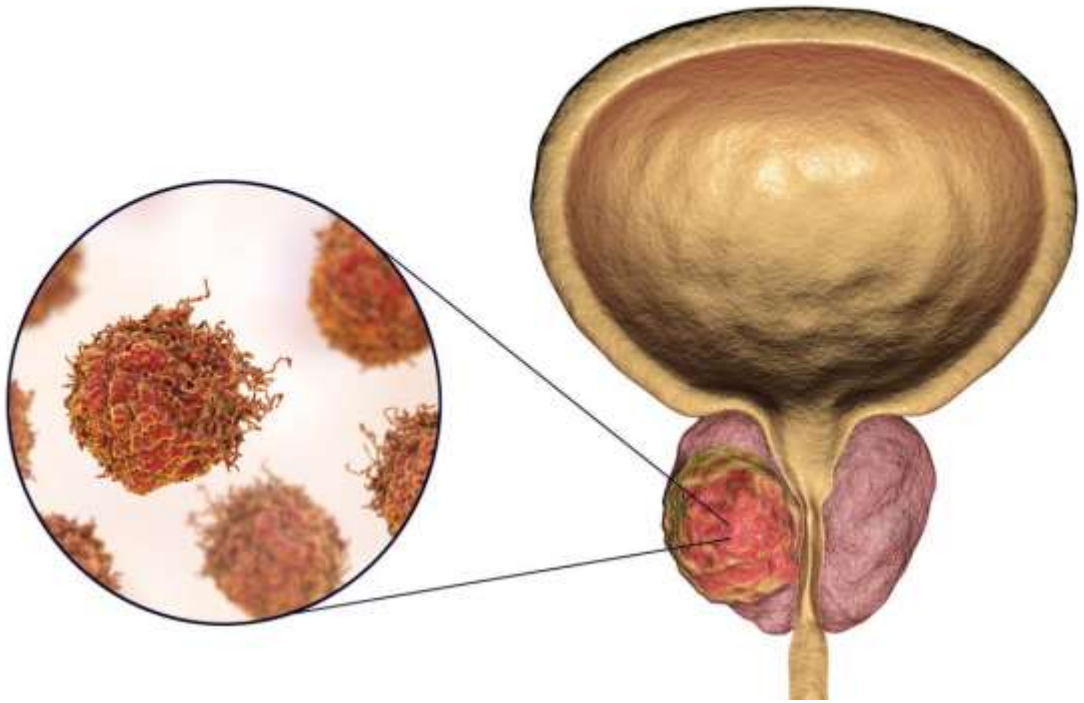
Tumori genito-urinari

Il punto di vista dell'esperto

Fabio Calabrò

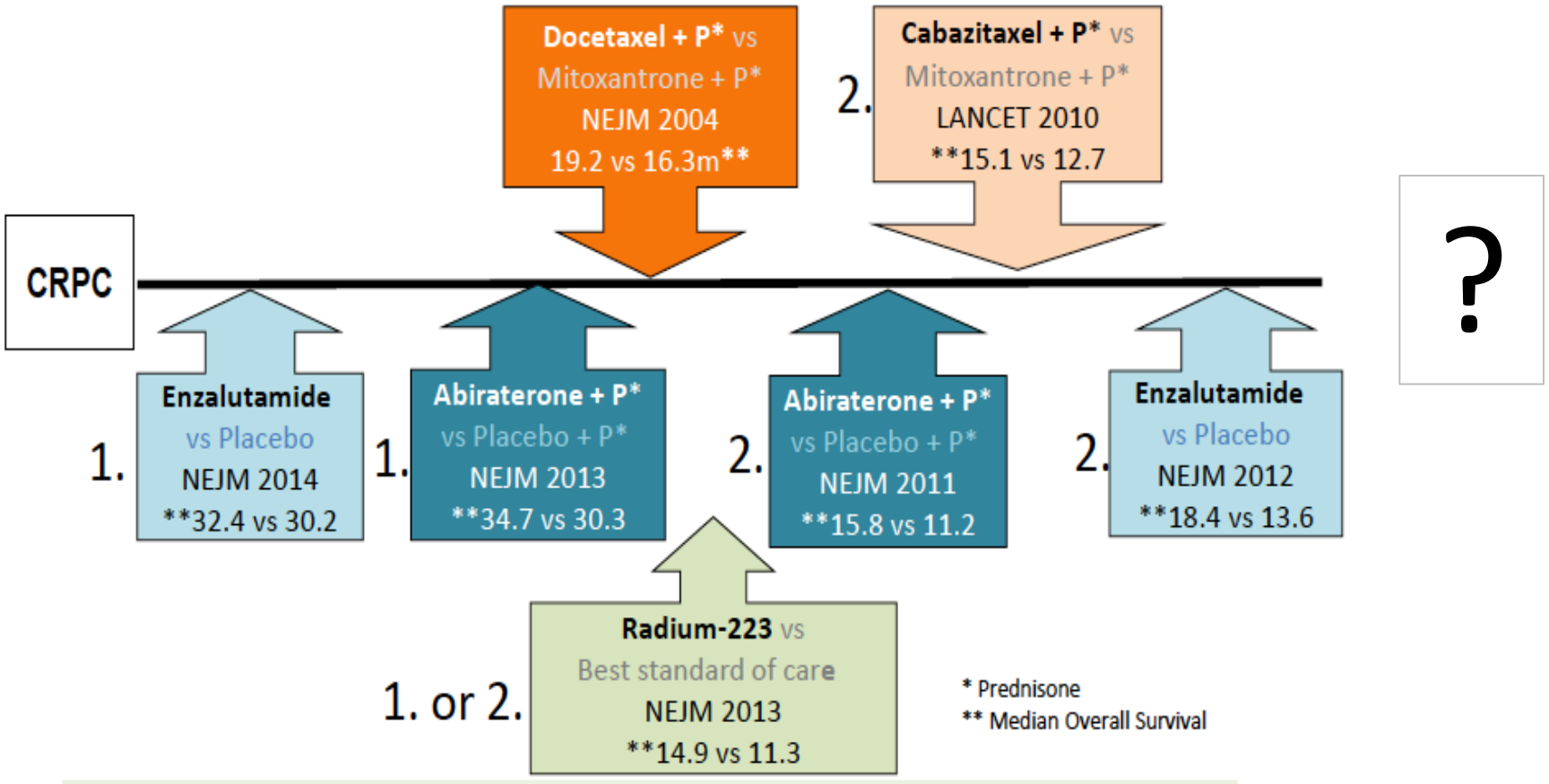
Azienda Ospedaliera San Camillo Forlanini
Roma

Roma, 2-3 Dicembre 2019

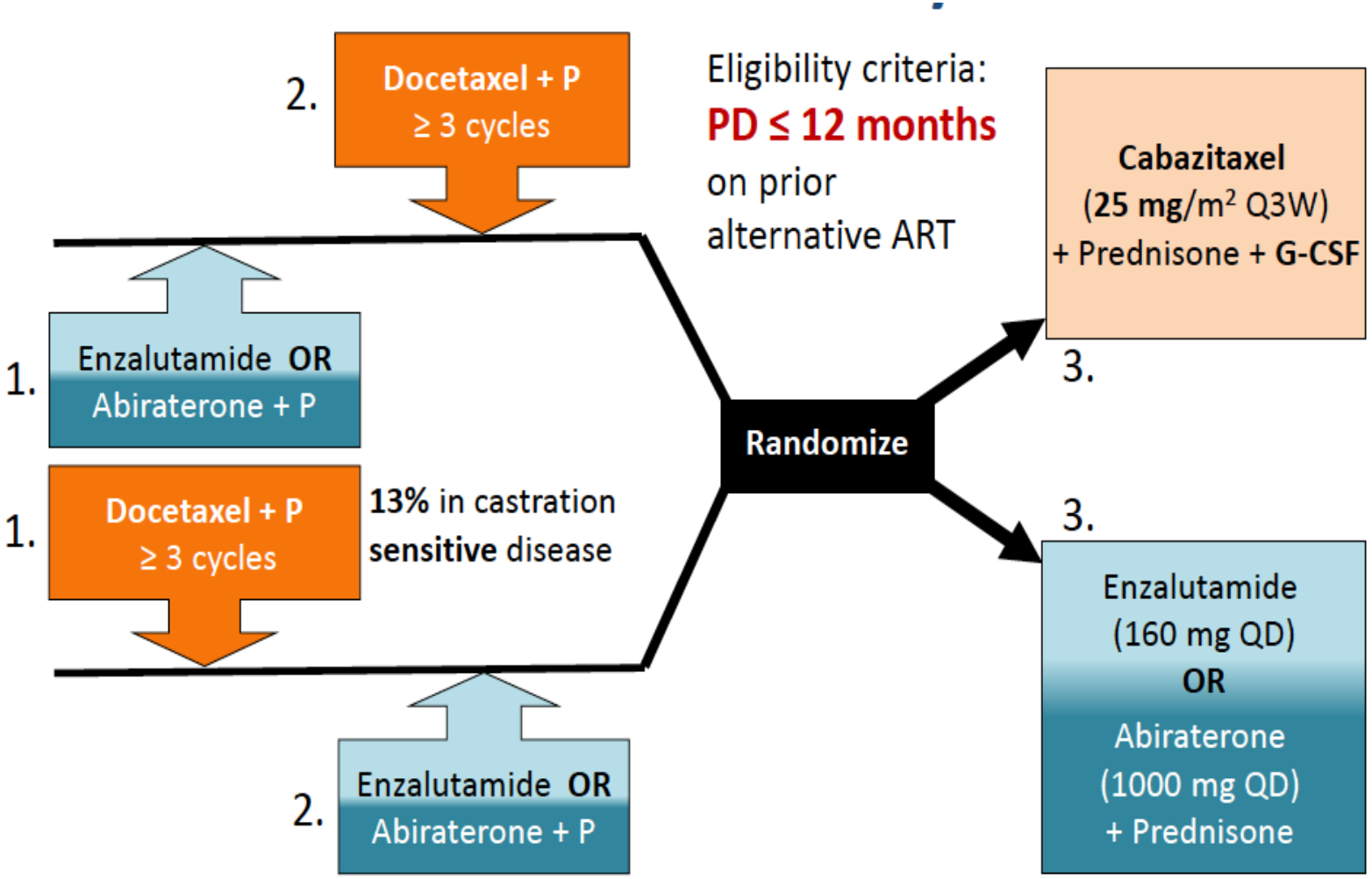


Prostate cancer

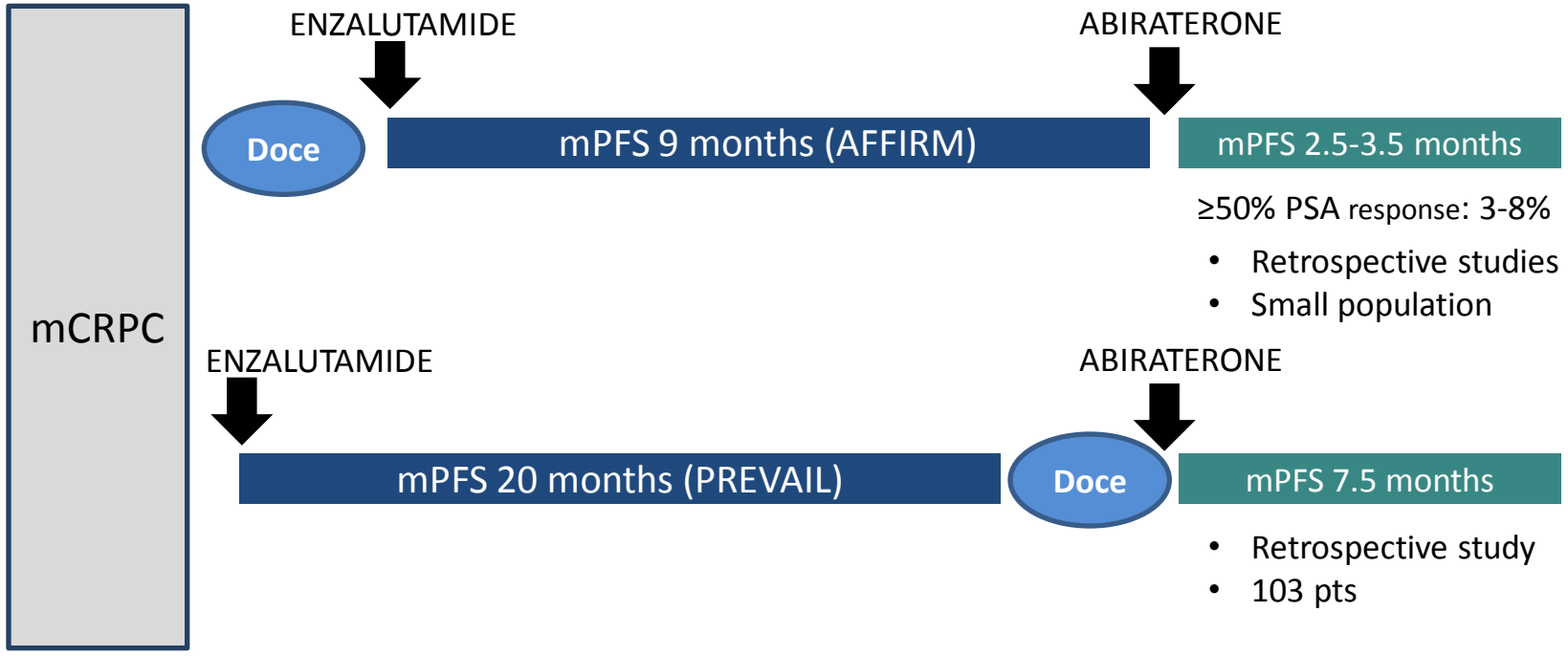
The landscape of mCRPC



The CARD Trial

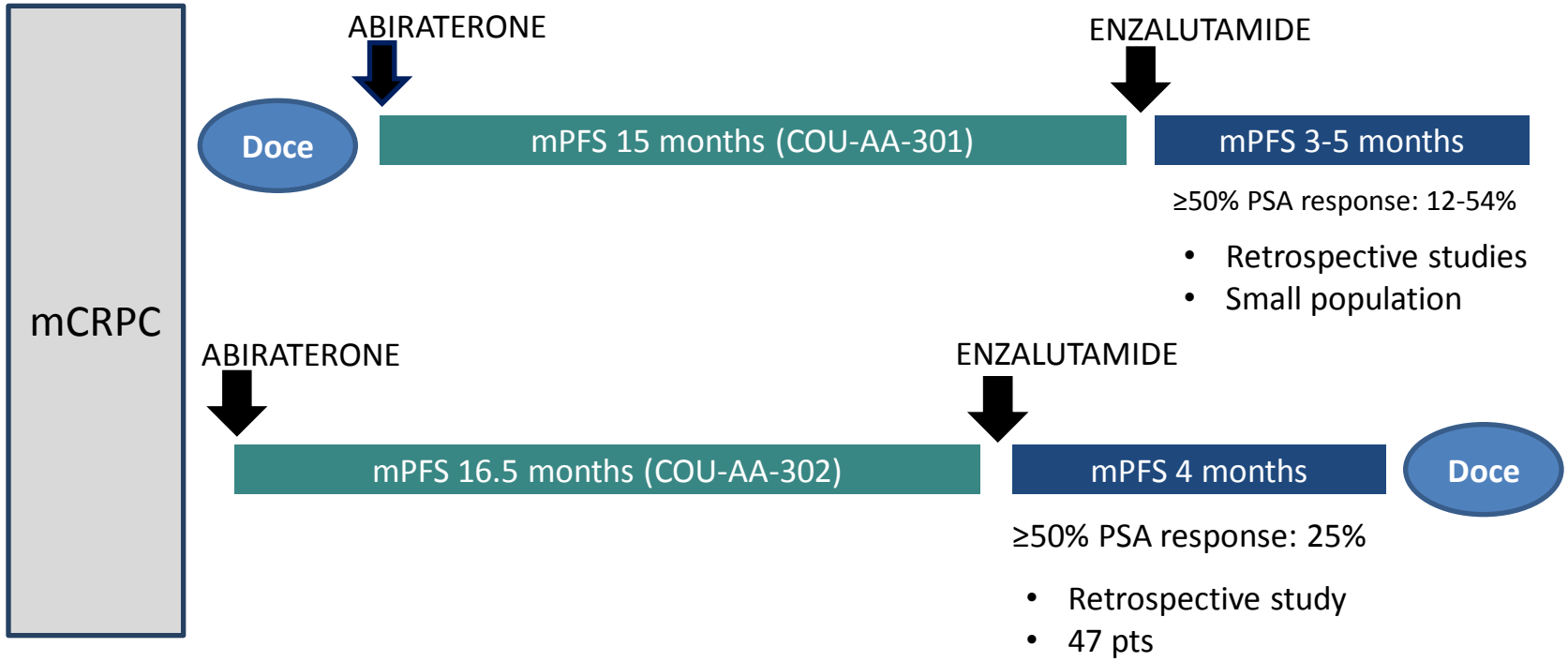


ENZA-to-ABI in mCRPC



Scher HI, et al. NEJM 2012; Noonan KL, *et al.* Ann Oncol 2013; Loriot Y, *et al.* Ann Oncol 2013 4. Beer TM et al. NEJM 2014

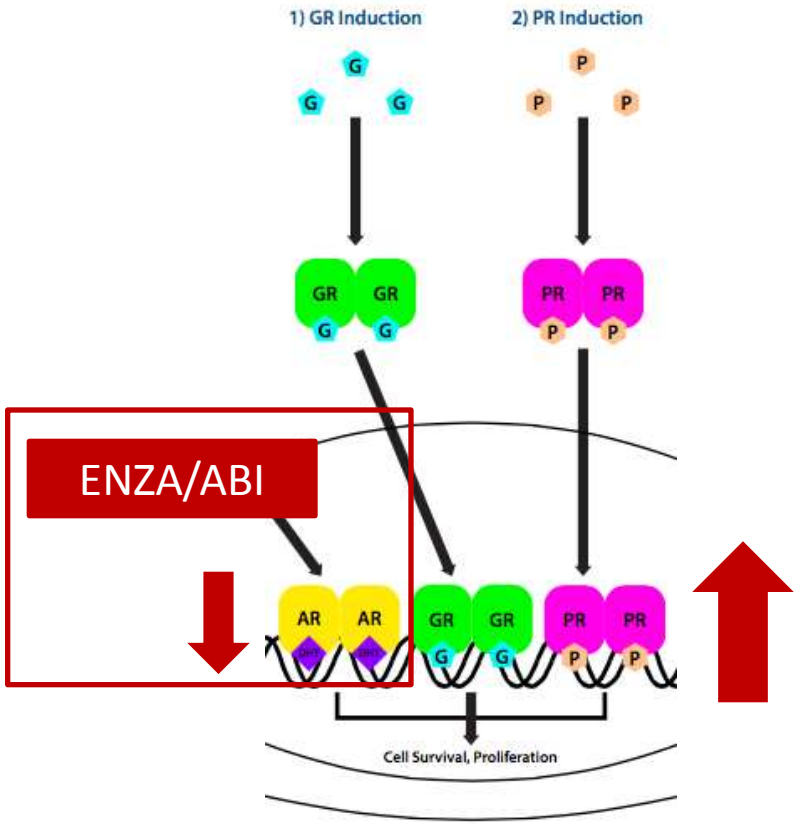
ABI-to-ENZA in mCRPC

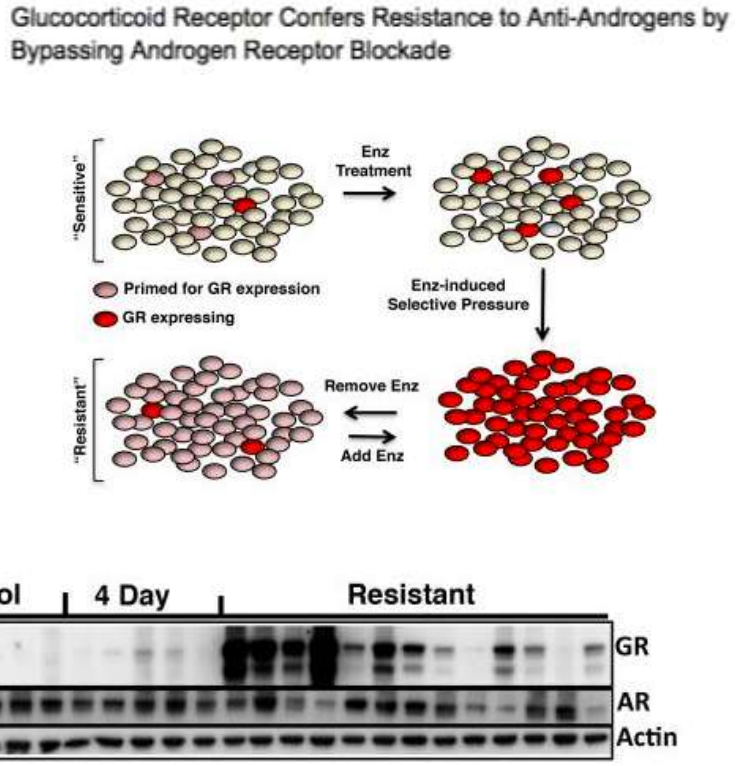


De Bono J, et al. NEJM 2011; Schmid SC, et al., Adv Ther 2014; Bianchini D, et al., Eur J Cancer 2014; Ryan J, et al. NEJM 2013; Azad AA, et al. 2014

Acquired cross-resistance mechanisms to Enzalutamide and Abiraterone

1. AR Bypass Pathway

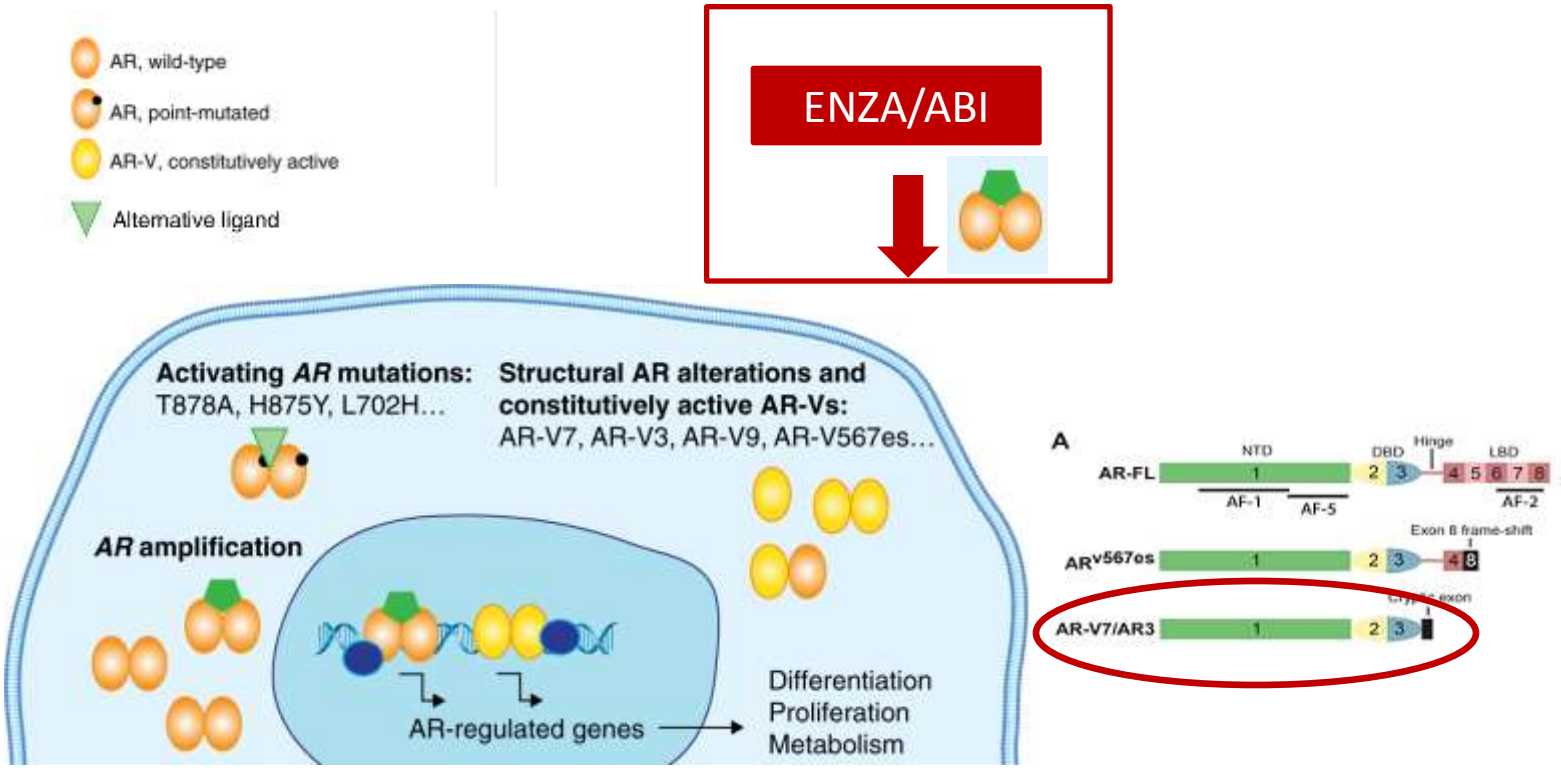




Arora VK et al. Cell 2013

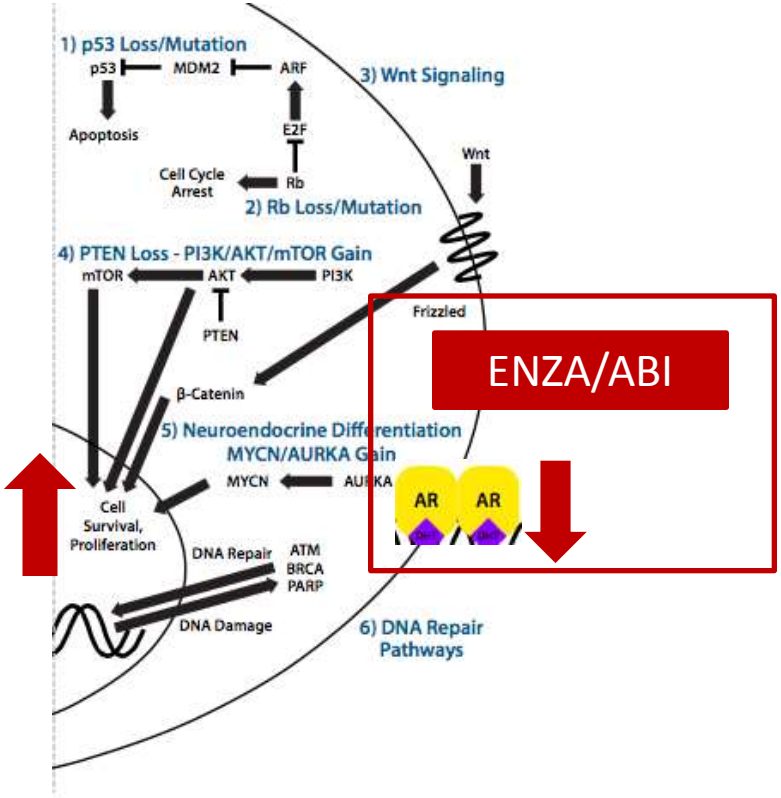
Acquired cross-resistance mechanisms to Enzalutamide and Abiraterone

2. Persistent AR signaling



Acquired cross-resistance mechanisms to Enzalutamide and Abiraterone

3. AR Independent Mechanisms



99% of the mCPRC harbored gene aberrations

65% of cases harbored targetable genomic alterations (when *AR* was not considered)

49% → PI3K pathway
19% → DNA repair pathway
5% → WNT pathway
7% → CDK inhibitors
3% → RAF kinases

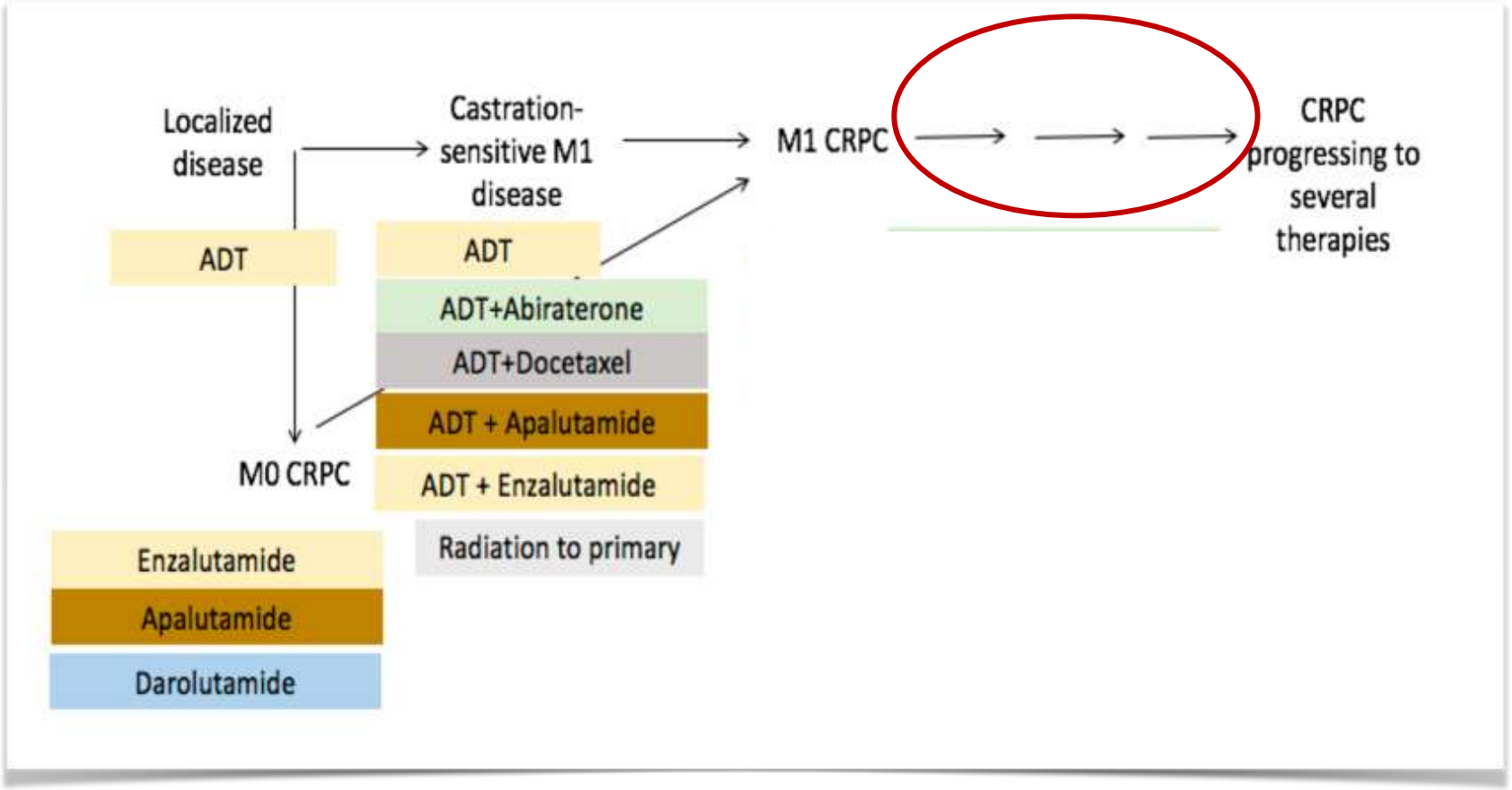
Robinson et al. Cell 2015

CARD Trial

Comments

- ✓ Well designed addressing an unmet clinical need
- ✓ Patient population representative
- ✓ Toxicit did not seem worse (choose 20 mg/mq?)
  - ✓ Always consider G-CSF
- ✓ Unanswered questions
  - ✓ Extrapolation in castration sensitive?
  - ✓ Patients with PS=2 or worse
  - ✓ Patients responding to prior ART > 12 months

Prostate cancer treatment. A rapidly evolving field



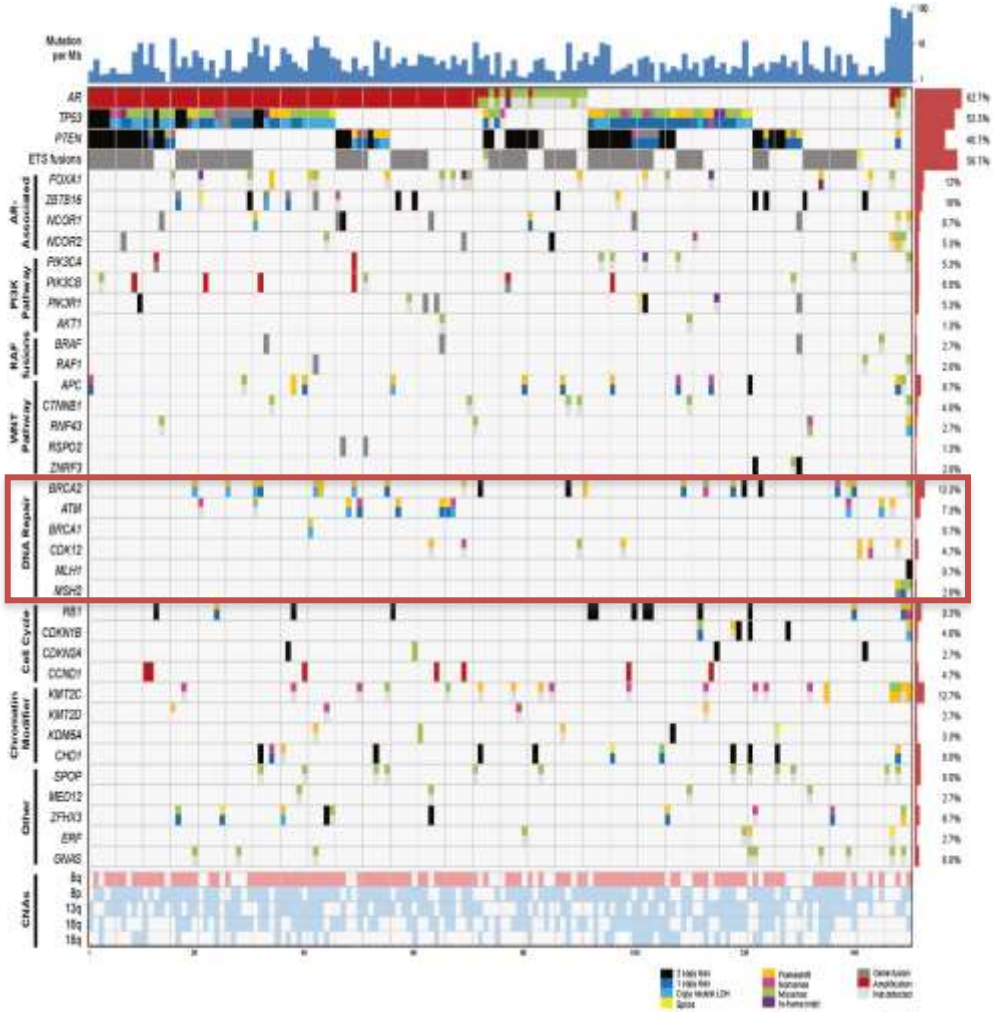
Ongoing trials in CSPC

Trial Name	Arms	# Pts.	1° Endpoint	NCT#	Ant. Read-Out
ENZAMET	ADT +/- DOCE + Enza	1100	OS	NCT02446405	2020
31216	Bicalutamide	1304	OS	NCT01809691	2022
PEACE-1	ADT +/- DOCE, +/- RT, +/- Abi	916	OS, rPFS	NCT01957436	2020

- ✓ The PEACE-1 is a positive trial
- ✓ It will certainly carry costs and toxicities
- ✓ It will also beg the question at what point is clinical benefit, overshadowed by costs, praticality and toxicity

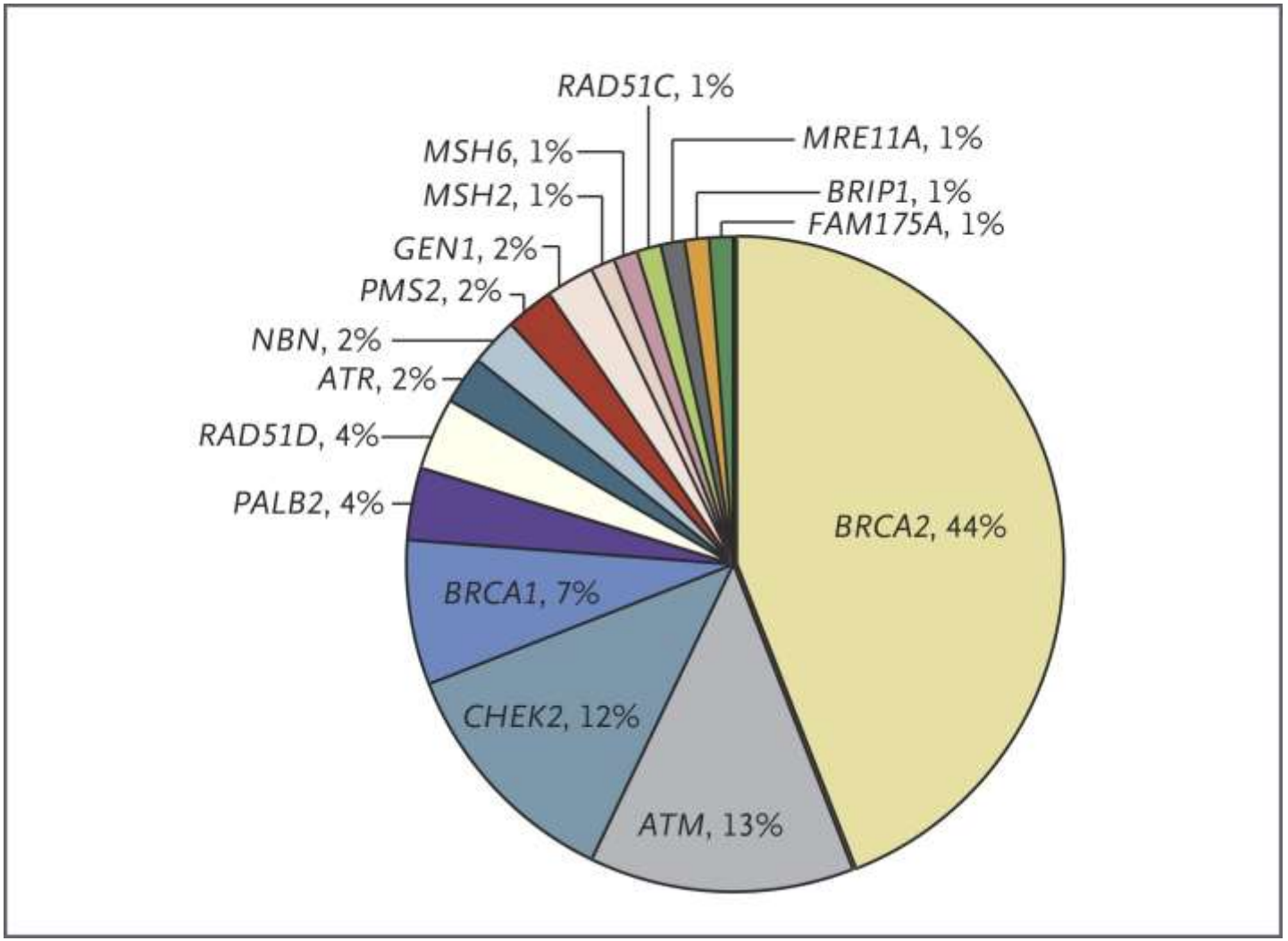
Integrative landscape analysis of somatic and germline aberrations in mCRPC

- 90% of mCRPC harbor clinically actionable molecular alterations
- 20% of mCRPC harbor DNA repair pathway aberrations
- 8% harbor germline mutations



Robinson D et al. *Cell*. 2015;161:1215-28

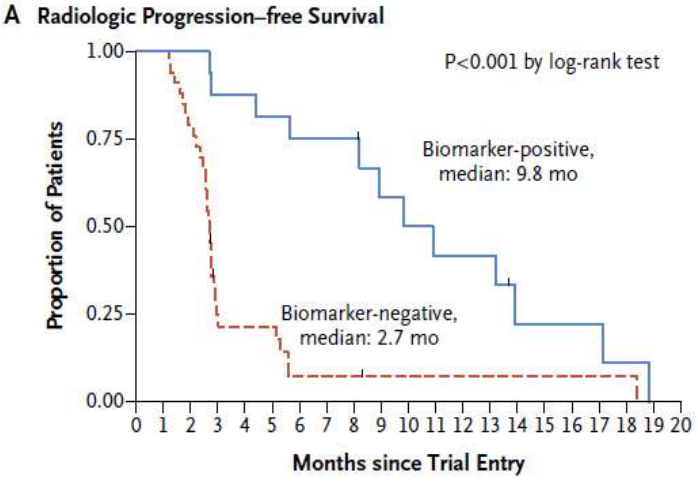
Distribution of Presumed Pathogenic Germline Mutations

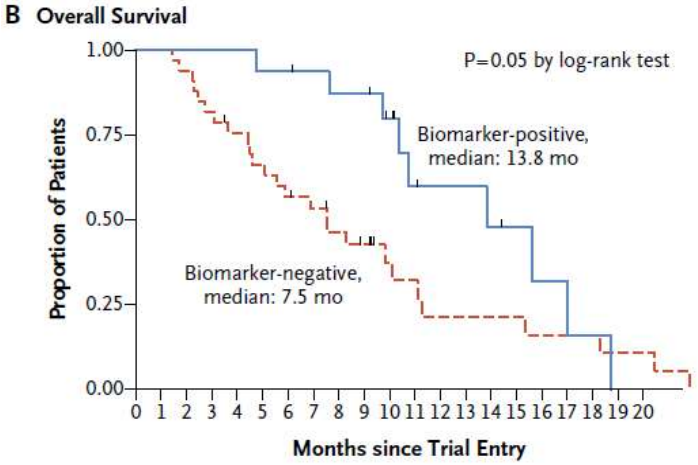


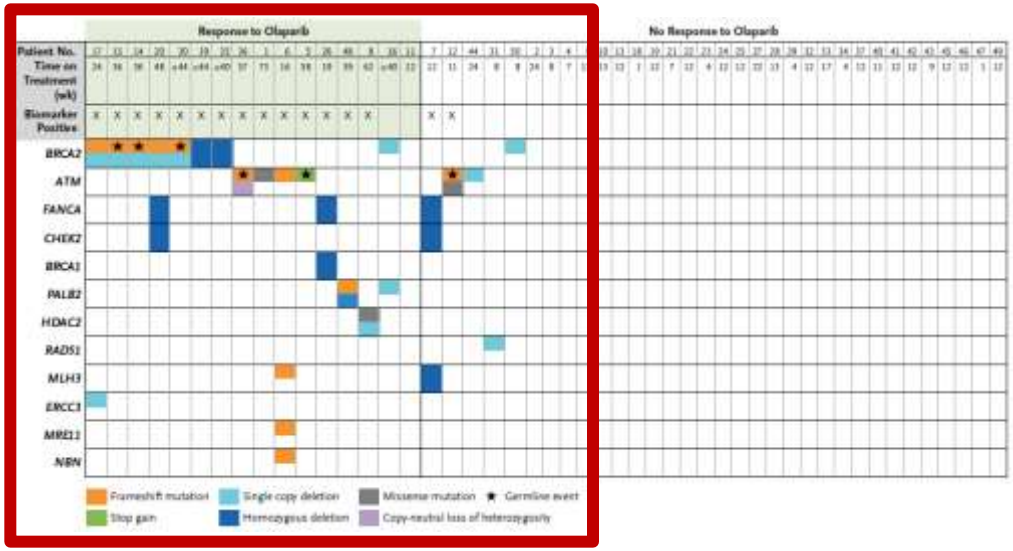
Shown are mutations involving 16 DNA-repair genes

Pritchard CC. N Engl J Med 2016

Defects in DNA repair genes associated with PARPi sensitivity





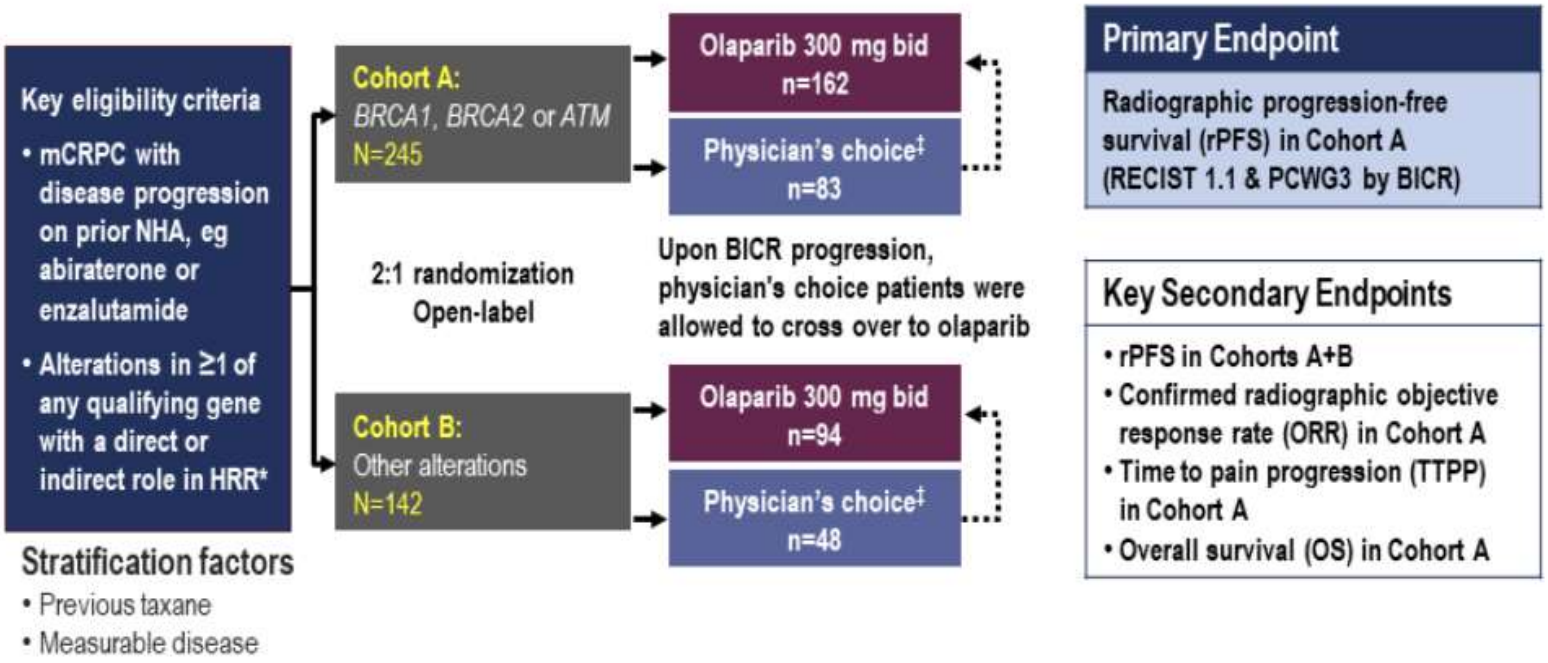


- ✓ 49 heavily pretreated mCRPC men
- ✓ PARP inhibitor (olaparib 400 mg BID)
- ✓ Genomic signature of PARP inhibitor sensitivity in **16**/49 (33%) pts
  - ✓ BRCA2, ATM, BRCA1, PALB2, CHEK2, FANCA, HDAC2
  - ✓ **Response to PARP in 14/16**

Mateo J et al. New Engl J Med. 2015;373:1697-708

PROFOUND trial

Study design

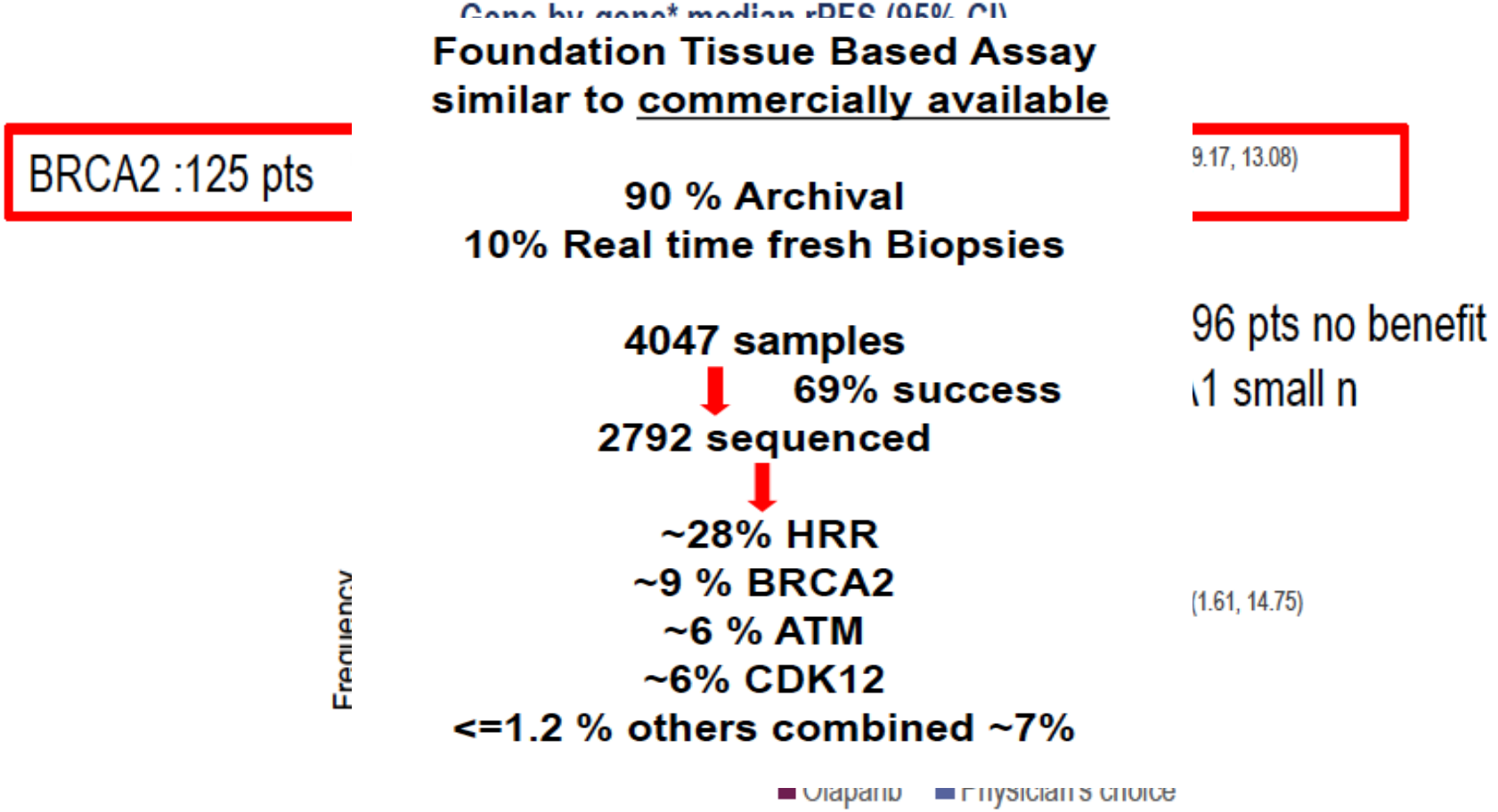


PROFOUND Trial

A truly practice changing study

- ✓ DDR and BRCA2m associated with poor prognosis
  - ✓ BRCAness may be biologically neutral
- ✓ Extrapolation of germline and somatic mutations
  - ✓ % are similar
  - ✓ Responsiveness appears similar

Efficacy outcomes driven by BRCA2m enrichment

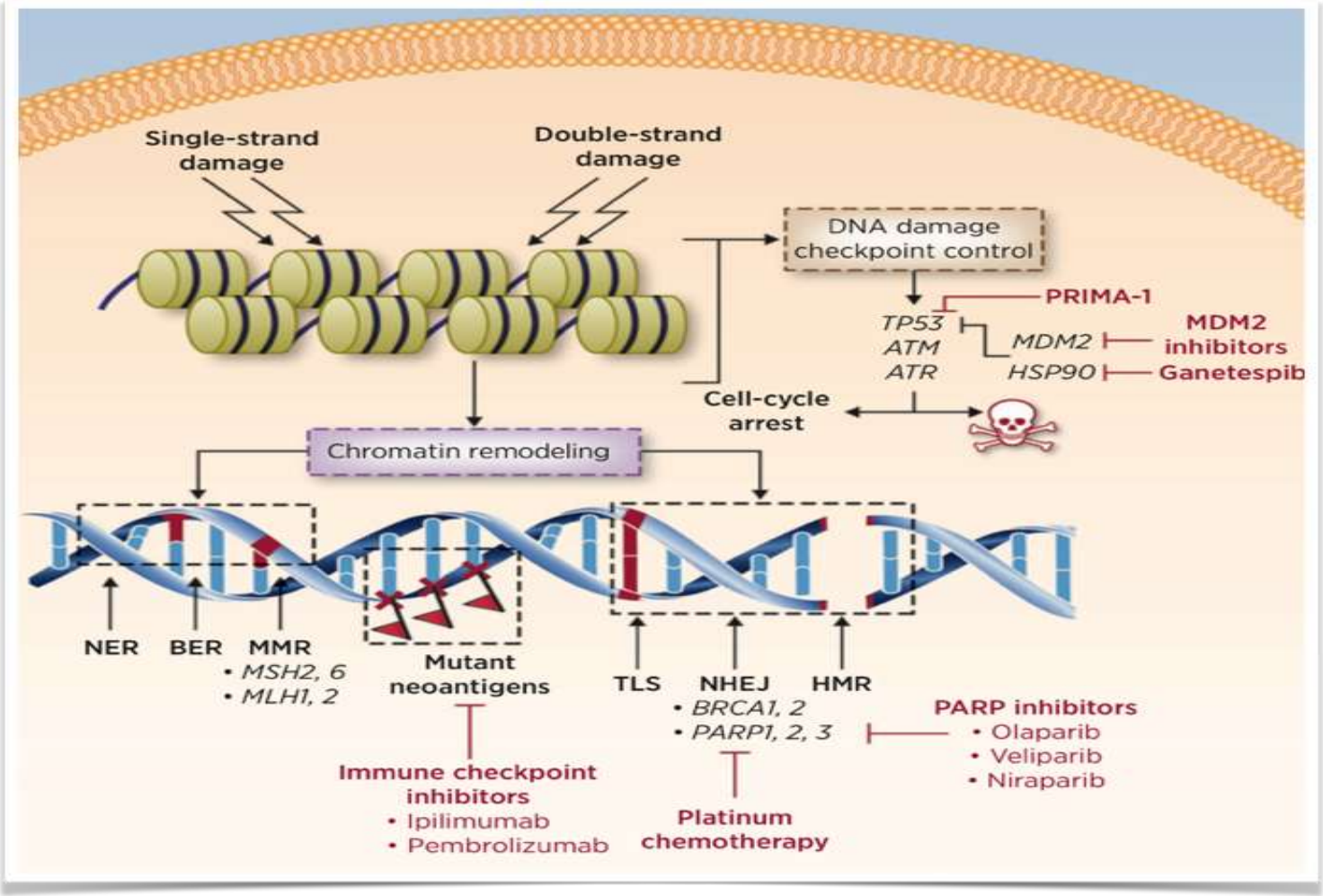


PROFOUND Trial

A truly practice changing study

- ✓ Well designed addressing an unmet clinical need
- ✓ Patient population representative
- ✓ Positive outcomes that are clinically meaningful
- ✓ Reproducible results
  - ✓ Need of validated genomic analysis essay
  - ✓ Room for liquid biopsy?
- ✓ Role of other genes?
- ✓ Targeted therapy era initiation
  - ✓ Abandon sequential use of novel androgen signaling inhibition

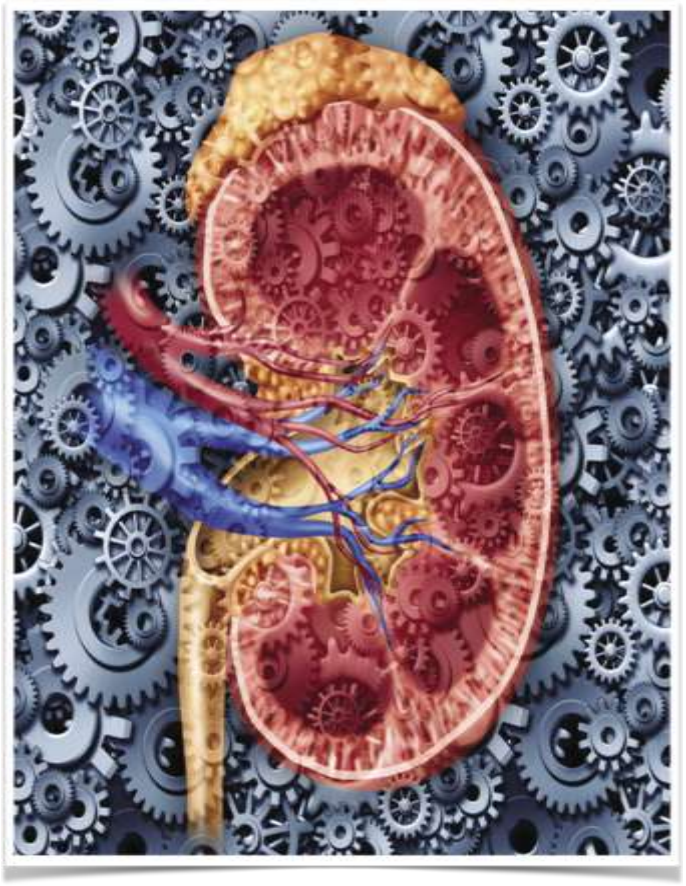
DNA damage repair pathways



Olaparib + Durvalumab in mCRPC

Patient Number	DNA Damage Repair (DDR) Pathway Mutation(s)	Other Genomic Aberration(s)	Maximum % PSA Decline
1	BRCA2	None	-79%
2	BRCA2	ASXL1	-99%
3	None	TP53, RB1	15%
4	None	AR amplification	35%
5	None	MYD88, CCND3, BIRC3	-79%
6	BRCA2 (germline)	SPOP, 13q deletion, AR amplification	-89%
7	Insufficient specimen	Insufficient specimen	-99%
8	BRCA2 (germline)	13q deletion, PKP2	-93%
9	Insufficient specimen	Insufficient specimen	-23%
10	BRCA2	TP53, KAT6A	-85%
11	BRCA2 (germline)	Copy number loss and allelic imbalance on 13q	-50%
12	None	RYR2, PIK3CA	37%
13	Insufficient specimen	Insufficient specimen	9%
14	BRCA2	HRAS	-80%
15	None	PIK3CA, ADGRB3, TP53	4%
16	None	TP53, STAG1	-46%
17	None	BRAF, AR amplification, ASXL1, MYH11	-10%

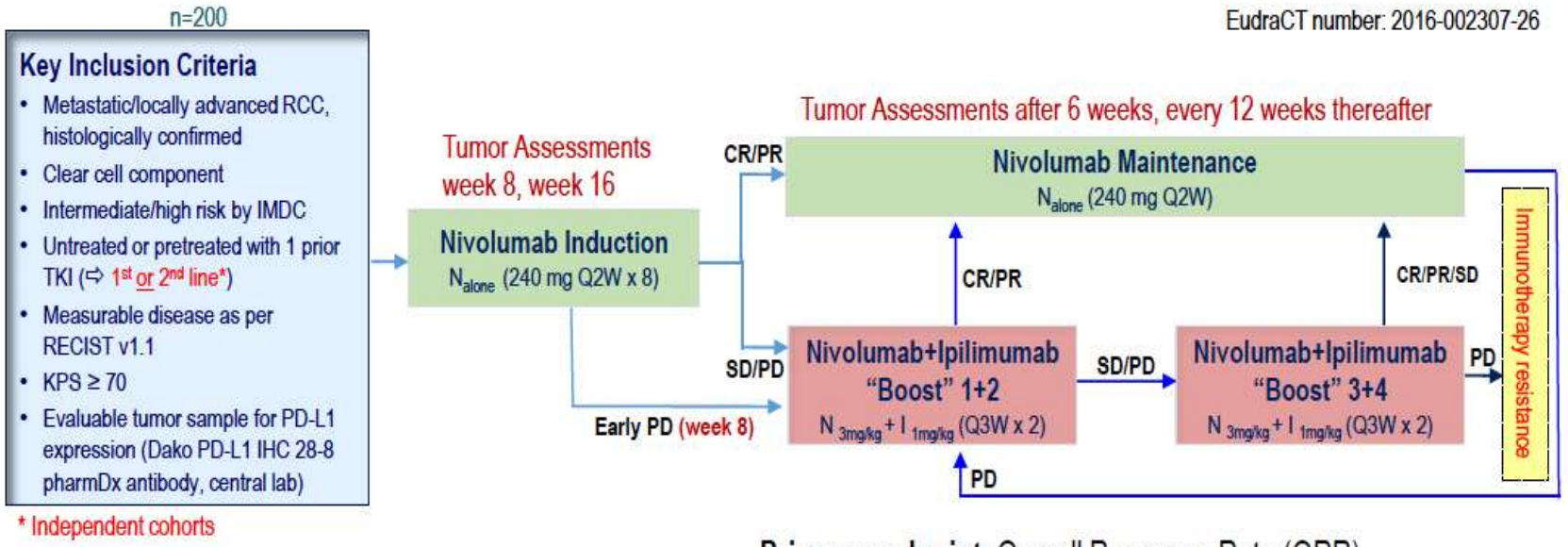
Karzai F, ASCO-GU 2018



Renal cell carcinoma

TITAN

Study design



Primary endpoint: Overall Response Rate (ORR)
Secondary endpoints: PFS, OS, RR after Nivo+Ipi "Boosts"
Safety (TRAE), QoL (FKSI-19)

27 July 2018
EMA/513784/2018
EMEA/H/C/WS/1278

Refusal of a change to the marketing authorisations for Opdivo (nivolumab) and Yervoy (ipilimumab)

On 26 July 2018, the Committee for Medicinal Products for Human Use (CHMP) adopted a negative opinion, recommending the refusal of a change to the marketing authorisations for the medicinal products Opdivo and Yervoy. The change concerned adding the use of both medicines in combination for the treatment of renal cell carcinoma (kidney cancer).

The company that applied for the change to the authorisation is Bristol-Myers Squibb Pharma EEIG. It may request a re-examination of the opinion within 15 days of receipt of notification of this negative opinion.

TITAN trial Trial

A truly practice changing study?

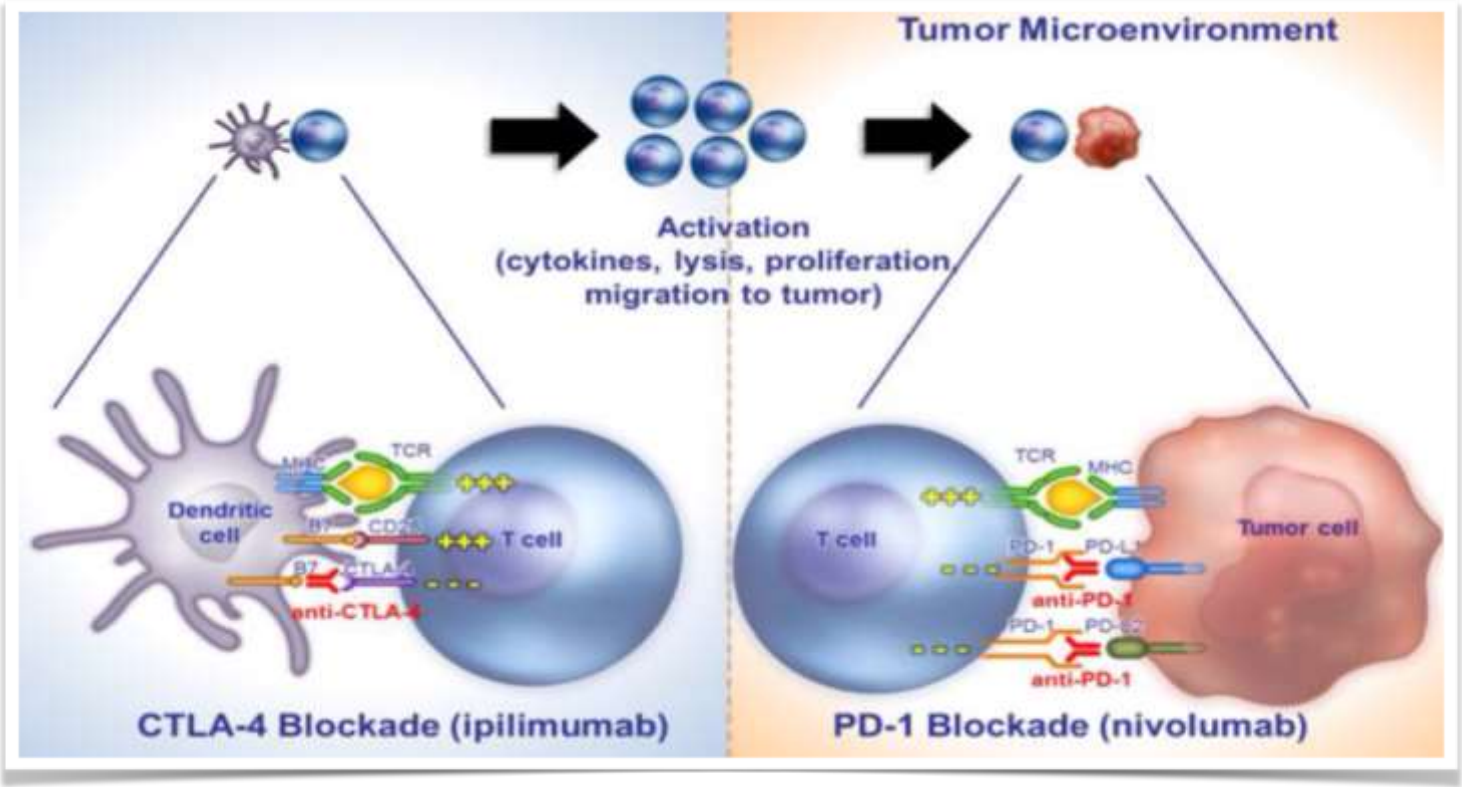
- ✓ Boosting improved ORR in first line (from 28,7% to 37%)
- ✓ Boosting improved ORR in second line (from 18,2% to 28,3%)
- ✓ Ipilimumab boost can rescue 10% of patients

Combination trials

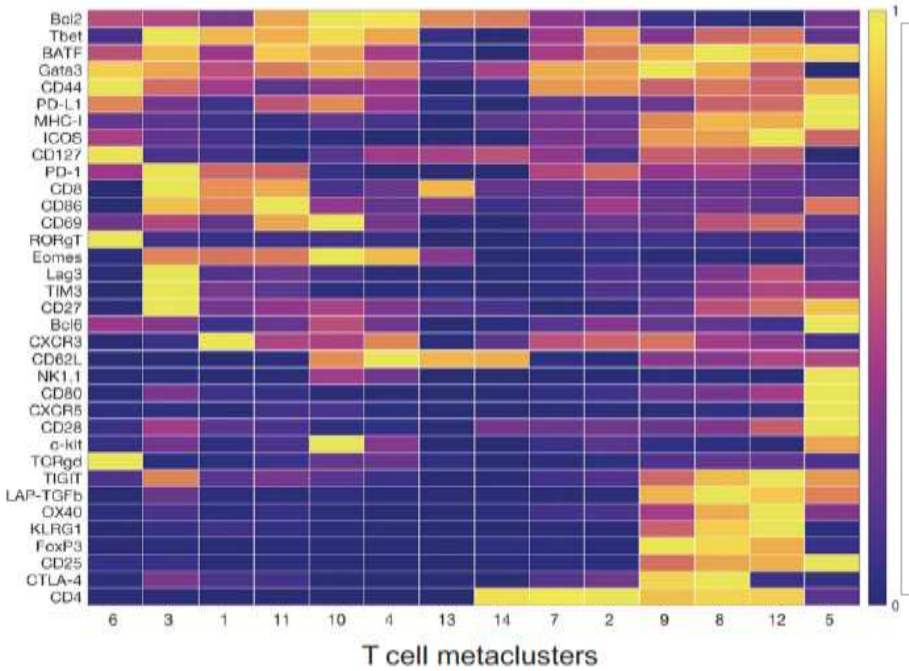
Variable	Trial of Pembrolizumab plus Axitinib vs. Sunitinib[5] (N=861)	Trial of Avelumab plus Axitinib vs. Sunitinib[4] (N=886)	Trial of Nivolumab plus Ipilimumab vs. Sunitinib[3] (N=1096)
IMDC prognostic risk (% of patients)†			
Favorable	31.2	21.4	23
Intermediate	56.2	61.8	61
Poor	12.6	16.2	17
Quantifiable tumor PD-L1 expression ≥1% (% of patients)	60.5	63.2	24
Overall survival			
Hazard ratio for death	0.53	0.78	0.68
CI	95% CI, 0.38–0.74	95% CI, 0.55–1.08	99.8% CI, 0.49–0.95
P value	<0.0001	0.14	<0.001
Median progression-free survival (mo)			
Combination therapy group	15.1	13.8	12.4
Sunitinib group	11.1	8.4	12.3
Objective response in combination-therapy group (% of patients)	59.3	51.4	39.0
Complete response in combination-therapy group (% of patients)	5.8	3.4	10.2
Median follow-up (mo)	12.8	11.6	25.2

CTLA-4 and PD-1 blockade

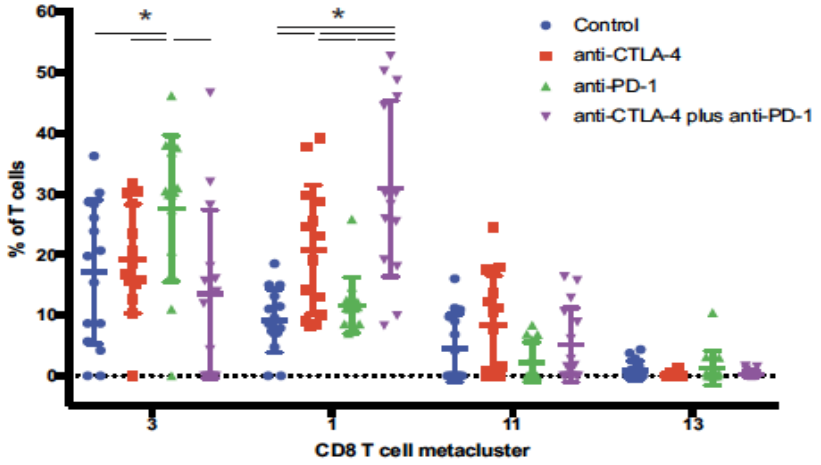
Rationale for combinations

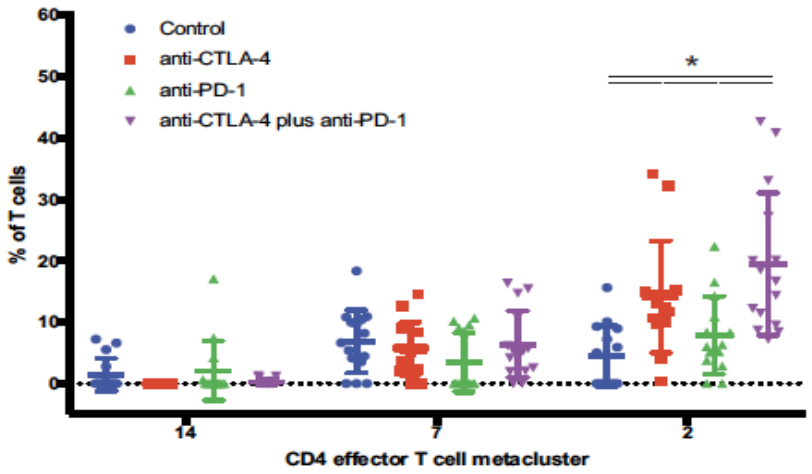


Anti–CTLA-4 plus anti–PD-1 utilizes cellular mechanisms distinct from monotherapies



- ✓ Highly phenotypically exhausted cluster of differentiation 8 (CD8) T cells expand in frequency following anti–PD-1 monotherapy but not combination
- ✓ Activated terminally differentiated effector CD8 T cells expand only following combination therapy.
- ✓ Combination therapy also led to further increased frequency of T helper type 1 (Th1)-like CD4 effector T cells even though anti–PD-1 monotherapyis not sufficient to do so.





Wei SC, PNAS 2019

TITAN trial Trial

A truly practice changing study?

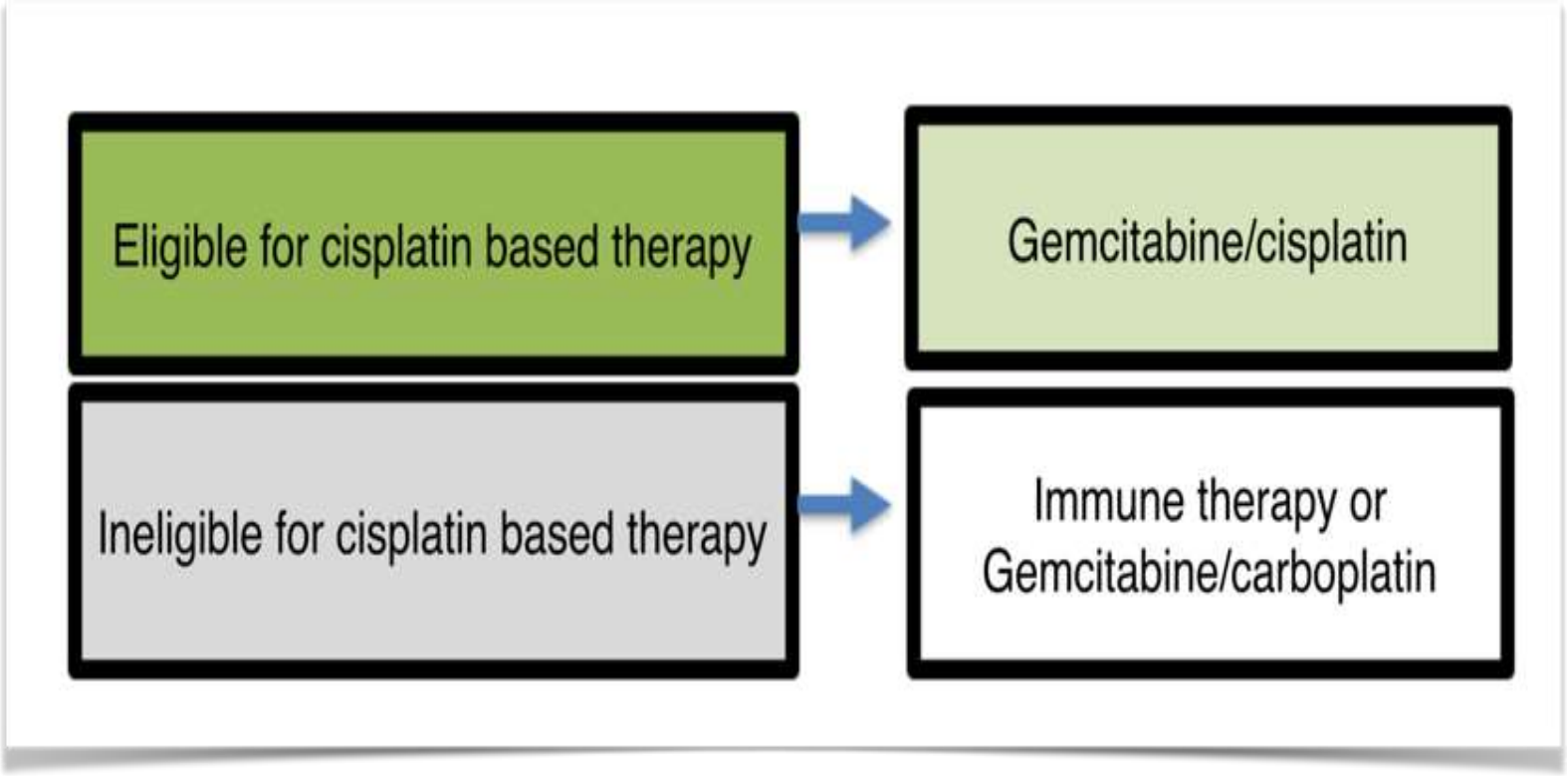
- ✓ CR rates with this strategy is lower than with other combination
- ✓ Not all candidates could finally receive the boost (77% in first line)
- ✓ PFS and OS are still immature
- ✓ Is this the right moment for monotherapy?

Urothelial carcinoma

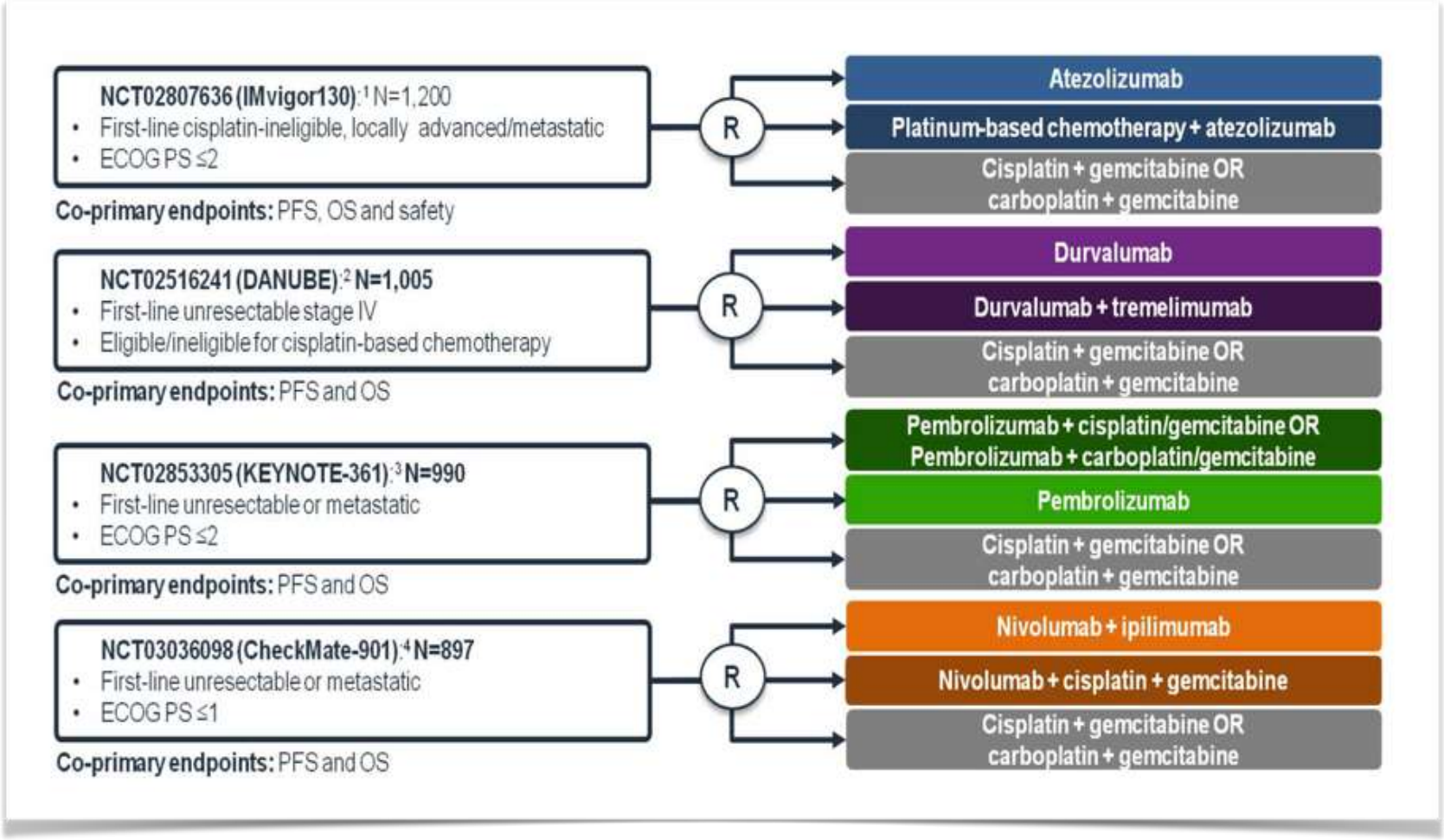
FDA approval	EMA approval
1st line	
Atezolizumab Pembrolizumab	Atezolizumab pembrolizumab
2nd line	
Atezolizumab Pembrolizumab (benefit on OS) Nivolumab Avelumab Durvalumab	Nivolumab Atezolizumab pembrolizumab

Algorithm for first line therapy in metastatic UC

Until recently



Phase III trials of anti PD-1/PD-L1 antibodies



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1 June 2018
EMA/364553/2018

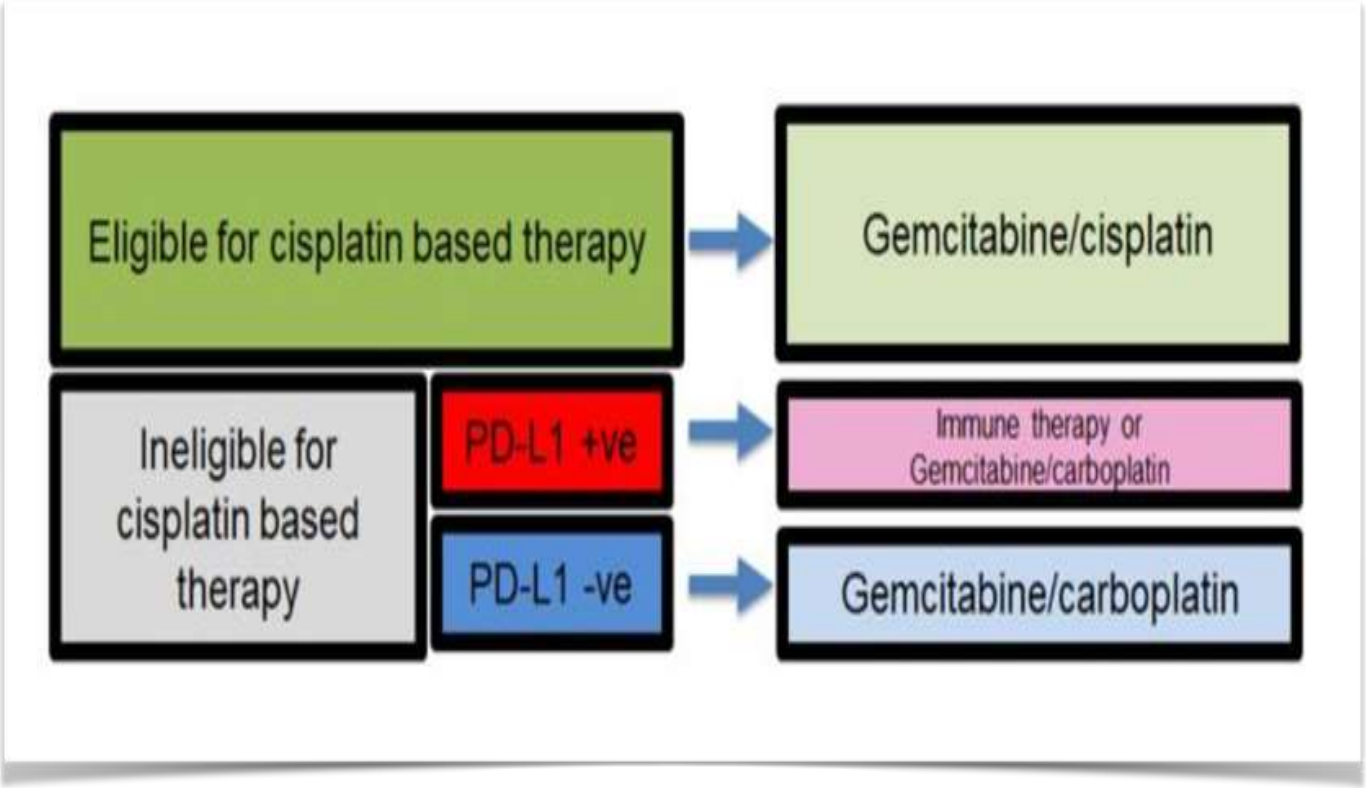
EMA restricts use of Keytruda and Tecentriq in bladder cancer

Data show lower survival in some patients with low levels of cancer protein PD-L1

Early data from two clinical trials[1] show reduced survival with Keytruda (pembrolizumab) and Tecentriq (atezolizumab) when used as first-line treatments for urothelial cancer (cancer of the bladder and urinary tract) in patients with low levels of a protein called PD-L1. The data indicate that Keytruda and Tecentriq may not work as well as chemotherapy medicines in this group of patients.

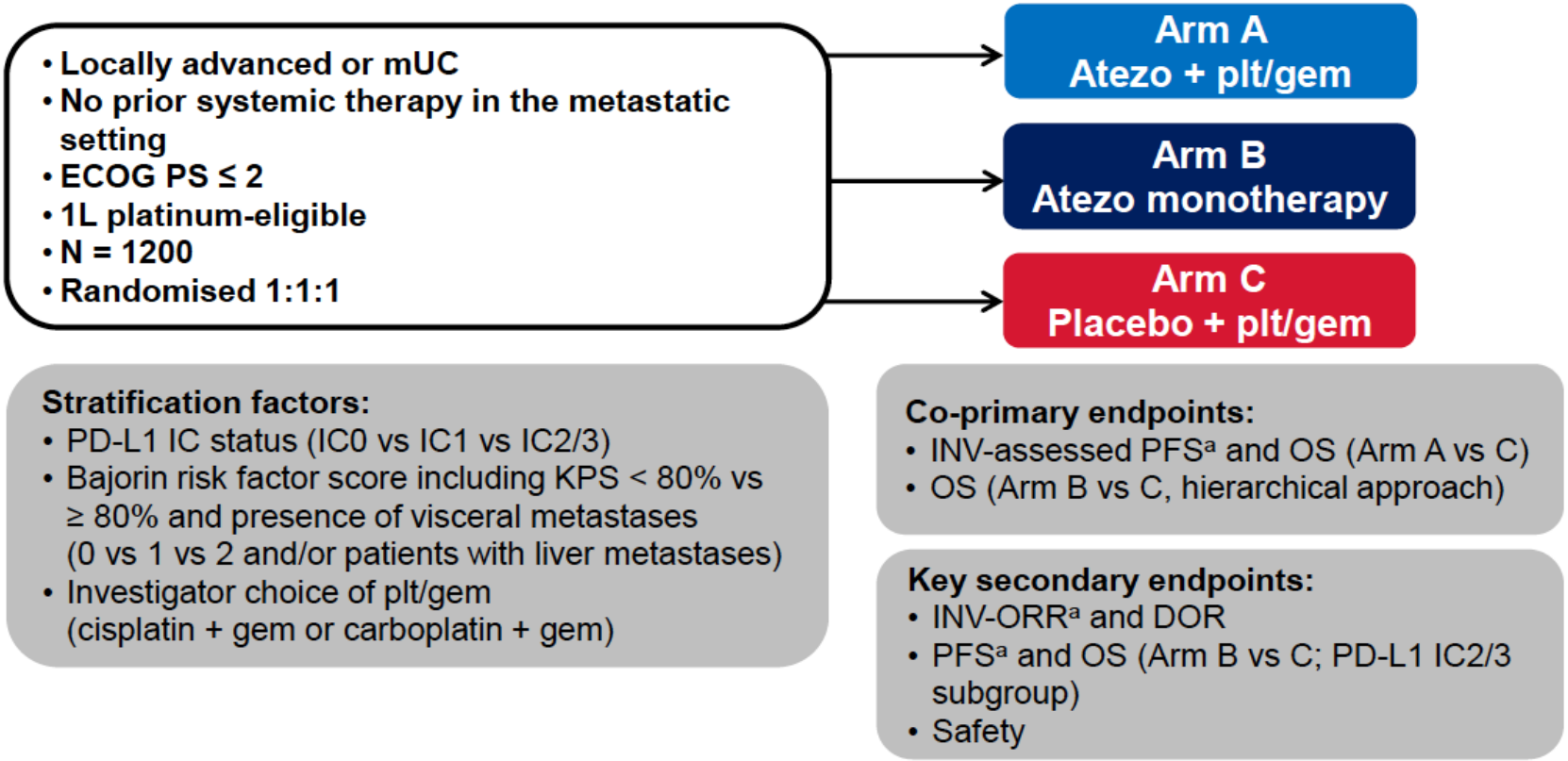
Algorithm for first line therapy in metastatic UC

From July 2018



IMvigor130

Study design



IMvigor130

Key protocol amendments

Arms	Randomization	Platinum eligibility	Monotherapy	Enrolment (n)
2	2:1	Cisplatin-ineligible only	No	129

Rationale: IMvigor210 results provided proof-of-concept for testing atezo monotherapy and including cisplatin-eligible patients

3	1:1:1	Cisplatin-ineligible/ Cisplatin-eligible	Yes	1078

Rationale: IDMC recommended change based on early assessment of the atezo monotherapy arm

3	1:1:1	Cisplatin-ineligible/ Cisplatin-eligible	Only PD-L1 IC2/3[a]	6

Imvigor 130

- 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

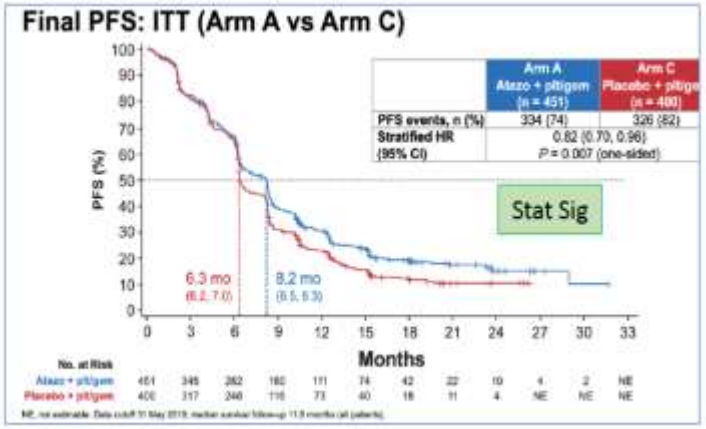
→ **Arm B** Atezo monotherapy

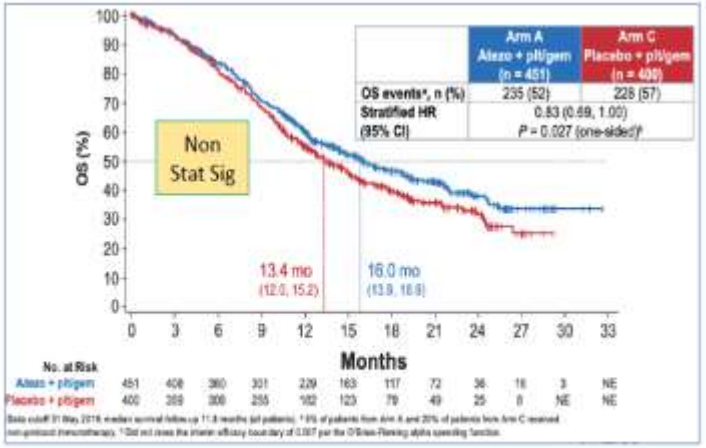
→ **Arm C** Placebo + plt/gem

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





- Is this a positive study?
- Is this a clinically meaningful study?

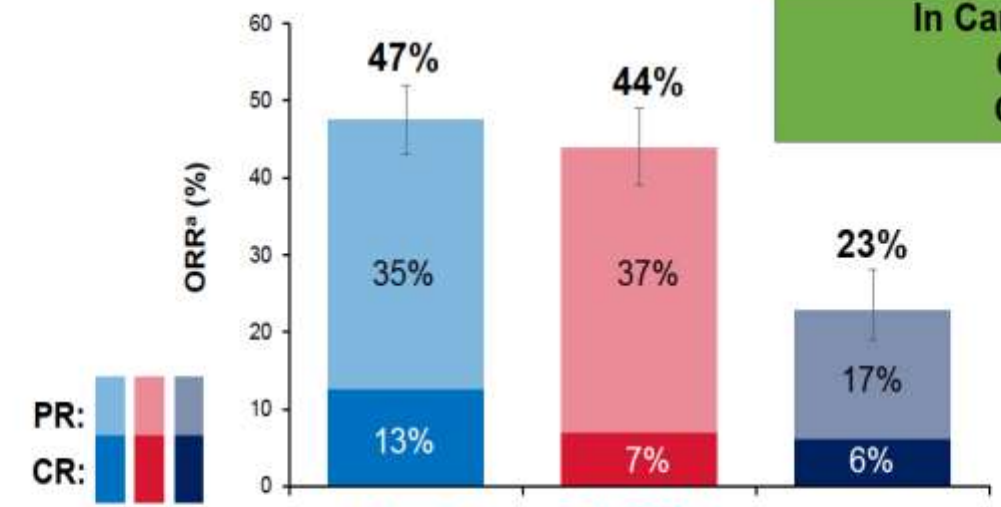
Imvigor 130

A comparative view

Confirmed ORR and DOR:
A comparative view

Investigator-assessed ORR in CG Vs MVAC were:
(GC **54.3%,** MVAC 55.0%). **12% CR**

In Carbo-Gem study
ORR 41%
CR 6-12%



DOR[b], median (95% CI), mo	8.5 (7.2,10.4)	7.6 (6.3, 8.5)	NE (15.9, NE)

Imvigor 130

Open questions

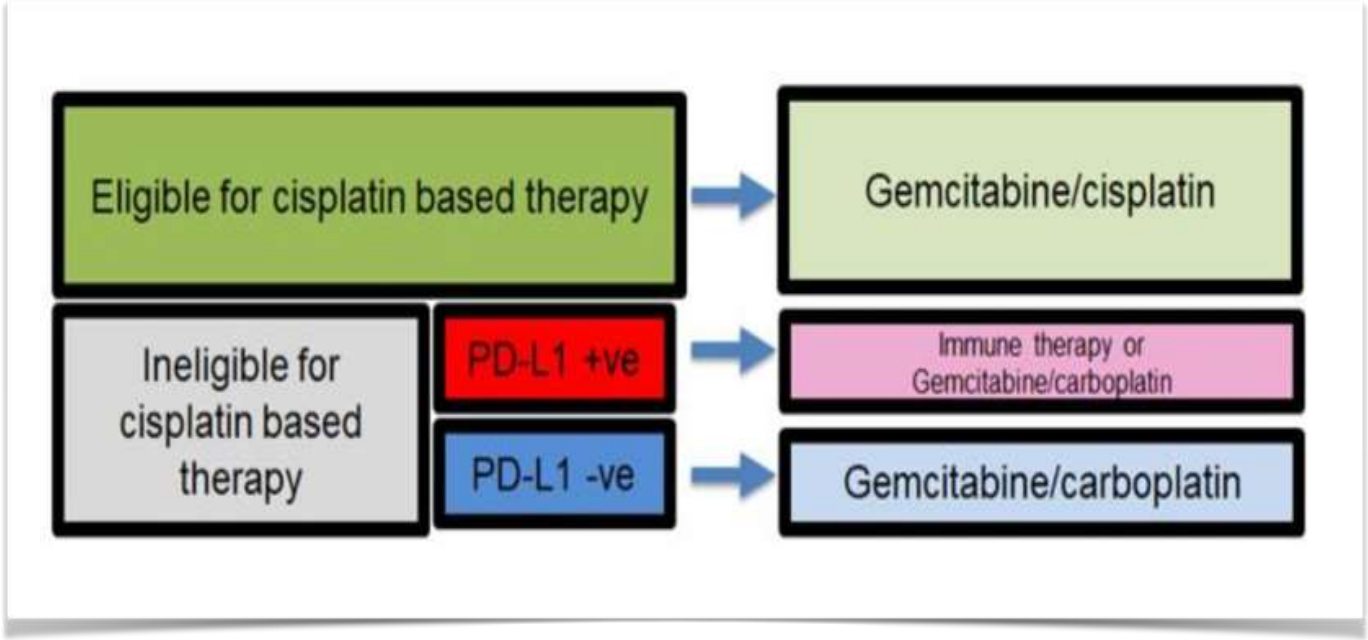
Characteristic	Atezo + plt/gem (n = 451)	Placebo + plt/gem (n = 400)[a]	Atezo (n = 362)
Median age (range), y	69 (31-87)	67 (33-89)	67 (36-87)
ECOG PS, n (%)			
0	182 (40)	173 (43)	157 (43)
1	209 (46)	187 (47)	174 (48)
2	60 (13)	40 (10)	31 (9)
Bajorin risk factor score, n (%)			
0	176 (39)	162 (41)	151 (42)
1	169 (37)	149 (37)	134 (37)
2 and/or liver mets	106 (24)	89 (22)	77 (21)
PD-L1 status on IC, n (%)			
IC2/3	108 (24)	91 (23)	88 (24)
IC1	195 (43)	179 (45)	160 (44)
IC0	148 (33)	130 (33)	114 (31)
Cisplatin ineligibility[b]	204 (45)	140 (35)	107 (30)
Renal impairment	113 (25)	94 (24)	65 (18)
Investigator choice of chemotherapy[c]	25%	31%	33%
Carboplatin	314 (70)	264 (66)	227 (63)
Cisplatin	137 (30)	136 (34)	135 (37)

How did the overuse of Carbo influenced the final outcomes?

Is a HR of 0.82 enough to regulatory authorities?

Is the % of subsequent treatments representative of our practices?

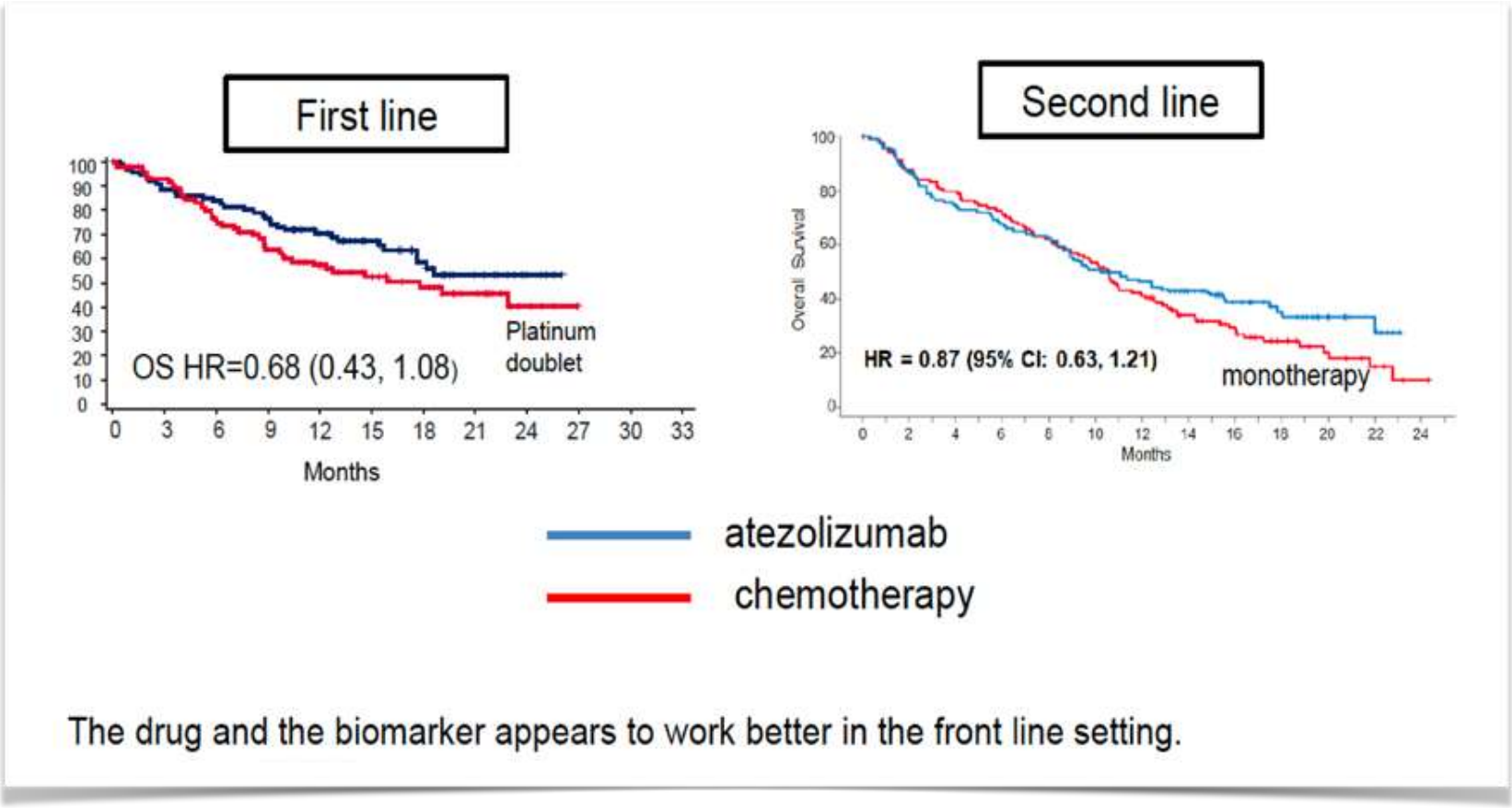
Do the combination results change the algorithm?



For	Against
Significant delay in PFS	PFS HR 0.82 (0.7-0.96)
OS trending the right way	But not significant yet.
CR of 13% vs 7%	Response rates of 47 vs 44%
No increase in AEs for the combo	No QOL/PRO data

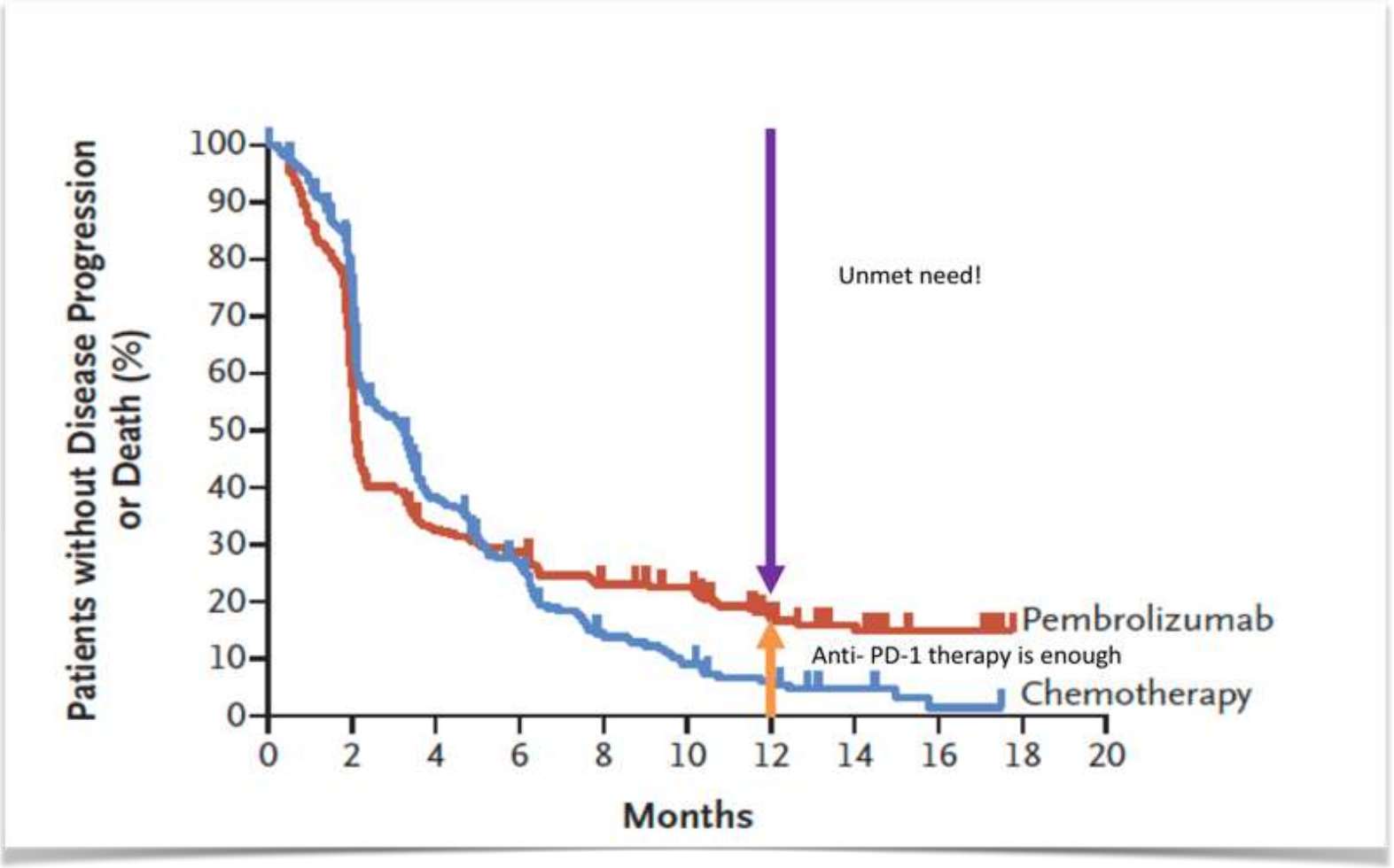
Atezolizumab

Results in first line and DDP-refractory PD-L1 positive

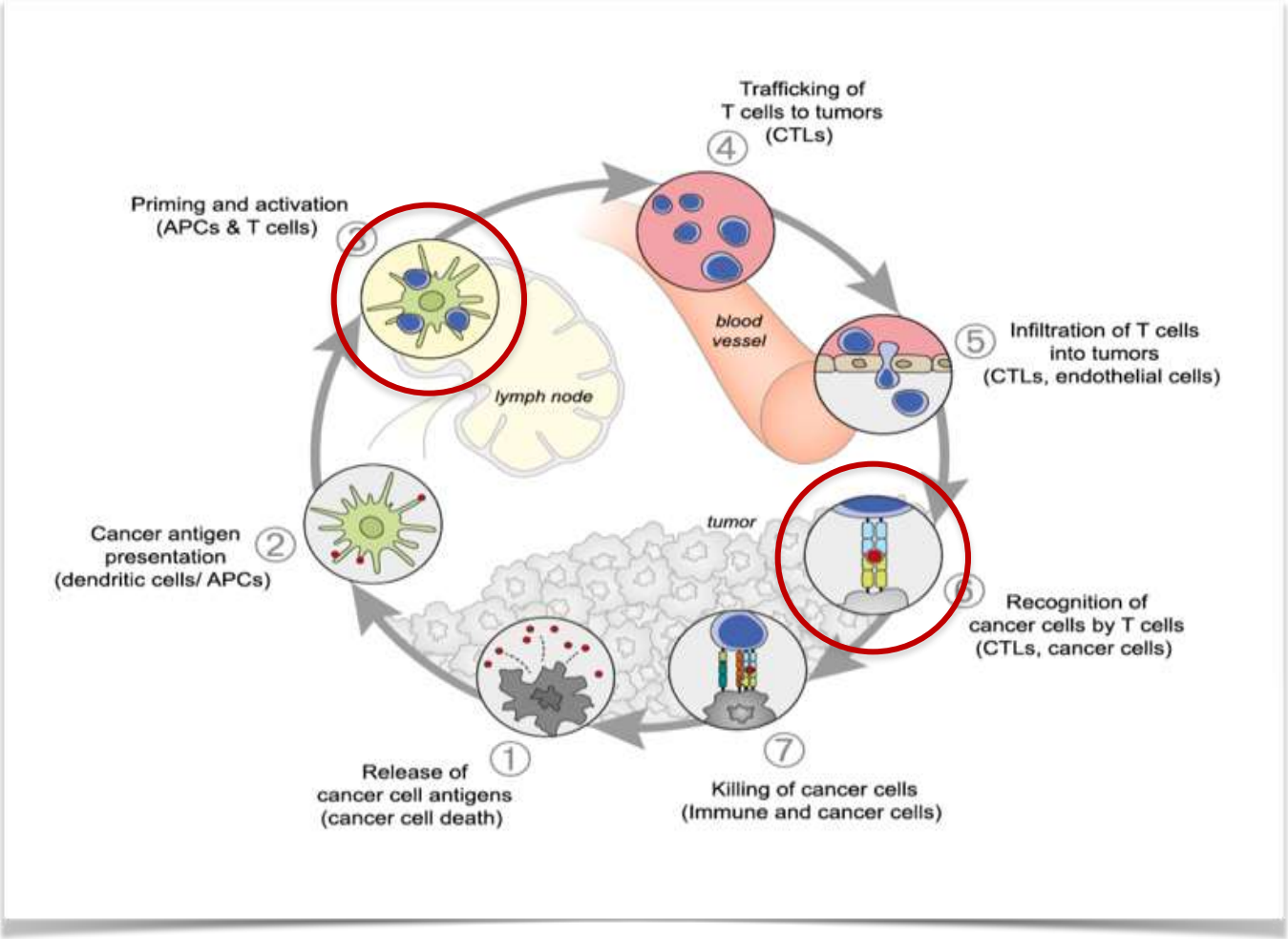


The drug and the biomarker appears to work better in the front line setting.

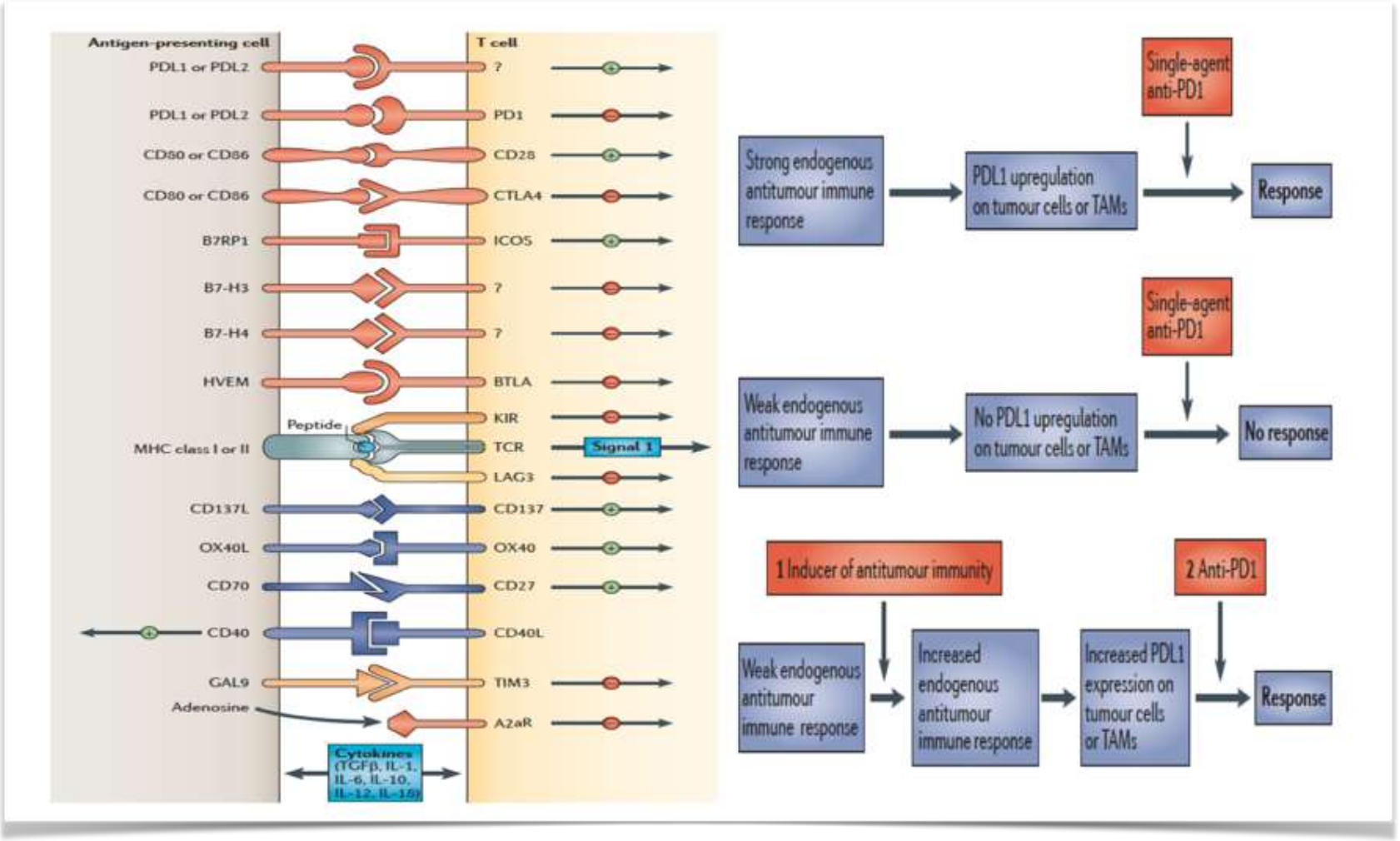
Is anti-PD-1 therapy enough?



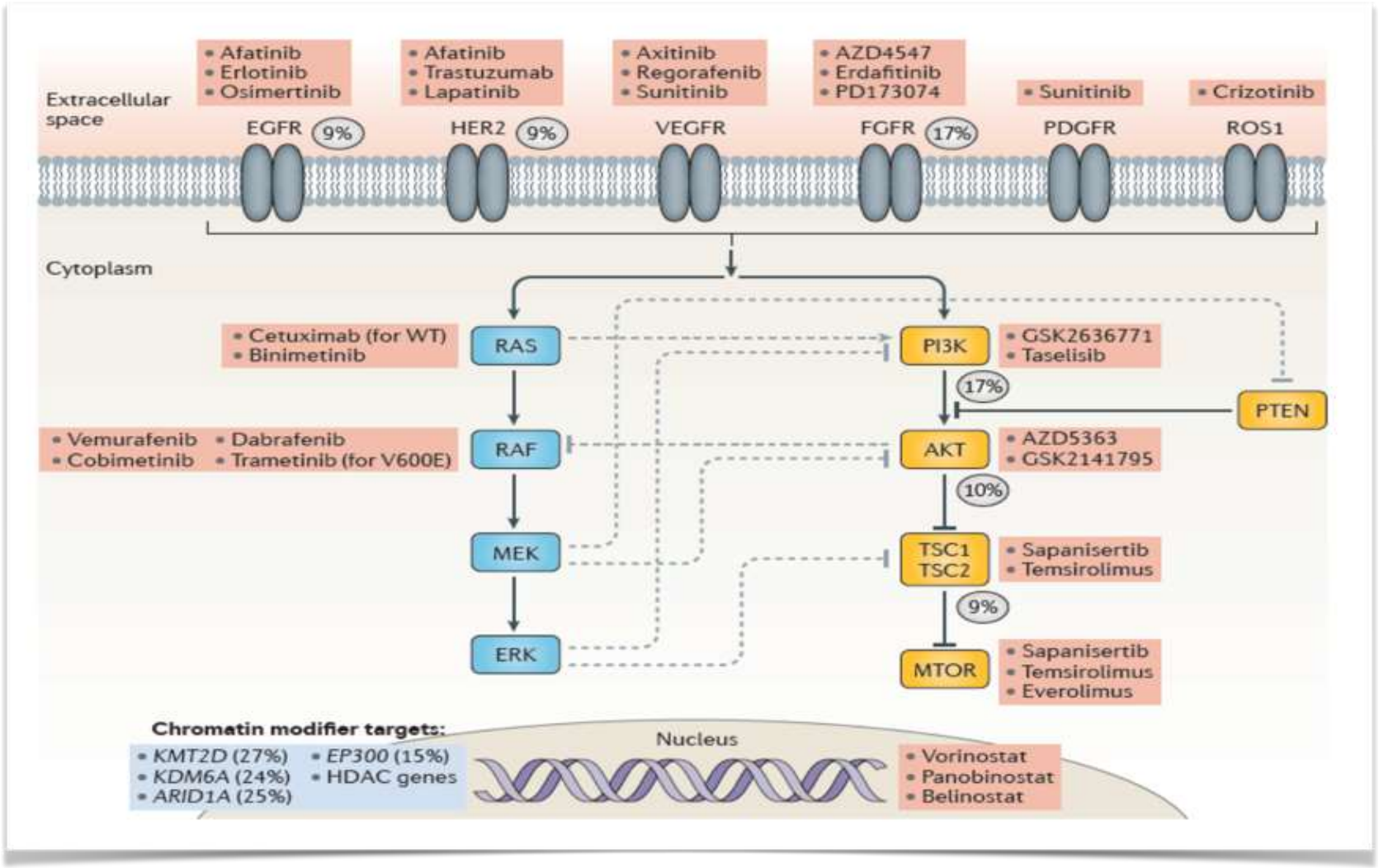
The immunity cycle



A rationale for combinations



Potentially actionable mutations in bladder cancer



Felsenstein KN, Nature Rev Urol 2017

Ongoing trials

Study	Arms	Line of therapy	n	Phase
IMvigor 130	Atezolizumab vs atezolizumab + platinum based CT vs platinum based CT	1st	1200	3
KEYNOTE 361	Pembrolizumab +/- platinum based combination CT vs CT	1st	990	3
BISCAY	Durvalumab +/- targeted agent matched to tu or profile FGFR, PARP, PI3K inhibitor	1, 2, 3	140	1b/2
NCI	Nivolumab + Cabozantinib +/- ipilimumab	2nd	66	1/2
BMS CA224-020	Anti-LAG3 +/- nivolumab	2nd	30	1
Celldex CDX1127-06	Varlilumab + atezolizumab	2nd	55	1
CORVUS CPI-444-001	CPI-444 +/- atezolizumab	2nd	534	1
PsiOxus Therapeutics	Enadenotucirec (oncolytic virus) + nivolumab	2nd	30	1
Yale	Ramucirumab + pembrolizumab	2nd	155	1
Plexxicon	CSF1R, KIT or FLT3 inhibitor + pembrolizumab	2nd	400	1/2
USC	Pembrolizumab + sEphB4-HSA	2nd	60	2

Imvigor 130

Conclusions

- Currently, **chemotherapy** [GC/DD MVAC] remains the option with more solid data for systemic treatment in **1st line mUC in platinum- eligible patients**

- **More mature data** from IMVIGOR-130 and the **completion of the other ongoing studies** (i.e. KN 361) is necessary to assess the real impact of combining chemo and I-O in 1st lines

- Immunotherapy in the **EU in 1st line** should be **restricted** for those **patients** who are **NOT eligible for cisplatin-containing chemotherapy,** and whose tumors **highly express PD-L1**
  - Combined positive score **(CPS) ≥10** or tumours with a **PD-L1 expression ≥5%**