced survival in PDL1- patients

Adapted T Powles ESMO 2018

E Grande LBA14, ESMO 2019

CISPLATIN ELIGIBLE PATIENTS WERE INCLUDED IN THIS MONOTHERAPY ARM

Should we use atezolizumab for all PDL1+ pts ?

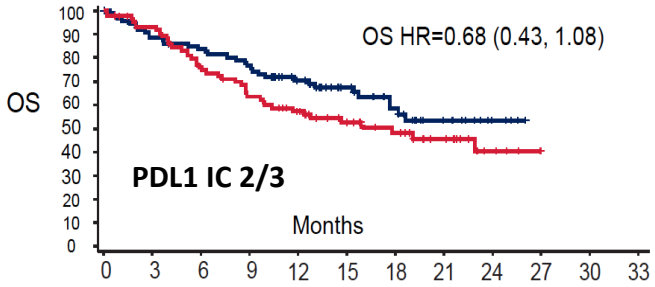
Data support the use of atezolizumab for PDL1 + CDDP ineligible pts (but not for CDDP eligible pts yet)

PD-L1 –ve

Gemcitabine/Cisplatin

Atezolizumab

Cisplatin based therapy



RR atezo vs CT: 2

Toxicity : 16% vs 82 % grade

No subset analysis available

Adapted T Powles ESMO 2018

E Grande LBA14, ESMO 2019

ÌMVIGOR 130 STUDY DESIGN

- Locally advanced or mUC
- No prior systemic therapy in the metastatic setting
- ECOG PS ≤ 2
- 1L platinum-eligible
- N = 1200
- Randomised 1:1:1

Arm A
Atezo + plt/gem

Arm B
Atezo monotherapy

Arm C
Placebo + plt/gem

Should we add IO to CT ?

Stratification factors:
- PD-L1 IC status (IC0 vs IC1 vs IC2/3)
- Bajorin risk factor score including KPS < 80% vs ≥ 80% and presence of visceral metastases (0 vs 1 vs 2 and/or patients with liver metastases)
- Investigator choice of plt/gem (cisplatin + gem or carboplatin + gem)

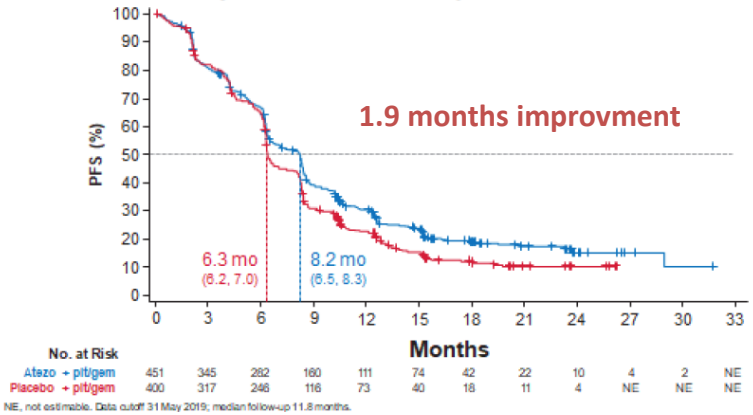
Co-primary endpoints:
- INV-assessed PFS[a] and OS (Arm A vs C)
- OS (Arm B vs C, hierarchical approach)

Key secondary endpoints:
- INV-ORR[a] and DOR
- PFS[a] and OS (Arm B vs C; PD-L1 IC2/3 subgroup)
- Safety

E Grande LBA14, ESMO 2019

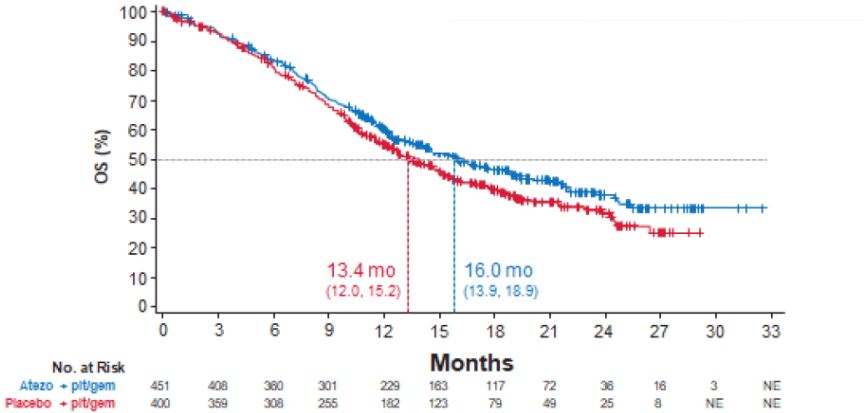
IMVIGOR 130 PFS AND OS RESULTS : ATEZO/CT VS CT

Final PFS: ITT (Arm A vs Arm C)



	Arm A Atezo + plt/gem (n = 451)	Arm C Placebo + plt/gem (n = 400)
PFS events, n (%)	334 (74)	326 (82)
Stratified HR (95% CI)	**0.82 (0.70, 0.96)** *P* = 0.007 (one-sided)	

Interim OS: ITT (Arm A vs Arm C)



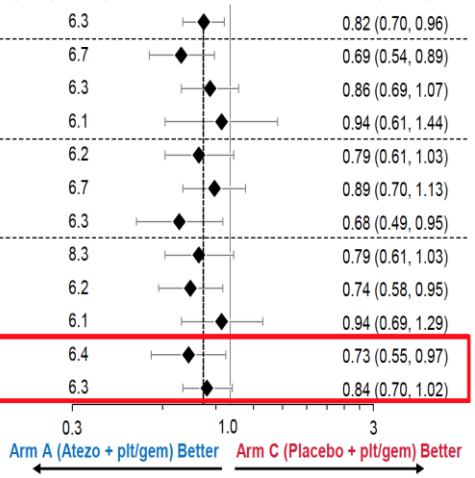
	Arm A Atezo + plt/gem (n = 451)	Arm C Placebo + plt/gem (n = 400)
OS events[a], n (%)	235 (52)	228 (57)
Stratified HR (95% CI)	**0.83 (0.69, 1.00)** *P* = 0.027 (one-sided)[b]	

Not statistically significant due to one sided- and alpha spend 0.024

SUBGROUP ANALYSIS : CDDP VS CARBO

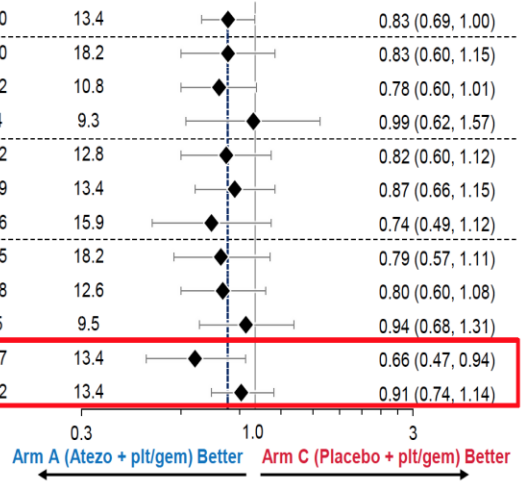
PFS

Characteristic		Patients (n)	Arm A mPFS, mo (n = 451)	Arm C mPFS, mo (n = 400)	HR (95% CI)[a]
All patients		851	8.2	6.3	0.82 (0.70, 0.96)
ECOG PS	0	355	9.4	6.7	0.69 (0.54, 0.89)
	1	396	6.8	6.3	0.86 (0.69, 1.07)
	2	100	4.8	6.1	0.94 (0.61, 1.44)
PD-L1 status	0	278	6.5	6.2	0.79 (0.61, 1.03)
	1	374	8.1	6.7	0.89 (0.70, 1.13)
	2/3	199	8.6	6.3	0.68 (0.49, 0.95)
Bajorin risk factor score	0	338	9.8	8.3	0.79 (0.61, 1.03)
	1	318	8.2	6.2	0.74 (0.58, 0.95)
	2 and/or liver mets	195	5.0	6.1	0.94 (0.69, 1.29)
Investigator choice of chemo	Cisplatin	273	8.8	6.4	0.73 (0.55, 0.97)
	Carboplatin	578	7.1	6.3	0.84 (0.70, 1.02)



OS

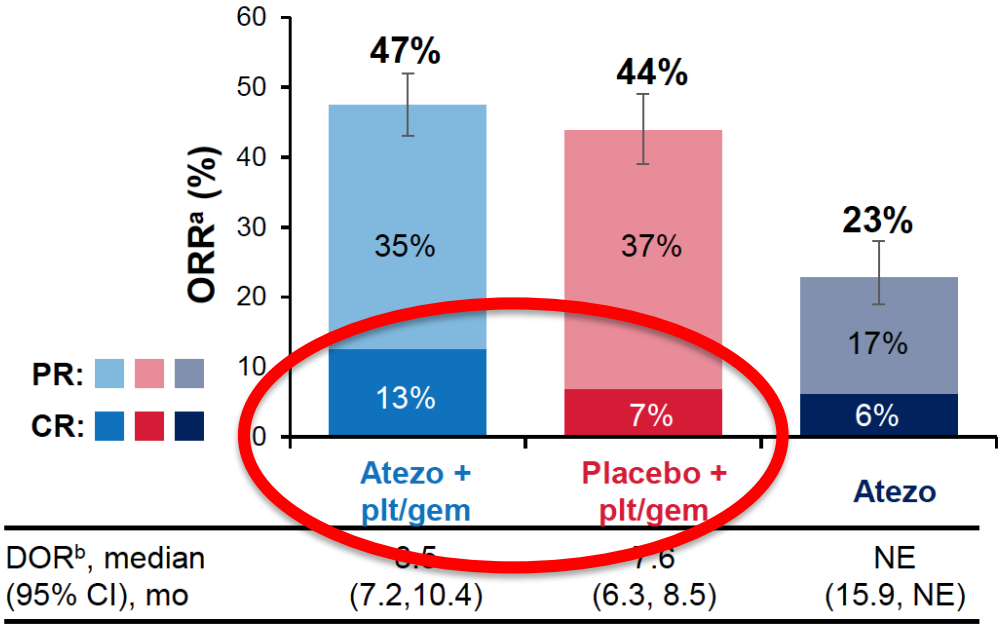
Characteristic		Patients (n)	Arm A mOS, mo (n = 451)	Arm C mOS, mo (n = 400)	HR (95% CI)[a]
All patients		851	16.0	13.4	0.83 (0.69, 1.00)
ECOG PS	0	355	22.0	18.2	0.83 (0.60, 1.15)
	1	396	14.2	10.8	0.78 (0.60, 1.01)
	2	100	7.4	9.3	0.99 (0.62, 1.57)
PD-L1 status	0	278	14.2	12.8	0.82 (0.60, 1.12)
	1	374	14.9	13.4	0.87 (0.66, 1.15)
	2/3	199	23.6	15.9	0.74 (0.49, 1.12)
Bajorin risk factor score	0	338	24.5	18.2	0.79 (0.57, 1.11)
	1	318	15.8	12.6	0.80 (0.60, 1.08)
	2 and/or liver mets	195	9.5	9.5	0.94 (0.68, 1.31)
Investigator choice of chemo	Cisplatin	273	21.7	13.4	0.66 (0.47, 0.94)
	Carboplatin	578	14.2	13.4	0.91 (0.74, 1.14)



Improved PFS and OS mainly in pts treated with CDDP

E Grande LBA14, ESMO 2019

WHAT ABOUT RESPONSE RATE ?



	Atezo + plt/gem	Placebo + plt/gem	Atezo
DOR[b], median (95% CI), mo	[illegible] (7.2,10.4)	7.6 (6.3, 8.5)	NE (15.9, NE)

DO THE RESULTS CHANGE THE ALGORITHM ?

Eligible for Cisplatin based therapy		**Gemcitabine/Cisplatin**
Ineligible for Cisplatin based therapy	PD-L1 +ve*	IO or Gemcitabine/Carboplatin
	PD-L1 –ve	Gemcitabine/Carboplatin

For
Significant delay in
OS trending the right
CR of 13% vs 7%
No increase in AEs for th

NO

PHASE III RANDOMIZED TRIALS SUPPORTING PEMBROLIZUMAB AND TO A LESSER EXTENT ATEZOLIZUMAB

	First line cisplatin ineligible, PD-L1 postive	Platinum refractory	Platinum and ICIs refractory
Pembrolizumab	IIIB	IA	
Atezolizumab	IIIB	IIB	
Nivolumab		IIIB	
Avelumab		IIIC*	
Durvalumab		IIIC*	
Enfortumab vedotin			IIIB*
Erdafitinib		IIIB*	IIIB*

*Not EMA approved as of 18th Aug 2019.
UC: urothelial cancer; ICIs: Immune checkpoint inhibitors; ADC: antibody drug conjugate; FGFR: fibroblast growth factor receptor;
Numbers represent levels of evidence according to ESMO guidelines.

Pembrolizumab[1]	
RR	21%
OS HR	0.73 (0.53-0.91)

Atezolizumab[2]	
RR	13%
OS HR	0.83 (0.73-0.99)
Supportive phase II and IV data	

J Bellmunt et al NEJM 2017 ; T Powles et al Lancet 2018 Feb 24

TOWARDS PRECISION MEDECINE

	First line cisplatin ineligible, PD-L1 postive	Platinum refractory	Platinum and ICIs refractory
Pembrolizumab	IIIB	IA	
Atezolizumab	IIIB	IIB	
Nivolumab		IIIB	
Avelumab		IIIC*	
Durvalumab		IIIC*	
Enfortumab vedotin			IIIB*
Erdafitinib		IIIB*	IIIB*

*Not EMA approved as of 18th Aug 2019.
UC: urothelial cancer; ICIs: Immune checkpoint inhibitors; ADC: antibody drug conjugate; FGFR: fibroblast growth factor receptor;
Numbers represent levels of evidence according to ESMO guidelines.

ADC

Enfortumab vedotin Phase II - III
IMMU-132 phase II

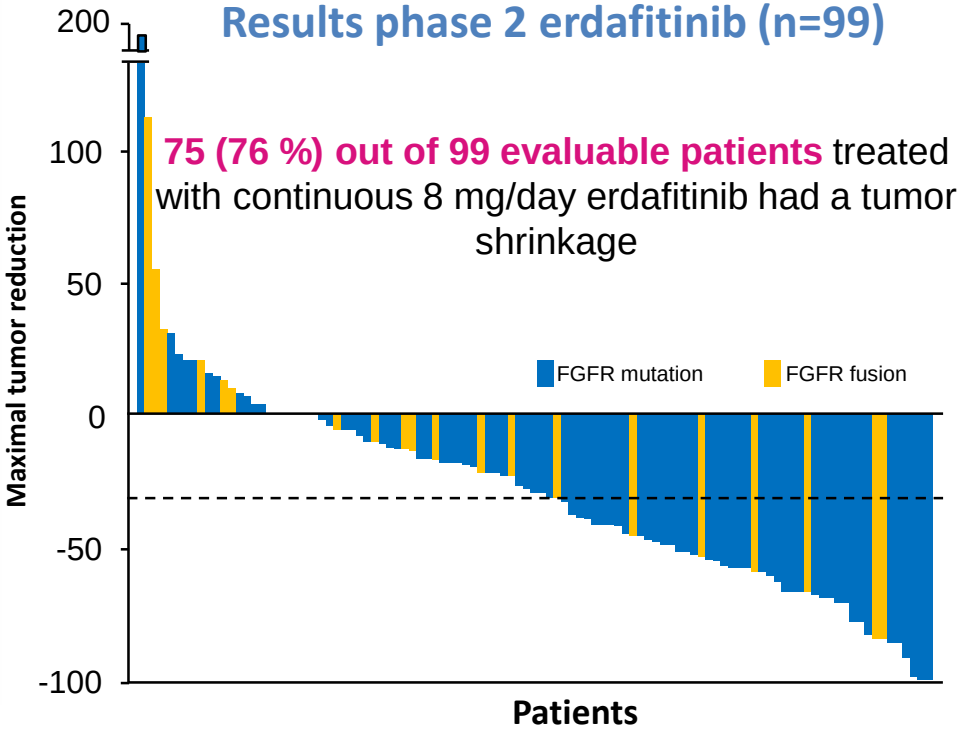
FGFRi

Erdafitinib phase II - III
INCB 054828 phase II

T Powles ESMO 2019

FGFR INHIBITORS IN UC

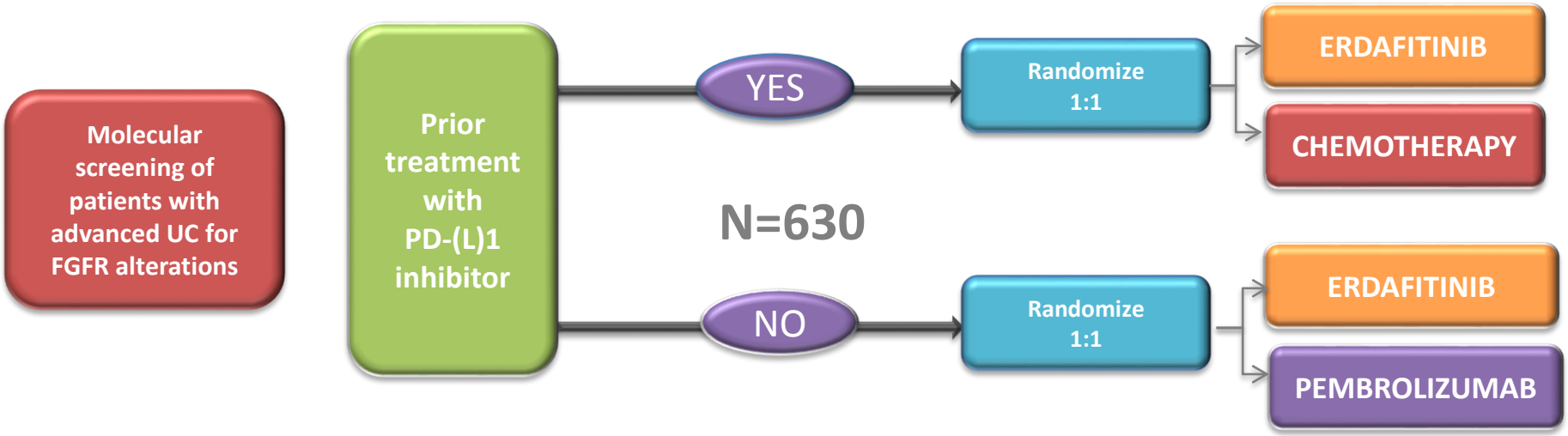
	Erdafitinib	INCB054828
Population	Platinum refractory	Platinum refractory
Number	99	100
Phase	II	II
biomarker	Mutations and fusions	Mixed (2 cohorts)
RR	40%	25%
PFS months	5.5 months (4.2-6)	na
Toxicity (grade 3)	Stomatitis Nail tox. Hypophosphatemia	Alopecia Fatigue Hypophoshatemia.
Median OS	9 .5 months (8-19)	NA



Y Loriot et al NEJM August 2019 ; A Necchi et al ESMO 2018

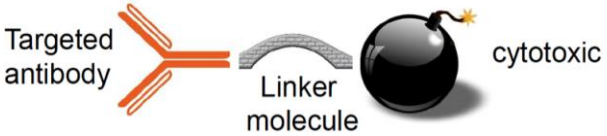
ONGOING PHASE III THOR STUDY : ERDAFITINIB

2nd line trial



Primary endpoint : Overall survival

ANTIBODY DRUG CONJUGATES (ADC) IN UC

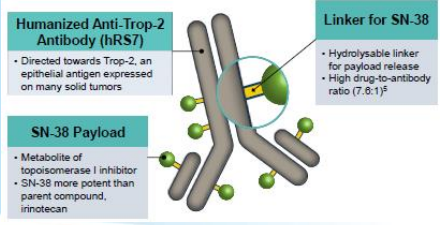


	Efortumab Vedotin	Sacitumab govitecan	ASG-ISME	Chemo. (>1st line)
mAb Target	Nectin	TROP-2	SLITRK6	microtubule
Payload	MMAE	SN-38	MMAE	NA
Phase	II	I	I	III
Patients	112	41	42	442
RR (%)	41%	34%	33%	13
Toxicity (grade 3)	Hyponatramia (7%)	Neutropoenia (39%)	Fatigue (44%)	Neutropaeia (13%)
Median OS	13.6 months 11-15.8	NA	NA	8.0 months 7.6-8.4

ESMO 2019 : IMMU-132
Preliminary Phase II results

Rosenberg ASCO 2018
Petrylak Ann Onc 2016
Tagawa ESMO 2017
Powles Lancet 2018

TROPHY 01 : PHASE II PRELIMINARY RESULTS



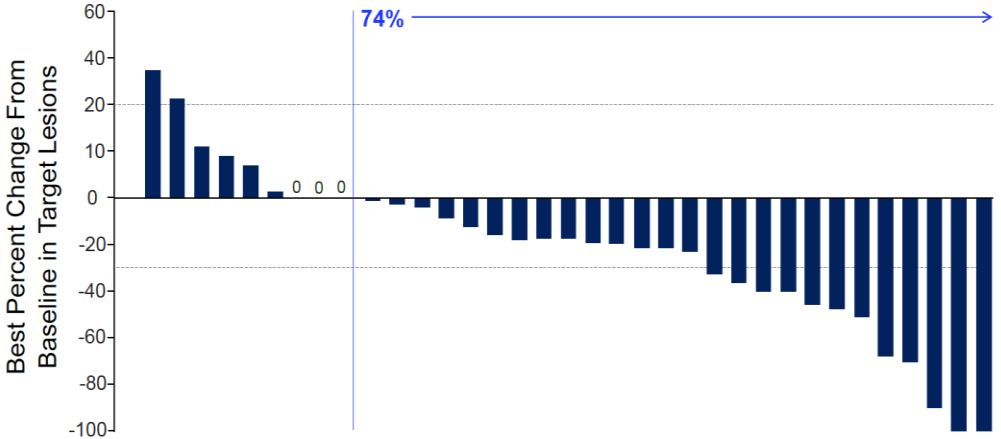
Platinum/CPI refractory

N=35 ; ORR=29%

Response Outcomes

Endpoint	Cohort 1 (N=35)
Median follow-up, mon	**4.1**
Pts continuing treatment, n (%)	20 (57)
ORR, n (%) [95% CI]	10 (29) [15, 46]
CR, n (%)	2 (6)
PR, n (%)	6 (17)
uPR pending confirmation, n (%)[a]	2 (6)
Median time to onset of response, (range), mon	1.5 (1.2–2.8)

Tumor shrinkage



=> Promising results

Tagawa et al, Abstract LBA55 présenté à l'ESMO 2019

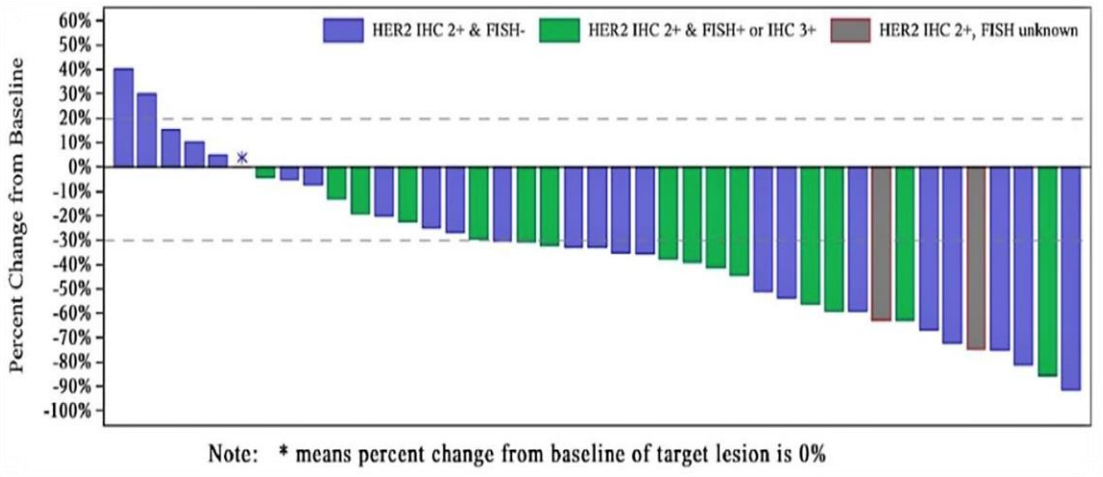
RC48-ADC : PHASE II PRELIMINARY RESULTS

HER2 2+ or 3+ ; UC 2nd line

HER2 status	
IHC3+ (n,%)	11 (25.6%)
IHC2+FISH+ (n,%)	4 (9.3%)
IHC2+FISH- (n,%)	24 (55.8%)
IHC2+FISH unknown (n,%)	3 (7.0%)
Primary Lesion	
Bladder (n,%)	22 (51.2%)
Renal pelvis (n,%)	13 (30.2%)
Ureter (n,%)	11 (25.6%)
Visceral metastases (n,%)	37 (86.0%)
Lung (n,%)	21 (48.8%)
Liver (n,%)	20 (46.5%)
Prior chemotherapy	
1 Line (n,%)	31 (72.1%)
≥2 Lines (n,%)	12 (27.9%)
Prior PD-1/PD-L1 therapy (n,%)	8 (18.6%)

N=43

ORR=60.5% ; DCR = 90.7%



=> Promising results

X Sheng et al ASCO 2019

OUTLINE

- *Recommandations*
  - *1st line and second line*
- 2019 reported data
  - 1st line setting : IMvigor 130
  - 2nd line setting and beyond
- **Future**

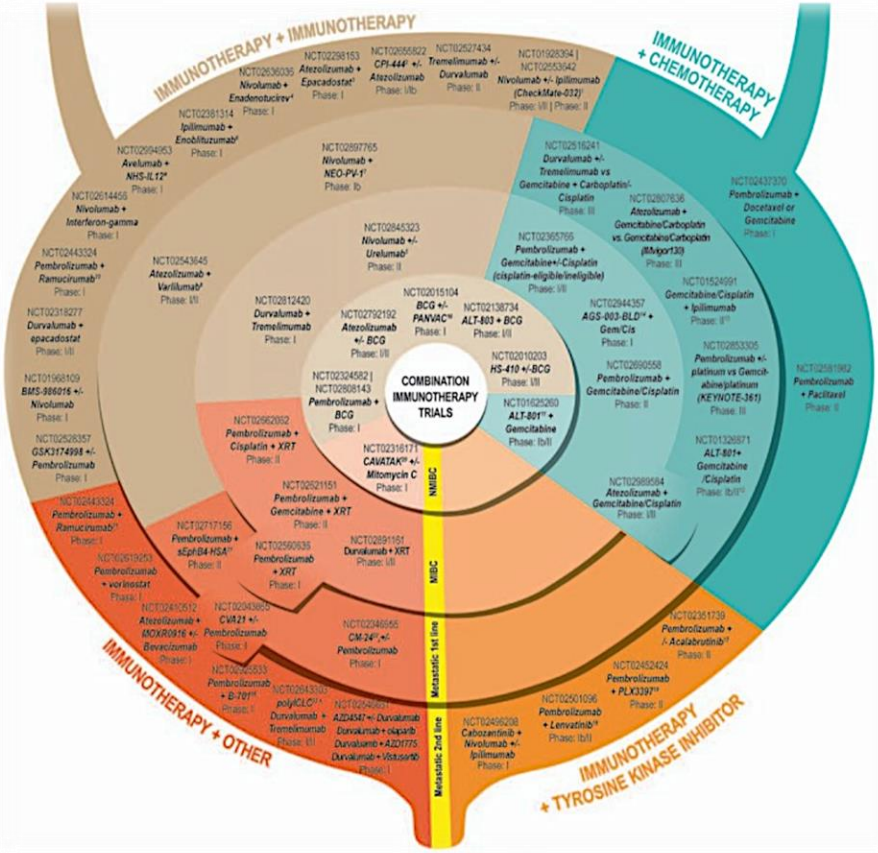
WHAT IS THE NEXT STEP ?

Identifying the best setting to use each drug

Identifying predictive biomarkers

How to combine the different agents

IDENTIFYING THE BEST IO COMBINATION : THE BEST PARTNER ?



Immunotherapy ?

Chemotherapy ?

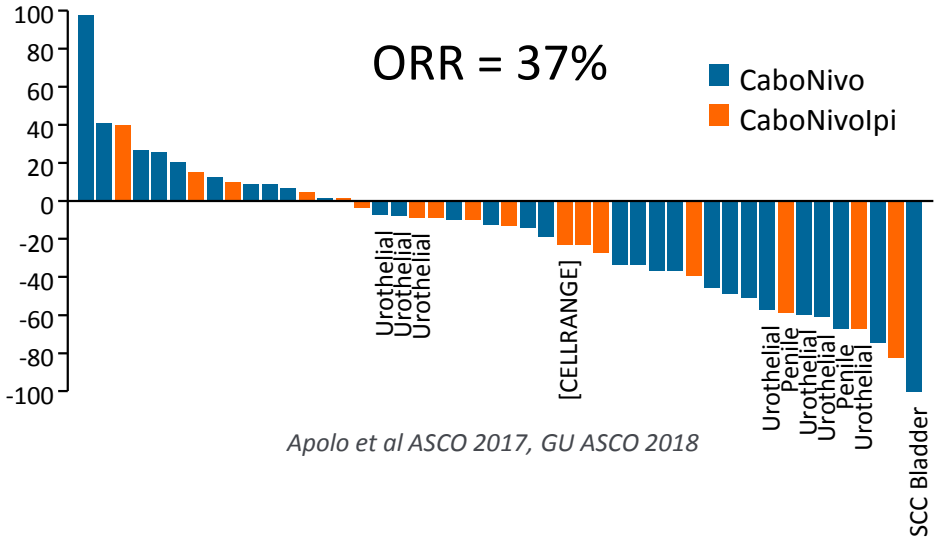
TKI : Antiangiogenics ?

Targeted therapy : ADC ?

J Rosenberg et al ESMO 2018

IO AND ANTI-ANGIOGENICS

Cabozantinib + nivolumab +/- Ipilimumab for mUC and other GU tumors



Apolo et al ASCO 2017, GU ASCO 2018

Lenvatinib + Pembrolizumab for mUC

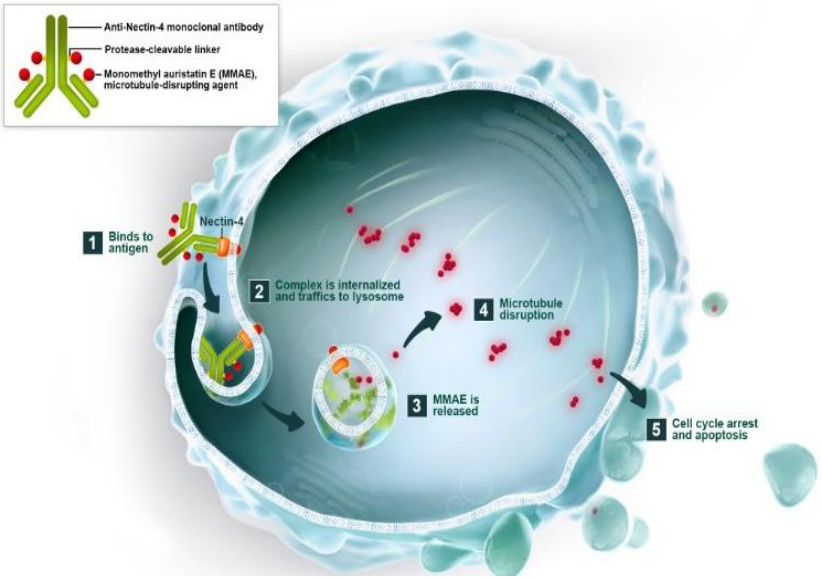
Vogelzang et al ASCO SITC 2019

- Recent data of trials assessing antiangiogenics

Rosenberg J E, *et al*. CALGB 90601 (Alliance): Randomized, double-blind, placebo-controlled phase III trial comparing gemcitabine and cisplatin with bevacizumab or placebo in patients with metastatic urothelial carcinoma.

EV103 PHASE 1 ENFORTUMAB VEDOTIN – PEMBROLIZUMAB IN ADVANCED UC

Enfortumab vedotin



Design

Patient Population	Dose Escalation[1]	Dose Expansion
Locally Advanced or Metastatic Urothelial Cancer (la/mUC)	EV 1.25 mg/kg + pembro cis-ineligible 1L (n=5)	Cohort A EV + pembro cis-ineligible 1L (n=40)

Primary endpoints: AEs, lab abnormalities

Key secondary endpoints: DLTs, ORR, DCR, DOR, OS

RESULTS : CLINCAL BENEFIT RATE = 93%

Pts characteristics

40% PDL1 –

91% visceral M+

33% liver M+

ORR per RECIST v1.1 by investigator 18 Jun 2019 data cut-off	Patients (N=45) n (%)
Confirmed Objective Response Rate (ORR)	**32 (71)**
95% confidence interval	(55.7, 83.6)
Best Overall Response per RECIST v. 1.1	
Complete response	6 (13)
Partial response	26 (58)
Stable disease	10 (22)
Progressive disease	1 (2)
Not evaluable[1]	2 (4)

[1] Two patients did not have post-baseline response assessments before end-of-treatment: 1 withdrew consent and 1 died before any post-baseline response assessment

TAKE HOME MESSAGE :

- **First line setting**
  - Chemotherapy remains a SOC in CDDP eligible pts
  - IO is an (the best?) option for CDDP ineligible PDL1+ pts
  - IO/CT combination is not ready for prime time (yet?)

- **2nd line and beyond**
  - IO monotherapy (Pembrolizumab) is 2nd line SOC
  - New drugs are underway : FGFRi, ADC….

- **Future**
  - Combinations : IO – ADC ? IO-FGFRi ?
  - Precision medecine approach : Molecular screening

Thanks for your attention

Urology
Hervé Lang
Pierre Munier
Christian Saussine
Thibault Tricard

Pathology Department
Véronique Lindner

Radiology
Catherine Roy
Pierre Leyendecker

Radiotherapy
Ines Menoux
Yvan Pin
Gianni Pietta

Medical Oncology
Philippe Barthélémy
Mickael Burgy
Gabriel Malouf
Laure Pierard
Caroline Schuster
Philippe Trensz

Interventional Radiology
Afshin Gangi
Pierre Auloge
Jean Caudrelier
RL Cazzato
Julien Garnon
Guillaume Koch