Data Changing practice in solid tumors

Urothelial Carcinoma

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DISCLOSURES

- Advisory board
  - ROCHE, PFIZER, MSD, BMS, IPSEN, SANOFI, JANSSEN CILAG, NOVARTIS
- Honoraria
  - EISAI, ASTELLAS

OUTLINE

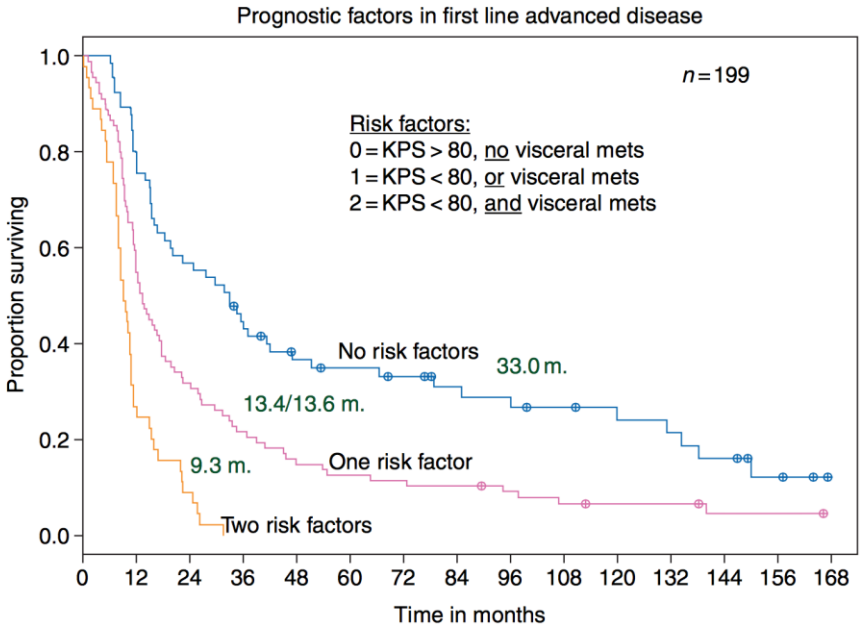
Past

- *What have we learnt …*

Present and future

- *Chemotherapy*
  - *Adjuvant UTUC*
- *Immunotherapy*
  - *Where are we know, where are we going …*
- *Precision medecine*
  - *New drugs*

WHAT WE KNOW ABOUT UC:



Bajorin, D.F. et al. J Clin Oncol 1999; 17: 3173–3181

UC is an **agressive disease** - **poor prognosis**

Prognostic factors :

- Performans Status
- Visceral metastases

Heterogeneous population

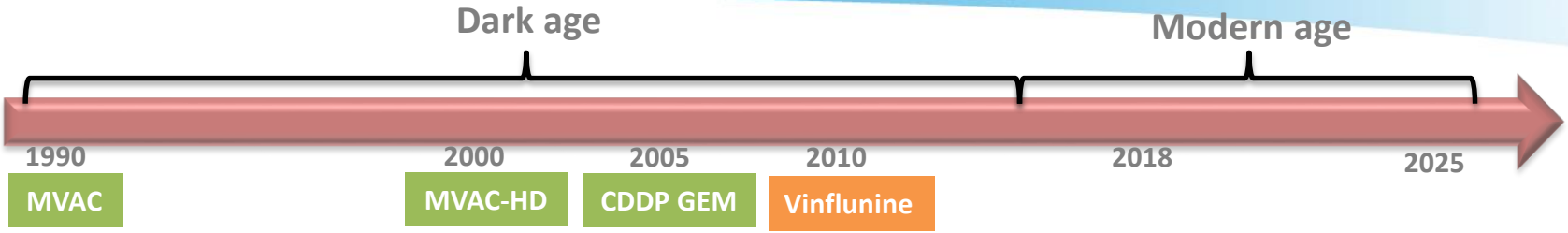
CDDP eligible vs ineligible (unfit)

UC is chemosensitive :

+/- 7% long-term remission can be achieved

What about the therapeutic landscape ?

WHAT HAPPENED OVER THE LAST DECADES



Localized bladder UC : **neoadjuvant CDDP based chemotherapy (fit pts)**

upper tract UC : **surveillance**

First line treatment algorithm in 2016

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

Second line treatment

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

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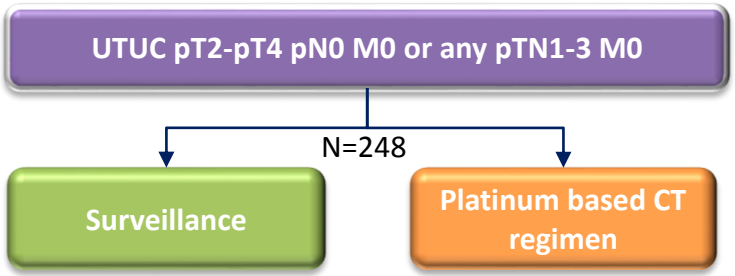
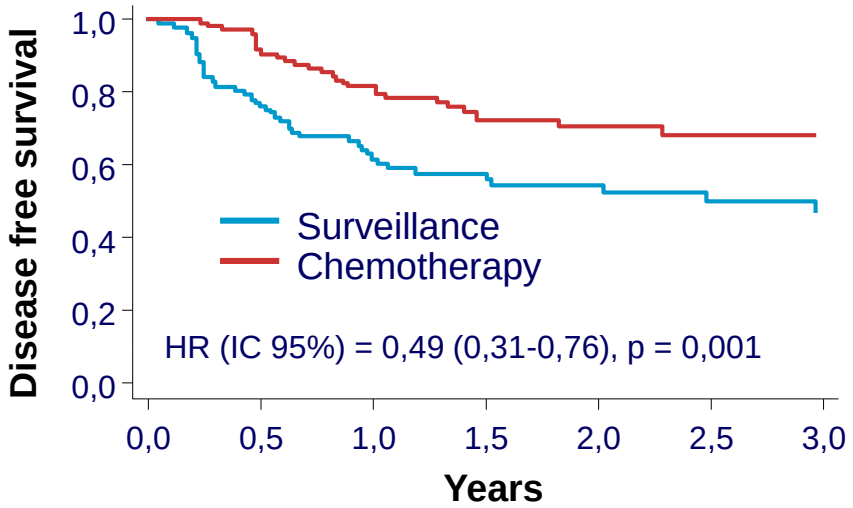
ADJUVANT CHEMOTHERAPY IN UPPER TRACT UC : POUT - PHASE IIIR TRIAL : A NEW SOC





- **Primary endpoint: Disease free survival**
- Treatment
  - Gemcitabine : 1000 mg/m² J1 and J8
    - + cisplatine : 70 mg/m² J1 if Clcreat ≥ 50 ml/mn
    - or carboplatine AUC 4.5/AUC5 J1 if Clcreat : 30-49 ml/mn

=> Platinum based CT regimen : new adjuvant SOC in UTUC

ASCO GU 2018 - D'après AJ Birtle et al Abst 407

EVOLVING LANDSCAPE : THE MODERN AGE

- **IMMUNOTHERAPY**
  - CHECKPOINT INHIBITORS : PD(L)-1
- **TARGETED THERAPIES**
  - FGFR inhibitors
  - Drug conjugates

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T Powles , ASCO GU 2018

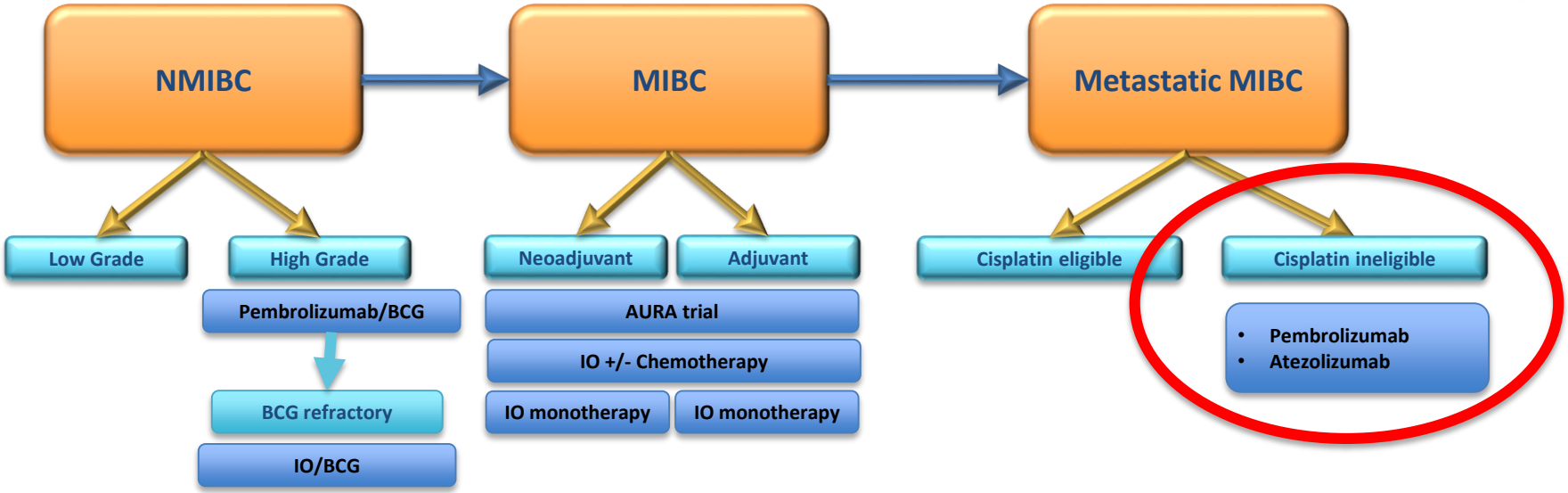
IMMUNOTHERAPY : THE ACTORS

Immunotherapy (IO)	Atezolizumab[1,2]	Nivolumab[3]	Pembrolizumab	Durvalumab[5]	Avelumab[6]
Target for inhibition	PD-L1	PD-1	PD-1	PD-L1	PD-L1
Studies performed	Phase 1-3	Phase 1 and 2	Phase 1 and 3	Phase 1b	Phase 1b
Cell types scored for PD-L1 status	IC	TC	TC + IC	IC + TC	IC + TC
FDA + EMA Licence	Platinum refractory and platinum ineligible.	Platinum refractory	Platinum refractory and platinum ineligible	Platinum refractory	Platinum refractory
Estimated PD-L1 prevalence in urothelial cancer trials					

IC, immune cells; IHC, immunohistochemistry; IO, immuno-oncology; PD-L1, programmed death ligand-1; TC, tumour cells.

1. Rosenberg JE et al. *Lancet* 2016;387:1909–1920; 2. Hoffman-Censits JH et al. *J Clin Oncol* 2016;34(Suppl. 2S):Abstract 355; 3. Sharma P et al. *J Clin Oncol* 2016;34(Suppl.):Abstract 4501; 4. Bellmunt J et al. *N Engl J Med* 2017;376:1015–1026; 5. Powles C et al. *J Clin Oncol* 2016;34:3119–3125; 6. Apolo AB et al. *J Clin Oncol* 2016;34(Suppl.):Abstract 4514.

IMMUNOTHERAPY DEVELOPMENT IN UC



ASCO® GU 2015 – Adapted from Andrea B. Apolo

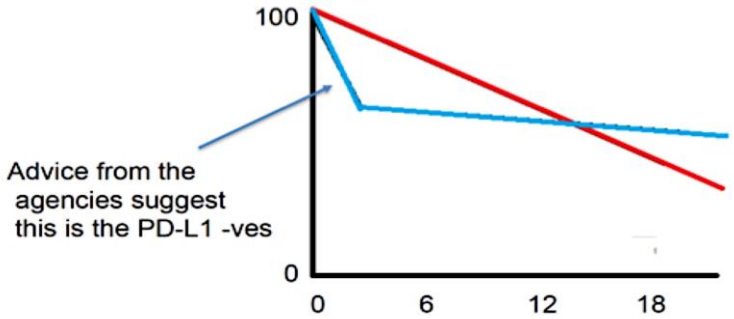
1ST LINE PEMBROLIZUMAB AND ATEZOLIZUMAB

	IMvigor110	Keynote-052		
	atezolizumab	pembrolizumab	Chemotherapy median ranges	Chemotherapy (mean of medians)
Number	119	370	100s	NA
PS 2	20%	42%	0-45%	NA
Visceral mets	65%	85%	43-53	NA
RR	23%	24%	34-53	~45%
PFS	2.1 months	2.3 months	5.9-6.1	~5months
OS	15.9 months (10.4- NE)	11.5 months 10.0-13.3)	12.8-14.0	~11 months

Bellmunt et al. J Clin Oncol. 2012;30:1107–13
De Santis et al. Ann Oncol. 2016;27:449–54
De Santis et al. J Clin Oncol. 2012;30:191–9
Jones et al ESMO 2016
Balar Lancet 2017
Balar Lancet 2016

EMA RESTRICTION : REDUCED SURVIVAL IN PDL1- PATIENTS

KEYNOTE 361 AND IMVIGOR 130 PRELIMINARY DATA



IO may not work as well as CT in this subset

Recommended new Algorithm

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

*CPS score > 10%
PD-L1 > 5%

	Atezolizumab IMvigor110		Pembrolizumab Keynote-052	
ORR	24%		24%	
	IC0	21%	PD-L1<1%	18%
	IC1	23%	PD-L1 (1-10%)	15%
	IC2/3	28%	PD-L1 >10%	37%

Adapted T Powles ESMO 2018

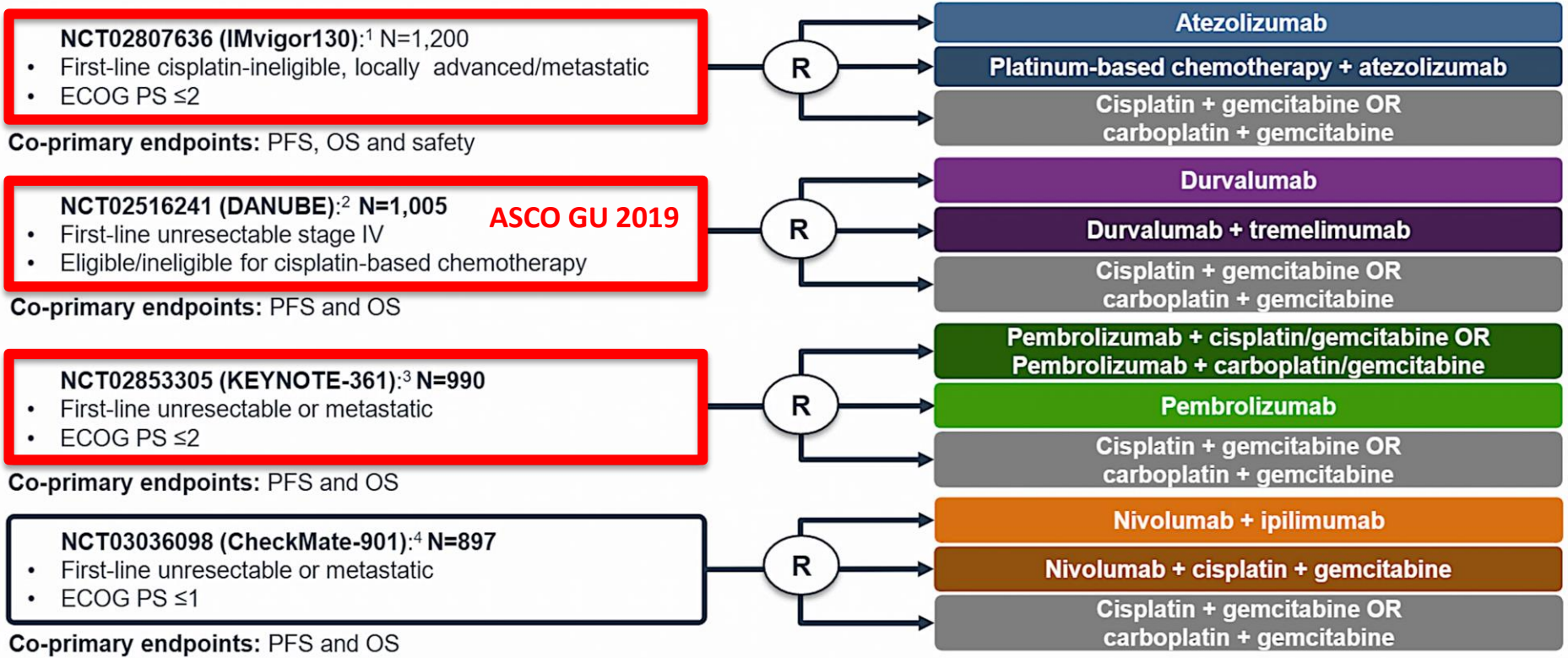
CONCLUSION : SINGLE AGENT IO IN 1ST LINE

- **Pembrolizumab et atezolizumab**
  - Associated with well tolerated long-term responses which is attractive for patients
  - Remaining questions : identify subset of responder ? biomarkers? => ***currently only recommended for PD-L1 +ve pts***

- **Chemotherapy is active** in this setting

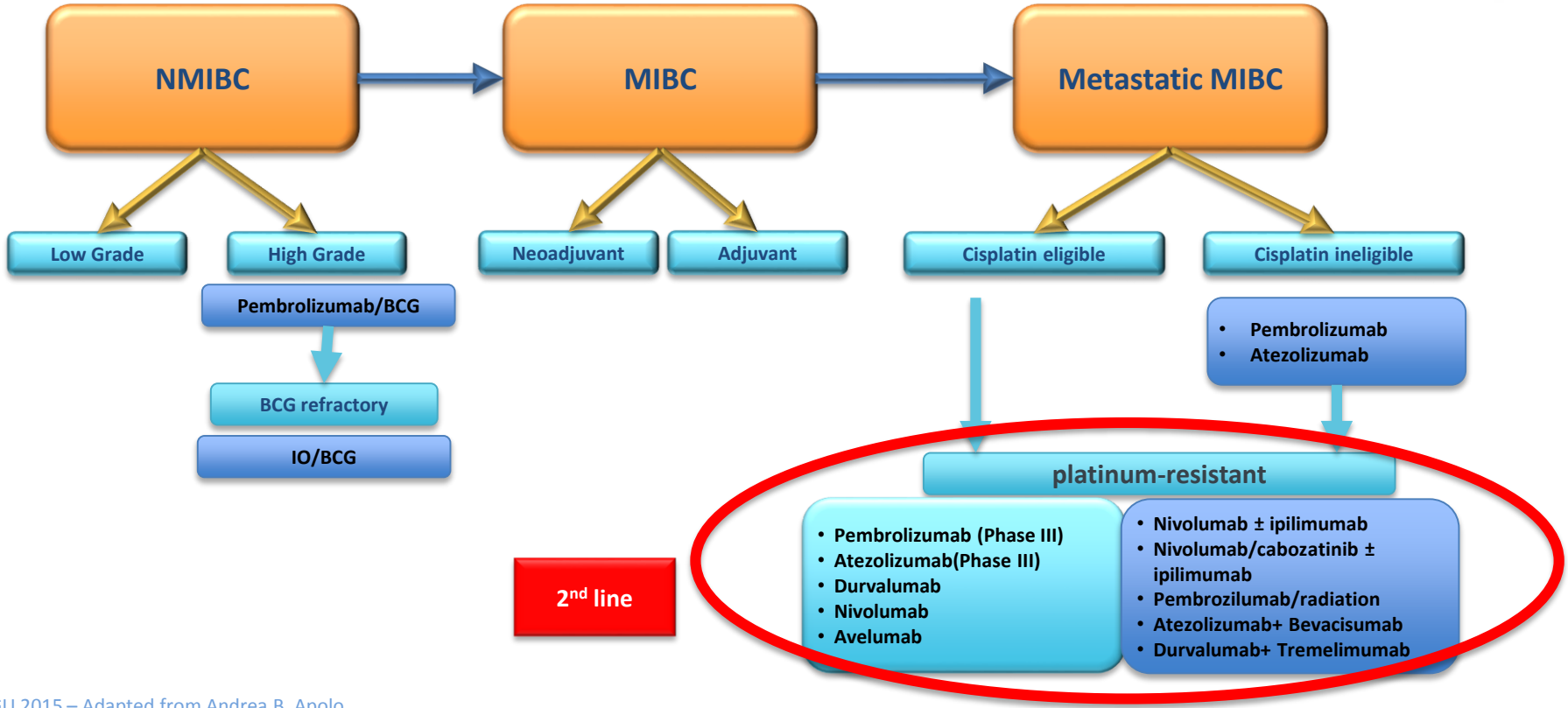
- **NEXT STEP => Combinations**

PHASE III TRIALS IN PROGRESS IN FIRST LINE



- 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).

IMMUNOTHERAPY DEVELOPMENT IN UC



ASCO® GU 2015 – Adapted from Andrea B. Apolo

PHASE III TRIALS: PLATINUM REFRACTORY/RESISTANT

KEYNOTE 045

Eligibility criteria

- UC bladder or upper tract
- Progression after >1-2 lines of chemotherapy including platinum regimen or recurrence < 12 months after perioperative chemotherapy
- ECOG 0-2

R

- Pembrolizumab 200 mg IV /3w
- Paclitaxel 175 mg/m² /3w or Docetaxel 75 mg/m² /3w or Vinflunine 320 mg/m² /3w

✓

IMvigor 211

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✗

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

UPDATED RESULTS IN 2ND LINE

	Trial	OS	ORR	1 year- OS
Nivolumab*	*CheckMate 275*	*8.74 mois*	***19,6%***	*NA*
Pembrolizumab (2 y FU)	**KEYNOTE-045**	**10.3mois**	**21%**	**44.4 %**
Atézolizumab	**IMvigor 211**	**11.1 mois**	**23%**	**46 %**
Durvalumab	*Etude 1108*	-	***31%***	-
Ipilimumab-nivolumab	*CheckMate 032*	-	***38,5%***	-
Chemotherapy		**7mois**	**12%**	**26%**

* *Improved OS in PD-L1+ (≥1%) pts*

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

ASCO GU 2017 - Milowsky M

CONCLUSION : IO IN CDDP REFRACTORY PATIENTS

- **The main goal is to achieve long term remission**

  => This appear possible with all 5 PD/PD-L1 inhibitors

- **All agents should be considered as attractive alternatives to chemotherapy**

- **Pembrolizumab: The only agent with positive phase IIIR data supporting its use (negative for atezolizumab)**

- **No biomarker available yet**

FUTURE : WHAT IS THE NEXT STEP ?

Identifying the best setting to use the drugs

WHAT IS THE NEXT STEP ?

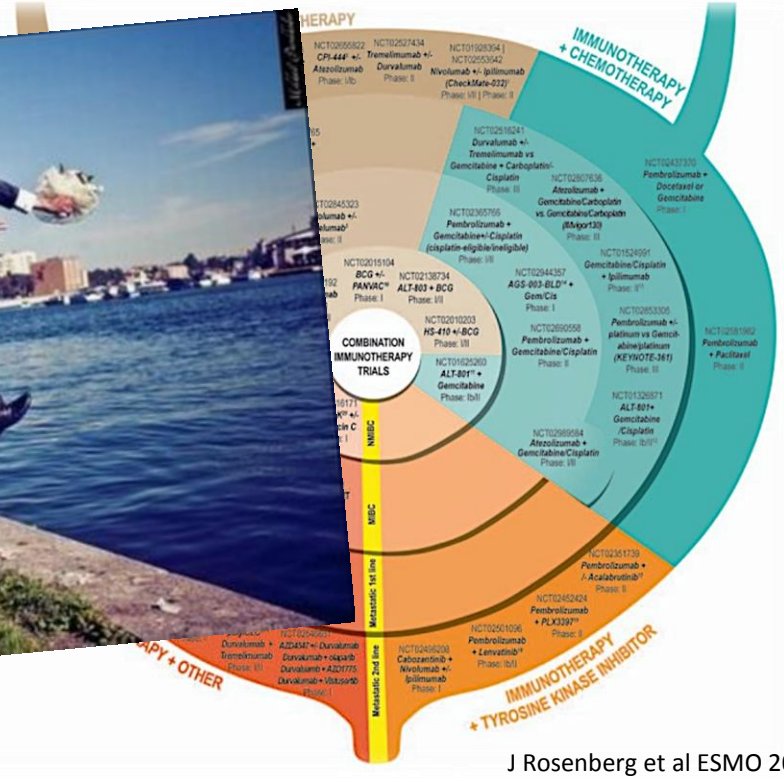
Identifying the best setting to use the drugs

Identifying the best combination of agents

IDENTIFYING THE BEST COMBINATION : THE BEST PARTNER ?

IO – IO Combinations

	Durvalumab Tremelimumab	Nivolumab 3 Ipilimumab 1	Nivolumab 1 Ipilimumab 3	Pembrolizumab
Population	Platinum refractory	R r		
Number	168	9		
Phase	II	I		
RR	21%	38		
RRPD-L1+	29%	58%		
PFS	1.9	4.3		
Toxicity (grade3)	28%	39%		
Median OS	9.5 months (8-19)	15.3 (10-27)	(5-11)	10.3months (8-12)



J Rosenberg et al ESMO 2018

WHAT IS THE NEXT STEP ?

Identifying the best setting to use the drugs

Identifying the best combination of agents

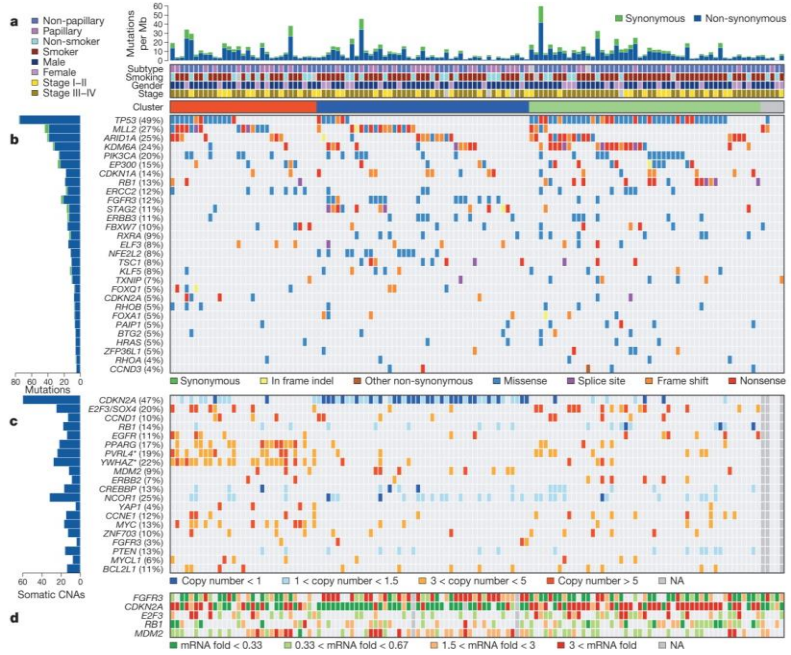
Identifying predictive biomarkers

EVOLVING LANSCAPE : THE MODERN AGE

- IMMUNOTHERAPY
  - CHECKPOINT INHIBITORS : PD(L)-1, CTLA4

- **TARGETED THERAPIES**
  - **FGFR inhibitors**
  - **Drug conjugates**

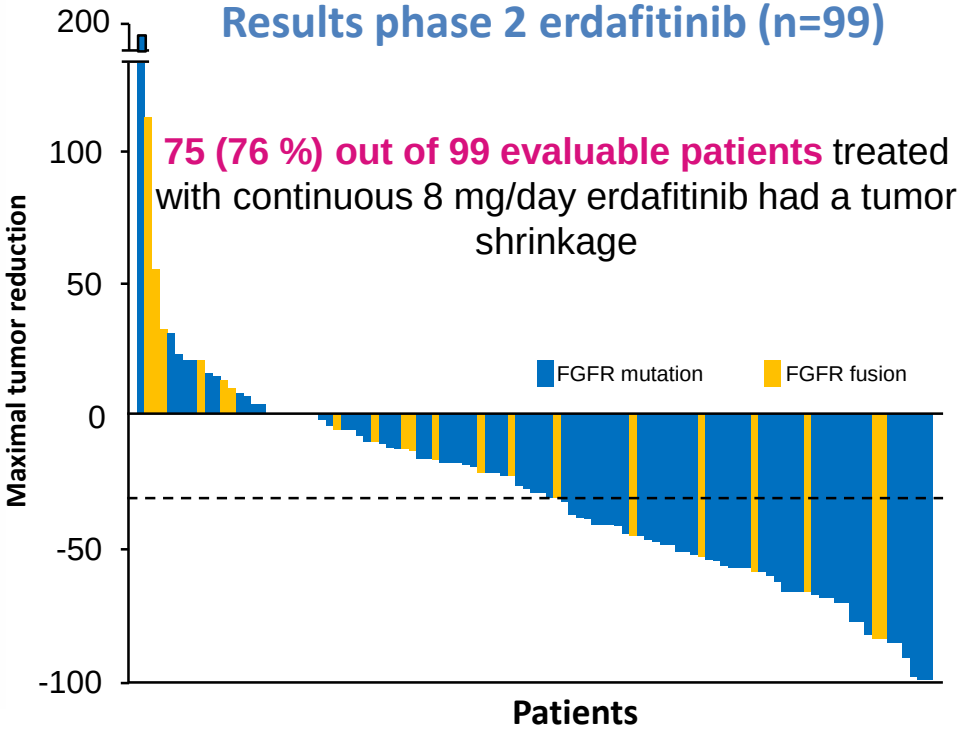
THE GENOMIC LANDSCAPE OF BLADDER CANCER



TP53 (49%)	RB1 (13%) Del 15%	NFE2L2 (8%)	FOXA1 (5%)
MLL2 (27%)	ERCC2 (12%)	ERBB2 (5%)	PAIP1 (5%)
ARID1A (25%)	FGFR3 (11%)	TSC1 (8%) TSC2 (2%)	HRAS (5%)
KDM6A (24%)	STAG2 (11%)	KLF (8%)	BTG2 (5%)
PI3KCA (15%)	ERBB3 (11%)	TXNIP (7%)	ZFP36L1 (5%)
EP300 (15%)	FBXW7 (10%)	FOXQ1 (5%)	RHOA (4%)
ATM (15%)	RXRA (9%)	P16/CDKN2A (5%) Del 50%	CCDN3 (4%)
P21/CDKN1A (14%) Del 6%	ELF3 (8%)	RHOB (5%)	CTNNB1 (2%)

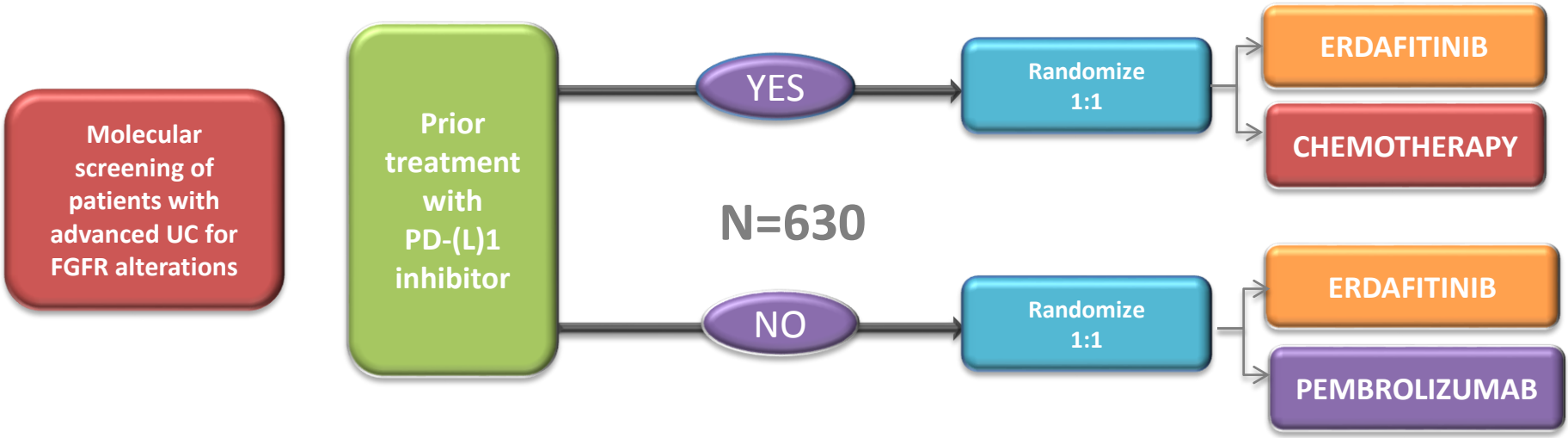
FGFR INHIBITORS IN UC

	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



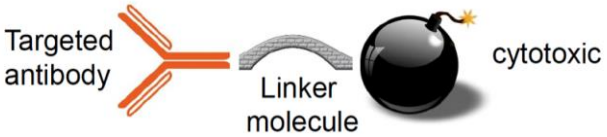
Y Loriot et al ASCO 2018 ; A Necchi et al ESMO 2018

ONGOING PHASE III THOR STUDY : ERDAFITINIB



Primary endpoint : Overall survival

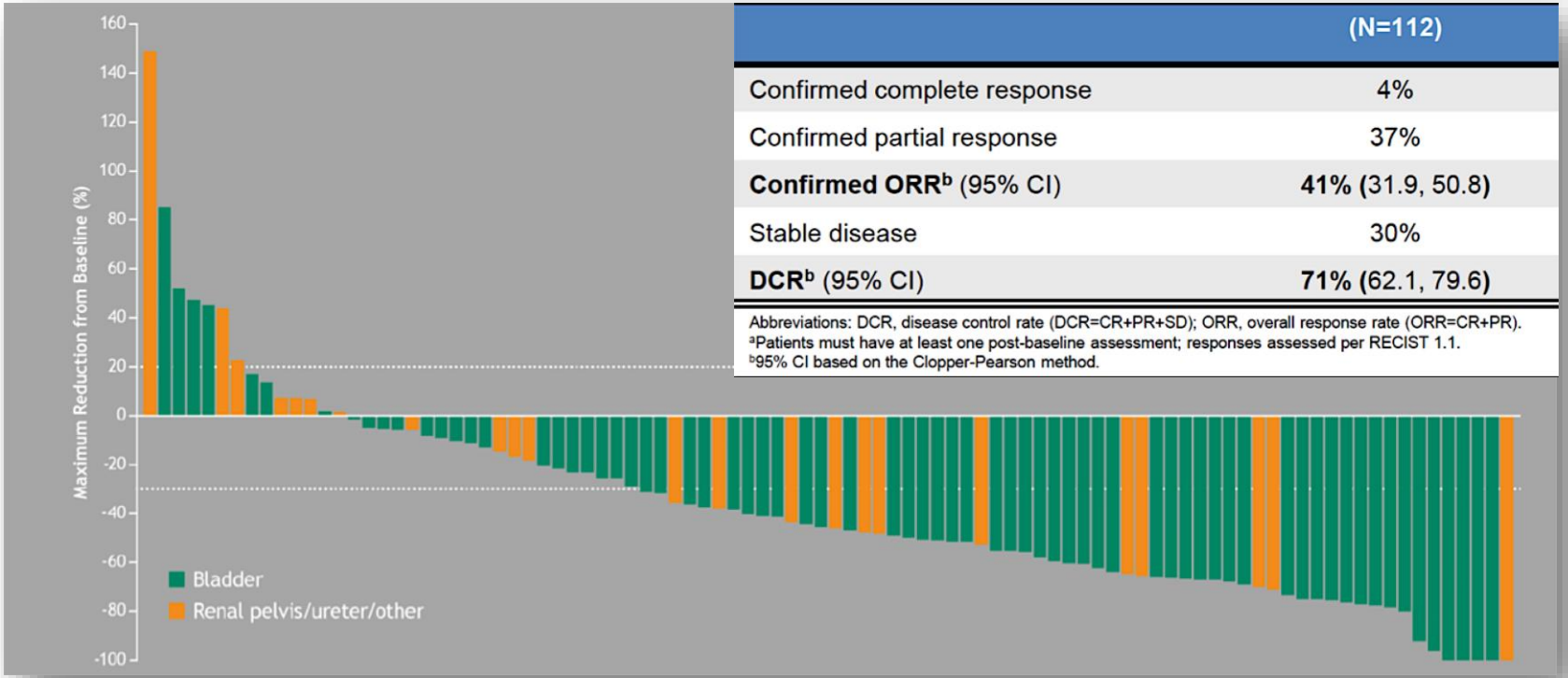
ANTIBODY DRUG CONJUGATES (ADC) IN UC



	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

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

ENFORTUMAB VEDOTIN IN HEAVILY PRETREATED PATIENTS WITH METASTATIC UC

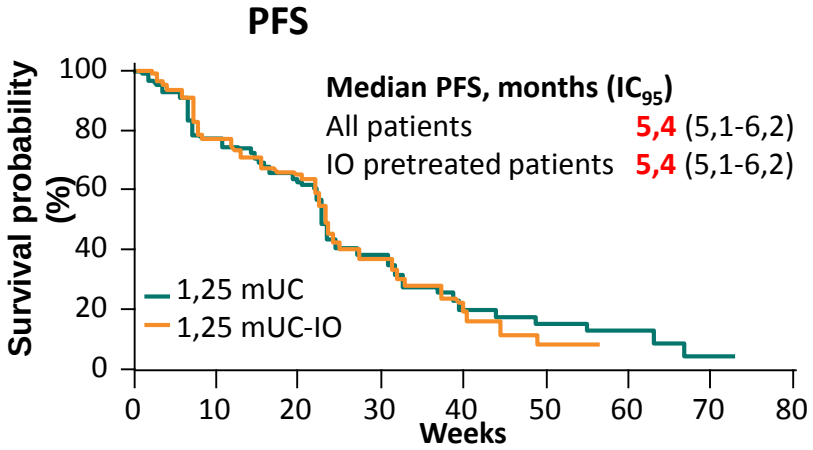


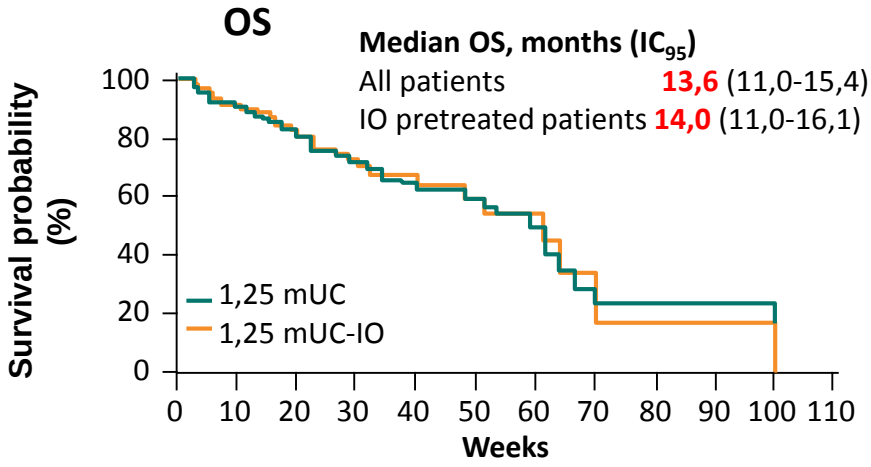
	(N=112)
Confirmed complete response	4%
Confirmed partial response	37%
Confirmed ORR[b] (95% CI)	**41%** (31.9, 50.8)
Stable disease	30%
DCR[b] (95% CI)	**71%** (62.1, 79.6)

Abbreviations: DCR, disease control rate (DCR=CR+PR+SD); ORR, overall response rate (ORR=CR+PR).
[a]Patients must have at least one post-baseline assessment; responses assessed per RECIST 1.1.
[b]95% CI based on the Clopper-Pearson method.

ASCO 2018 - Rosenberg JE et al., abstr. 4504

ENFORTUMAB VEDOTIN IN HEAVILY PRETREATED PATIENTS WITH METASTATIC UC





KEYNOTE-045	Pembrolizumab	Paclitaxel/docetaxel/ vinflunine	Enfortumab védotin
ORR (%)	21	11	40
PFS median (months)	2,1	3,3	5,4
OS median (months)	10,3	7,4	13,6
Response duration (months)	NA (1,6-15,6+)	4,3	5,75

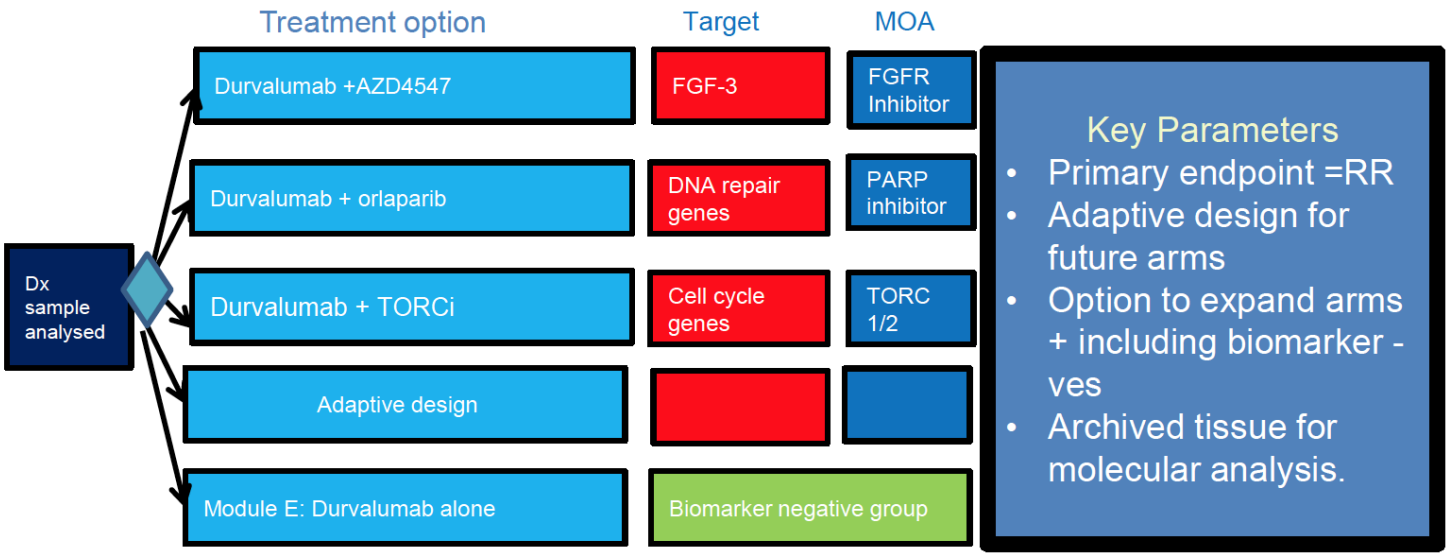
ASCO 2018 - Rosenberg JE et al., abstr. 4504

CONCLUSION : PRECISION MEDECINE

- **New targets :**
  - FGFR, HER2…
- **New drugs in development:**
  - FGFR inhibitors (phase III)
- **ADC : promising results**
  - Enfortumab vedotin (phase III)

NEAR FUTURE : GOLDEN AGE

Targeted therapy with immune therapy) A personalised approach.



Assignment to module dependent on presence of molecular biomarker (gene mutations/alterations)

TAKE HOME MESSAGE :

- **Chemotherapy**
  - Remains active in UC
  - Neoadjuvant setting
  - Adjuvant setting (upper tract- Pout trial)

- **Immunotherapy**
  - Monotherapy : 1st line PDL1+ve pts, SOC 2nd line
  - Combination strategies in the future

- **Precision medecine**
  - The beginning of the history : personalised approach

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ONCODISTINCT NETWORK

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Thank you for your attention

Philippe Barthélémy
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Institut Régional Cancer Alsace