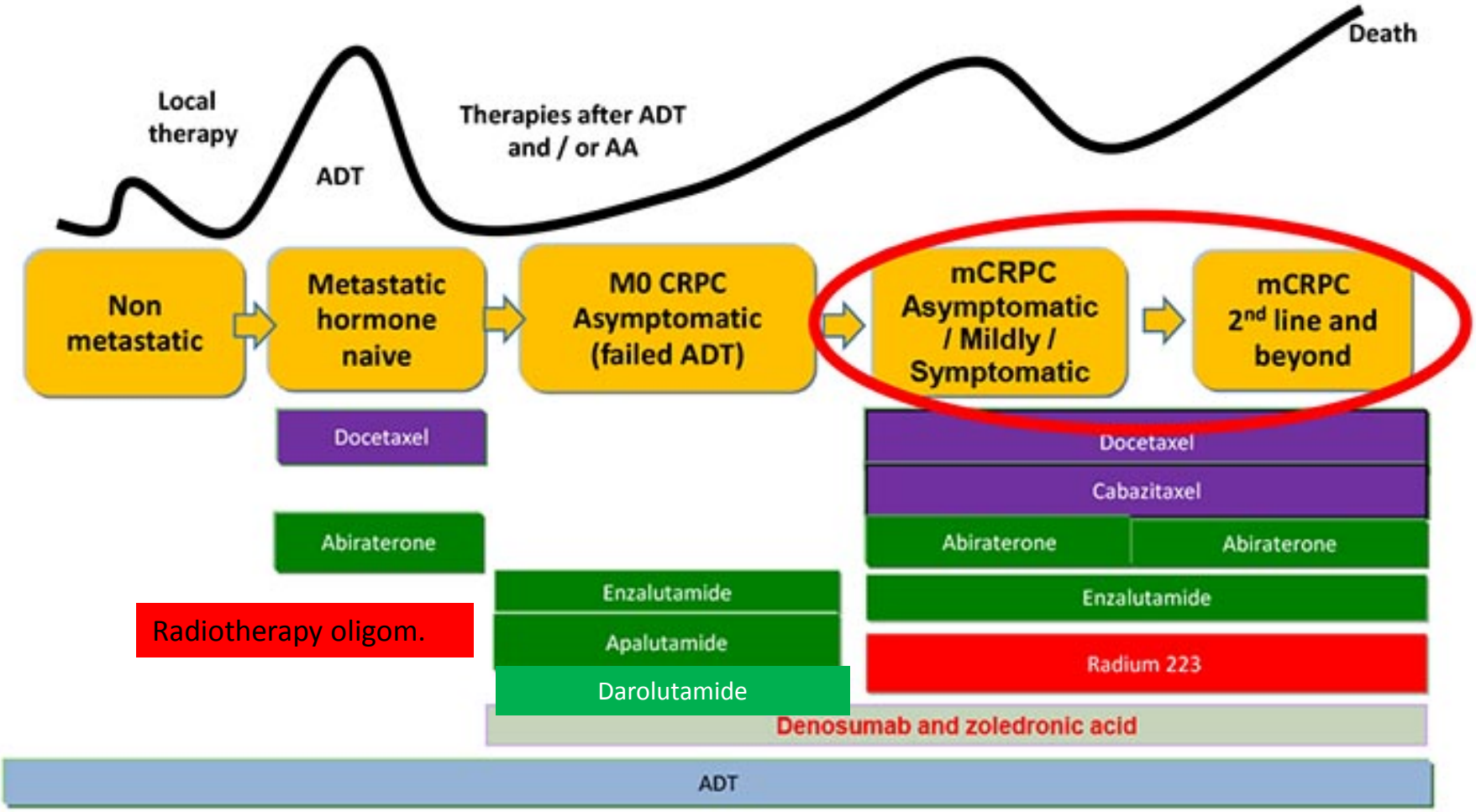
III Incontro TMD Uro-Onco 2018

Nuovi Farmaci: Potenzialità e criticità

Dott. G. Di Lorenzo

Azienda Ospedaliera Universitaria Federico II

PROSTATE CANCER CONTINUUM DRUGS



TREATMENT IN METASTATIC HORMONE-SENSITIVE PROSTATE CANCER:

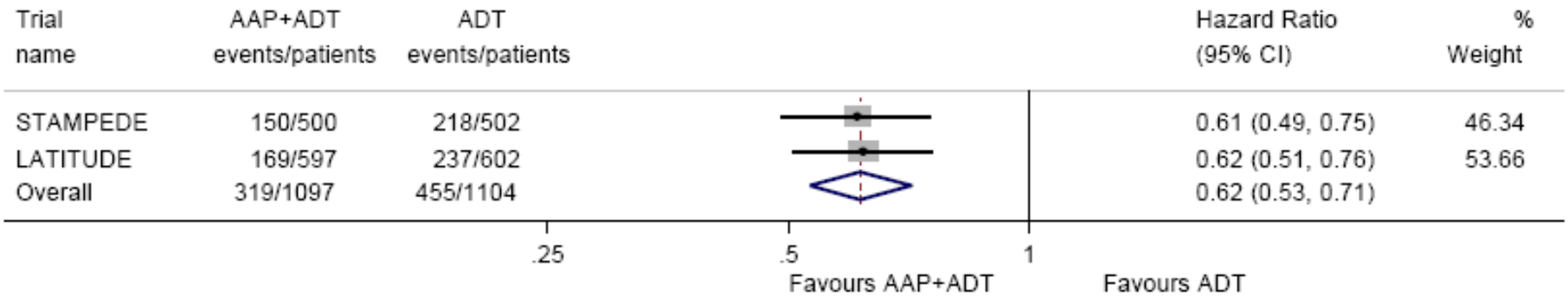
Vantaggi

- Aumento in OS
- Miglioramento QoL e PRO
- Somministrazione orale
- Gestione ambulatoriale del paziente
- Minor impatto psicologico

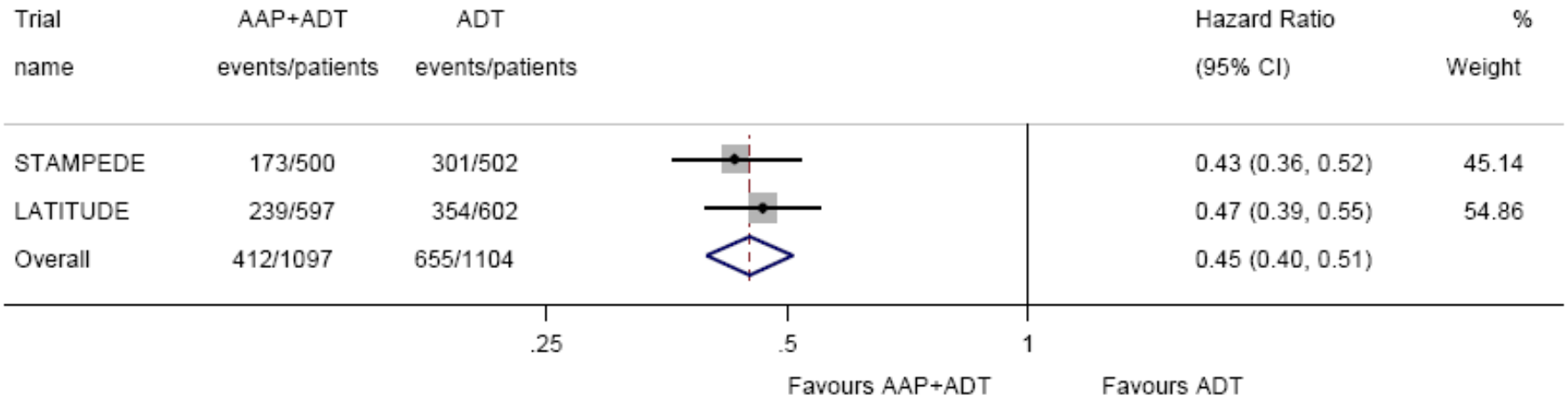
Adding abiraterone to andro… …n therapy in men with meta… …prostate cancer: A systematic re… …meta-analysis

38% risk of death reduction
14% survival improvment at 3y

Overall Survival in M1



Progression-free survival in M1 (clin/radiol)



Rydzewska et Al. Eur J Canc 2017

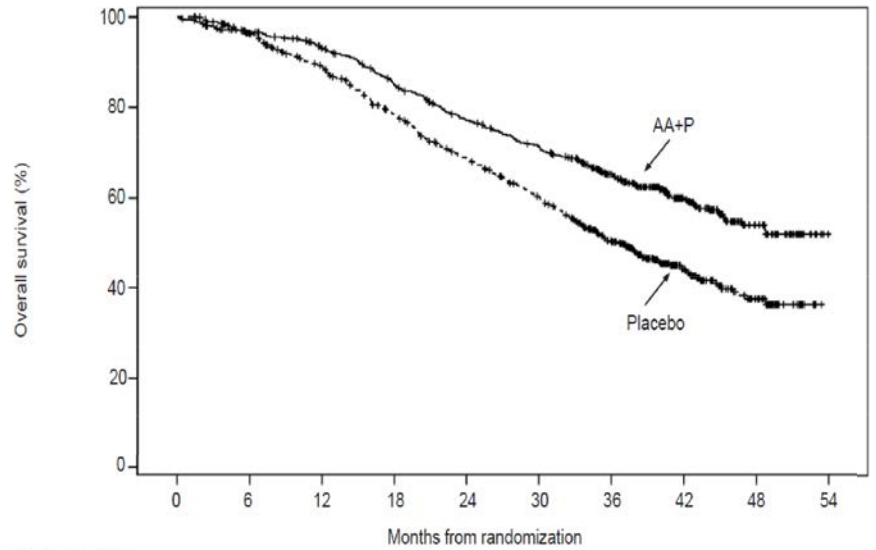
5023

Longer Term Preplanned Efficacy and Safety Analysis of Abiraterone Acetate + prednisone (AA + P) in patients (pts) With Newly Diagnosed High-Risk Metastatic Castration-Naïve Prostate Cancer (NDx-HR mCNPC) From the Phase 3 LATITUDE Trial

Karim Fizazi,[1*] Susan Feyerabend,[2] Nobuaki Matsubara,[3] Mustafa Özgüroğlu,[4] Luis Fein,[5] Alfredo Rodriguez-Antolin,[6] Boris Y. Alekseev,[7] Giri Sulur,[8] Andrew Protheroe,[9] Peter De Porre,[10] Susan Li,[11] Youn C. Park,[12] Suneel Mundle,[12†] NamPhuong Tran,[8] Kim N. Chi[13]

FOLLOW UP MEDIANO 41.4 MESI

Figure 3: Kaplan-Meier Plot of Overall Survival (Intent-to-treat population)



No. of patients at risk

AA+P	597	565	529	479	425	389	314	170	61	0
Placebo	602	564	505	432	368	314	227	113	39	0

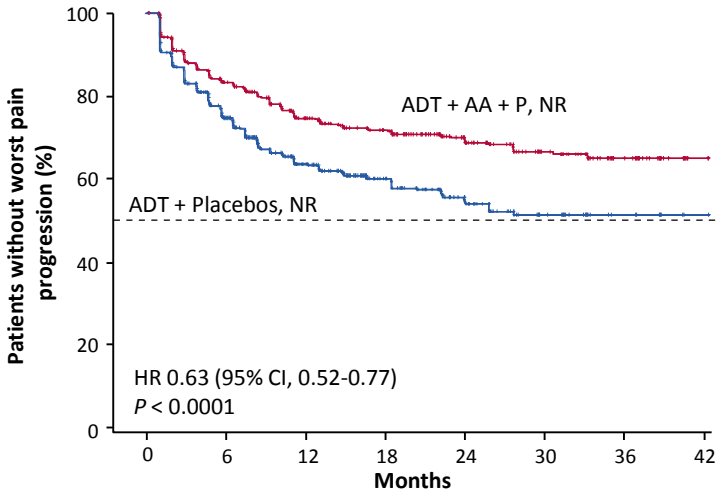
AA+P: Abiraterone acetate + prednisone; ADT: Androgen deprivation therapy

- **Riduzione del rischio di morte del 38 % nel braccio ABI**
- **Mediana OS non raggiunta nel braccio ABI vs 36.7 mesi nel braccio ADT**
- **Piu' del 50 % dei pazienti ancora in vita a 41.4 mesi di mediana di follow-up**

Fizazi K. et al, Poster presented at ASCO 2018, abstact 5023

ADT + AA + P Significantly Improved Pain

37% Risk Reduction for Worst Pain Progression



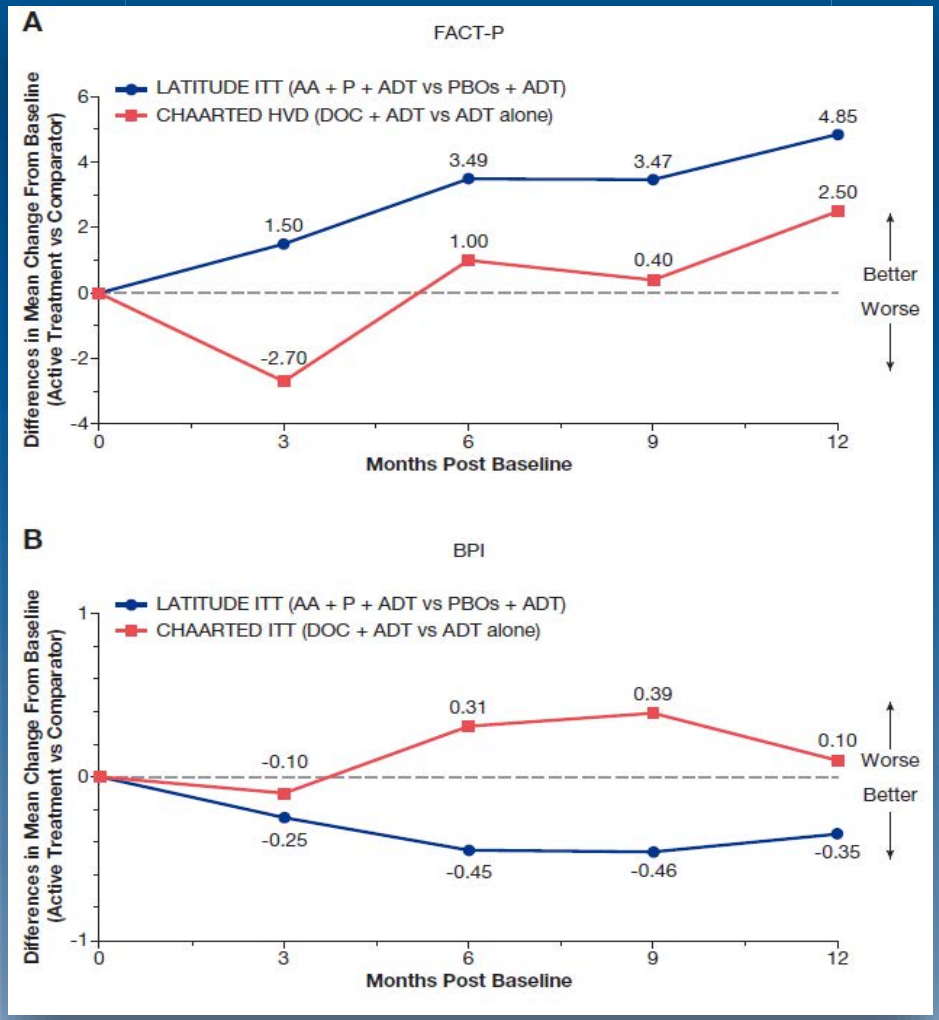
Patients at risk								
ADT + AA + P	597	456	356	299	218	115	47	2
ADT + Placebos	602	387	246	162	99	44	10	1

*1 cycle = 28 days.

Chi K, et al. Abstract 783O presented at ESMO 2017

Indirect treatment comparison (ITC) of AA + P and Doc on PROs in mCNPC

Mean Change in PRO Scores from Baseline for FACT-P (A) and BPI (B) from LATITUDE and CHAARTED



Aim: The objective of this study was to compare ITCs with AAP + ADT vs Doc + ADT on HRQoL and pain PROs in patients with mCNPC.

ITC analysis showed that patients receiving AAP + ADT had improvements in HRQoL after 3 months, compared with Doc + ADT; these effects were sustained up to 1 year after treatment.

ASCO GU 2018

Feyerabend S, et al. Poster presented at ASCO-GU 2018; abstract 200.

What patient populations were included?

Total sample size, n	ADT+AA+P vs ADT		ADT+Doce vs ADT		
	LATITUDE*[1]	STAMPEDE (Arm G)[2,3]	GETUG-AFU 15[4]	CHAARTED[5,6]	STAMPEDE (Arm C)[7]
Total sample size, n	1199	1917	385	790	1776
Patients with mHSPC	100%	52%	100%	100%	61%
Patients with high-risk/high volume mHSPC	100%	NE	47.5% (183)	65 % (513)	NE
Patients with *de novo* M1	100%	49%	71%	72.8%	58%
Patients with visceral metastasis	17.3%	3%	14.5%	15.6%	3.8%
Patients with Gleason Score ≥8	98%	74.9%	56.1%	61.3%	70.1%

HIGH RISK (HR)[1]

At least 2 of 3:

- **≥3 bone lesions**
- **Visceral metastasis**
- **Gleason score ≥8**

HIGH VOLUME (HV)[4,5]

At least 1 of 2:

- **≥4 bone lesions with ≥1 beyond the vertebral bodies / pelvis**
- **Visceral metastasis**

Not head-to-head compariso

1. Fizazi K, et al. New Engla
Abstract Session; 3. James
2016 Aug;70(2):256-62; 5.
2016;27(suppl 6):Abstract

Efficacy in mHSPC de novo high-volume disease

Post hoc Latitude[1]

	Patients with high-volume disease		Patients with low-volume disease		Overall population	
Clinical outcomes	AA+P+ADT n=487	PBOs+ADT n=468	AA+P+ADT n=110	PBOs+ADT n=133	AA+P+ADT n=597	PBOs+ADT n=602[a]
Overall survival						
Median, months	NR	33.1	NR	NR	NR	34.7
HR (95% CI)	0.57 (0.46-0.71)[b]		0.81 (0.48-1.34)[c]		0.62 (0.51-0.76)[d]	
rPFS[e]						
Median, months	30.7	14.7	NR	22.4	33.0	14.8
HR (95% CI)	0.43 (0.36-0.52)[b]		0.53 (0.35-0.80)[f]		0.47 (0.39-0.55)[d]	

[a]Includes 1 patient with missing baseline scan. [b]p < 0.0001. [c]p = 0.4052. [d]p < 0.001. [e]Sequential radiographic imaging to assess rPFS (CT or MRI and bone scanning) was performed every 4 months, starting at Week 16. [f]p = 0.0024.
NR, not reached.

CHARTEED long term[2]

Overall survival	ADT + DOC	ADT alone	P value HR (95% CI)
Whole Study Population (mo.)	57.6	47.2	0.0017 0.73 (0.59 – 0.89)
High volume (mo.)	51.2	34.4	<0.001 **0.63** (0.50 – 0.79)
Low Volume (mo.)	63.5	NR	0.86 [illegible]70 – 1.55)
de novo metastatic prostate cancer			
High volume (mo.)	48.0	33.1	0.0004 **0.63** (0.49 - 0.81)
Low Volume (mo.)	58.3	59.8	0.55 0.86 (0.52 – 1.42)
Metastatic after prior local therapy*			
High volume (mo.)	66.9	51.7	0.37 0.72 (0.36 – 1.46)
Low Volume (mo.)	69.6	NR	0.55 1.25 (0.60 – 2.60)

mo: months, NR: not reached

1.Fizazi K, et al. Poster presented at ASCO-GU 2018; abstract 182. 2.Sweeney C, et al. Ann Oncol 2016;27(suppl 6):Abstract (and poster) 720PD

Stampede-Abiraterone retrospective analysis

	ADT+AA+P vs ADT		ADT+Doce vs ADT		
Total sample size, n	LATITUDE*[1]	STAMPEDE (Arm G)[2,3]	GETUG-AFU 15[4]	CHAARTED[5,6]	STAMPEDE (Arm C)[7]
Total sample size, n	1199	**1917**	385	790	1776
Patients with mHSPC	100%	**52%**	100%	100%	61%
Patients with high-risk/high volume mHSPC	100%	**NE**	47.5% (183)	65 % (513)	NE
Patients with *de novo* M1	100%	**49%**	71%	72.8%	58%
Patients with visceral metastasis	17.3%	**3%**	14.5%	15.6%	3.8%
Patients with Gleason Score ≥8	98%	**74.9%**	56.1%	61.3%	70.1%

HIGH RISK vs Low risk

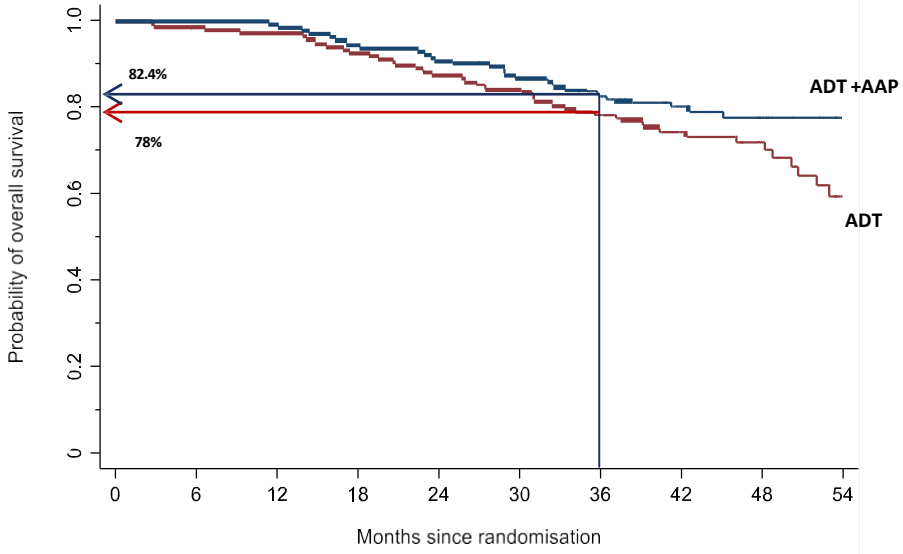
At least 2 of 3:

- **≥3 bone lesions**
- **Visceral metastasis**
- **Gleason score ≥8**

RESULTS:

OVERALL SURVIVAL

Low Risk

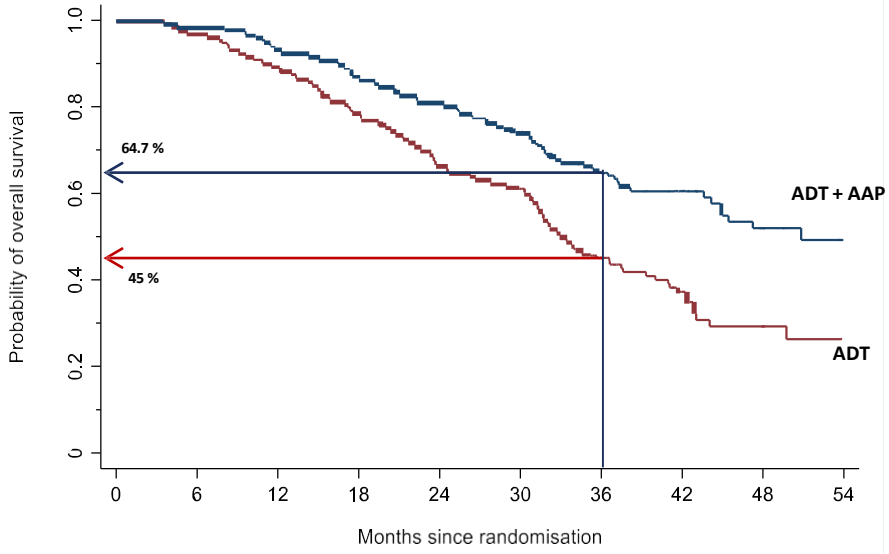


No. of patients (Events)

AAP	208	(2)	205	(17)	186	(16)	131	(5)	45
ADT alone	220	(6)	210	(21)	186	(19)	125	(7)	43

OS - 4.4%
HR 0.66 (0.44-0.98)
p=0.041

High Risk



No. of patients (Events)

AAP	241	(17)	220	(29)	190	(35)	106	(12)	28
ADT alone	232	(25)	204	(51)	148	(44)	71	(15)	13

OS – 19.7%
HR 0.54 (0.41-0.70)
p<0.001

Docetaxel or Abiraterone Summary

	Docetaxel	Abiraterone
Efficacy FFS		Probably better
Efficacy OS	Equally appropiate	Equally appropiate
High Volume Dis.		
Low Volume Dis.		
Tollerability	Occasionally preferred	Often preferred
Duration	4 months	2 years
Costs	More affordable	Less affordable

Current Landscape of available CRPC treatments

Drugs with proven survival benefit | **Supportive drug**

AR Inhibitors	Targeted Alpha Therapy	Chemotherapy	Supportive Therapy
ADT Abiraterone Enzalutamide Apalutamide Darolutamide	Radium-223 dichloride	Docetaxel Cabazitaxel	Zoledronic acid Denosumab Steroids

AIOM Italian guidelines for Prostate Cancer 2017

CRPC scelta del farmaco

- Fattori legati al paziente: sintomi, comorbidità, PS, età
- Fattori legati alla malattia: sedi (viscerali vs ossee), «tumor burden», progressione rapida vs indolente
- Fattori legati alla terapia: dati di letteratura
  - timing di progressione
  - tossicità dei trattamenti precedenti
  - cross resistenza tra ARTA
- Preferenze del paziente
- Preferenze del clinico

mCRPC e trattamento:

Vantaggi

- Aumento in OS
- Cronicizzazione della malattia e trattamenti sequenziali
- Miglioramento QoL e PRO
- Somministrazione orale
- Gestione ambulatoriale del paziente
- Minor impatto psicologico

Median OS in Advanced Prostate Cancer

1990s	Prednisone (P) alone (mCRPC):	12.6 mo[1]
2004	TAX327 (DOC/P – mCRPC):	18.9 mo[2]
2010	TROPIC (DOC/P → CAB/P – mCRPC)*:	29.4 mo[3-4]
2011	COU-AA-301 (DOC/P → ABI/P – mCRPC)*:	32.6 mo[5]
2013	COU-AA-302 (ABI/P pre-DOC – mCRPC):	34.7 mo[6]
2014	PREVAIL (ENZA pre-DOC – mCRPC):	35.3 mo[7]
2015	STAMPEDE – M1 (DOC/P + ADT – mHSPC):	65.0 mo[8]
2016	CHAARTED – M1 (DOC/P + ADT – mHSPC):	57.6 mo[9]
2017	LATITUDE & STAMPEDE (ABI/P +ADT –mHSPC):	not yet reached

*Median OS calculated from first DOC cycle

1. Kantoff PW. J Clin Oncol. 1999;7:2506–13; 2. Tannock IF. N Engl J Med. 2004;351:1502–12; 3. de Bono JS et al. Lancet. 2010;376:1147–54; 4. Sartor O. J Clin Oncol. 2011;29(S15):abstract 4525 (podium presentation); 5. Fizazi K . Lancet Oncol. 2012;13:983–92 (supplementary appendix); 6. Ryan CJ. Lancet Oncol. 2015;16:152–60; 7. Beer TM. Eur Urol. 2017;71:151–54; 8. James ND et al. Lancet. 2016;387:1163–77; 9. Sweeney C et al. Ann Oncol. 2016;27(suppl 6):

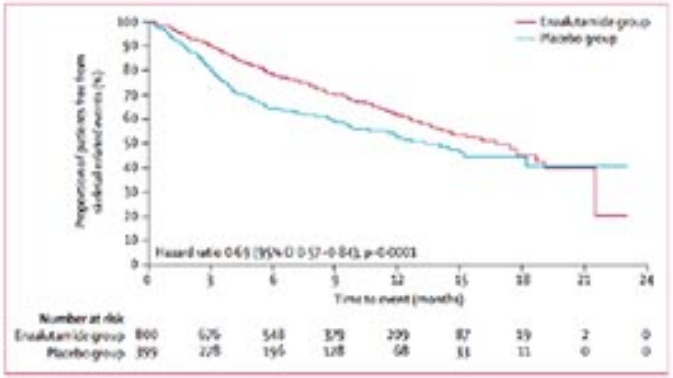
ABIRATERONE: Patient Reported Outcomes (PROs)

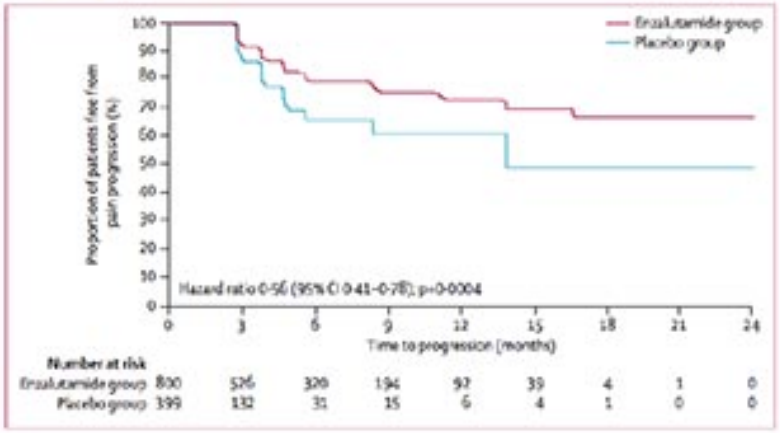
COU-AA-301 Logothetis *et al.* (2012)[25] **Pain palliation**	Phase III RCT; abiraterone + prednisone (797 patients) versus placebo + prednisone (398 patients) post-docetaxel treatme… PROs measured using the BPI–SF at sc… (baseline), day 15 of cycle one, and da… subsequent treatment cycle until the … treatment	In patients with clinically significant pain at baseline, those receiving	Good exploratory analysis of pain data with …lso
COU-AA-301 Harland *et al.* (2013)[26] **FACT-P total score improvement**	QoL aspect of phase III RCT; PROs me… using FACT–P at baseline and on day 1 of cycles 1, 4, 7, 10 and every six cycles until end of study treatment	significant improvements FACT–P total score 48% versus 32% ($P<0.0001$); longer median time to deterioration in FACT–P total score ($P<0.0001$); similar differences were observed in all FACT–P subscales, with the exception of the social/family wellbeing domain, median time to improvement in the physical wellbeing domain; trial outcome index was significantly shorter ($P<0.01$)	impaired HRQoL considered for the improvement analyses, could have shown numbers of patients that improved, declined or stayed the same over time, more frequent assessments needed
COU-AA-301 Sternberg *et al.* (2013)[27] **Fatigue improvement**	Pain and fatigue aspect of phase III RCT; PROs measured using the BFI at baseline (~14 days before the first dose of study treatment) and on the first day of each treatment cycle until treatment discontinuation	Abiraterone + prednisone superior in terms of improvement in clinically significant fatigue at baseline (58% versus 40%, $P=0.0001$), improved fatigue interference (55% versus 38%, $P=0.0075$), and accelerated improvement in fatigue intensity ($P=0.0155$)	Good study but again, analyses confined to those with fatigue at baseline
COU-AA-302 Basch *et al.* (2013)[28] **Delayed time to deterioration**	Phase III RCT; abiraterone + prednisone (546 patients) versus placebo + prednisone (542 patients) in chemotherapy-naive patients; PROs measured using BPI-SF at screening, day 1 of each treatment cycle and at treatment end; FACT–P on the first day of cycles 1, 3, 5, 7 and then the first day of every third cycle and at treatment discontinuation	Abiraterone + prednisone superior in terms of: median time to mean pain intensity, 26.7 versus 18.4 months ($P=0.049$); and median time to pain interference with daily activities, 10.3 versus 7.4 months ($P=0.005$); abiraterone + prednisone significantly delayed time to QoL deterioration as assessed by FACT–P total score, general function and trial outcome index composite scores, prostate-cancer-specific scores, and all subscale scores ($P<0.001$) except for social and family wellbeing. Median times to progression of worst pain intensity were similar between groups	Good reporting of data from BPI, but only reported overall QoL scores

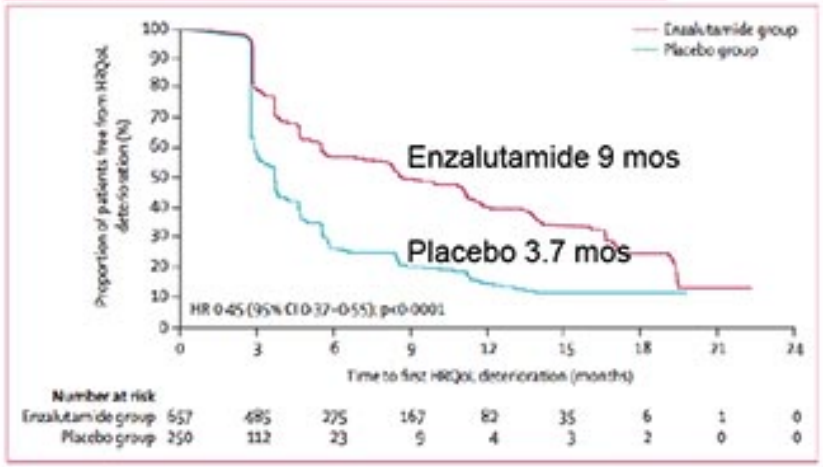
Improvement in all PRO nel CRPC

Fallowfield, Critical rev in Clin Oncol 2016

ENZALUTAMIDE: significantly longer time to first SRE, pain progression and HRQoL deterioration - AFFIRM study

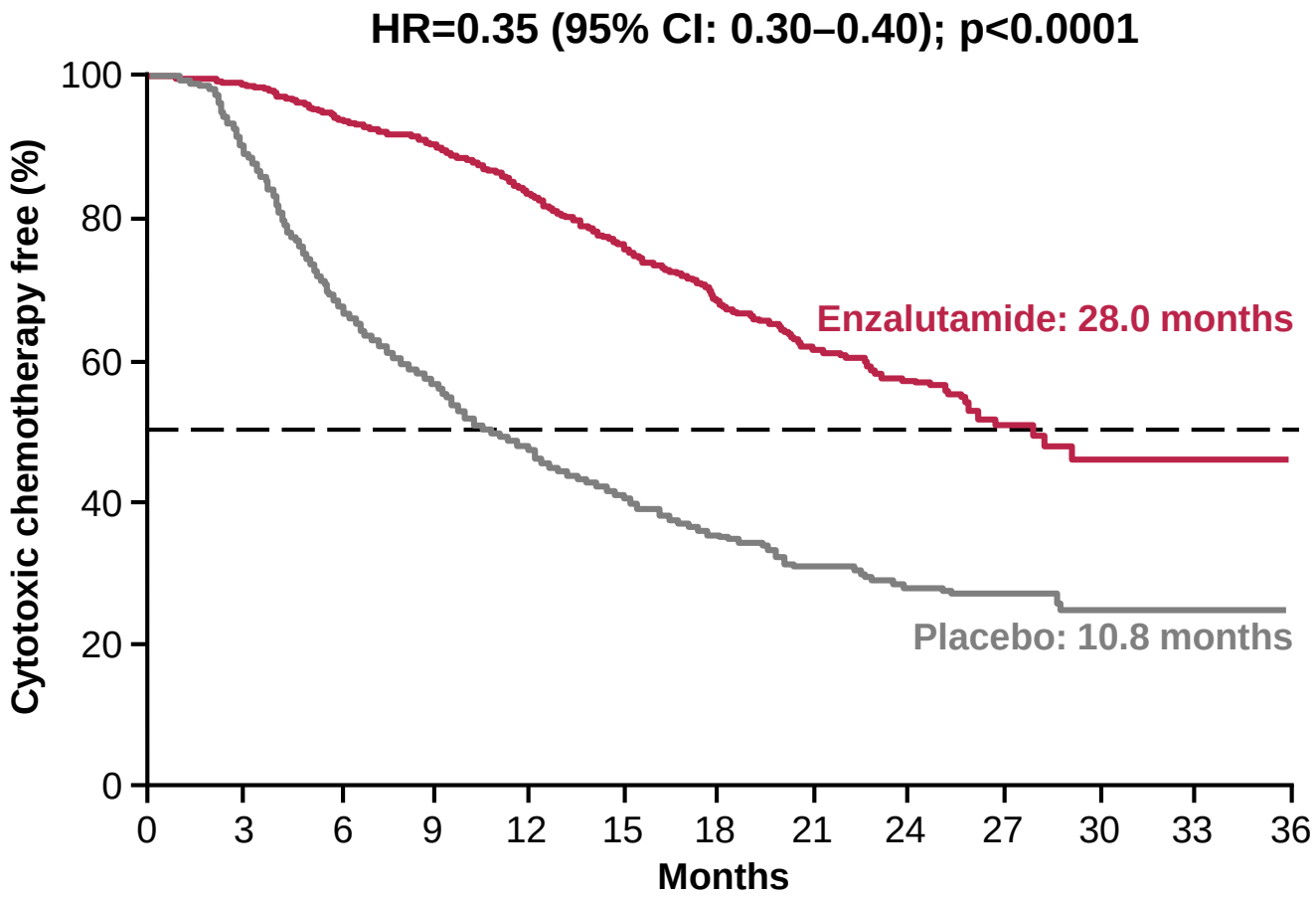






Fizazi K, *et al. Lancet Oncol* 2014;15:1147–56

Enzalutamide delayed median time to chemotherapy by 17 months



Enzalutamide, n	872	854	799	751	665	575	388	252	158	78	21	2	0
Placebo, n	845	734	518	415	324	257	165	103	64	25	9	0	0

CI=confidence interval; HR=hazard ratio.

Beer TM, *et al.* ASCO-GU 2014; Oral presentation.

PRO:

- Somministrazione orale
- Gestione ambulatoriale del paziente
- Minor impatto psicologico

Opzione 1

Stia tranquillo…
domani va da dall'oncologo
che le darà una pastiglietta
da prendere

Opzione 2

Domani andrà dall'oncologo
che le farà un po' di
chemioterapia

COSA HA SCELTO IL PAZIENTE

Buongiorno!
Oggi preferisco iniziare
la terapia in pastiglie,
che mi farà GUARIRE!

mCRPC e trattamento:

Criticità:

1. Tossicità dei nuovi farmaci

2. Combinazione dei nuovi farmaci

3. Cost-effectiveness

4. Difficoltà nella personalizzazione dei farmaci ad alto costo

	CHAARTED	STAMPEDE-Docetaxel ($n = 1776$)		GETUG-AFU 15	
	Docetaxel group	Docetaxel group	ADT alone	Docetaxel group	ADT alone
	($n = 397$)[a]	($n = 592$)	($n = 1184$)	($n = 189$)	($n = 186$)
Grade 3, 4, or 5 adverse event	29.6%	52%	32%	NR	NR
Neutropenia	12.1%	12%	0%	32%	0%
Febrile neutropenia	6.1%	15%	1%	~7%	0%
Fatigue	4.1%	NR; 7% had "general disorder", including lethargy, fatigue, asthenia	NR; 4% "general disorder"	7%	1%
Infection with neutropenia	2.3%	NR	NR	~2%	0%
Allergic reaction	2.1%	NR	NR		

Grade 2,4 or 5 toxicity Associated with Abiraterone or Docetaxel in phase III trials for mHSPC

	LATITUDE		STAMPEDE-Abiraterone	
	Abiraterone group ($n = 597$)	Placebo group ($n = 602$)	Abiraterone group ($n = 948$)	ADT alone ($n = 960$)
Grade 3, 4, or 5 adverse event[a]	63%	48%	47%	33%
Hypertension	20%	~10%	5%	1%
Hypokalemia	10%	~1%	1%	<1%
Hyperglycemia	~4%	3%	1%	0%
Elevated ALT	~5%	1%	6%	<1%
Elevated AST	~4%	1%	1%	1%
Cardiac disorders[b]				
Any	4%	1%	5%	3%
Atrial fibrillation	<1%	<1%	NR	NR
Myocardial infarction	NR	NR	1%	1%
Cardiac dysrhythmia	NR	NR	1%	<1%
Fatigue	2%	2%	2%	2%
Respiratory disorders	NR	NR	5%	2%

ABIRATERONE

- Emivita:

  t1/2= 15 Ore
- Distribuzione:

  Tessuti periferici
- Metabolismo:

  Epatico
- ELIMINAZIONE

  88% feci - 5 % urine

ENZALUTAMIDE

- Emivita:

  t1/2= 5,8 Giorni

Distribuzione:

Passa la BEE

- Metabolismo:

  Epatico
- ELIMINAZIONE

  71% urine - 13,6% feci

Riassunto delle caratteristiche del prodotto di Xtandi
Riassunto delle caratteristiche del prodotto di Zytiga

Interazioni con altri medicinali (da RCP)

Abiraterone	Enzalutamide
Analgesici (es. codeina, ossicodone, tramadolo)	**Analgesici** (es. fentanyl, tramadolo)
Antibiotici (es. rifampicina, rifapentina, rifabutina, telitromicina)	**Antibiotici** (es. claritromicina, doxiciclina)
Antineoplastici NON RIPORTATO*	**Antineoplastici** (es. cabazitaxel)
Anticoagulanti NON RIPORTATO*	**Anticoagulanti** (es. acenocumarolo, warfarin)
Antiepilettici (es. fenitoina, carbamazepina, fenobarbitale)	**Antiepilettici** (es. carbamazepina, clonazepam, fenitoina, primidone, valproato)
Antipsicotici (es. Erba di San Giovanni, aloperidolo, risperidone, tioridazina)	**Antipsicotici** (es. aloperidolo)
Betabloccanti (es. metoprololo, propranololo)	**Betabloccanti** (es. bisprololo, propranololo)
Calcioantagonisti NON RIPORTATO*	**Calcioantagonisti** (es. diltiazem, felodipina, nicardipina, nifedipina, verapamil)
Glicosidi cardiaci NON RIPORTATO*	**Glicosidi cardiaci** (es. digossina)
Corticosteroidi NON RIPORTATO*	**Corticosteroidi** (es. desametasone, prednisolone)
Antivirali HIV NON RIPORTATO*	**Antivirali HIV** (es. indinavir, ritonavir)
Ipnotici e antidepressivi (es. desipramina, venlafaxina)	**Ipnotici e antidepressivi** (es. diazepam, midazolam, zolpidem)
Statine NON RIPORTATO*	**Statine metabolizzate da CYP3A4** (es. atrovastatina, simvastatina)
Farmaci tiroidei NON RIPORTATO*	**Farmaci tiroidei** (es. levotiroxina)
Antiaritmici (es. propafenone, flecanide)	**Antiaritmici NON RIPORTATO***

Riassunto delle caratteristiche del prodotto di Xtandi
Riassunto delle caratteristiche del prodotto di Zytiga

Six-month patient-reported outcome (PRO) results from AQUARIUS, a prospective, observational, multicenter phase 4 study in patients (Pts) with metastatic castration-resistant prostate cancer (mCRPC) receiving abiraterone acetate + prednisone (AAP) or enzalutamide (ENZ) – Abstract ASCO 2018

Vuillemin AT et al

Premessa

AQUARIUS è uno studio osservazionale, attualmente in corso, condotto con l'obiettivo di analizzare i Patient Report Outcome (PRO) nei pazienti con mCRPC che iniziano un trattamento di prima linea con abiraterone acetato e prednisone (AAP) o enzalutamide (ENZ).
In tutti i 211 pazienti arruolati è stata determinata l'incidenza del peggioramento clinicamente significativo (CMW) durante i primi 6 mesi di trattamento con AAP (n=105) o ENZ (n=106).

Risultati

Durante i primi 6 mesi una percentuale significativamente inferiore di pazienti in terapia con AAP ha manifestato CMW rispetto a quelli trattati con ENZ in ogni parametro valutato (vedi tabella nella slide successiva): Functional Assessment of Cancer Therapy-Cognitive Function (FACT-Cog), Brief Fatigue Inventory (BFI) e European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30).

	Pts with ≥ 1 episode of CMW during first 6 mos of treatment			
	AAP, %	ENZ, %	Odds ratio[a] (95% CI)	*p*
FACT-Cog Perceived cognitive impairments Comments from others	27 20	56 39	0.27 (0.13-0.56) 0.38 (0.17-0.85)	0.0004 0.0191
BFI Fatigue right now Usual level of fatigue	42 40	55 55	0.46 (0.22-0.95) 0.42 (0.20-0.86)	0.0365 0.0174
EORTC QLQ-C30 Fatigue Appetite loss	31 20	53 46	0.36 (0.18-0.73) 0.28 (0.13-0.61)	0.0047 0.0013

[a]AAP vs ENZ.

Evolution of neuropsychiatric adverse events of enzalutamide and AA and ENZ treatments reported in EudraVigilance in mCRPC patients

Analisi delle ADR riportate nel DB europeo della Farmacovigilanza EUDRAVIGILANCE

- **ADR analizzate**: headache, seizure, fall, dizziness, hallucination, restless, anxiety, and insomnia.

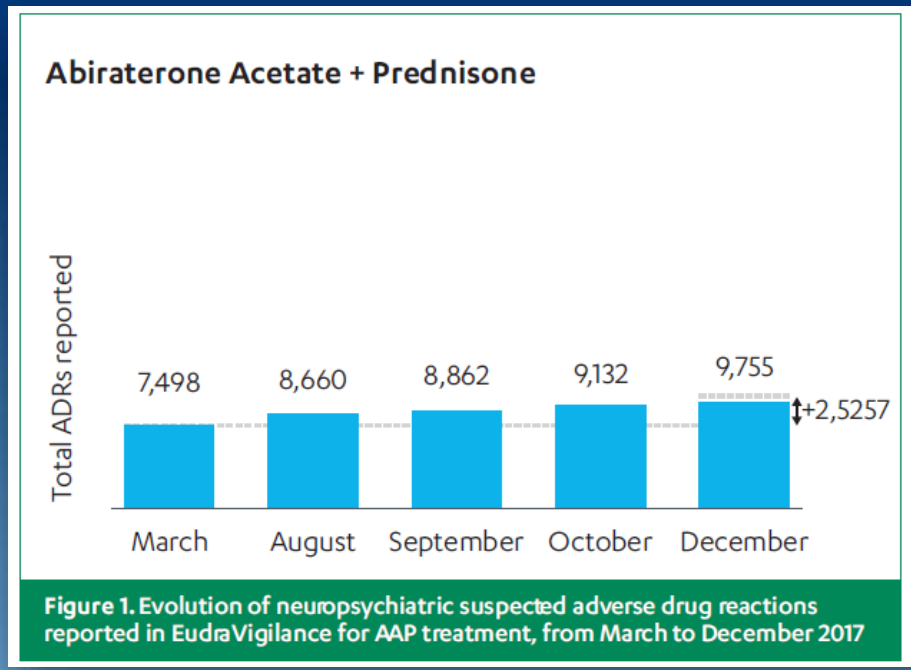


Figure 1. Evolution of neuropsychiatric suspected adverse drug reactions reported in EudraVigilance for AAP treatment, from March to December 2017

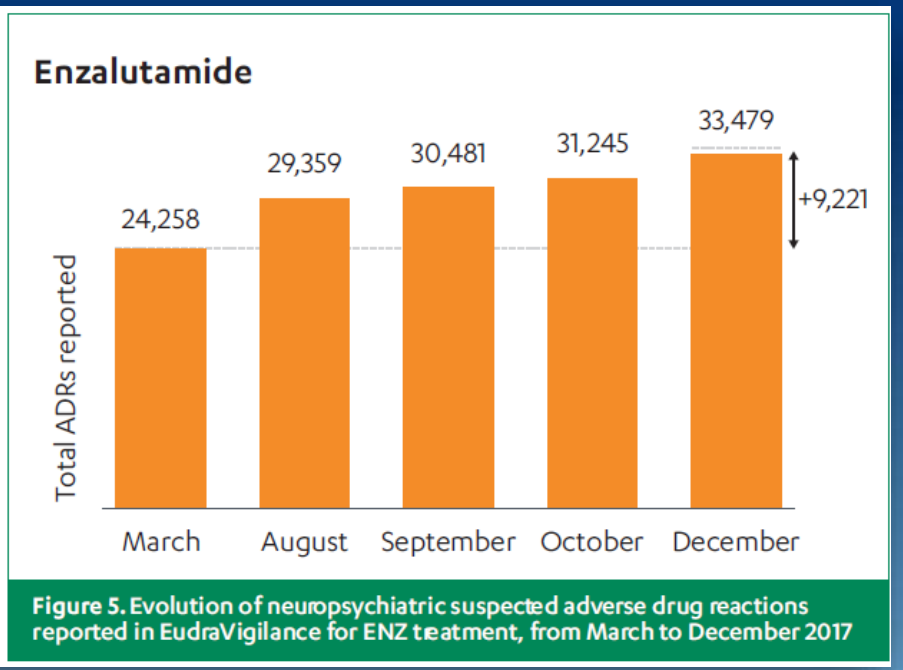


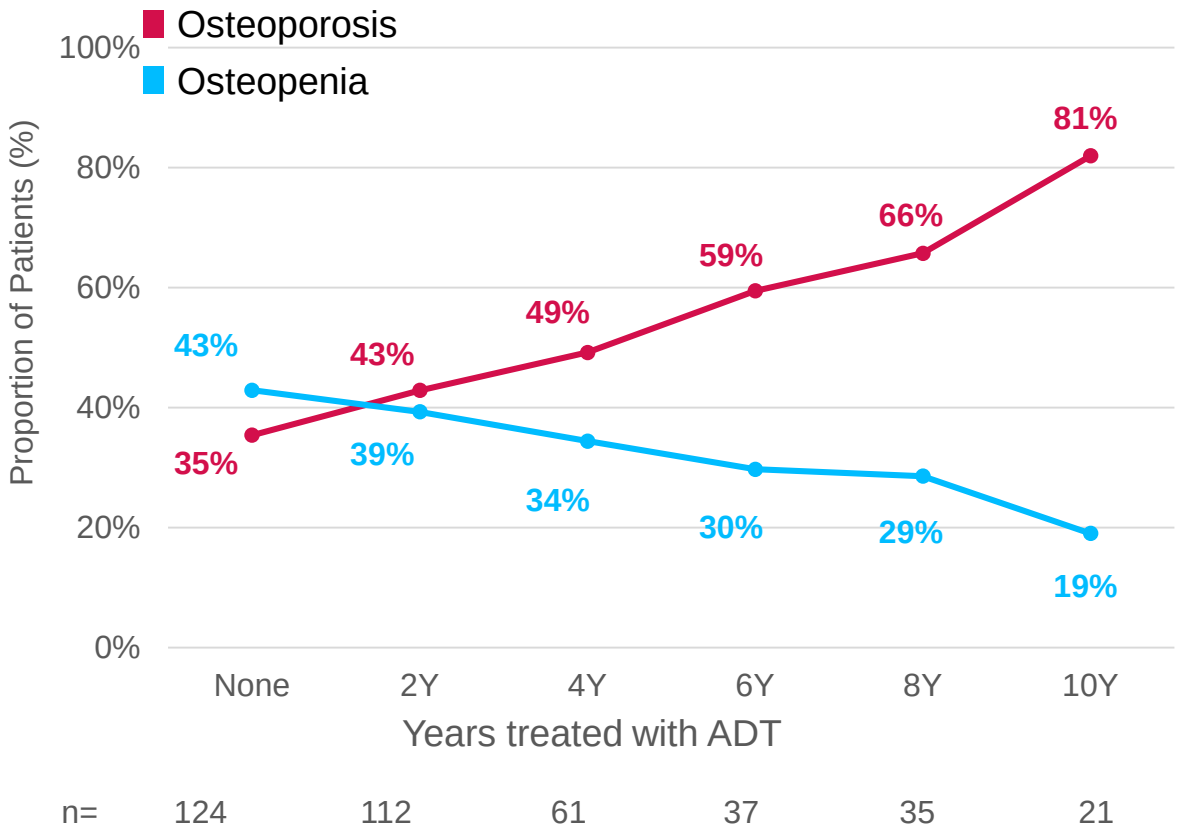
Figure 5. Evolution of neuropsychiatric suspected adverse drug reactions reported in EudraVigilance for ENZ treatment, from March to December 2017

Moreno P, et al. Poster presented at ASCO-GU 2018; abstract 343.

Prostate Cancer Patients Are at an Elevated Risk of Osteoporosis Due to Standard Androgen Deprivation Therapy

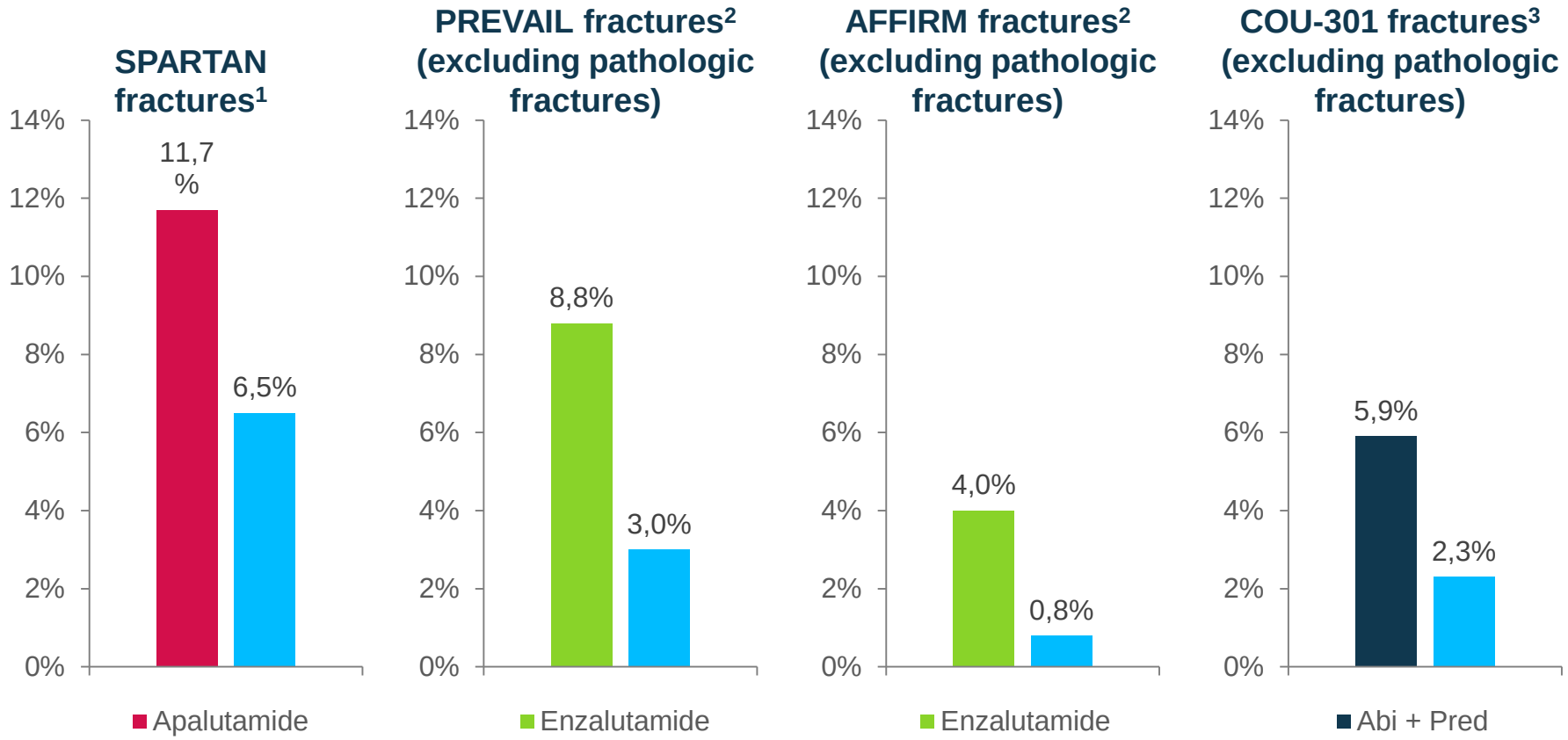
The rate of osteoporosis in men treated with ADT increases over time*,[1]

// Prevalence of poor bone health in ADT-treated prostate cancers is high, and increases with duration of ADT treatment



1. Morote J *et al. Urology* 2007;69:500–504. **2.** Saad F *et al. J Clin Oncol* 2008;26:5465–5476.

Apalutamide, Enzalutamide, Abiraterone + Prednisone: aumento del rischio di fratture non patologiche



// The apalutamide USPI contains a warning and precaution to monitor and manage patients at risk of fractures according to treatment guidelines and consider the use of bone-targeted agents[4]

// In the PROSPER trial, 17% of enzalutamide-treated patients reported falls and fractures compared with 8% of placebo-treated patients[5]

Monitoraggio dello stato osseo nei pazienti con tumore della prostata

ADT e NAHs utilizzati più a lungo portano a aumento del danno osseo [1]

E’ raccomandato che gli uomini in trattamento ormonale per tumore della prostata vengano periodicamente valutati per lo stato di salute dell’osso [1–3]

Una supplementazione di calcio (1200 mg die) e vitamina D3 (800–1000 IU die) è raccomandata per gli uomini >50 anni[3,4]

ADT, androgen deprivation therapy; **NAH**, novel anti-hormonal.

1. Rachner TD et *al. Lancet Diabetes Endocrinol.* 2018;doi: 10.1016/S2213-8587(18)30047-0 [Epub ahead of print]. **2.** Parker C *et al. Ann Oncol* 2015;26(Supplement 5):v69–v77. **3.** Gillessen S *et al. Eur Urol* 2018;73:178–211. **4.** Cosman F *et al. Osteoporos Int* 2014;25:2359–2381.

mCRPC: linee guida per prevenire SSE

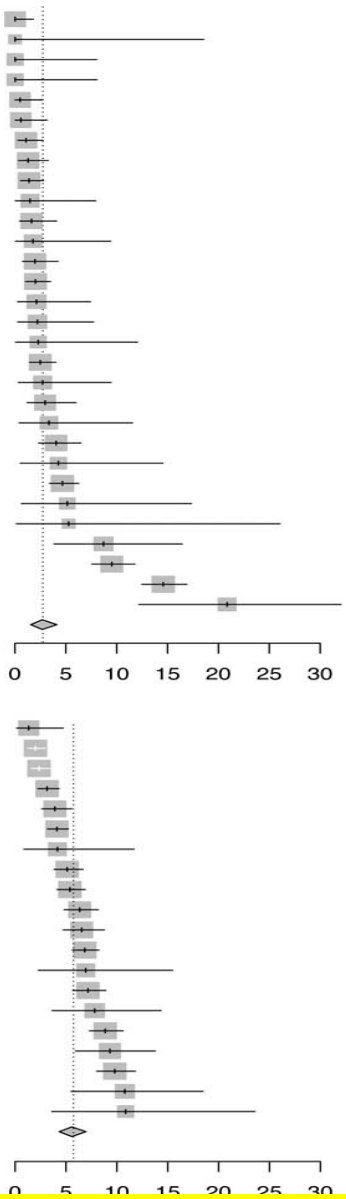
- mHSPC: BHA raccomandati solo per prevenzione osteoporosi[1]
- Il trattamento con denosumab o bifosfonati è raccomandato per pazienti con mCRPC e metastasi ossee per prevenire o ritardare gli eventi scheletrici[1,3]

BMD, bone mineral density; **CRPC**, castration-resistant prostate cancer; **mHSPC**, metastatic hormone-resistant prostate cancer.

1. Gillessen S *et al. Eur Urol* 2018;73:178–211. **2.** Parker C *et al. Ann Oncol* 2015;26(Supplement 5):v69–v77. **3.** National Comprehensive Cancer Network. Prostate Cancer V2.2018; Available at: https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf; Accessed March 2018. **4.** Cosman F *et al. Osteoporos Int* 2014;25:2359–2381. **5**. Tsourdi E *et al. Bone* 2017;105:11–17.

FATIGUE and CORTICOSTEROIDS

Study ID	Nr of patients	Nr of patients with grade 3–4 Fatigue			
NO chronic use of corticosteroids					
Yu, Evan Y 2015	205	0	0.00	[0.00; 1.78]
Ward JE 2012	18	0	0.00	[0.00; 18.53]
Bradley DA 2011	44	0	0.00	[0.00; 8.04]
M. Dror Michaelson 2006	44	0	0.00	[0.00; 8.04]
Pili R 2011	206	1	0.49	[0.01; 2.67]
Beer TM 2011	175	1	0.57	[0.01; 3.14]
Neal D Shore 2016	372	4	1.08	[0.29; 2.73]
Nicholas D. James 2009	312	4	1.28	[0.35; 3.25]
Kantoff PW 2010	512	7	1.37	[0.55; 2.80]
Steven Attia 2008	68	1	1.47	[0.04; 7.92]
Eric J. Small 2004	248	4	1.61	[0.44; 4.08]
Noguchi M 2010	57	1	1.75	[0.04; 9.39]
Randall E. Millikan 2008	306	6	1.96	[0.72; 4.22]
Tomasz M. Beer 2016	598	12	2.01	[1.04; 3.48]
Orazio Caffo 2008	95	2	2.11	[0.26; 7.40]
J.–C. Eymard 2007	91	2	2.20	[0.27; 7.71]
Freytag SO 2014	44	1	2.27	[0.06; 12.02]
Smith MR 2013	645	16	2.48	[1.42; 4.00]
William L. Dahut, 2004	74	2	2.70	[0.33; 9.42]
William D. Figg 2009	237	7	2.95	[1.20; 5.99]
Keizman D 2010	60	2	3.33	[0.41; 11.53]
Sweeney CJ 2015	397	16	4.03	[2.32; 6.46]
Richard Cathomas 2016	47	2	4.26	[0.52; 14.54]
Hoskin P 2014	901	42	4.66	[3.38; 6.25]
Azad AA 2014	39	2	5.13	[0.63; 17.32]
James L. Gulley 2005	19	1	5.26	[0.13; 26.03]
Matthew D. Galsky 2005	92	8	8.70	[3.83; 16.42]
Kwon ED 2014	789	75	9.51	[7.55; 11.77]
Matthew Smith 2016	1023	149	14.57	[12.46; 16.88]
THOMAS NELIUS 200	72	15	20.83	[12.16; 32.02]
pooled Estimate	7790		2.67	[1.53; 4.11]
Heterogeneity: I^2 = 92%	0.0113, $p < 0.01$			
YES chronic use of corticosteroids				
Jean–Pascal Machiels 2008	150	2	1.33	[0.16; 4.73]
Karim Fizazi 2017	1199	24	2.00	[1.29; 2.96]
Stèphane Oudard 2017	1147	27	2.35	[1.56; 3.41]
Mario Eisenberger 2017	1175	37	3.15	[2.23; 4.31]
de Bono JS 2010	742	29	3.91	[2.63; 5.57]
Saad F 2015	1554	64	4.12	[3.19; 5.23]
WILLIAM D. FIGG 2005	72	3	4.17	[0.87; 11.70]
Ian F. Tannock 2004	997	51	5.12	[3.83; 6.67]
Fizazi K 2015	1095	59	5.39	[4.13; 6.90]
Michaelson MD 2014	866	55	6.35	[4.82; 8.19]
Tomasz M Beer 2017	627	41	6.54	[4.73; 8.77]
Araujo JC 2013	1518	104	6.85	[5.63; 8.24]
Petrioli R 2011	72	5	6.94	[2.29; 15.47]
Petrylak DP 2015	1046	75	7.17	[5.68; 8.91]
Fleming MT 2012	115	9	7.83	[3.64; 14.34]
de Bono JS 2011	1185	105	8.86	[7.30; 10.62]
de Bono JS 2014	236	22	9.32	[5.93; 13.77]
Kim N Chi 2017	1000	98	9.80	[8.03; 11.81]
Dreicer R 2013	102	11	10.78	[5.51; 18.48]
Emmanuel S. Antonarakis 2017	46	5	10.87	[3.62; 23.57]
pooled Estimate	14944		5.58	[4.33; 6.98]
Heterogeneity: I^2 = 89%, τ^2 = 0.0029, $p < 0.01$				



Test for between group differences (Random Effect Model)

	Q	*df*	*p-value*
Between-groups	*9.65*	*1*	*0.002*

Di Lorenzo et al, submitted

mCRPC e trattamento:

Criticità:

Combinazione dei nuovi farmaci

ERA 223: Concomitant Treatment of Asymptomatic or Mildly Symptomatic CRPC with Bone Metastases with Radium-223 in Combination with Abiraterone and Prednisone

	Radium-223 + abiraterone + prednisone	Placebo + abiraterone + prednisone
SSE-FS events, no. patients with event	49% (196/401)	47% (190/405)
Median (95% CIs) SSE-FS, months	**22.3**	**26** p=0.2636
Survival analysis		
Deaths	39% (155/401)	35% (141/405)
P-value	0.128	
HR (95% CIs)	1.195 (0.950- 1.505)	
Median OS (95% CIs), months	**30.7 (25.8, NE)**	**33.3 (30.2, 41.1)**

A, value cannot be estimated due to censored data.

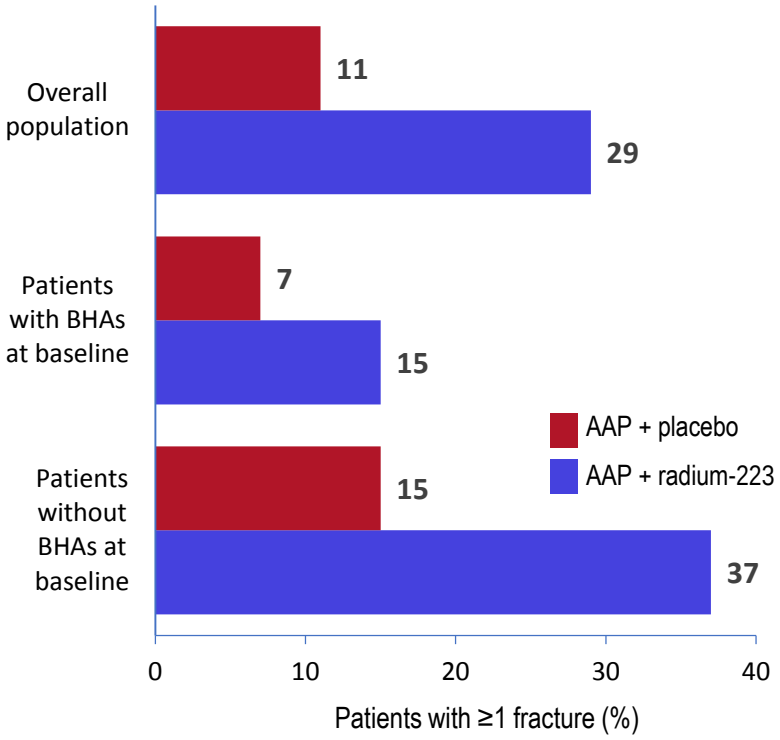
Unplanned interim analysis; data cutoff November 24, 2017.

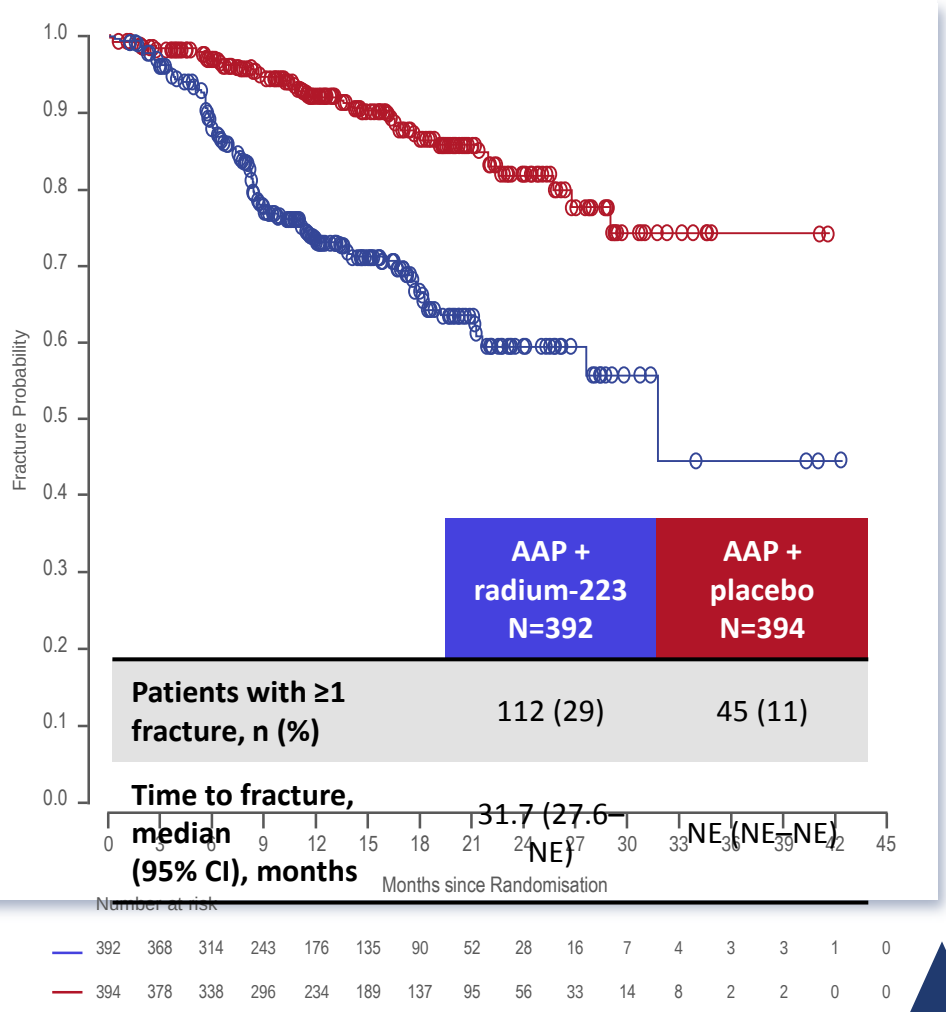
CI, confidence interval; **HR**, hazard ratio; **OS**, overall survival; **SSE-FS**, symptomatic skeletal event-free survival.

European Medicines Agency: Pharmacovigilance Risk Assessment Committee (PRAC). Assessment Report on Provisional Measures (Xofigo): EMA/170170/2018; 2018. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/002653/WC500246181.pdf. Accessed April 2018.

Studio ERA-223

Fractures Occurring after Date of the First Dose (Investigator Assessment)





	AAP + radium-223 N=392	AAP + placebo N=394
Patients with ≥1 fracture, n (%)	112 (29)	45 (11)
Time to fracture, median (95% CI), months	31.7 (27.6–NE)	NE (NE–NE)

AAP, abiraterone acetate and prednisone/prednisolone; BHA, bone health agent; NE, not estimable.

mCRPC e trattamento:

Criticità:

1. Cost-effectiveness

6514 - Cost-effectiveness of abiraterone versus docetaxel in metastatic hormone naïve prostate cancer.

- Chethan Ramamurthy et al.

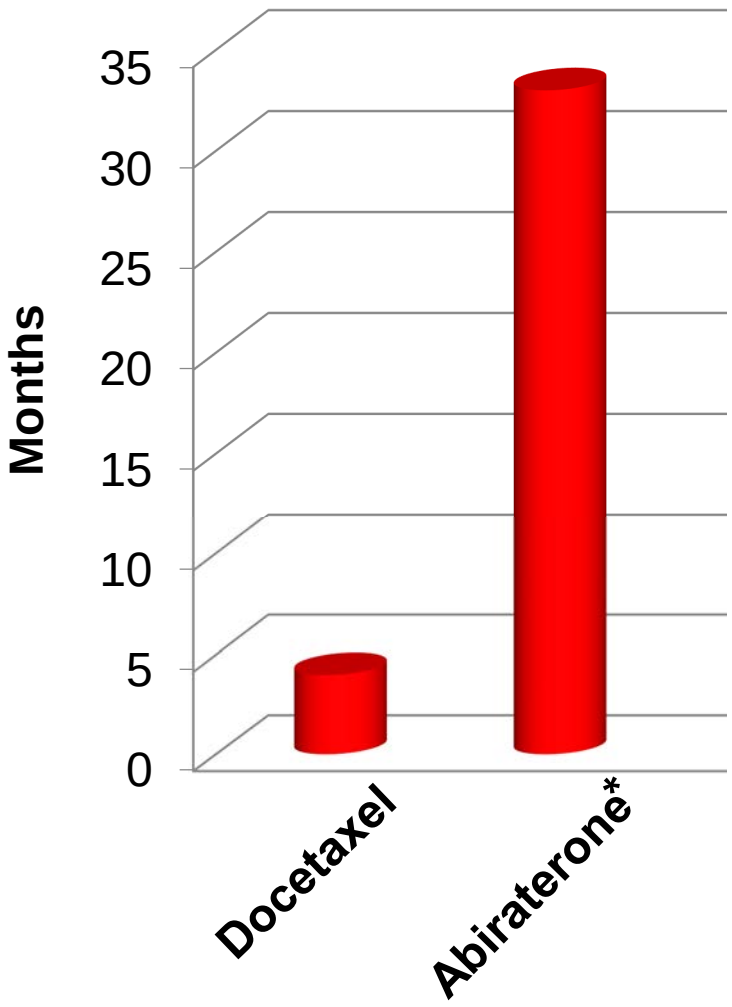
Markov Model

- Inputs
  - Survival - progression/death from the CHAARTED and LATITUDE studies.
  - AEs were modeled
  - Utility values - obtained from the literature.
  - Costs - obtained from a range of sources (Average Wholesale Price and VA costs).
- Outputs
  - Effectiveness PFS quality adjusted life years (PFS QALYs)
  - Incremental cost-effectiveness ratios (ICER).

Table 2. Results of Cost Effectiveness Markov Model

	Docetaxel	Abiraterone
PF QALY gained	0.32	0.48
Cost Increase	$12,500	$208,000
ICER (base case)	$39,600/PF QALY	$434,000/PF QALY

Treatment duration and costs



Two different treatment strategies

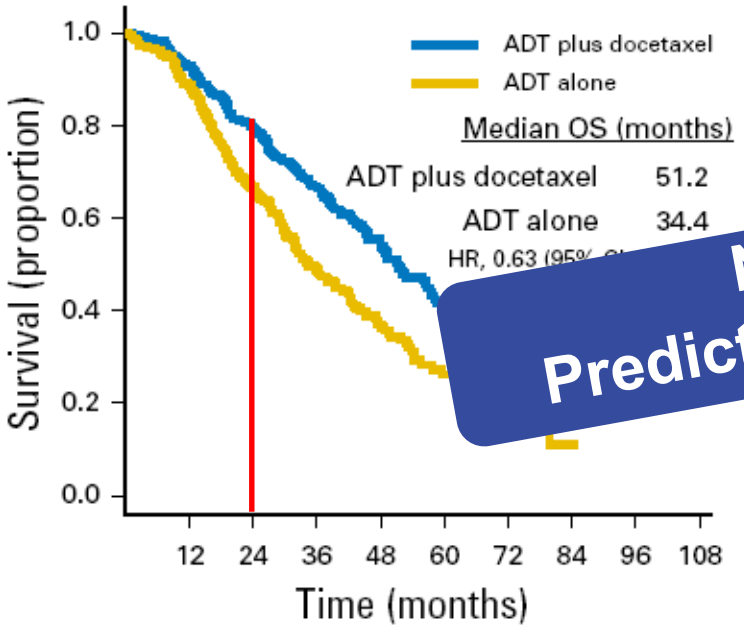
Fixed Term **Vs** **Until Progression**

Cost and sustainability is an issue

*33 months median radiographic PFS in LATITUDE

Despite early Docetaxel or Abiraterone 20% of patients die after 24 months

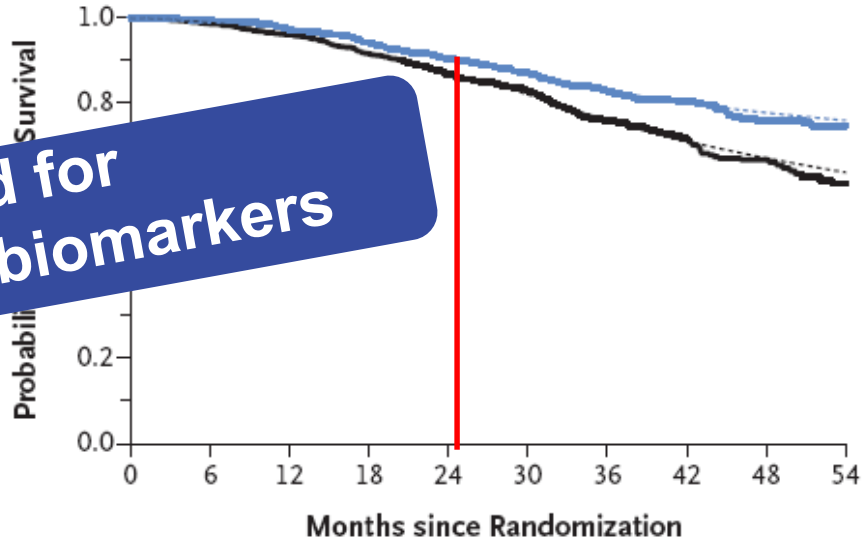
CHAARTED
Overall Survival High-volume



No. at risk:

ADT plus docetaxel	263	239	202	151	91	41	16	5	2	0
ADT alone	250	215	156	104	59	19	9	1	0	0

LATITUDE
Overall Survival High-risk



No. of Patients (no. of deaths)									
Combination therapy	960	(26)	917	(63)	840	(67)	541	(25)	161
ADT alone	957	(37)	909	(88)	806	(92)	491	(36)	123

Need for Predictive biomarkers

Kyriakoupulos et Al. JCO 2018

James et Al. NEJM 2017

Despite early Docetaxel or Abiraterone 20% of patients die after 24 months

Plan to combine the data from trials that stratified by docetaxel

	ENZAMET	PEACE-1*	Combined
Overall	**N**	**N**	**N**
ADT+D	**252**	**290**	**542**
ADT+Doc + Enz /Abi	**252**	**290**	**542**
High Volume			
ADT+D	**180**	**232**	**412**
ADT+D+E/A	**180**	**232**	**412**

Plus: Some patients from STAMPEDE and TITAN (ADT +/- apalutamide)

Hypothesis:
Targeting both AR positive & AR negative clones could lead to incremental benefit with ADT + docetaxel + abiraterone + pred

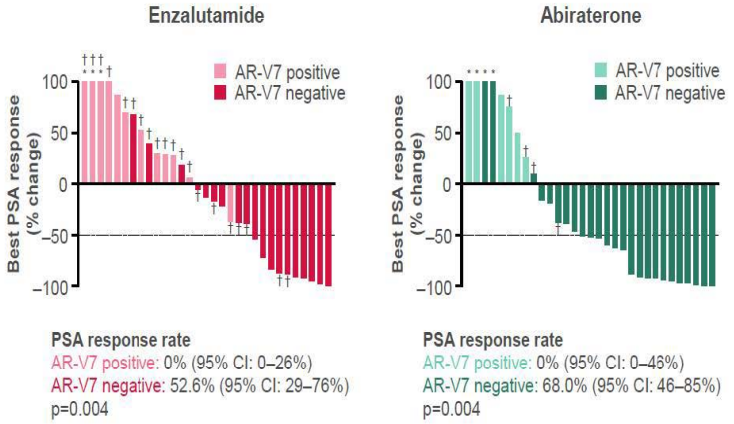
mCRPC e trattamento:

Criticità:

1. Difficoltà nella personalizzazione dei farmaci

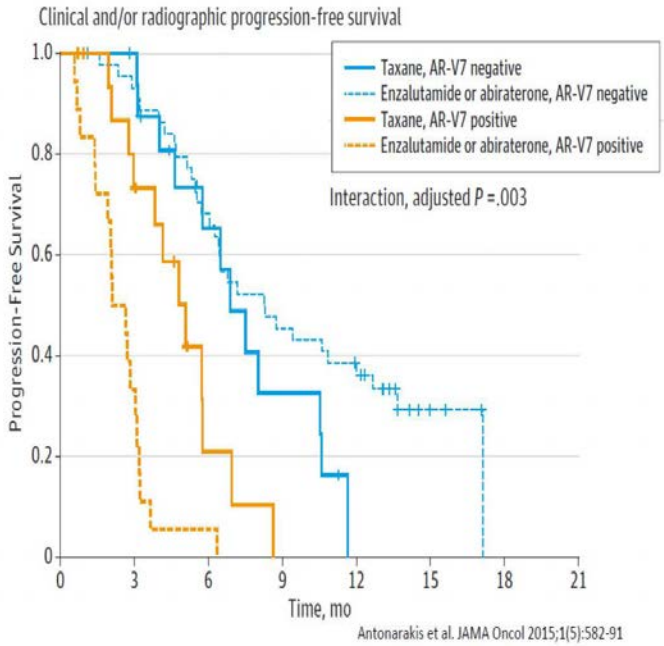
PSA responses according to AR-V7 status

- Patients previously receiving chemotherapy, abiraterone or enzalutamide were included



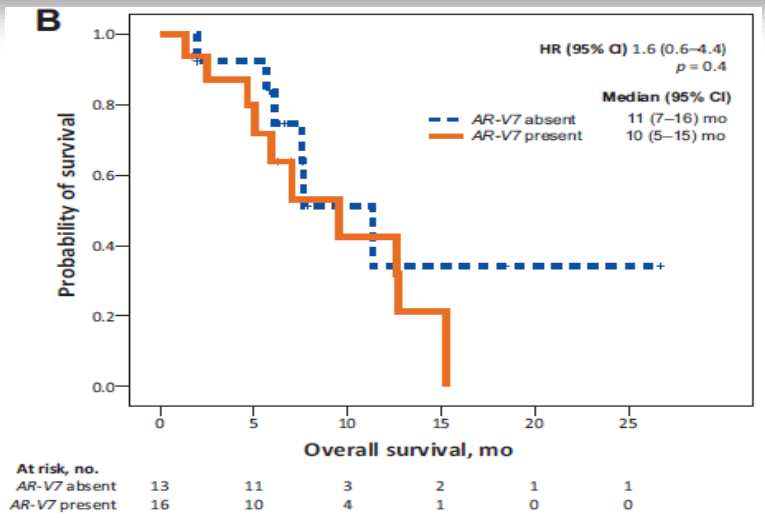
*Increase of more than 100% in best PSA response. †Patients in the enzalutamide cohort who had previously received abiraterone and patients in the abiraterone cohort who had previously received enzalutamide.
Antonarakis ES, *et al. N Engl J Med* 2014;371:1028–38.

AR-V7 and taxanes in mCRPC



Antonarakis et al. JAMA Oncol 2015;1(5):582-91

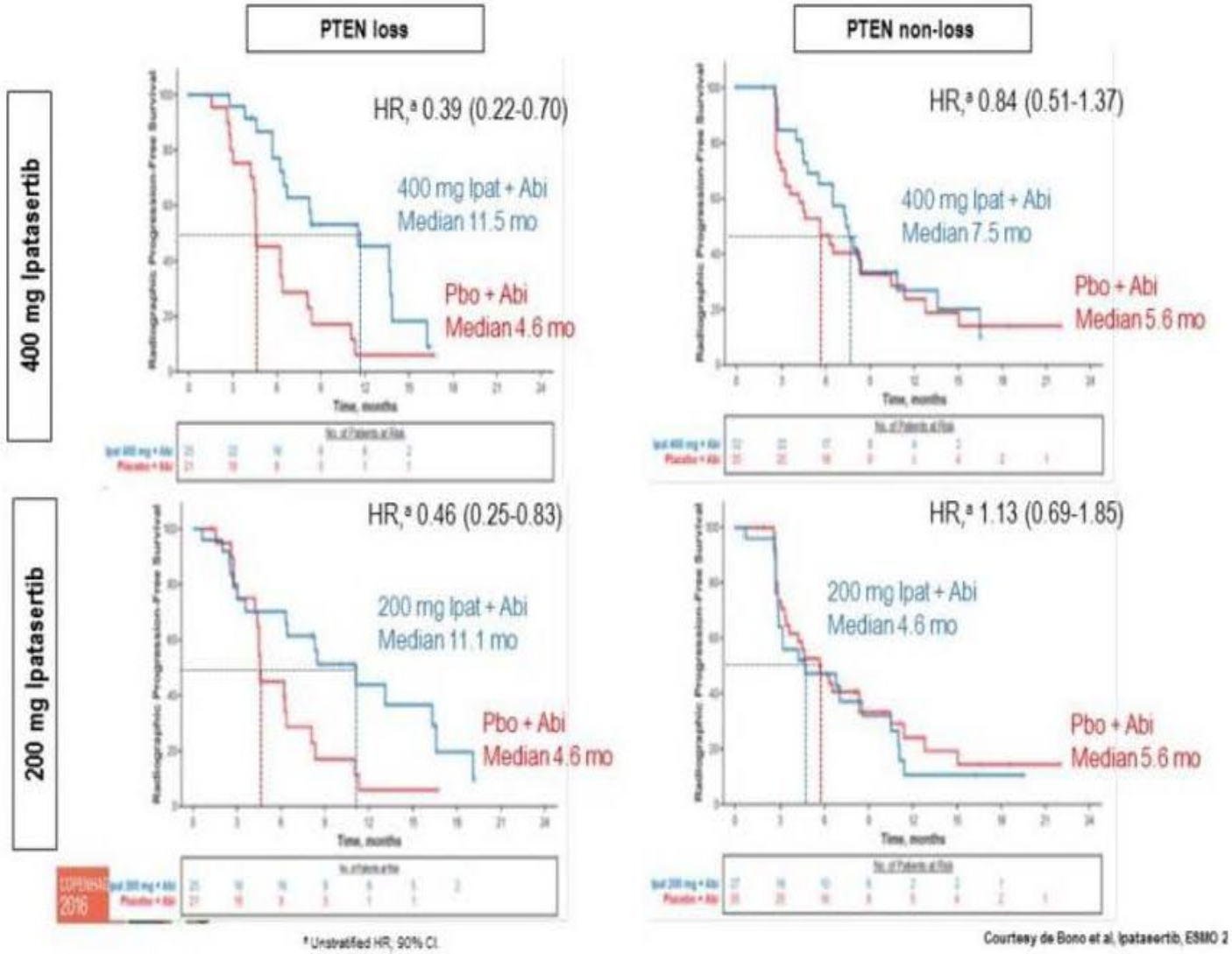
Cabazitaxel efficacy does not seem influenced by ARV7 status in mCRPC patients



ARV7 as biomarker

- ARV7 expression growth during CRPC evolution;
- Prognostic role;
- No predictive role;
- Differences among CTC-CDNA and tissue;
- Differences among intrapatient metastases;
- Node metastases : higher ARV7 than bone.

CO-PRIMARY ENDPOINT: RPFS WITH IPATASERTIB OR PLACEBO + ABIRATERONE BY ICR IHC



ª Unstratified HR, 90% CI.

Courtesy de Bono et al, Ipatasertib, ESMO 2

A Randomized Phase 2 Study of Cabazitaxel vs Abiraterone or Enzalutamide in Poor Prognosis Metastatic Castration-Resistant Prostate Cancer

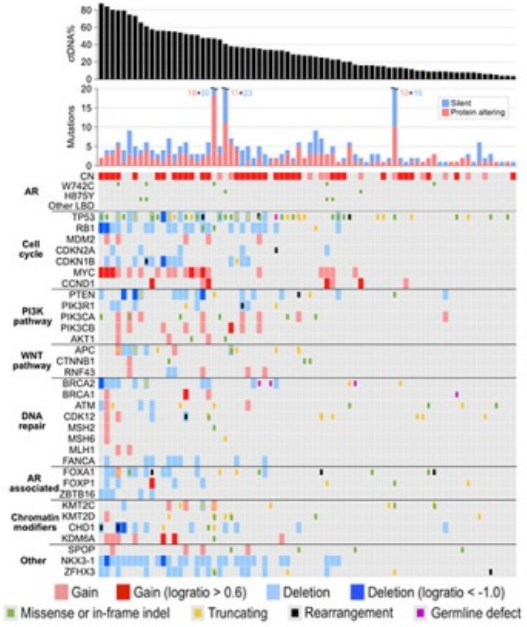
Kim N. Chi[1,2], Sinja Taavitsainen[2], Nayyer Iqbal[3], Cristiano Ferrario[4], Michael Ong[5], Deepa Wadhwa[6], Sebastien J. Hotte[7], Gregory Lo[8], Ben Tran[9], Arun Azad[10], Lori Wood[11], Joel R. Gingerich[12], Scott North[13], Carmel J. Pezaro[14], Dean Ruether[15], Srikala S. Sridhar[16], Matti Annala[2], Jack Bacon[2], Alexander W. Wyatt[2]

[1]BC Cancer - Vancouver Centre, [2]Urologic Sciences, University of British Columbia, [3]Saskatoon Cancer Centre, [4]Jewish General Hospital , [5] Ottawa Hospital Cancer Centre, [6]BC Cancer - Kelowna Centre, [7]Juravinski Cancer Centre, [8]Durham Regional Cancer Centre, [9]Peter MacCallum Cancer Centre, [10]Monash Health [11]QEII Health Sciences Centre, [12]CancerCare Manitoba, [13]Cross Cancer Institute, [14]Eastern Health, [15]Tom Baker Cancer Centre, [16]Princess Margaret Hospital

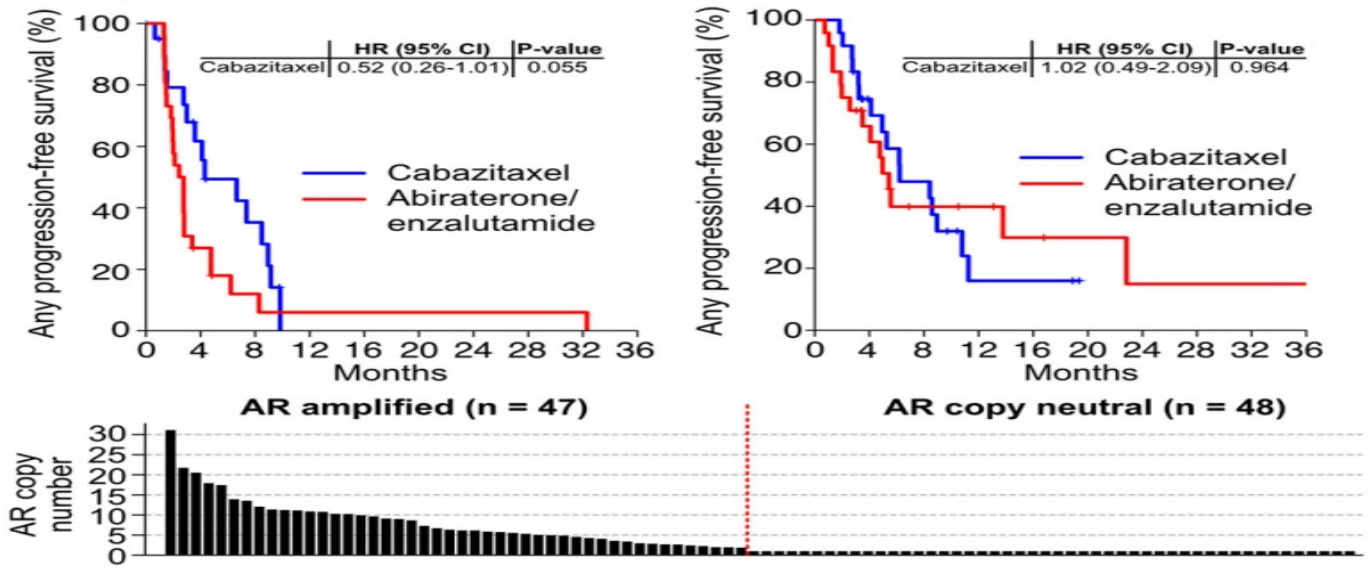
ctDNA and genomic alterations

Alteration	Current Study "Poor Prognosis" (n = 95)	"All Comers" Cohort[1] (n = 202)	P-value
ctDNA > 2%	74 / 95 (78%)	115 / 202 (57%)	0.0005
TP53 mutation	38 / 95 (40%)	66 / 202 (33%)	0.2413
AR amplification	47 / 95 (49%)	67 / 202 (33%)	0.0103
SPOP mutation	4 / 95 (4%)	12 / 202 (6%)	0.7835
Any DNA repair (BRCA2, ATM, CDK12, MSH2, MSH6)	25 / 95 (26%)	22 / 202 (11%)	0.0011

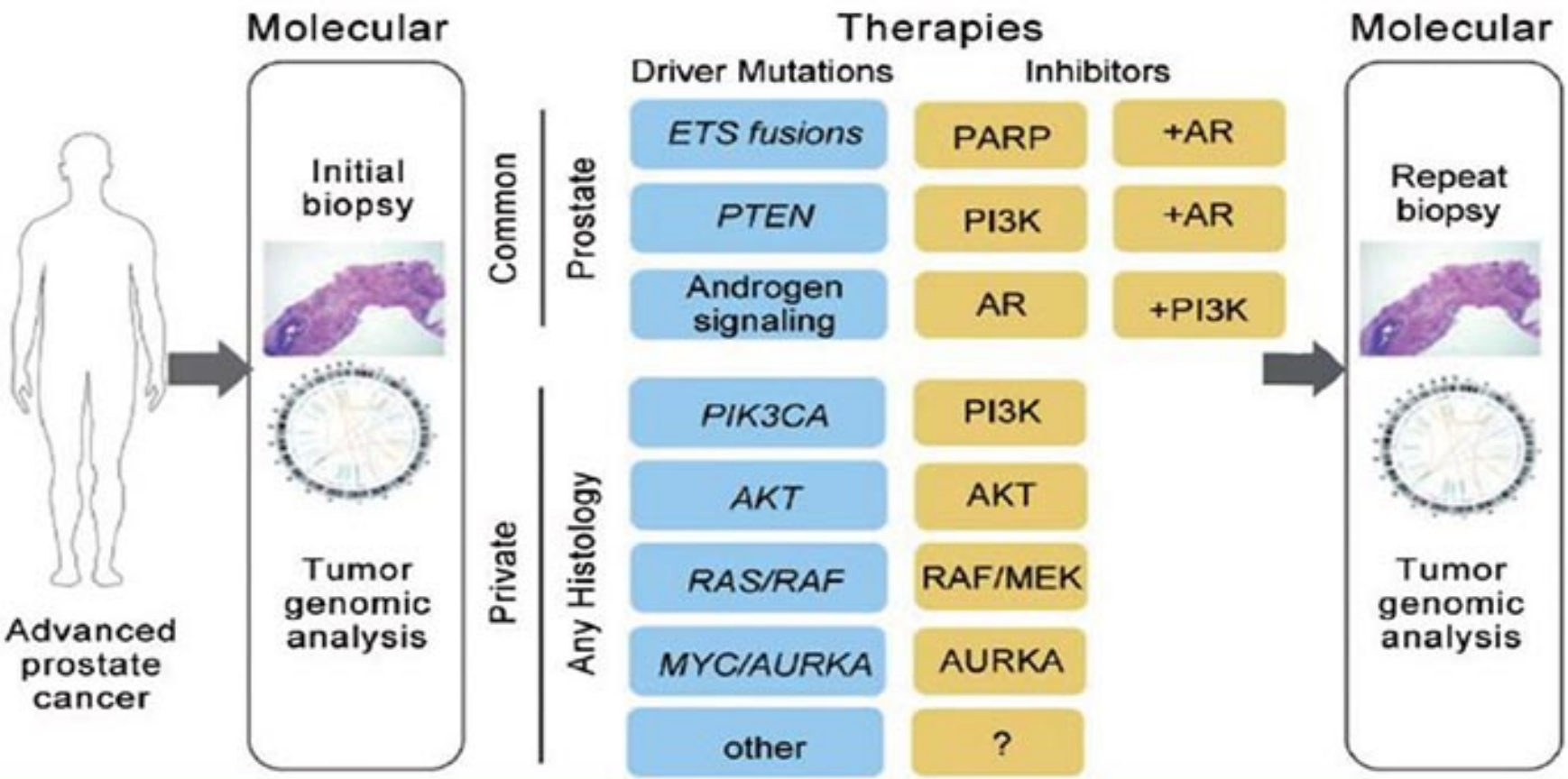
[1]M Annala, et al. Cancer Discov, 8:1–14, 2018



AR Amplification and PFS



The future choice: genomics-driven treatments



Shevrin, Asian Journal of Andrology(2016)18, 586–591

NEOPLASIE UROTELIALI

Take home messages (1)

1) Urothelial cancers are a molecularly heterogeneous disease;

2) Role of immunotherapy in different settings;

3) **Combinations Immunotherapy and immuno-Chemotherapy could improve efficacy** but *toxicity* !!!!!

4) Patients unlikely to respond to ICI remain important unanswered questions;

Take home messages (2)

5) First, caution should be used with results of phase 1-2 studies;

6) Research of predictive biomarkers is a primary issue (*PDL1…. cut off : 1, 10, >10%* …..also with cfDNA, IFY sign, TMB);

7) **Patient selection is the challenge**

UROTHELIAL CANCER

1. Role of the chemotherapy

2. Characterization of urothelial cancers

3.Immunotherapy results

4.Future directions

Flowchart for the management for T1-T4a N0M0 urothelial bladder cancer

Diagnosis
- Cystoscopy and tumour resection
- Evaluation of urethra
- CT imaging of abdomen, chest, UUT
- MR can be used for local staging

80%

Instillations BCG and Mitom.
in Ta, T1, CIS.....based on Grading..not only

Findings:
- pT2-3, clinical N0M0 urothelial carcinoma of the bladder

pT2N0M0 selected patients
- Multimodality bladder sparing therapy can be considered for T2 tumours

(Note: alternative, not the standard option)

Neoadjuvant chemotherapy
- Should be considered in selected patients
- 5-7% 5 year survival benefit

2 - *neoadjuvant radiotherapy is not recommended*

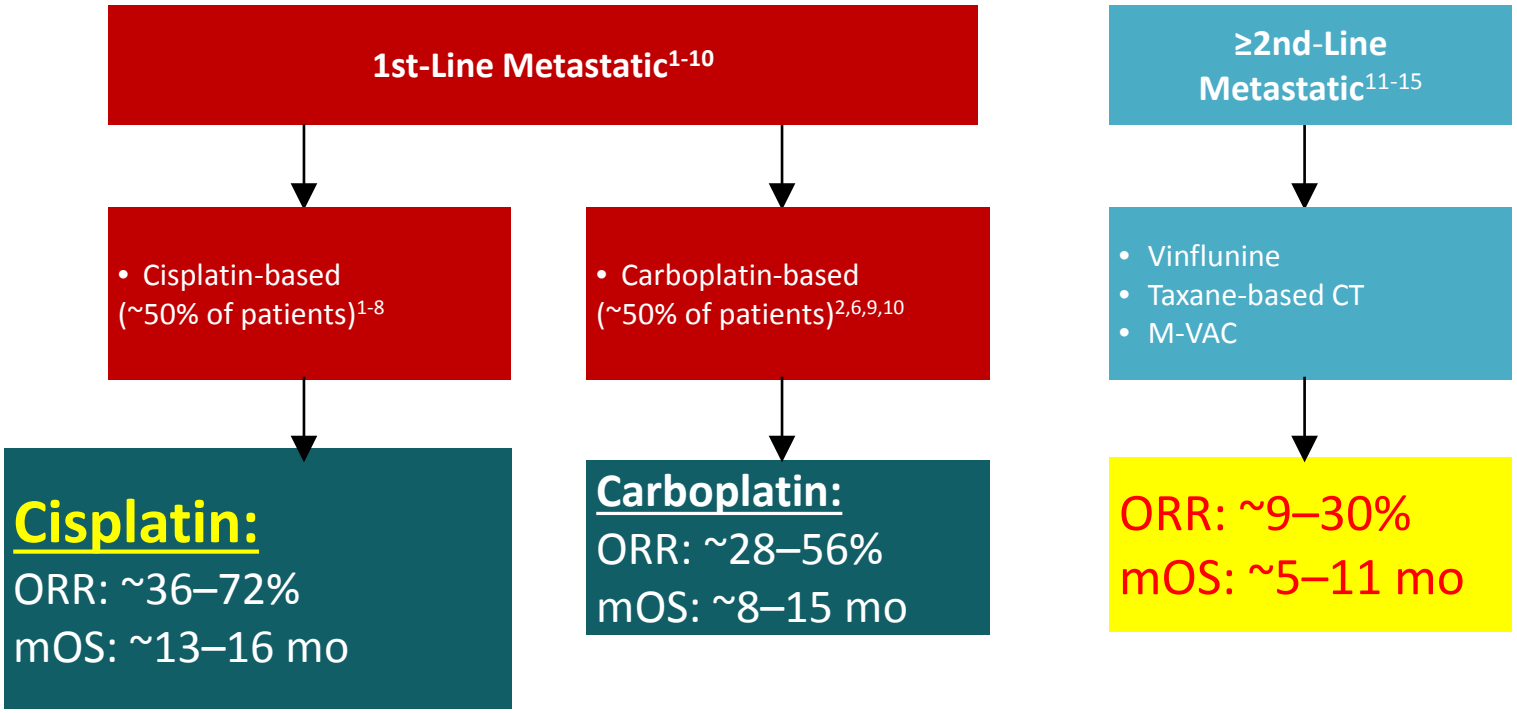
Radical cystectomy
- Know general aspects of surgery
  - o Preparation
  - o Surgical technique
  - o Integrated node dissection
  - o Urinary diversion
  - o Timing of surgery
- A higher case load improves outcome

Endpoint	HR	95% CI	P-value
OS	0.77	0.59-0.99	0.049
OS in LN (+)	0.66	0.45-0.91	0.014
DFS	0.66	0.48-0.92	0.014

Direct adjuvant chemotherapy
- Not indicated after cystectomy

Limited role

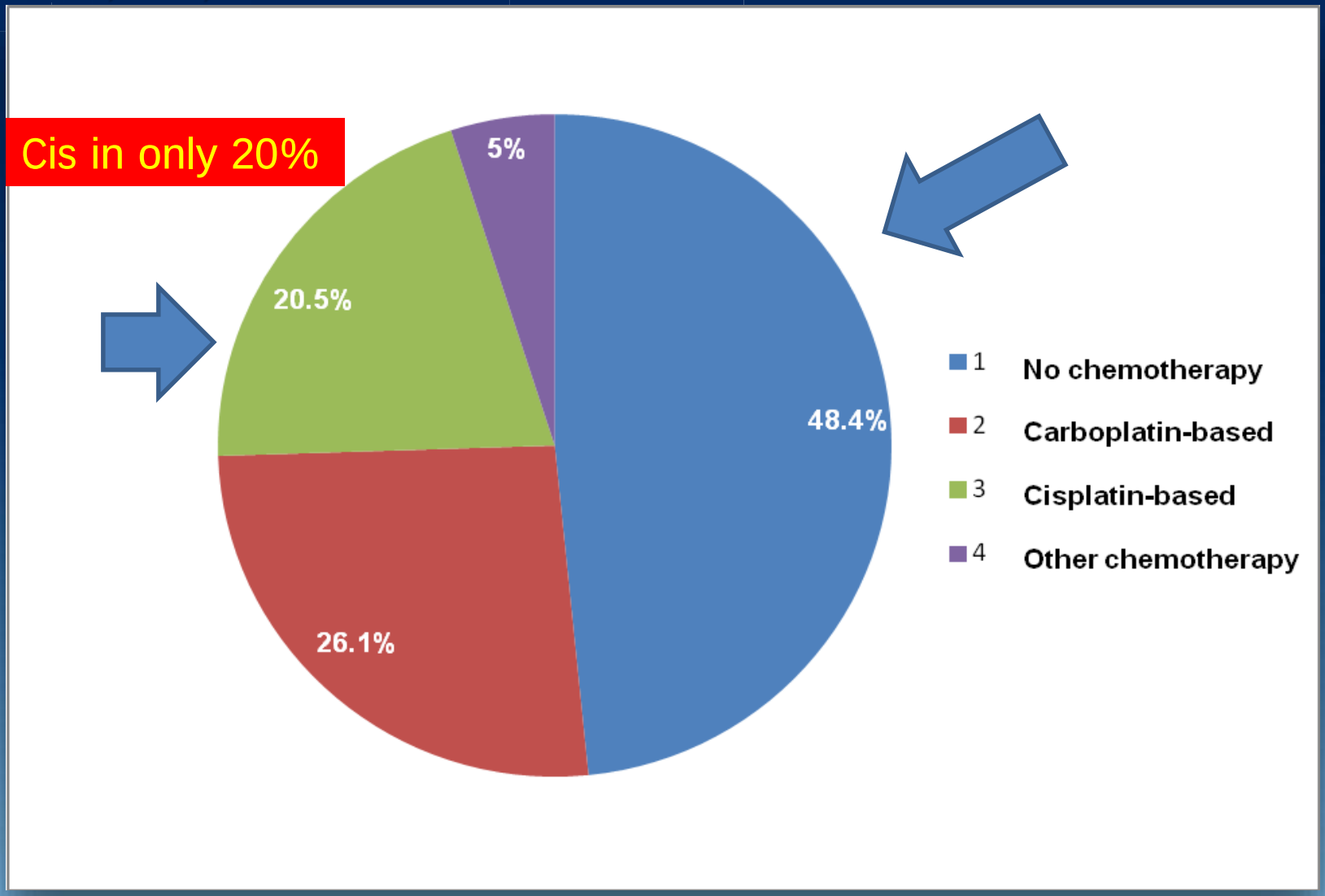
Prognosis of Metastatic Bladder Cancer Patients Treated with Chemotherapy



5-year survival rate of mBC: ~15%

Therapeutic regimens in patients presenting with metastatic urothelial carcinoma (N=1031)

Sonpavde G, et al, Clin Genitourin Cancer 2014



Cisplatin ineligibility

Galsky MD, Rosenberg JE, Hahn N, Sonpavde G, Bellmunt J, et al. JCO 2011.

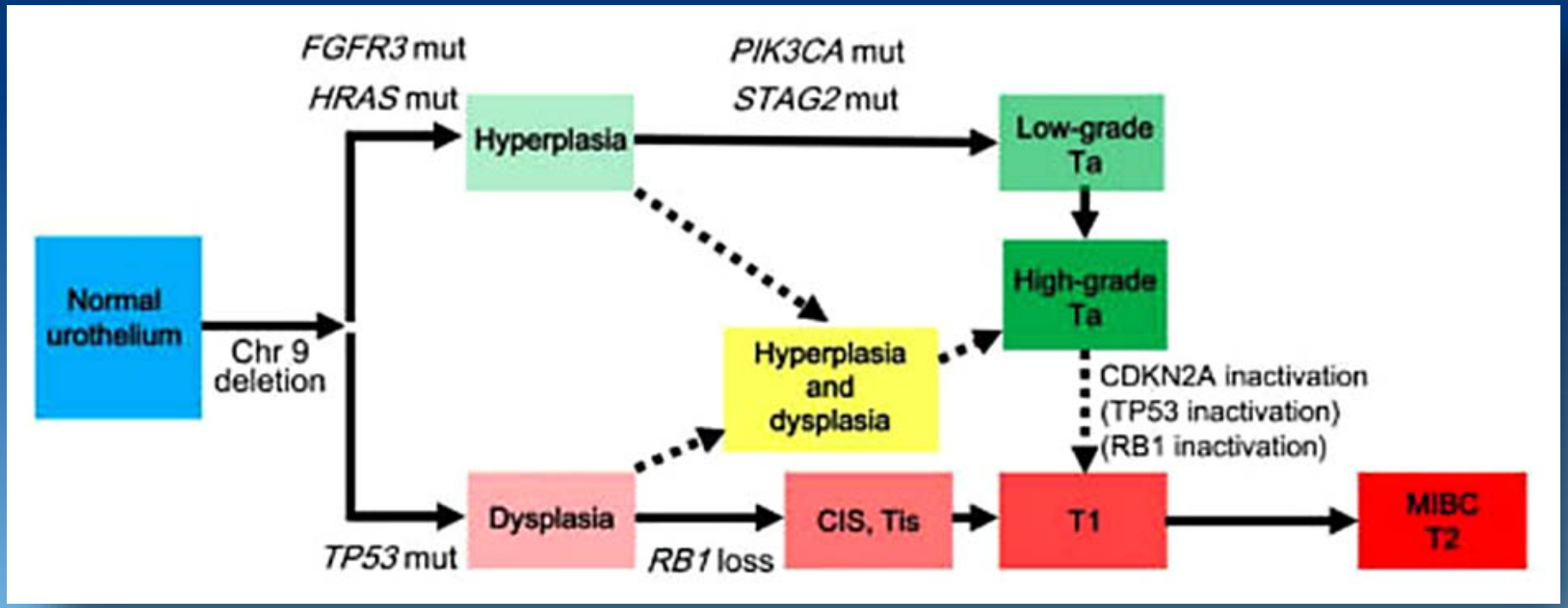
≥1 of the following:

- Estimated creatinine clearance <60 ml/min
- Performance status = 2
- Cardiac dysfunction class 3
- Peripheral neuropathy >grade 1
- Severe hearing impairment >grade 1
- ?Age (≥80 years)
- ?Solitary kidney
- ?Incurable by cisplatin: visceral metastasis

1. Chromosomal alterations;

2. FGFR3, PI3K, RAS: superficial urothelial cancer and low grade;

3: TP53, RB1: most common in high grade, muscle invasive



Molecular subtypes in 2411 tumors

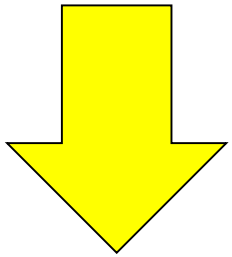
6 molecular subtypes were identified:

- Neural like: high WNT/B catenin signaling
- HER-2 like: ERBB2 amplification
- Papillary like: FGFR3 mutations
- Luminal like: kras mutations
- Mesenchymal like: AXL signaling
- Squamous cell carcinoma like: high PD1, CTL4 signaling

Tuan et al, EUR UROL 2018

Molecular subtypes in 2411 tumors

6 molecular subtypes were identified:



Different OS

-Non muscle-invasive shows predominantly PAPILLARY-LIKE and good prognosis;

-20% non muscle-invasive shows muscle invasive subtypes and lower 5 –yr OS rate (81% vs 96%)

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Topics to discuss

Characterization of muscle-invasive urothelial cancers

ARTICLE Nature 1/29/2014; 507:315-22, 2014 OPEN
doi:10.1038/nature12965

Comprehensive molecular characterization of urothelial bladder carcinoma

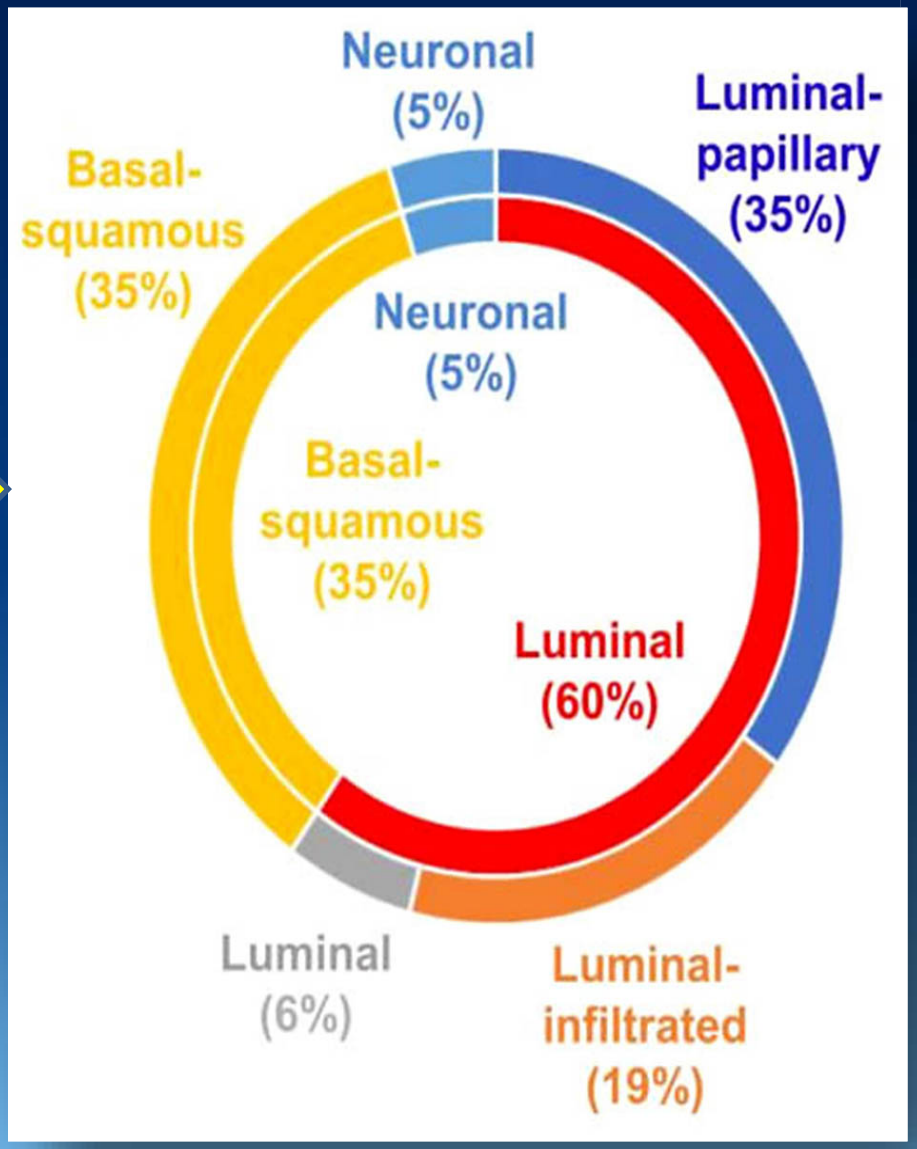
The Cancer Genome Atlas Research Network. Nature 507:315, 2014
Corresponding authors: John N Weinstein, Seth P Lerner, David Kwiatkowski

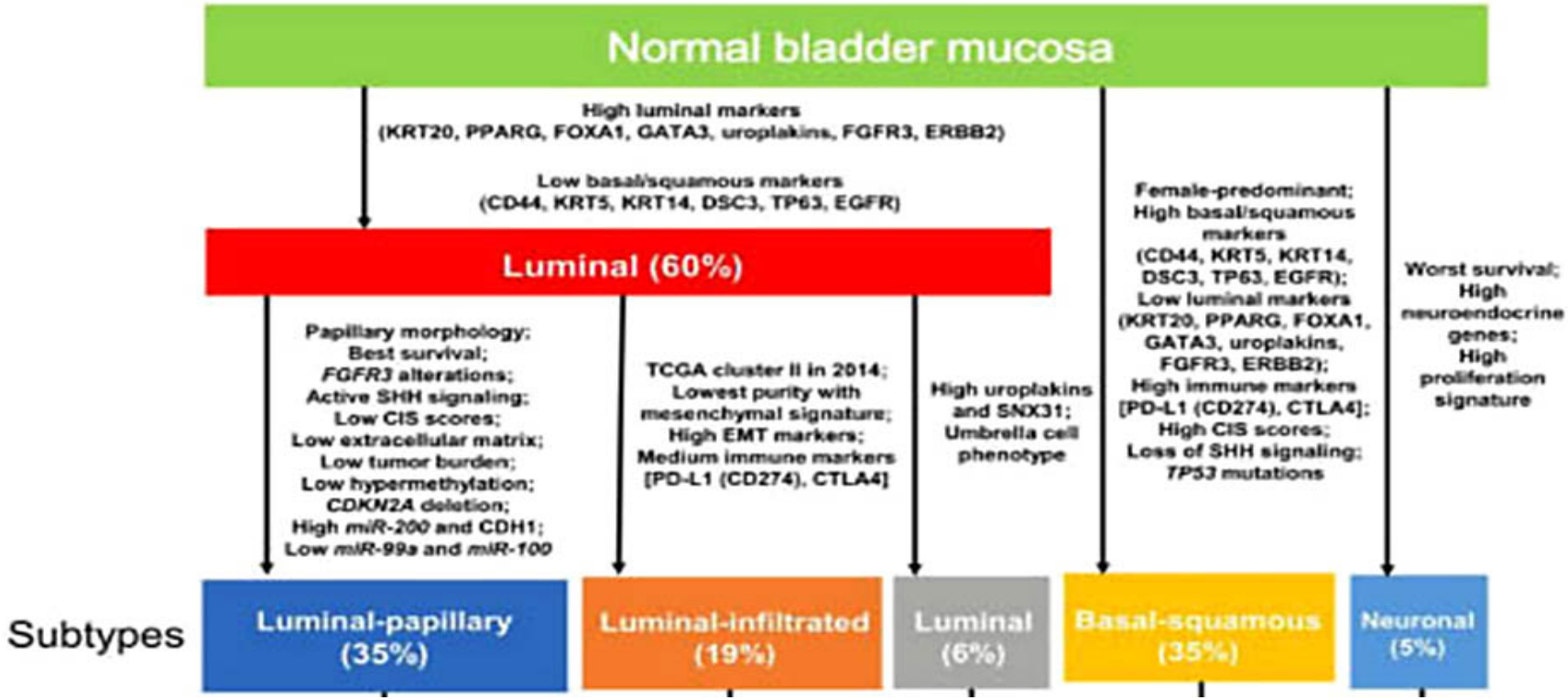
- Key findings: 131 tumors (T2-T4, N any, M any, < 50% divergent histology)
  - Mean and median somatic mutation rate per tumor 7.7 and 5.5 per megabase
  - 32 significantly mutated genes
    - 9 not previously reported in bladder cancer
  - Pathway alterations in cell-cycle regulation (93%), chromatin regulation (89%), and kinase signaling pathways (72%)
    - 69% of tumors with potentially actionable mutations
  - 4 expression subtypes (mRNA, miRNA, protein) – similarities to breast, lung and head and neck squamous

https://gdc.nci.nih.gov

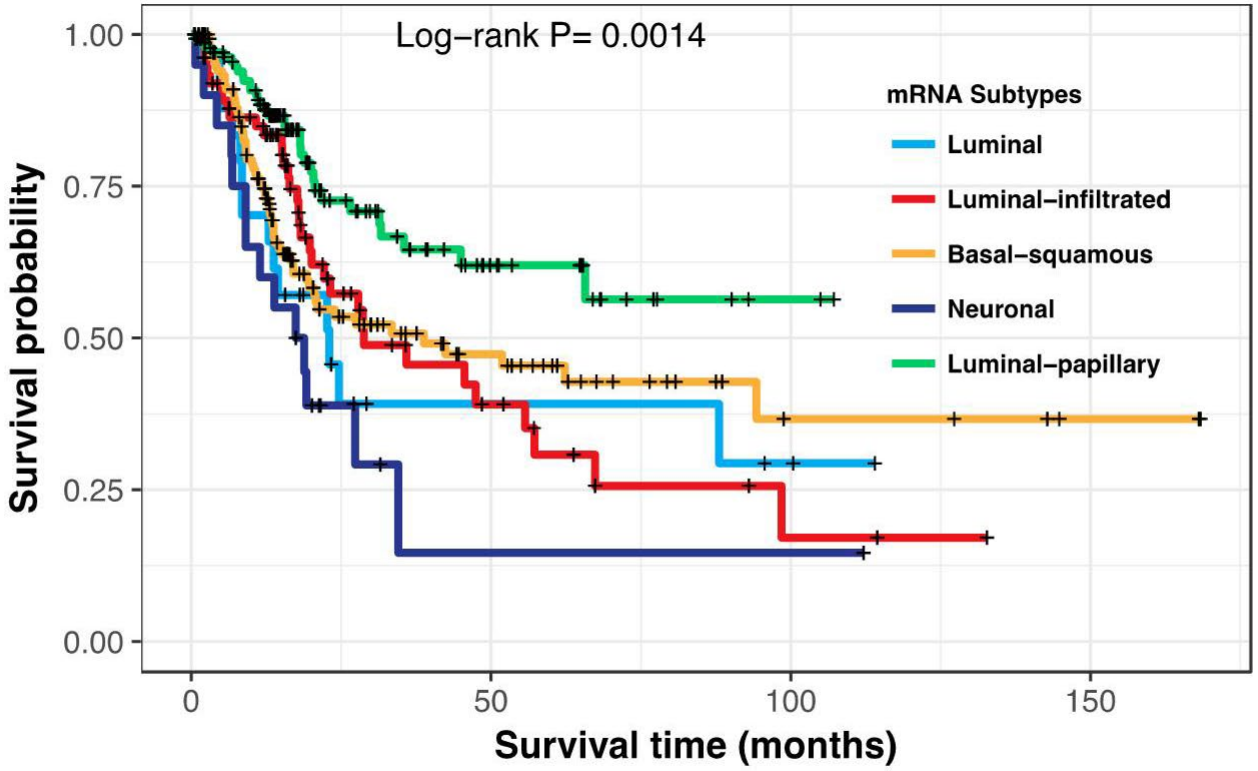
mRNA expression subtypes

5 types




Normal bladder mucosa
High luminal markers
(KRT20, PPARG, FOXA1, GATA3, uroplakins, FGFR3, ERBB2)
Low basal/squamous markers
(CD44, KRT5, KRT14, DSC3, TP63, EGFR)
Luminal (60%)
Papillary morphology;
Best survival;
FGFR3 alterations;
Active SHH signaling;
Low CIS scores;
Low extracellular matrix;
Low tumor burden;
Low hypermethylation;
CDKN2A deletion;
High miR-200 and CDH1;
Low miR-99a and miR-100
TCGA cluster II in 2014;
Lowest purity with
mesenchymal signature;
High EMT markers;
Medium immune markers
[PD-L1 (CD274), CTLA4]
High uroplakins
and SNX31;
Umbrella cell
phenotype
Female-predominant;
High basal/squamous
markers
(CD44, KRT5, KRT14,
DSC3, TP63, EGFR);
Low luminal markers
(KRT20, PPARG, FOXA1,
GATA3, uroplakins,
FGFR3, ERBB2);
High immune markers
[PD-L1 (CD274), CTLA4];
High CIS scores;
Loss of SHH signaling;
TP53 mutations
Worst survival;
High
neuroendocrine
genes;
High
proliferation
signature
Subtypes
Luminal-papillary
(35%)
Luminal-infiltrated
(19%)
Luminal
(6%)
Basal-squamous
(35%)
Neuronal
(5%)

Molecular Subtypes and Outcome



Heterogeneous disease and several types

Presented By Seth Lerner at 2017 ASCO Annual Meeting

Topics to discuss

Immunotherapy results

Atezolizumab in UC – phase II study

IMvigor210 - study design and objectives

IMvigor210 is a phase 2, global, multicenter, single-arm trial conducted that evaluated efficacy and safety of atezolizumab in patients with advanced urothelial carcinoma

- Locally advanced or metastatic cancer of the bladder, renal pelvis, ureter, or urethra
- Predominant transitional cell histology
- **Tumour tissue evaluable for PD-L1 testing[a]**
- **No autoimmune disease or corticosteroid use**

Primary objective

- **ORR**

Secondary objectives

- PFS and DOR (IRF-assessed and investigator assessed[¶])
- ORR, DOR and PFS (investigator-assessed by RECIST 1.1)
- OS and 1-year OS
- Safety, tolerability, pharmacokinetics and ATAs.

Other objectives

- Potential biomarkers
- Biopsy measurement of tumour volume.

Cohort 1 (N ≈ 100): First-line cisplatin ineligible

Cohort 2 (N ≈ 300): Disease progression during or following ≥1 platinum-containing regimen

Atezolizumab 1200 mg IV q3 until:

PD

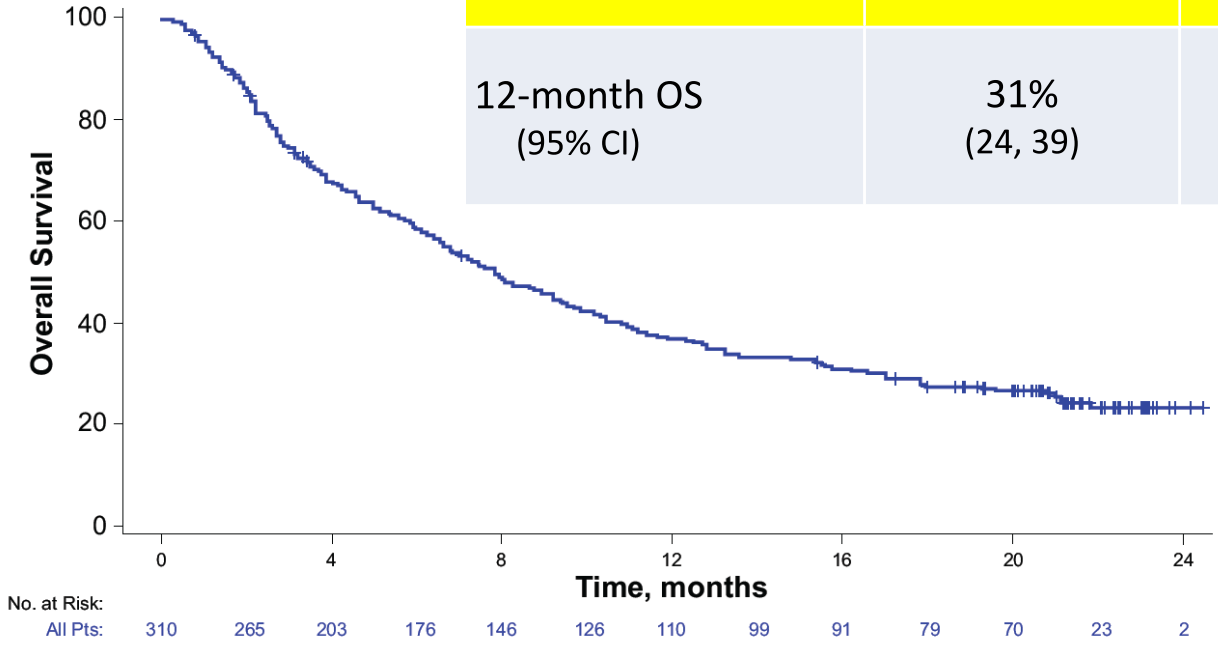
Loss of clinical benefit

IMvigor 210:

Overall Survival in mUC in pretreated pts

Kaplan-Meier OS Plot

	IC 0/1 n = 210	IC 2/3 n = 100	All n = 310
Median OS (95% CI)	6.7 mo (5.4, 8.0)	11.9 mo (9.0, NE)	7.9 mo (6.7, 9.3)
12-month OS (95% CI)	31% (24, 39)	50% (40, 60)	37% (31, 42)

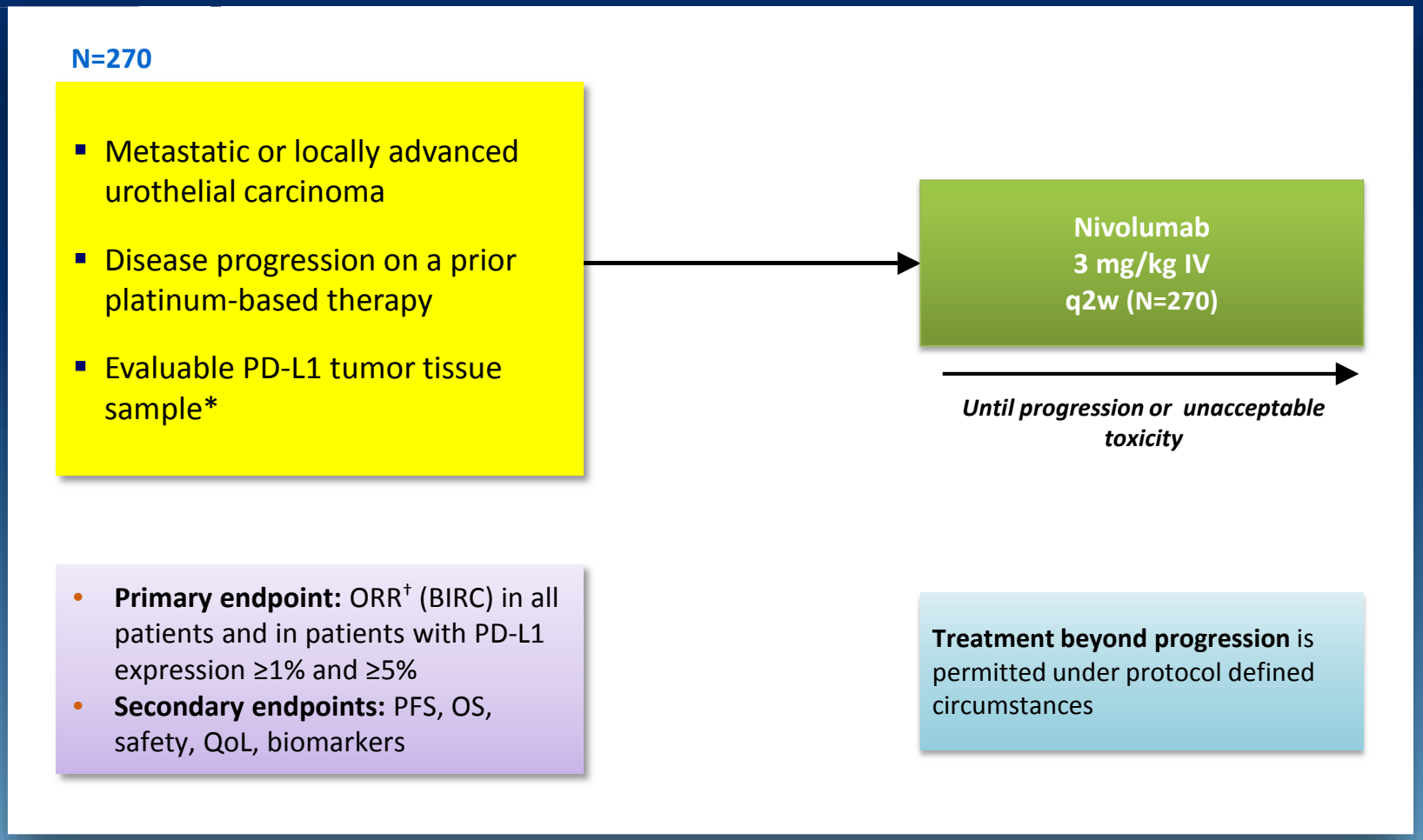


Atezolizumab vs CHEMOTHERAPY
IMVIGOR 211 phase 3

931 pts
Pretreated pts

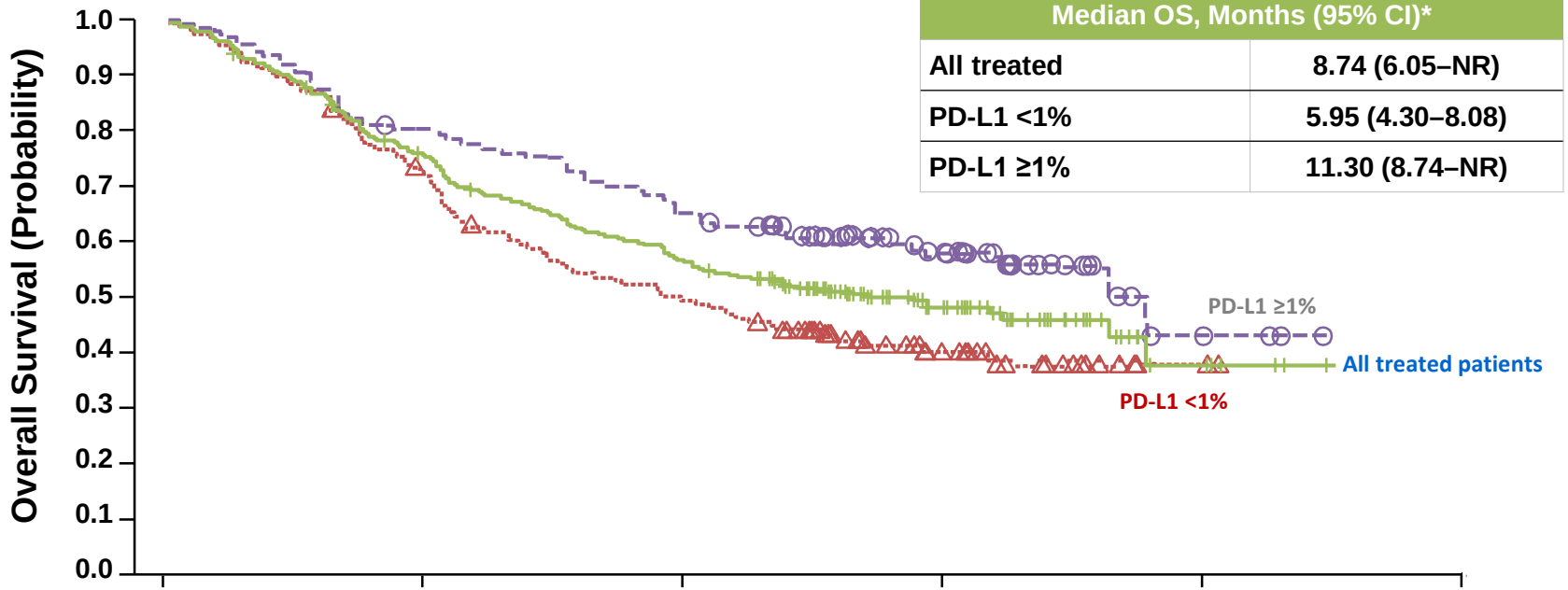
No different OS: 11.1 vs 10.6

Checkmate 275: Nivolumab in Metastatic or Unresectable Urothelial Cancer After Platinum Treatment (Ph 2)



Checkmate 275: Overall Survival

Median OS, Months (95% CI)*	
All treated	8.74 (6.05–NR)
PD-L1 <1%	5.95 (4.30–8.08)
PD-L1 ≥1%	11.30 (8.74–NR)



No. at Risk

All treated patients	265	198	148	63	5	0
PD-L1 <1%	143	101	69	26	2	0
PD-L1 ≥1%	122	97	79	37	3	0

Adapted from Galsky et al, 2016, ESMO.

- **Median OS in nivolumab-treated patients compares favorably to historical control**

Data reported as of October 2016.
* Similar results were seen using the 5% PD-L1 tumor expression cutoff.
CI, confidence interval; NR, not reached; OS, overall survival; PD-L1, programmed death ligand 1.
Galsky M et al. Oral presentation at ESMO 2016. LBA31_PR.

KEYNOTE-045 study design (NCT02256436)

•Key Eligibility Criteria

- •Urothelial carcinoma of the renal pelvis, ureter, bladder, or urethra
- •Transitional cell predominant
- •PD after 1-2 lines of platinum-based chemo or recurrence with 12 mo of perioperative platinum-based therapy
- •ECOG PS 0-2
- •Provision of tumor sample for biomarker assessment

R (1:1)
N = 542

N = 270 → **Pembrolizumab 200 mg IV Q3W for 2 years**

N = 272 → **Paclitaxel 175 mg/m² Q3W OR Docetaxel 75 mg/m² Q3W OR Vinflunine 320 mg/m² Q3W**

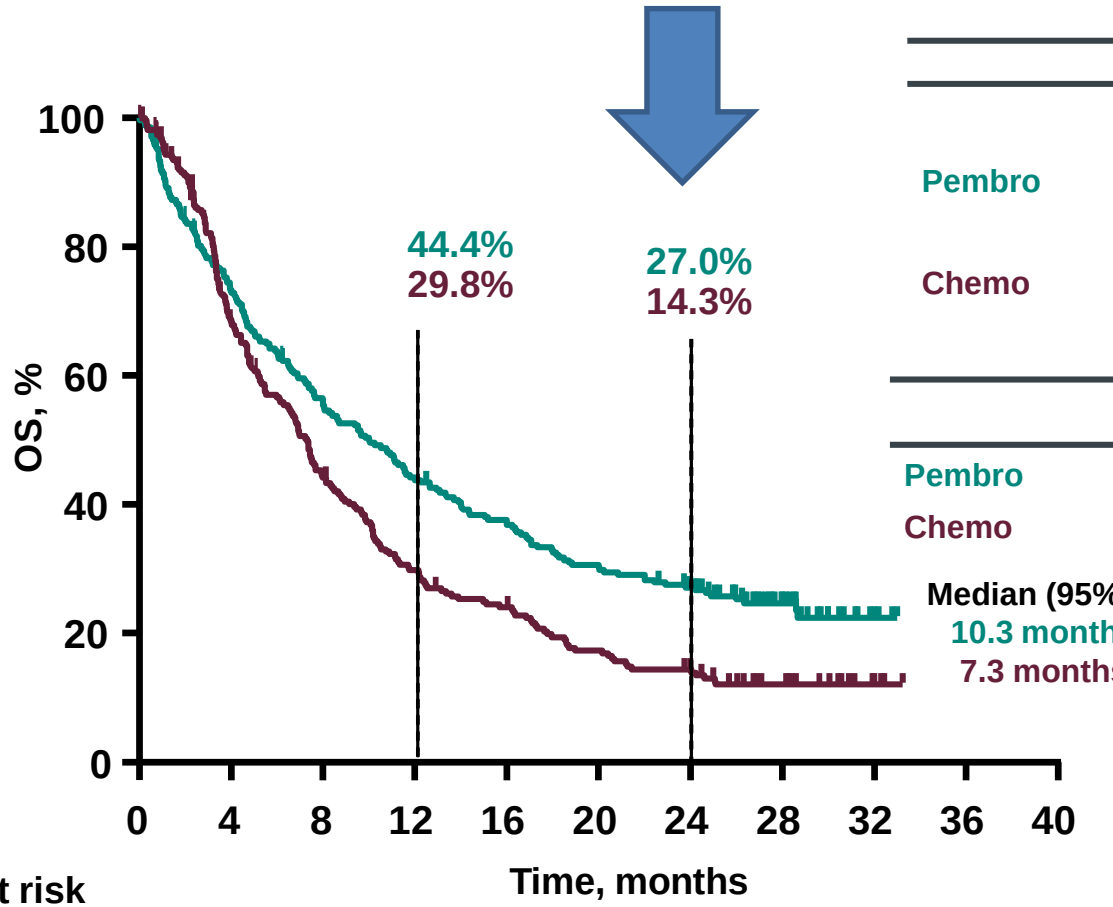
Stratification Factors

- **ECOG PS (0/1 vs 2)**
- **Hemoglobin level (<10 vs ≥10 g/dL)**
- **Liver metastases (yes vs no)**
- **Time from last chemotherapy dose (<3 vs ≥3 mo)**

Key Endpoints

- **Primary: OS and PFS in total and PD-L1 CPS ≥10% populations**
- Secondary: ORR and DOR in total and PD-L1 CPS ≥10% populations; safety in total population

Overall Survival: Total



No. at risk

Pembro	270	194	147	116	98	80	67	32	6	0	0
Chemo	272	173	109	73	58	41	33	18	4	0	0

14.1 months of follow-up[1]

	Events, n	HR (95% CI)[a]	*P*[b]
Pembro	155	0.73 (0.59-0.91)	0.0022
Chemo	179		

27.7 months of follow-up

	Events, n	HR (95% CI)[a]	*P*[b]
Pembro	199	0.70 (0.57–0.85)	0.00017
Chemo	218		

Median (95% CI):
10.3 months (8.0–12.3)
7.3 months (6.1–8.1)

60.6% at 24 months in the chemotherapy arm received an immunotherapeutic agent, including those who received pembrolizumab as part of the cross over.

[a]Based on Cox regression model with treatment as a covariate stratified by ECOG performance status (0/1 vs 2), liver metastases (yes vs no), hemoglobin (<10 vs ≥10 g/dL), and time from completion of chemotherapy (<3 vs ≥3 months). [b]One-sided *P* value based on stratified log-rank test. Data cutoff date: October 26, 2017.

1. Bellmunt J et al. *N Engl J Med*. 2017;376:1015-1026.

D.P. Petrylak[1], N.J. Vogelzang[2], Y. Fradet[3], D.F. Bajorin[4], R. de Wit[5], D.J. Vaughn[6], J.L. Lee[7], L. Fong[8], M.A. Climent[9], A. Necchi[10], W. Gerritsen[11], H. Gurney[12], D.I. Quinn[13], S. Culine[14], C.N. Sternberg[15], E.H. Jensen[16], M. Puhlmann[16], R.F. Perini[16], J. Bellmunt[17], T.K. Choueiri[17]

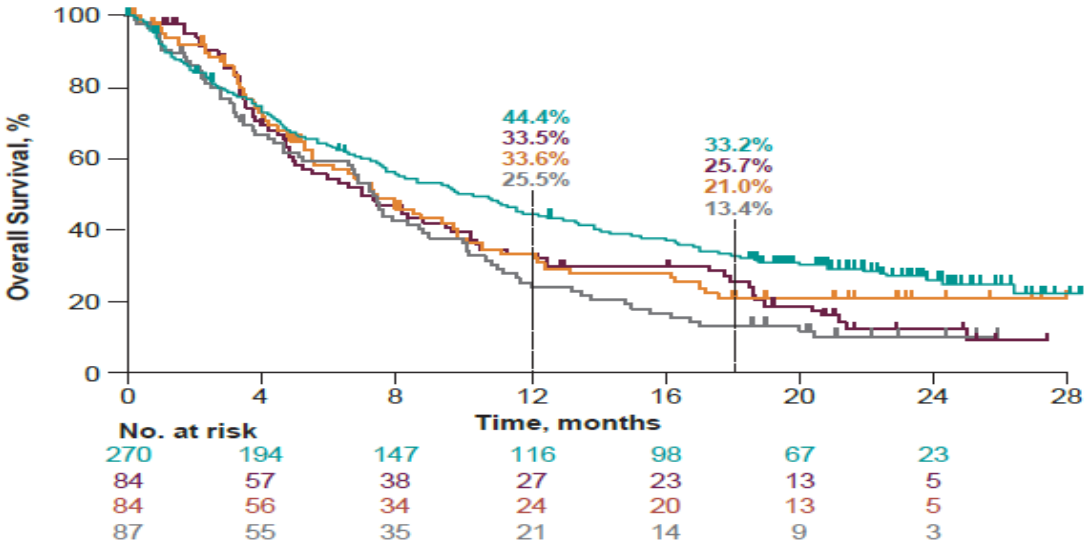
[1]Smilow Cancer Hospital at Yale University, New Haven, CT, USA; [2]Comprehensive Cancer Centers of Nevada, Las Vegas, NV, USA; [3]CHU de Québec-Université Laval, Québec City, QC, Canada; [4]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [5]Erasmus MC Cancer Institute, Rotterdam, Netherlands; [6]Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA, USA; [7]Asan Medical Center and University of Ulsan College of Medicine, Seoul, Republic of Korea; [8]University of California, San Francisco, San Francisco, CA, USA; [9]Fundacion Instituto Valenciano de Oncologia, Valencia, Spain; [10]Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [11]Radboud University Medical Center, Nijmegen, Netherlands; [12]Westmead Hospital and Macquarie University, Sydney, NSW, Australia; [13]University of Southern California Norris Comprehensive Cancer Center and Hospital, Los Angeles, CA, USA; [14]Hôpital Saint-Louis, Paris, France; [15]San Camillo Forlanini Hospital, Rome, Italy; [16]Merck & Co., Inc., Kenilworth, NJ, USA; [17]Dana-Farber Cancer Institute, Boston, MA, USA

Subgroup Analyses From KEYNOTE-045: Pembrolizumab Versus Individual Investigator's Choice of Chemotherapy (Paclitaxel, Docetaxel, or Vinflunine) in Recurrent, Advanced Urothelial Cancer

Efficacy

- Pembrolizumab demonstrated an OS benefit over each of the individual agents (hazard ratios [HRs] ranged from 0.65 to 0.79). Median OS was consistent across the 3 chemotherapy subgroups (**Figure 1**)

Figure 1. Overall Survival



	Events, n	OS, Median (range), Months	Pembro vs Chemo HR (95% CI)[a]
Pembrolizumab (n = 270)	191	10.3 (8.0-12.3)	—
Paclitaxel (n = 84)	70	7.0 (4.8-10.2)	
Docetaxel (n = 84)	59	7.4 (5.5-9.9)	
Vinflunine (n = 87)	74	7.4 (5.2-8.9)	65 (0.49-0.87)

Chemo, chemotherapy; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; OS, overall survival; Pembro, pembrolizumab.
[a]Based on a Cox regression model with treatment as a covariate stratified by ECOG performance status (0/1 vs 2), liver metastases (yes vs no), hemoglobin (<10 vs ≥10 g/dL), and time from completion of chemotherapy (<3 vs ≥3 months).

- No statistically significant difference in PFS was seen between pembrolizumab and each chemotherapy agent. A plateau can be seen in the tail of the curve in the pembrolizumab arm, which represents a subset of patients deriving long-term benefit (**Figure 2**)

O'Donnell, ASCO, Jun 2017

KEYNOTE-052 (NCT02335424): First-Line Pembrolizumab for Cisplatin-Ineligible Advanced Urothelial Cancer

Patients

- Advanced urothelial cancer
- No prior chemotherapy for metastatic disease
- ECOG PS 0-2
- Ineligible for cisplatin:
  - CrCl <60 mL/min
  - ECOG PS 2
  - Grade ≥2 neuropathy or hearing loss
  - NYHA class III heart failure

Pembrolizumab
200 mg Q3W
N = 370

Continue until

- 24 months of treatment
- Confirmed PD
- Intolerable toxicity
- Patient withdrawal

Pretreatment sample collection for biomarker analyses

- **Primary end points:** ORR
- **Secondary end points:** DOR, PFS, OS, safety; identification of cut point for high PD-L1 expression
- **Exploratory objective:** Relationship between candidate biomarkers and response
- **Data cutoff date:** March 9, 2017
  - Median follow-up: 9.5 months (range, 0.1-23 months)

O'Donnell, ASCO, Jun 2017

Confirmed Objective Response Rate

	Total Population N = 370		
	n	%	95% CI
Objective response rate	108	**29**	25-34
Complete response	27	7	5-10
Partial response	81	22	18-27
Stable disease	67	18	14-22
Progressive disease	155	42	37-47

With longer follow-up[a]:
- 5% increase in ORR
- 10 additional complete responses
- 9 additional partial responses

Data cutoff: March 9, 2017. Assessed per RECIST v1.1 by central imaging vendor review. An additional 31 patients had no postbaseline tumor assessment because of death, withdrawal of consent, loss to follow-up, or start of new anticancer therapy, and 9 patients had ≥1 postbaseline tumor assessment, none of which were evaluable.
[a]Compared with September 1, 2016, data cutoff.

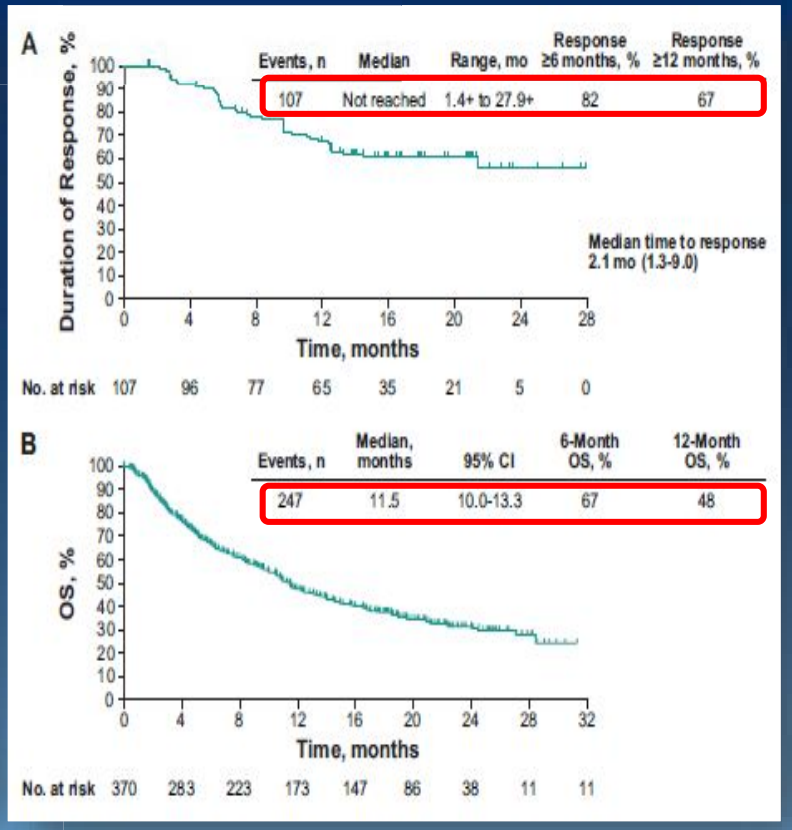
Updated Efficacy and Safety of KEYNOTE-052: A Single-Arm Phase 2 Study Investigating First-Line Pembrolizumab in Cisplatin-Ineligible Advanced Urothelial Cancer

J. Vuky[1]; A. V. Balar[2]; D. Castellano[3]; P. H. O'Donnell[4]; P. Grivas[5]; J. Bellmunt[6]; T. Powles[7]; D. Bajorin[8]; N. Hahn[9]; R. de Wit[10]; M. Savage[11]; L. Pang[12]; T. Frenkl[12]; S. M. Keefe[12]; E. R. Plimack[12]

[1]Oregon Health & Science University, Portland, OR, USA; [2]Perlmutter Cancer Center, NYU Langone Health, New York, NY, USA; [3]Hospital Universitario 12 de Octubre, Madrid, Spain; [4]The University of Chicago Medical Center, Chicago, IL, USA; [5]Cleveland Clinic, Cleveland, OH, USA; [6]Dana-Farber Cancer Institute, Boston, MA, USA; [7]Barts Cancer Institute, Queen Mary University of London, London, UK; [8]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [9]The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD, USA; [10]Erasmus MC Cancer Institute, Rotterdam, Netherlands; [11]Merck & Co., Inc., Kenilworth, NJ, USA; [12]Fox Chase Cancer Center, Philadelphia, PA, USA

Table 3. Overall Survival by Subgroups

	N	Events, n (%)	Median OS (95% CI), mo
PD-L1 subgroup			
PD-L1 CPS <10	251		10.0 (7.8-11.6)
PD-L1 CPS ≥10	110	57 (5…	18.5 (12.2 to NR)
Age, y			
<65	68	41 (60)	15.7 (6.9 to NR)
≥65	302	206 (68)	11.9 (9.7-12.8)
ECOG performance status			
0/1	214	134 (63)	13.1 (11.0-16.8)
2	156	113 (72)	9.7 (5.7-11.6)
Location of metastases			
Lymph node only	51	22 (43)	NR (12.4 to NR)
Visceral disease	315	223 (71)	10.8 (9.0-11.8)



Data cutoff was November 30, 2017; median follow-up was 11.5 months (range, 0.1-31.3 months)

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.

As a result, the European Medicines Agency (EMA) has recommended restricting the use of these medicines as first line-treatments for urothelial cancer.

Key entriq should now only be used for first-line treatment of urothelial cancer in patients with high levels of PD-L1 (see full indications below).

There are no changes to how these medicines should be used in patients with urothelial cancer who have had chemotherapy or in patients with other cancers for which these medicines are approved.

The two clinical trials are continuing but no new patients with low levels of PD-L1 will be given only Keytruda or Tecentriq. Patients in the trials who have any questions should speak to the doctor treating them.

The review of data on Keytruda and Tecentriq was carried out by EMA's Committee for Medicinal Products for Human Use (CHMP).

NOTA INFORMATIVA IMPORTANTE

CONCORDATA CON LE AUTORITA' REGOLATORIE EUROPEE

E L'AGENZIA ITALIANA DEL FARMACO (AIFA)

9 Luglio 2018

Keytruda (pembrolizumab): Restrizione dell'indicazione terapeutica per il trattamento del carcinoma uroteliale localmente avanzato o metastatico nei pazienti adulti non eleggibili alla chemioterapia contenente cisplatino

Gentile Dottoressa/Egregio Dottore,

MSD Italia S.r.l. in accordo con l'Agenzia Europea dei Medicinali (EMA) e l'Agenzia Italiana del Farmaco (AIFA), desidera informarLa di quanto segue:

Riassunto

- I dati preliminari derivanti da uno studio clinico in corso (KEYNOTE-361) mostrano una ridotta sopravvivenza con KEYTRUDA in monoterapia rispetto alla chemioterapia standard, quando utilizzato come trattamento di prima linea in pazienti con carcinoma uroteliale localmente avanzato o metastatico, il cui tumore presenta una bassa espressione del ligando 1 della proteina della morte programmata (PD-L1).

- Di conseguenza, l'indicazione terapeutica di KEYTRUDA per il trattamento del carcinoma uroteliale localmente avanzato o metastatico nei pazienti adulti che non sono eleggibili alla chemioterapia a base di cisplatino, è stata modificata come segue:

  "KEYTRUDA in monoterapia è indicato nel trattamento del carcinoma uroteliale localmente avanzato o metastatico negli adulti che non sono eleggibili alla chemioterapia contenente cisplatino e il cui tumore esprime PD-L1 con combined positive score (CPS) ≥ 10."

- L'indicazione terapeutica di KEYTRUDA per il trattamento del carcinoma uroteliale localmente avanzato o metastatico negli adulti che hanno ricevuto una precedente chemioterapia contenente platino, rimane invariata.

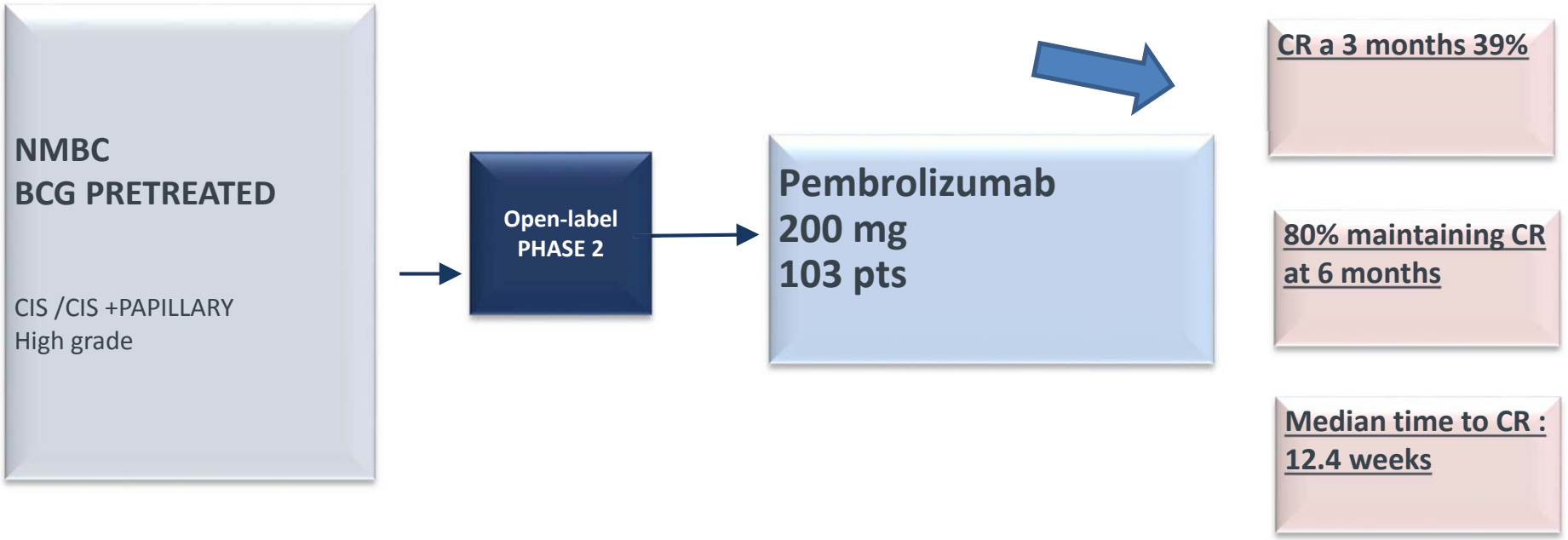
Topics to discuss

Only 15-25% of patients have durable response to ICI and efficacious agents are of urgent needs

improve the efficacy

KEYNOTE 057 Phase 2
PEMBROLIZUMAB IN NMBC

ESMO 2018 RESULTS



Pembrolizumab demonstrated encouraging anti-tumor activity, with a compelling, complete response rate and duration of response in patients with BCG-unresponsive CIS (with or without papillary disease), who refused or were ineligible for radical cystectomy. Importantly, in those patients who had a recurrence, none experienced progression to MIBC.

Table 3. Pathologic Response to Pembrolizumab

Response	All Treated Patients (N = 50)	PD-L1 CPS ≥ 10% (n = 35)	PD-L1 CPS < 10% (n = 15)
Primary end point			
Pathologic complete response, No. (%)	21 (42)	19 (54.3)	2 (13.3)
95% CI	28.2 to 56.8		
Secondary end point			
Pathologic downstaging to pT<2, No. (%)	27 (54)	23 (65.7	
95% CI*	39.3 to 68.2		
Treatment failure, No. (%)			
pT2N0	2 (3.8)		
pT3-4N0	6 (12)		
pTanyN+	10 (20)		
Additional MVAC chemotherapy†	5 (10)		
RECIST v1.1 PD	0		

Abbreviations: CPS, combined positive score; MVAC
tine, doxorubicin, cisplatin; PD, disease progression; PD
ligand-1.
*Including pTa (n = 3), pTis (n = 2), and pT1 (n = 1).
†As a result of investigator decision after the evid
response to pembrolizumab (n = 4) or because of the c
grade 3 transaminase increase (n = 1). These patient
pT2pN2 (n = 1), and pT3pN1 (n = 2) stage at radical c

JOURNAL OF CLINICAL ONCOLOGY RAPID COMMUNICATION

Pembrolizumab as Neoadjuvant Therapy Before Radical Cystectomy in Patients With Muscle-Invasive Urothelial Bladder Carcinoma (PURE-01): An Open-Label, Single-Arm, Phase II Study

Andrea Necchi, Andrea Anichini, Daniele Raggi, Alberto Briganti, Simona Massa, Roberta Lucianò, Maurizio Colecchia, Patrizia Giannatempo, Roberta Mortarini, Marco Bianchi, Elena Farè, Francesco Monopoli, Renzo Colombo, Andrea Gallina, Andrea Salonia, Antonella Messina, Siraj M. Ali, Russell Madison, Jeffrey S. Ross, Jon H. Chung, Roberto Salvioni, Luigi Mariani, and Francesco Montorsi

Table A3. Analysis With a Logistic Model of the Association Between Putative Genomic Biomarkers and Pathologic Response to Pembrolizumab

Variable	Statistics	Odds Ratio	95% CI	Wald Test *P*
TMB (mutation per megabase)	Continuous	Nonlinear effect; cutoff, ≥ 15 (80th quantile)		.0219
DDR and/or RB1 GA	Unadjusted	5.23	1.44 to 18.94	.0096
	Adjusted	3.41	0.76 to 15.24	.0989

Abbreviations: DDR, DNA damage response and repair; GA, genomic alterations; TMB, tumor mutation burden.

Nivolumab Alone or in Combination With Ipilimumab in Patients With Platinum-Pretreated Metastatic Urothelial Carcinoma, Including the Nivolumab 1 mg/kg + Ipilimumab 3 mg/kg Expansion From CheckMate 032

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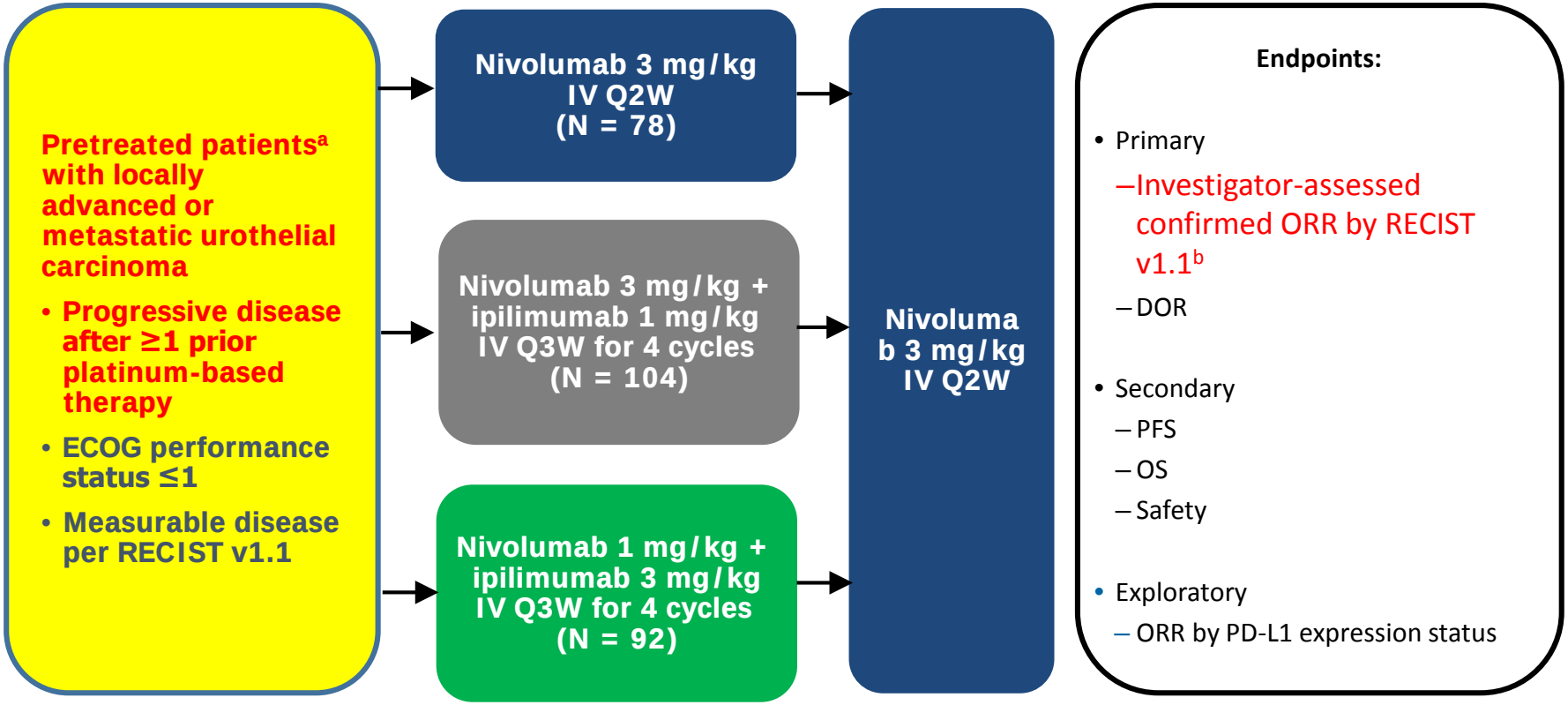
Italy Mercury Number 1506IT18NP04000-01

Study Design

Open-label, multicenter, phase 1/2 study (NCT01928394)



- Tumor measurements: CT or MRI every 6 weeks (±1 week) from first dose for the first 24 weeks, then every 12 weeks (±1 week)

[a]Patients could have refused chemotherapy. [b]Also evaluated per BICR for NIVO3 and NIVO1+IPI3

Treatment beyond progression was permitted if treatment was tolerated and prespecified clinical benefit was noted. Patients receiving combination treatment may undergo a re-exposure with nivolumab/ipilimumab if they had a subsequent documented progression after achieving an initial objective response (partial or complete response) or stable disease of ≥3 months, and met protocol-defined criteria

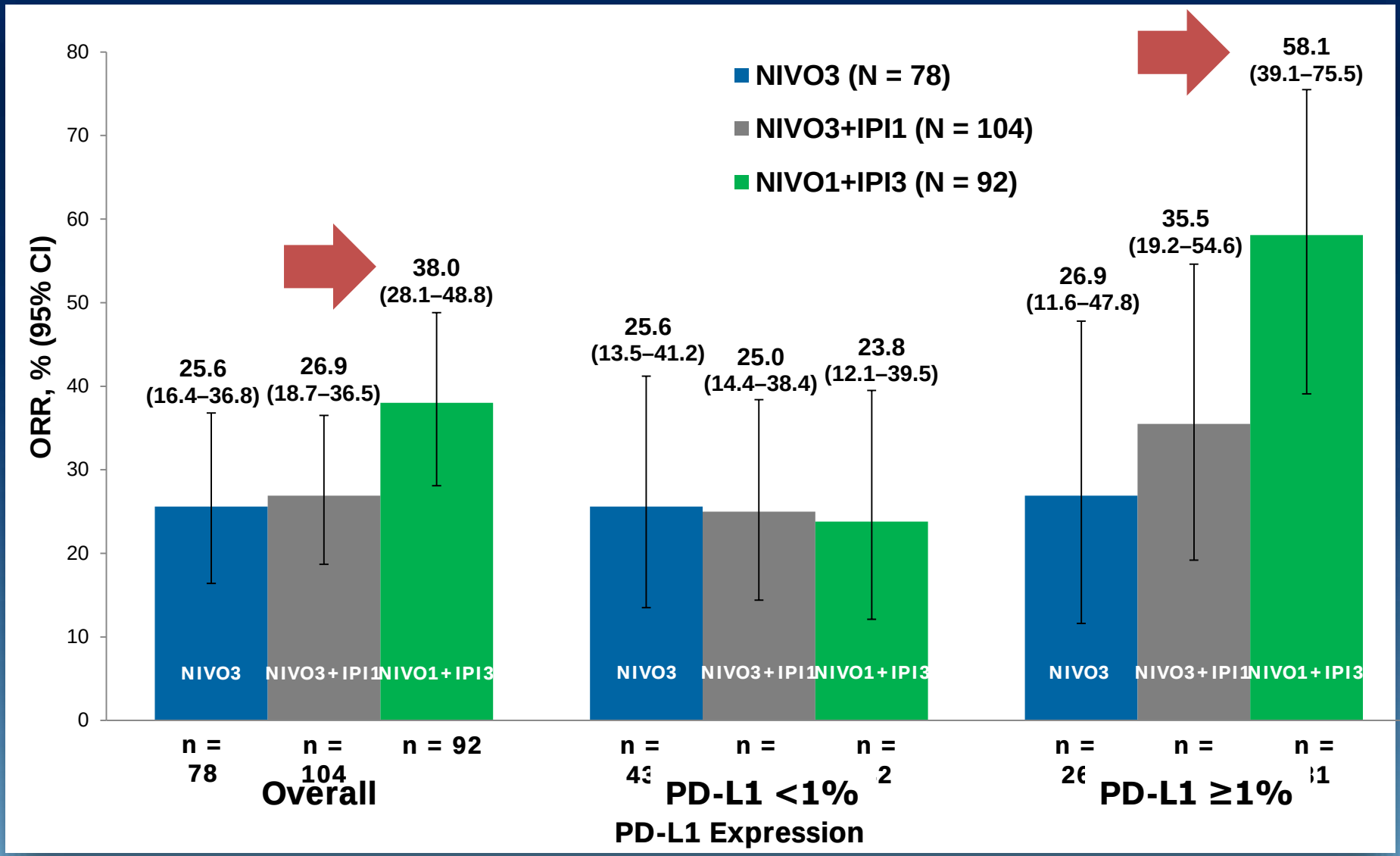
BICR, blinded independent committee review; DOR, duration of response; PD-L1, programmed death ligand 1

Sharma P, et al. *Lancet Oncol* 2016;17:1590–1598.

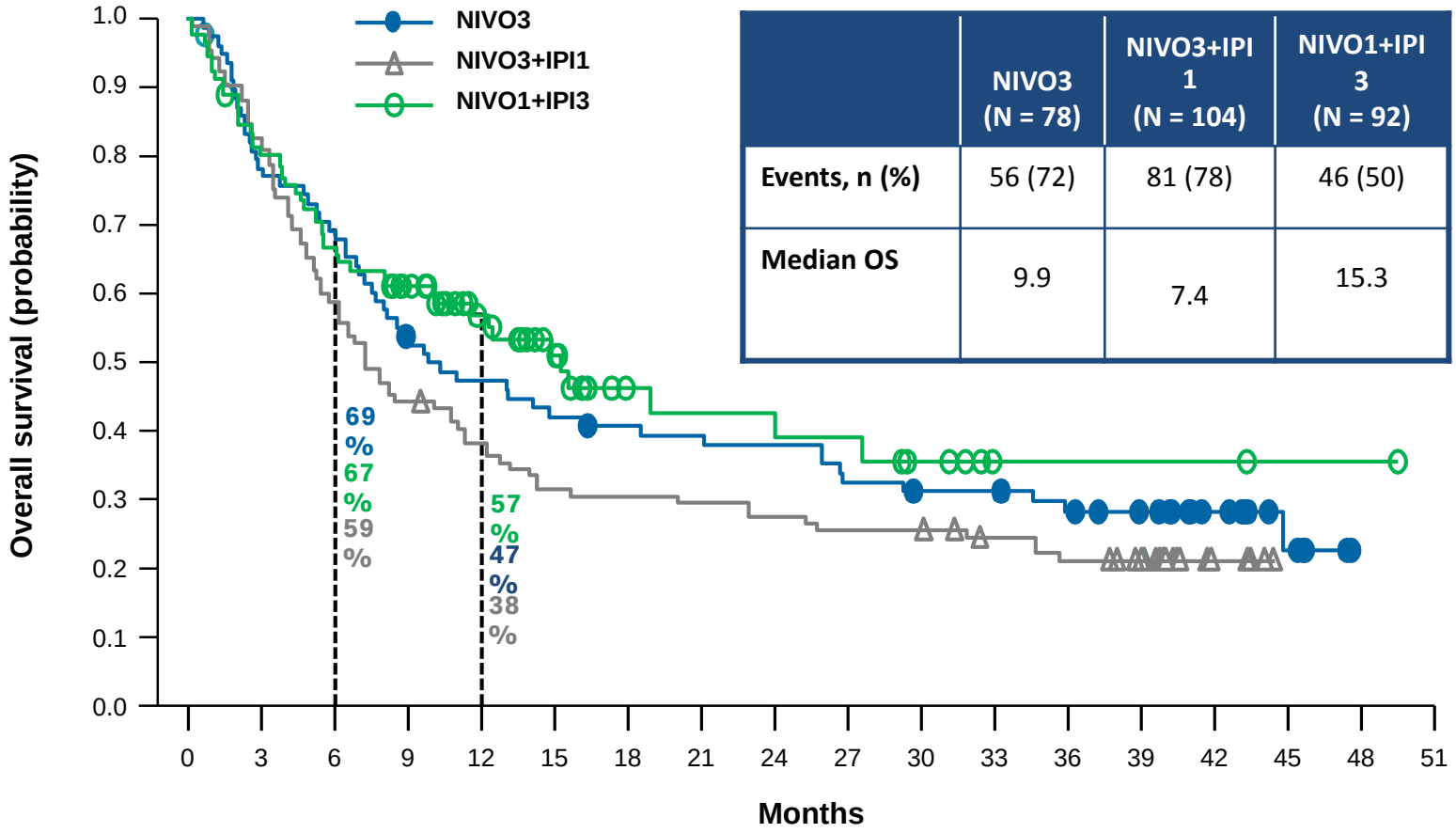
Best Overall Response per Investigator

Characteristic	NIVO3 (N = 78)	NIVO3+IPI1 (N = 104)	NIVO1+IPI3 (N = 92)
Confirmed ORR, %	25.6	26.9	38.0
Best overall response, %			
Complete response	10.3	7.7	6.5
Partial response	15.4	19.2	31.5
Stable disease	26.9	23.1	25.0
Progressive disease	38.5	42.3	21.7
Unable to determine	9.0	7.7	13.0
Not reported	0	0	2.2

ORR by Baseline Tumor PD-L1 Expression per Investigator



Overall Survival



	NIVO3 (N = 78)	NIVO3+IPI 1 (N = 104)	NIVO1+IPI 3 (N = 92)
Events, n (%)	56 (72)	81 (78)	46 (50)
Median OS	9.9	7.4	15.3

Number at risk

NIVO3	78	61	54	41	36	32	30	29	28	24	22	22	19	16	9	4	0	0
NIVO3+IPI1	104	86	61	46	39	32	31	30	28	26	26	22	19	15	5	0	0	0
NIVO1+IPI3	92	73	60	48	33	23	13	12	12	11	8	2	2	2	2	1	1	0

Treatment-Related Adverse Events

Event, %	NIVO3 (N = 78)		NIVO3+IPI1 (N = 104)		NIVO1+IPI3 (N = 92)	
	Any grade	Grade 3–4	Any grade	Grade 3–4	Any grade	Grade 3–4
Treatment-related AEs	85	27[a]	85	31[a]	80	39
Treatment-related AEs leading to discontinuation	4	4	13	12	13	11
Treatment-related AEs in ≥10% of patients						
Diarrhea	13	0	23	5	33	10
Pruritus	33	0	29	2	32	0
Fatigue	36	3	32	3	26	0
Decreased appetite	8	0	16	0	16	0
Maculopapular rash	22	4	18	2	16	3
Nausea	13	1	8	1	14	1
Hypothyroidism	8	0	13	0	13	0
Rash	8	0	13	2	13	1
Elevated ALT	4	0	19	6	13	7
Elevated AST	1	1	15	4	11	2
Lipase increased	17	6	10	6	5	4
Arthralgia	15	0	9	0	7	0
Anemia	12	1	12	1	7	0
Dyspnea	10	3	8	1	2	0
Dry skin	10	0	10	0	5	0
Hyperthyroidism	5	0	13	0	7	0
Amylase increased	9	5	11	1	7	2

[a]Two grade 5 pneumonitis events were reported: 1 in the NIVO3 group and 1 in the NIVO3+IPI1 group

NEW PATHWAYS

2018

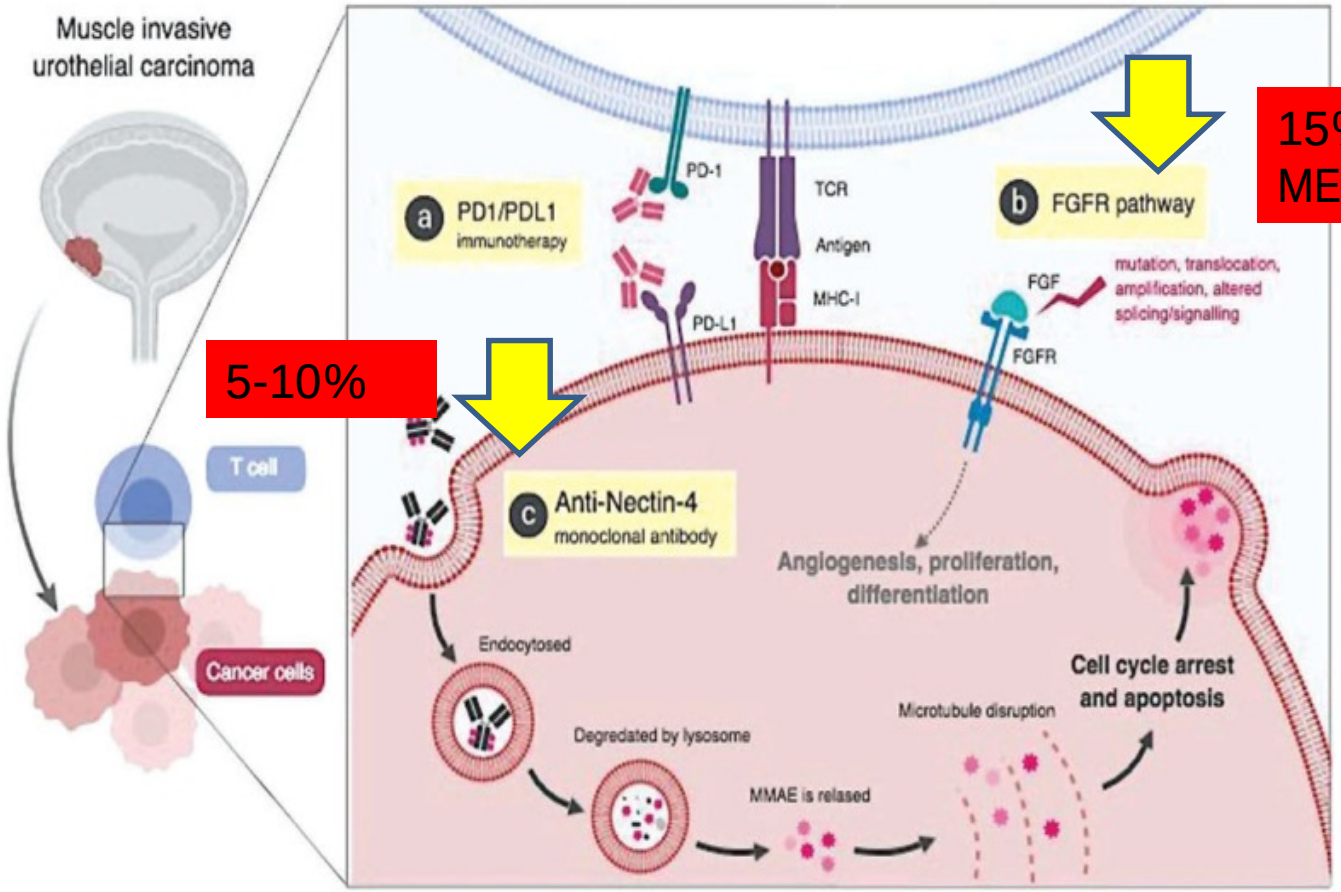


Figure 1. Selected targets of novel therapeutic agents for metastatic urothelial carcinoma: (a) the programmed death-1/programmed death ligand-1 (PD-1/PD-L1) pathway; (b) the fibroblast growth factor receptor (FGFR) pathway; (c) mechanism of action of anti-nectin-4 monoclonal antibody.

Table 1. Ongoing systemic phase-III studies in locally-advanced or metastatic urothelial carcinoma.

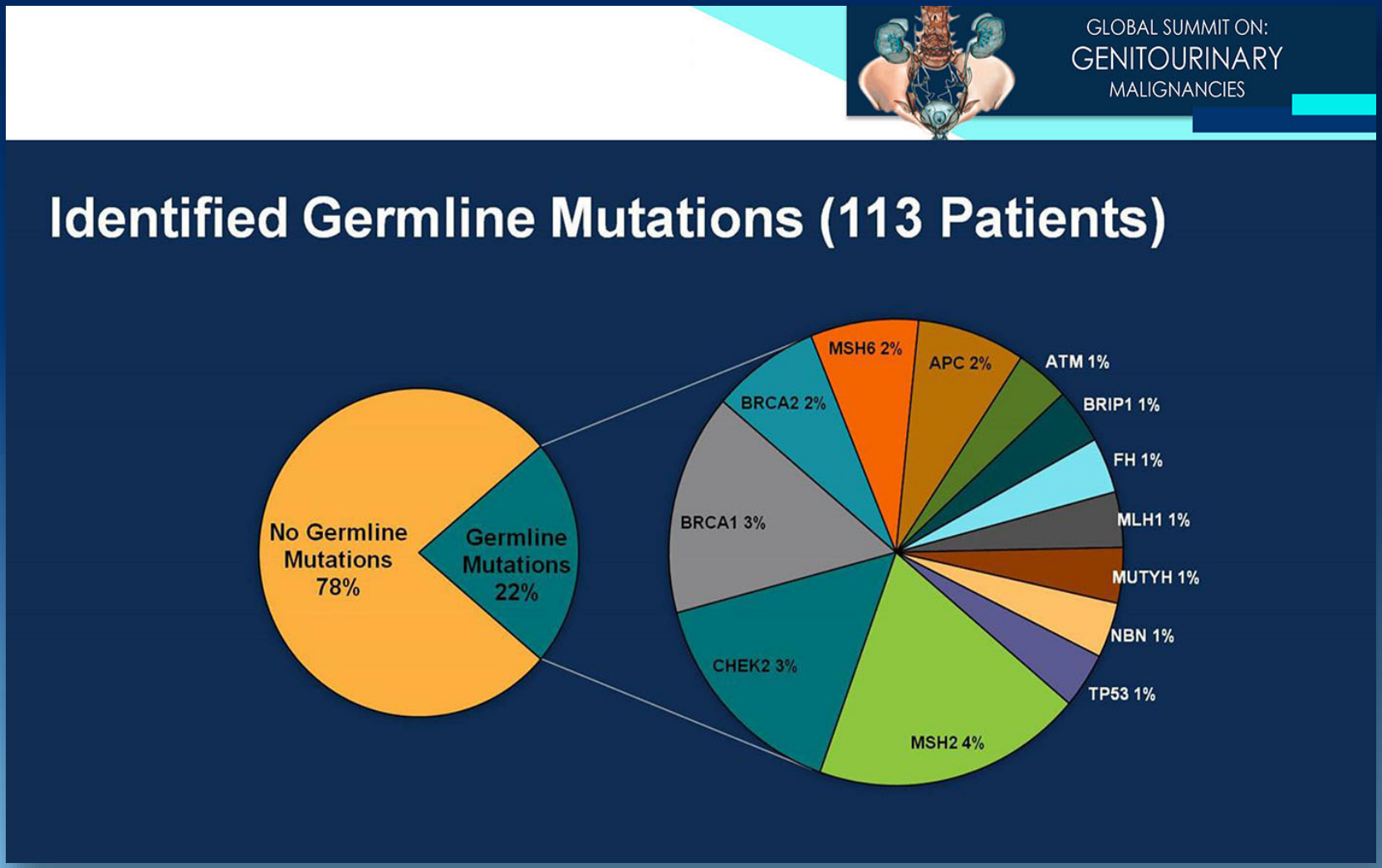
Study/trial number	Estimated enrollment	Control arm	Experimental arm(s)	Primary Endpoint(s)	Planned Completion Date
Subsequent-line setting					
NCT03474107 THOR* NCT03390504	631	Cohort 1 (PD-1 treated): docetaxel or vinflunine Cohort 2 (PD-1 naïve): pembrolizumab	Erdafitinib	OS	May 2021
FORT-1^ NCT03410693	400	Docetaxel, paclitaxel, or vinflunine	Rogaratinib	OS	April 2022

PFS, progression-free survival; OS, overall survival; PD-L1, programmed death-ligand 1; MVAC, methotrexate, vinblastine, doxorubicin, cisplatin; dd, dose-dense;
* Trial requires testing via Fibroblast Growth Factor Receptor inhibitor Clinical Trial Assay (FGFRi CTA) to determine molecular eligibility
^ Trial requires high FGFR1 or FGFR3 mRNA expression levels in archival or fresh tumor tissue

Emfortumab, anti nectina 4.....SECOND LINE Vs Vinflunine

Vicinium anti EPICAM + Durvalumab

Germline Mutations in Urothelial Ca pts



Example of novel clinical trials (PARPi)

ATLAS

RUCAPARIB IN PATIENTS WITH LOCALLY ADVANCED OR METASTATIC UROTHELIAL CARCINOMA

Eligibility

- Metastatic UC
- 1-2 prior standard regimens (platinum-based and/or immune checkpoint inhibitor)
- Mandatory tumor tissue collection at screening
- Measurable disease
- No prior PARPi
- No selection based on HRD status

Treatment

N=~200

Rucaparib

Primary EP:
ORR (RECIST v1.1)

Secondary EPs:
DOR, PFS, OS, Safety

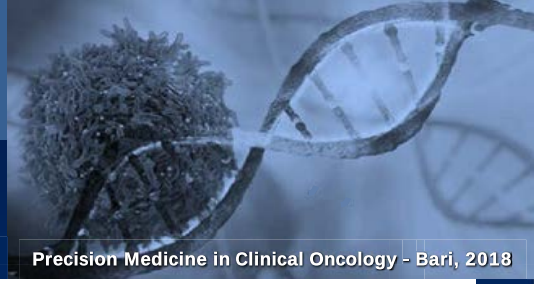
Treat with Rucaparib (600 mg BID) until progression or other reason for discontinuation

Analysis

HRD+ group and ITT

Di Lorenzo,
AOU Federico II,
Starting december 2018

ASCO 2018 *(Nassar et al)*



A 3-factor model that robustly predicted tumor regression with either first-line or post-platinum PD1/PD-L1 inhibitors.

- **NLR <5;**
- **No visceral metastasis;**
- **TMB ≥10**

IFNy,

CD8,

growth factors associated with resistance to PD1

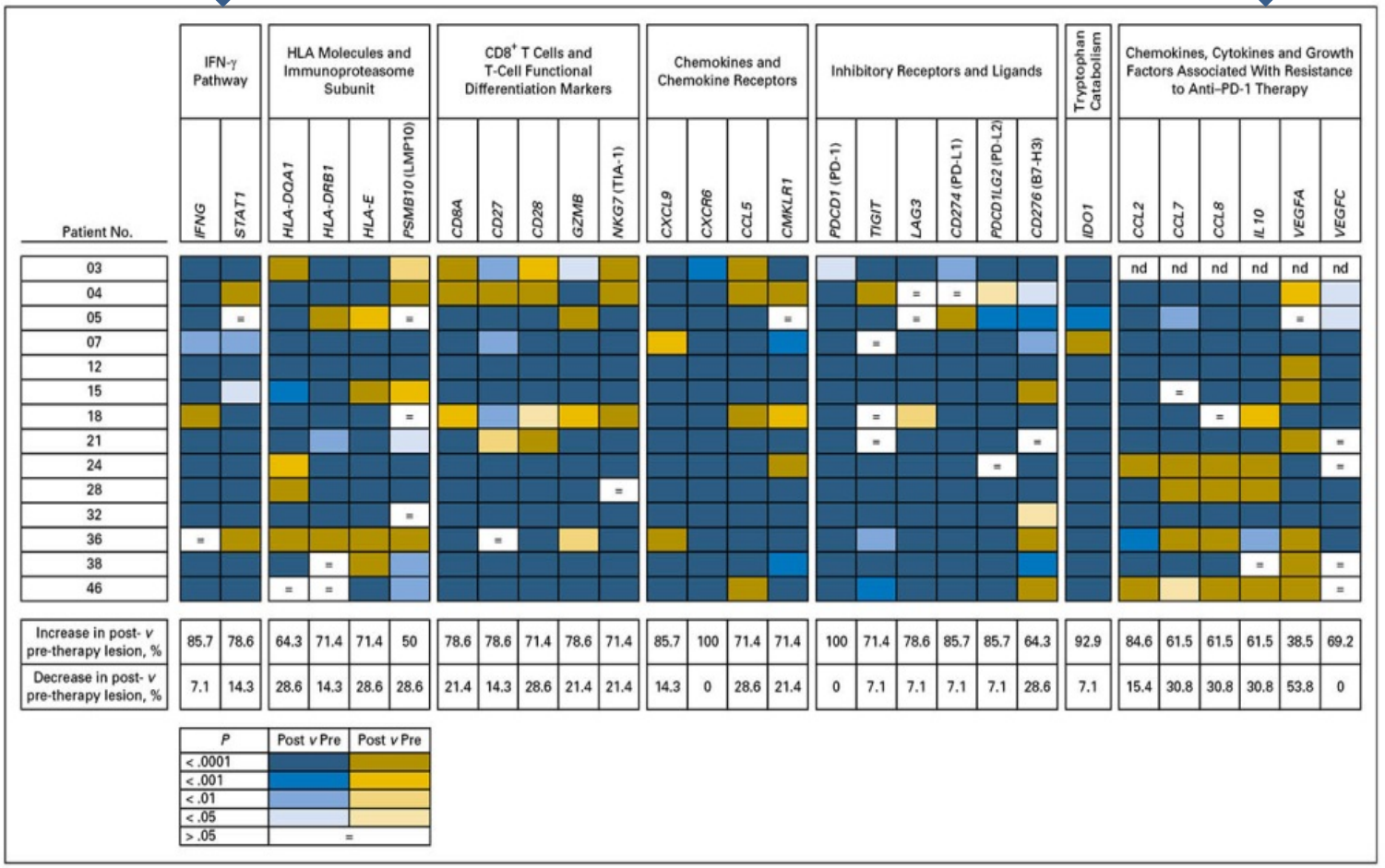


Fig 3. Neoadjuvant pembrolizumab modulates the expressions of immune-related genes associated with a response or resistance to programmed death 1 (PD-1) blockade. Formalin-fixed, paraffin-embedded sections from transurethral resection of the bladder and radical cystectomy samples of patients with pT≥2 tumor (n = 14) were compared using quantitative polymerase chain reaction (qPCR) for the expression of two sets of immune-related genes: a first set on the basis of the interferon gamma (IFN-γ)–related signature predicting response to the PD-1 blockade (from *IFNG* to *IDO1*), and a second set (from *CCL2* to *VEGFC*) on the basis of the signature of innate resistance to anti–PD-1. For each gene of interest, six qPCR replicate values obtained by analysis of the pretherapy (pre) and post-therapy (post) tissue samples in each patient are the result of independent technical procedures of reverse transcription, preamplification, and real-time PCR amplification, as described in Patients and Methods. Unpaired *t* test was used to compare gene expression in post- versus pretherapy lesions and corresponding *P* values are reported. Significant changes in gene expression observed in post- versus pretherapy lesions are shown by a color code on the basis of the *P* value, as shown by the legend (bottom; light blue to dark blue, significant increase in gene expression level in the post-therapy lesion compared with the pretherapy sample; light gold to dark gold, significant decrease in gene expression level in the post-therapy lesion compared with the pretherapy sample). Percentage of patients showing either an increase or a decrease in gene expression level in the post- versus pretherapy lesions are shown (bottom). nd, not done.

Neoadjuvant Chemotherapy Reinforces Antitumour T cell Response in Urothelial Urinary Bladder Cancer

David Krantz et al EUR UROL 2018 Nov.

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Patient summary:

The effect of chemotherapy on immune cell subsets of 40 patients with bladder cancer.

The patients with response:

1) Increase of Th1 e Th2 cells;

2) Decrease of Treg (CD39 and CD69);

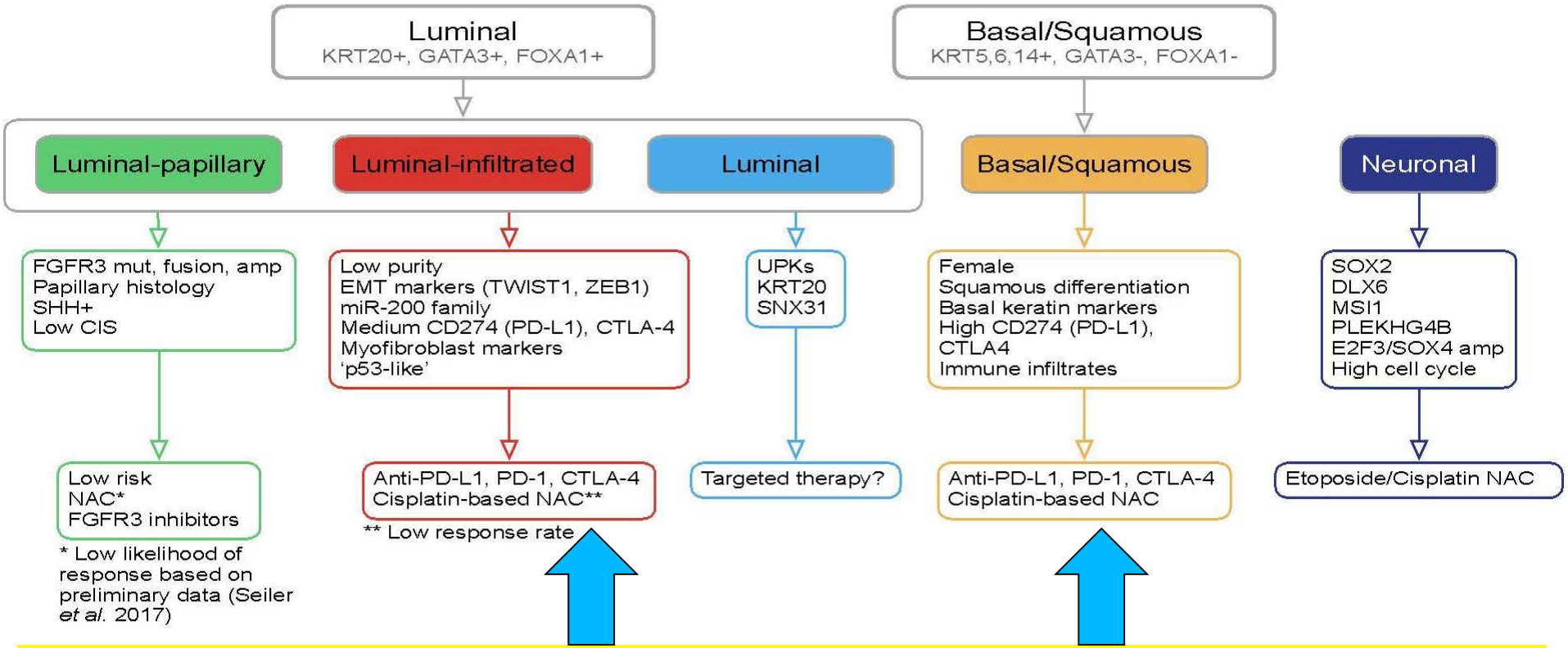
3) We conclude that neoadjuvant CT reinforces the antitumour immune response in bladder cancer patients

My opinion:

-The future landscape of treatment for UC may be more ***precisely genomically driven***, given encouraging early-phase data and is a focus of ongoing phase 3;

-**The collaborative, multidisciplinary approach *to care and clinical trial design* bodes well for our patients**

Future Treatment Paradigm for MIBC



Heterogeneous disease, several types and potential different therapies

Grazie