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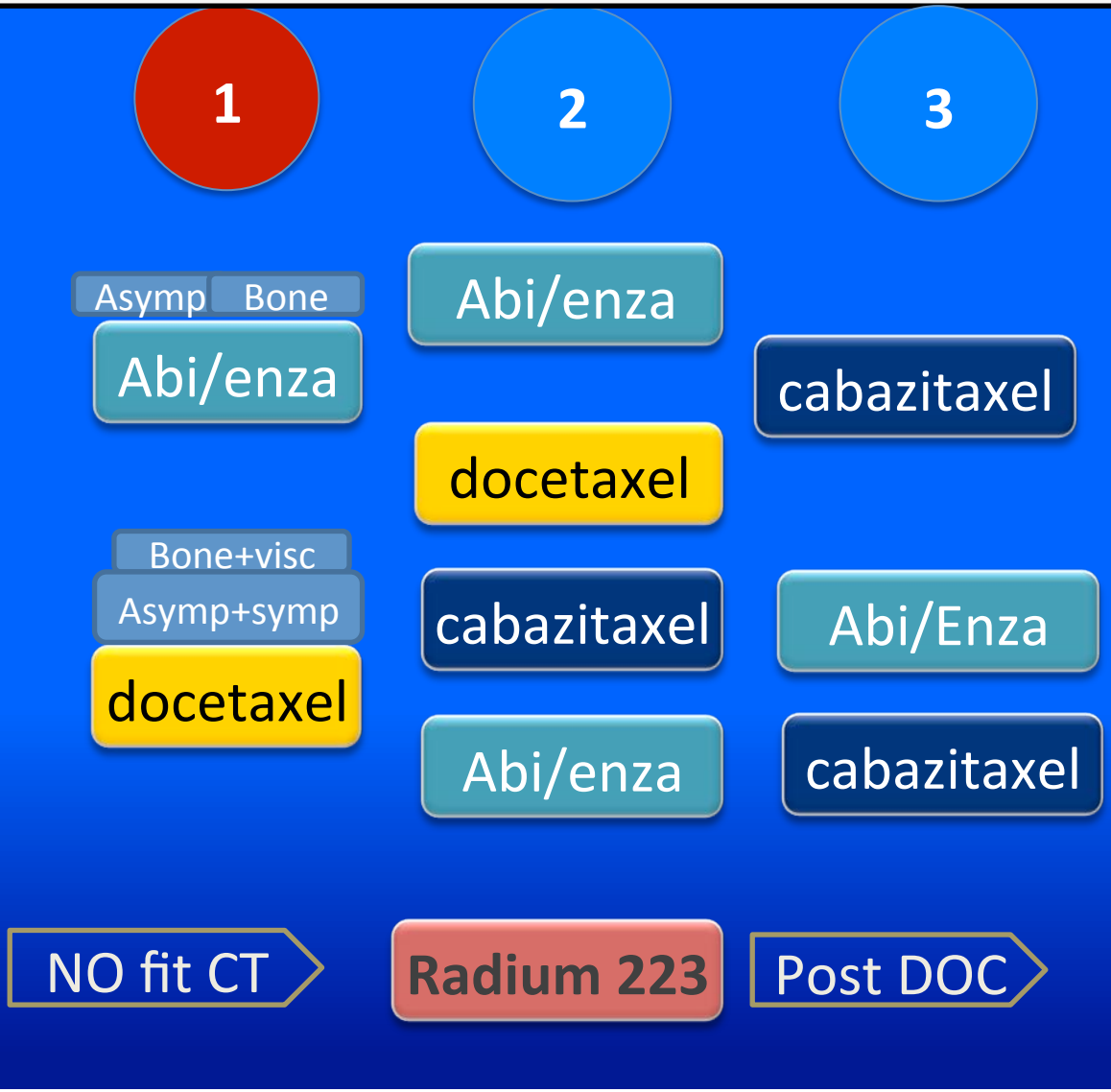
Terapie oncologiche nel paziente metastatico resistente alla castrazione: quali pazienti? Quando? Come?
G. Fornarini (Genova)

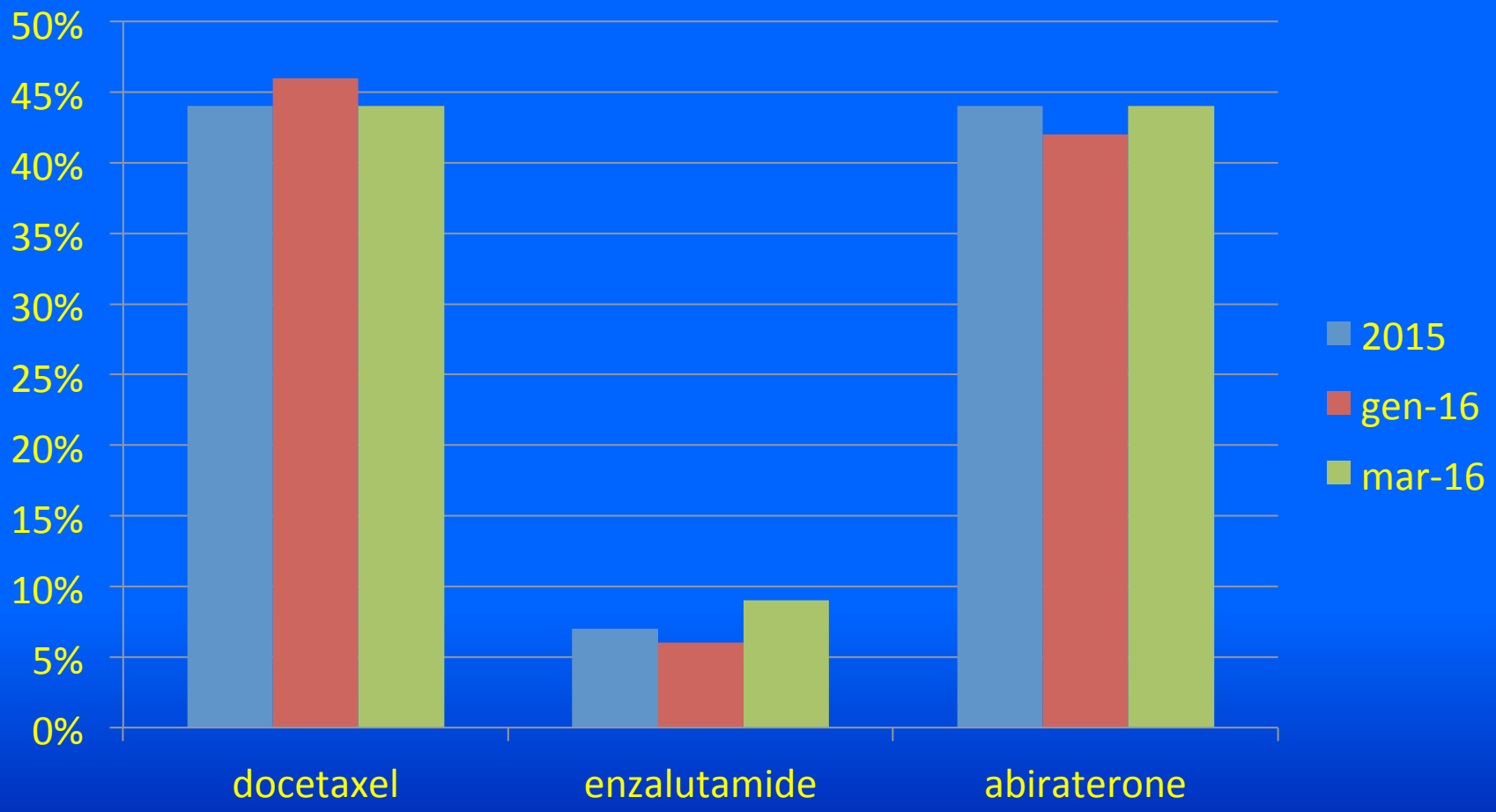
Phase III Trials Showing an OS Advantage in Metastatic Prostate Cancer

Study	Agents	N	Indication	HR (95% CI)	ΔOS (mo)
TAX-327[3]	DOC/P vs mito/ P	1,006	mCRPC, symptomatic or not	0.76 (0.62-0.94)	+2.9
TROPIC[5]	CABA/P vs mito/P	755	mCRPC (post-DOC)	0.70 (0.59-0.83)	+2.4
COU-AA-302[6]	ABI/P vs P	1,088	mCRPC (pre-DOC), mild/no symptoms - No visceral mets	0.81 (0.70-0.93)	+4.4
COU-AA-301[7]	ABI/P vs P	1,195	mCRPC (post-DOC)	0.74 (0.64-0.86)	+4.6
PREVAIL[8]	ENZA vs pbo	1,717	mCRPC (pre-DOC) mild/no symptoms , 11% visceral mets	0.71 (0.60-0.84)	+4.0
AFFIRM[9]	ENZA vs pbo (or P)	1,199	mCRPC (post-DOC)	0.63 (0.53-0.75)	+4.8
ALSYMPCA[10]	Radium-223 vs pbo	921	mCRPC (post-DOC or unfit for DOC)	0.70 (0.55-0.88)	+2.8

Esistono diversi pazienti con una diversa storia naturale….quindi!



La prima linea in Italia nel 2016



LE CERTEZZE DOPO IL DOCETAXEL

TROPIC (n=755)[7]	Cabazitaxel 25 mg/m^2 every 3 weeks (C)	Mitoxantrone 12 mg/m^2 every 3 weeks	Overall survival 15·1 months *vs* 12·7 months; HR 0·7, p=0·0001	PFS PSA response rate Radiographic response rate Pain response	Post docetaxel Significant haematologic toxicity with cabazitaxel No difference in pain response
COU-AA-302 (n=1088)[9]	Abiraterone acetate 1000 mg once a day plus prednisone 5 mg twice a day	Prednisone 5 mg twice a day plus placebo	Radiographic (PCWG2) PFS 16·5 months *vs* 8·3 months; HR 0·53 (p<0·001) Overall survival NR *vs* 27·2 months; HR 0·75, p=0·01	Time to opiate use Time to initiation of cytotoxic chemotherapy Time to ECOG performance status decrease PSA response rate Radiographic response rate Quality of life	Coprimary endpoint: overall survival plus radiographic PFS Chemotherapy naive patients No visceral metastases included Overall survival did not meet prespecified significance criteria
AFFIRM (n=1199)[10]	Enzalutamide 160 mg once a day	Placebo	Overall survival 18·4 months *vs* 13·6 months; HR 0·63, p<0·001	PSA response rate Pain response rate Quality of life (EQ-5D) PSA PFS Radiographic PFS Time to first SRE	Post docetaxel population Patients with risk factors for seizures excluded

… nel 2017 mCRPC… ormonoterapia o chemioterapia… questo è il problema!

Elementi da considerare nel decision making, presenti e ….

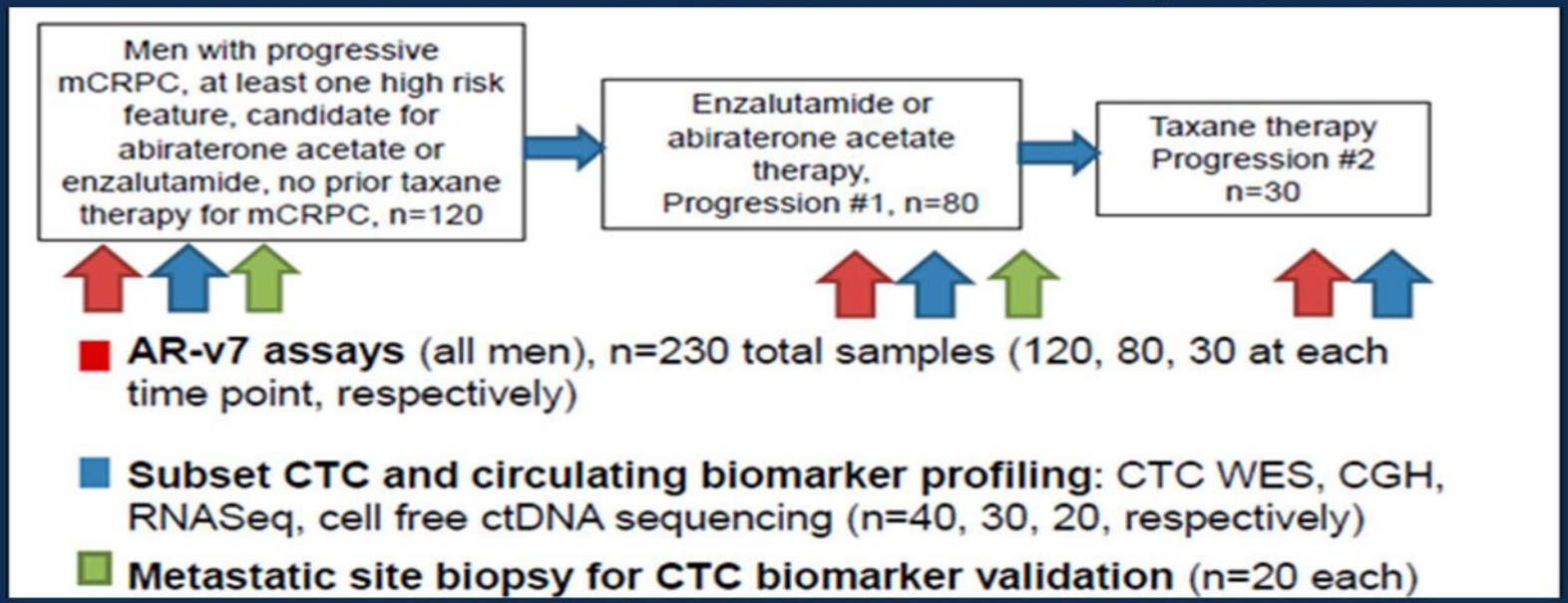
- Durata della risposta alla ormonoterapia di prima linea
- Comorbidità
- PSA DT
- GS – PSA pre-trattamento
- PS ECOG
- Burden tumorale
- ALP-HB
- Presenza di dolore
- Metastasi viscerali

Elementi da considerare nel decision making, ….futuri…

- Coesistenza di cloni AR- / AR+
- Amplificazione del AR WT
- Istologia neuroendocrina ab inizio
- Resistenze primarie e secondarie agli ARTA
  - CYP17A1, AKR1C3, GR and PR
  - ARV7 e tutte le varianti di splicing
  - HSD3B1
  - Mutazioni e/o perdita di RB1, TP53 and PTEN
  - alterazione germinale BRC 1-2 MMR

Prospective Validation of AR-V7

Primary objective: To develop and validate AR-V7 as a predictive biomarker of abi/enza resistance in a multicenter prospective trial



Courtesy of Andrew J. Armstrong, MD; Duke Cancer Institute

HSD3B1 and resistance to androgen-deprivation therapy in prostate cancer: a retrospective, multicohort study

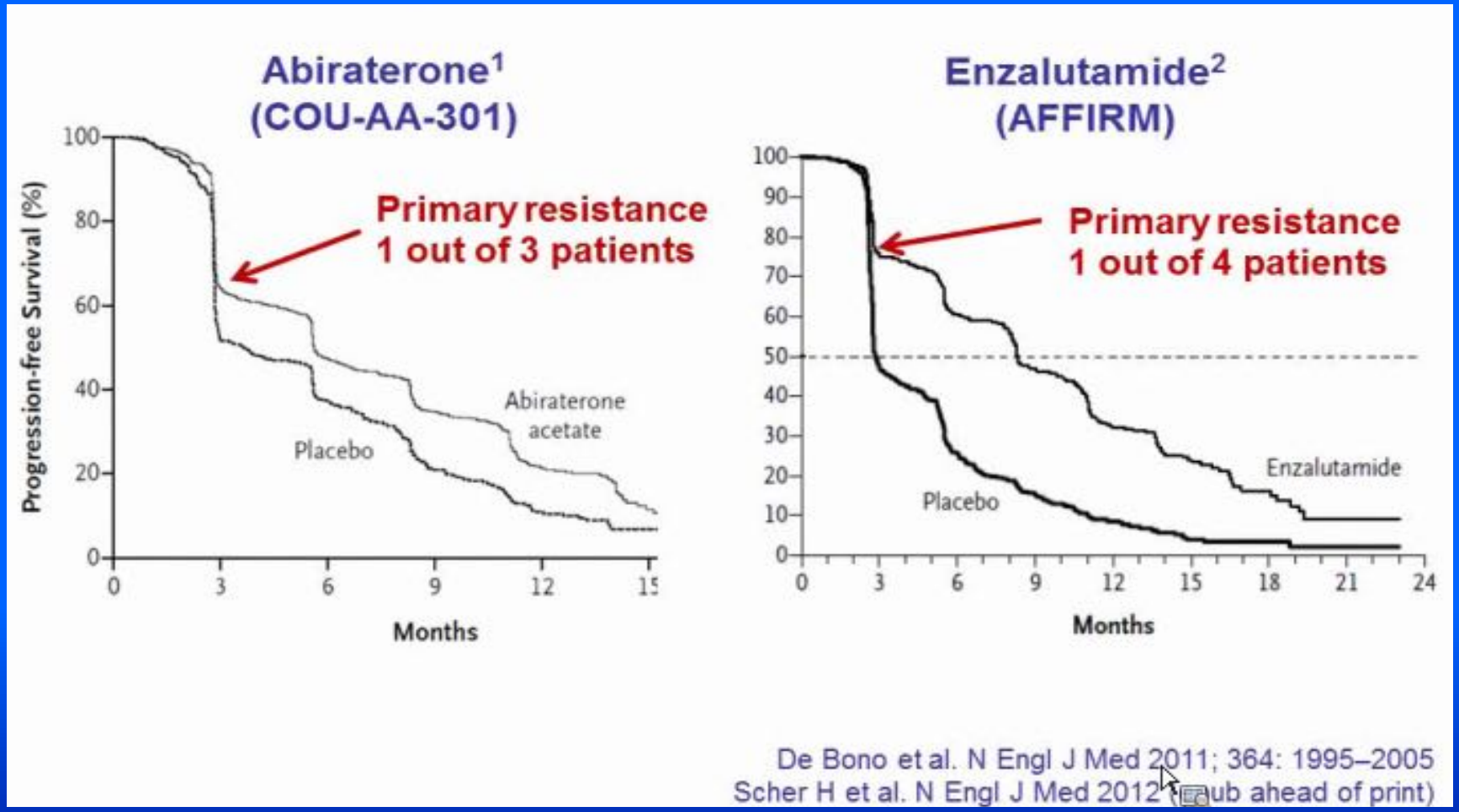
Un potenziale meccanismo di resistenza alla ADT potrebbe essere correlato ad un polimorfismo:

(1245A → C) nel gene HSD3B1. Questo gene codifica per l'isoenzima 3β-idrossisteroide deidrogenasi-1 (3βHSD1), che è il catalizzatore chiave responsabile della conversione degli androgeni surrenalici precursori in diidrotestosterone

L'incidenza di tale mutazione è variabile da 26 al 36% dei pazienti

JWD Hearn, G AbuAli, CA Reichard, *et al. HSD3B1* and resistance to androgen-deprivation therapy in prostate cancer: a retrospective, multicohort study
Lancet Oncol (2016) published online Aug 26

Resistenza primaria agli ARTA post docetaxel



De Bono et al. N Engl J Med 2011; 364: 1995–2005
Scher H et al. N Engl J Med 2012 (Epub ahead of print)

HSD3B1 and resistance to androgen-deprivation therapy in prostate cancer: a retrospective, multicohort study

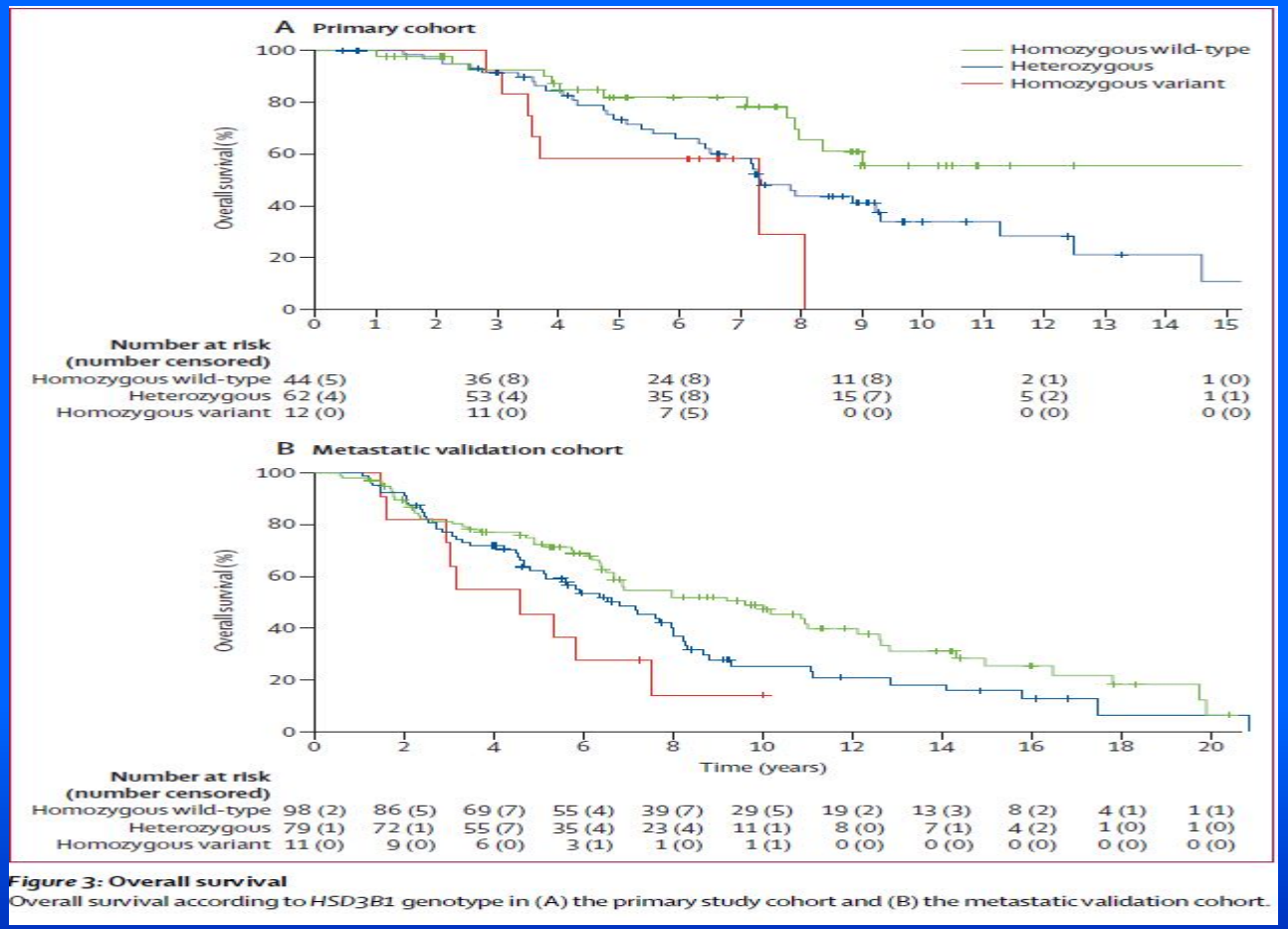


***Figure 3*: Overall survival**
Overall survival according to *HSD3B1* genotype in (A) the primary study cohort and (B) the metastatic validation cohort.

JWD Hearn, G AbuAli, CA Reichard, *et al. HSD3B1* and resistance to androgen-deprivation therapy in prostate cancer: a retrospective, multicohort study Lancet Oncol (2016) published online Aug 26

Attività di docetaxel post-abiraterone?

	VENICE[1] DOC/Pbo n=612	FIRSTANA[6] DOC N=391	De Bono[2] ABI→DOC n=35	Schweizer[3] DOC n=95	Schweizer[3] ABI→DOC n=24	Azad[4] ABI→DOC n=86	De Bono[5] (COU-AA-302) ABI→DOC n=261
DOC therapy line	1	1	2	1	2	2	2
Visceral mets	YES	Yes	YES	YES	YES	YES	NO
↓ PSA ≥50%	63.5%	68,4%	**25.7%**	63.0%	**38.0%**	**35.0%**	**47%**
Median PSA-PFS (mths)	8.1	5.3	4.6	6.7	4.1	4.0	7.6
OS, median (mths)	21.2	24.3	**12.5**	-	-	**11.7**	NA

[2-5] trials are retrospective studies

1. Tannock et al. Lancet Oncol 2013; 14:760-8; 2. Mezynski & De Bono Annal Oncol 2012. 23: 2943–2947; 3. Schweizer MT et al. Eur Urol 2014; 66:646-52; 4. Azad et al. The Prostate 2014; 74:1544-1550; 5. De Bono et al. ASCO GU 2015 (abstract 184); 6. Sartor et al. abs 5006 ASCO 2016

Attività di docetaxel post-abiraterone? Validità degli studi retrospettivi!!!

	Cohort size	Previous treatment: % of patient population	PSA response	Radiographic response	Survival	Comments
Docetaxel after abiraterone						
Mezynski et al[27]	35	Anti-androgens: 100% Dexamethasone: 71% Diethylstilboestrol: 46%	30% PSA decrease: 13/35 (37%) 50% PSA decrease: 9/35 (26%)	Partial response: 4/24 (17%)	Overall survival: 12·5 months (95% CI 10·6–19·4) PSA PFS: 4·6 months (95% CI 4·2–5·9)	None of the abiraterone refractory patients responded to docetaxel
Schweizer et al[28]	24	Anti-androgens: 92% Ketoconazole: 25%	30% PSA decrease: 13/24 (54·2%) 50% PSA decrease: 9/24 (38%)	NR	Overall survival: NR PSA PFS: 4·1 months (95% CI 2·8–5·8)	Significantly worse outcome compared to contemporary control group of abiraterone-naive patients 39% of abiraterone refractory patients achieved PSA response on docetaxel
Aggarwal et al[29]	23	Anti-androgens: 4%* Ketoconazole: 26% Diethylstilboestrol : 4%	30% PSA decrease: 15/23 (65%) 50% PSA decrease: 11/23 (48%)	NR	Overall survival: 12·4 months (95% CI 8·2–19·6)	Similar rate of response in patients with primary and acquired resistance to abiraterone
Azad et al[30]	86	Docetaxel: 57%	50% PSA decrease: 30/86 (35%)	NR	Overall survival: 11·7 months (95% CI 9·5–13·9) PFS: 4 months (95% CI 3·1–5·0)	No association between response to abiraterone and response to docetaxel

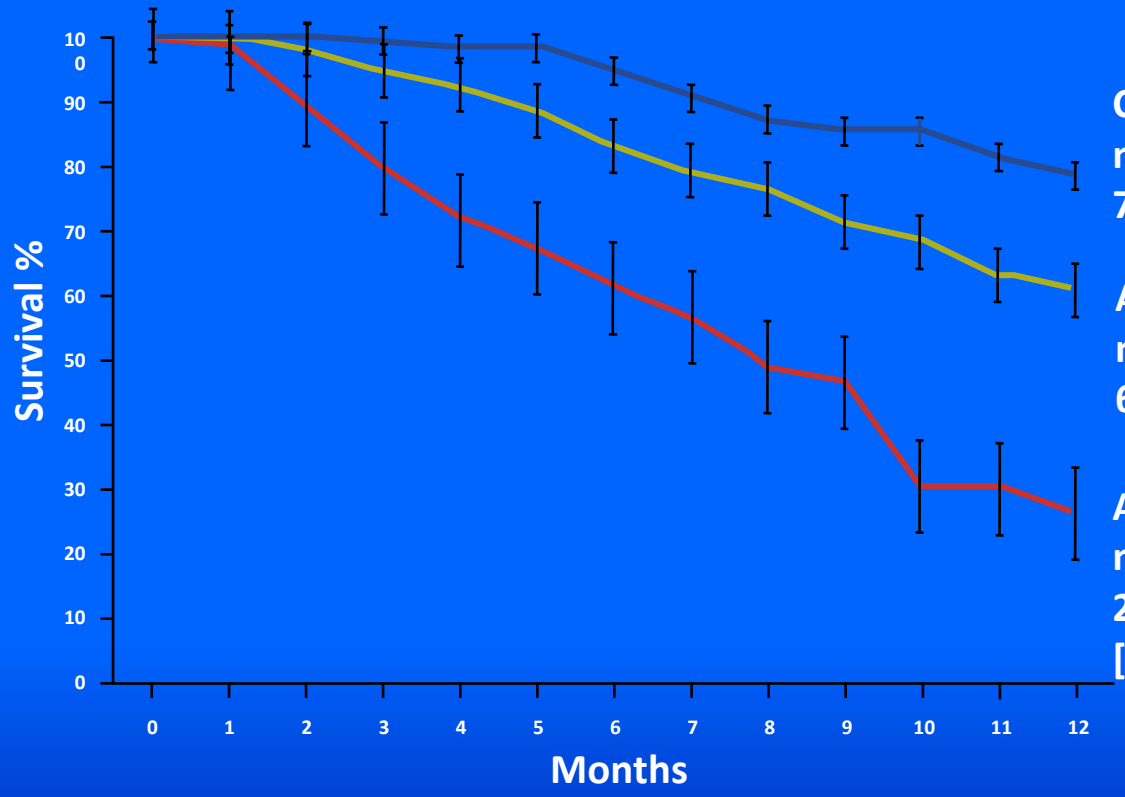
Sequenze ENZA-ABI / ABI -ENZA?

Author	Year published	N pts	Median ABI duration	↓ PSA ≥50%	Median PFS
No prior ENZA					
De Bono et al.[1] (COU-AA-302)	2011	797	8 mo	**29%**	**5.6 mo**
ENZA →ABI					
Loriot et al.[2]	2013	38	3 mo	8%	2.7 mo
Noonan et al.[3]	2013	30	3 mo	3%	3.6 mo

1. De Bono et al. NEJM 2011;364:1995-2005;
2. Loriot Y et al. Ann Oncol 2013;24:1807-12;
3. Noonan KL et al. Ann Oncol 2013;24:1802-7

Systematic Review of 13 Published Retrospective Studies in mCRPC (N=1,016)

12-month cumulative OS rate by sequence (post-DOC)



%, [95% CI]

CABA→ART, n=229
76.4% [70.9-81.9]

ART→CABA, n=318
61.3% [56.0-66.7]

ART→ART, n=397
28.5% [24.1-32.9]

Poor outcome when novel AR-targeted agents are prescribed in sequence

ART: novel AR-targeted agent (abiraterone acetate or enzalutamide)

Maines F et al. Crit Rev Hematol Oncol 2015;96:498-506

FLAC International Database (HEGP)

Retrospective analysis of 574 consecutive patients with mCRPC treated with **CABA (after DOC)** in 44 centers from 6 countries (France, Greece, Poland, Spain, Turkey, UK)

574 mCRPC pts treated with CABA

DOC → CABA →ART (N=124)

DOC → ART → CABA (N=183)

DOC → CABA (N=267)*

ART: novel AR-targeted agent (enzalutamide or abiraterone); HEGP: Hôpital Européen Georges-Pompidou
**Historical reference – First recruited patients (ART were not yet available)*

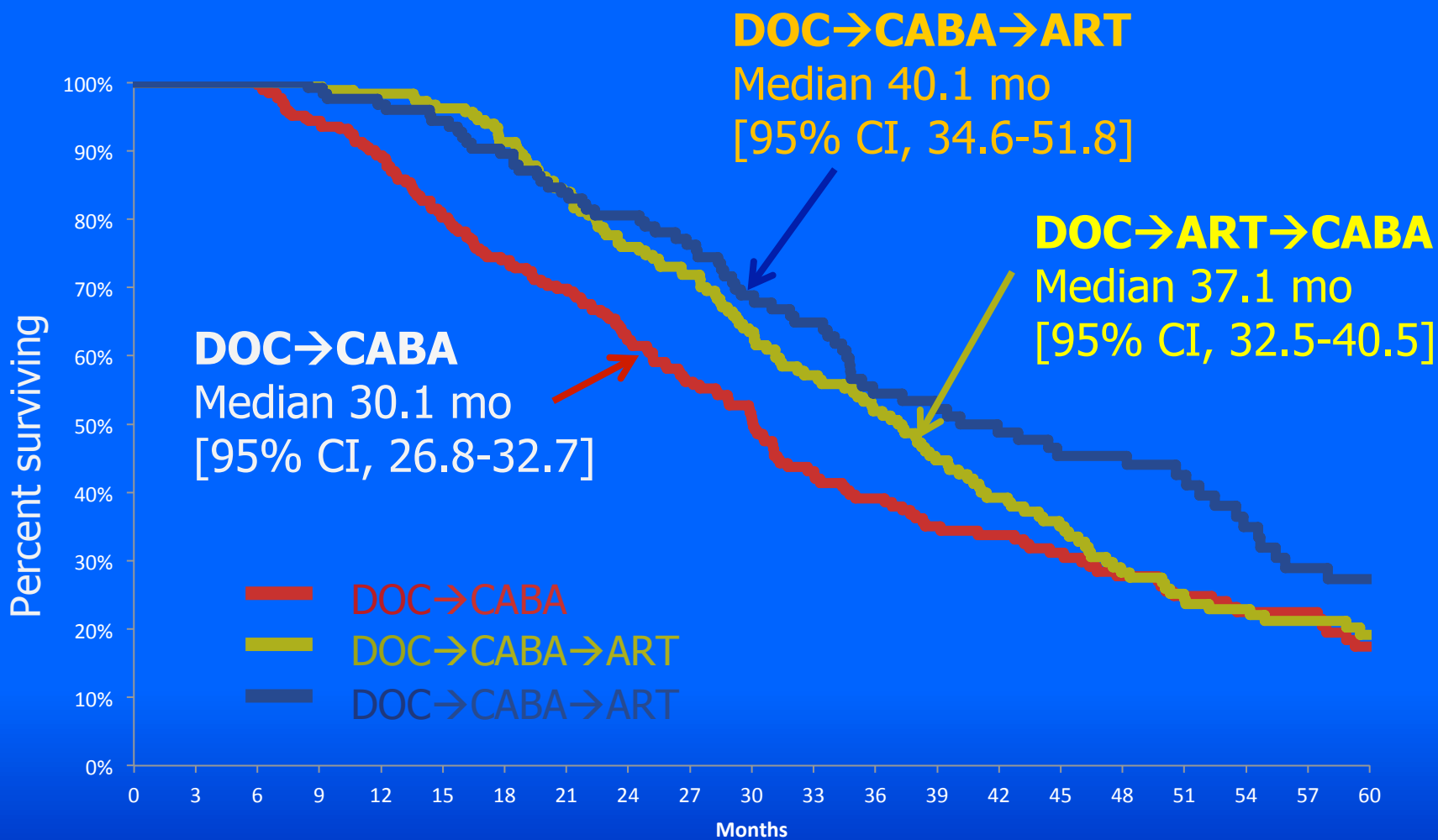
Delanoy N et al. J Clin Oncol 2017;35 (suppl 6S):abstract 267 (poster presentation)

FLAC - Patient Profile at DOC Initiation

	DOC→CABA→ART (N=124)	DOC→ART→CABA (N=183)	DOC→ CABA (N=267)
Gleason 8–10 at diagnosis	65.3 %	51.0 %	55.1 %
M1 at diagnosis	**51.5 %**	33.6 %	**51.9 %**
Patients characteristics at DOC initiation			
Median age, years	66	65	67.5
Duration of response to first ADT ≤ 12 mo	23.4 %	23.0 %	37.1 %
ECOG PS 2+	7.5 %	3.2 %	**15.9 %**
Pain	**43.7%**	33.5 %	**54.4 %**
Visceral mets	7.6 %	7.0%	**14.7%**
PSA level, ng/ml	59.0	42.0	60.3
Alkaline phosphatase ≥1.5 N	36.8	35.8	33.1
Hemoglobin <13 g/dl	47.5	50.0	48.2
Treatment modalities			
Median number of DOC cycles	7	6	7
Median number of CABA cycles	7	6	6
Median duration of ART, mo	5.9	4.4	NR

Delanoy N et al. J Clin Oncol 2017;35 (suppl 6S):abstract 267 (poster presentation)

FLAC - OS from First DOC Cycle



N at risk

DCA	266	266	266	248	229	197	175	162	139	118	97	75	68	58	52	46	40	34	27	22	14
DAC	183	183	183	182	180	176	165	148	131	122	102	88	79	67	58	47	37	32	27	23	19
DC	124	124	123	123	120	117	111	103	96	85	71	64	51	47	42	38	36	28	23	19	16

Delanoy N et al. J Clin Oncol 2017;35 (suppl 6S):abstract 267 (poster presentation)

FLAC - Factors Influencing OS (Multivariate Analysis)

Criterion at sequence initiation		HR [95% CI]	*P* value
Duration of response to first ADT	≤12 mo >12 mo	Ref 0.52 [0.40; 0.67]	<0.001
Clinical progression	No Yes	Ref 1.51 [1.16; 1.97]	0.002
Baseline PSA (log 10)		1.35 [1.14; 1.60]	<0.001
Sequence after DOC	CABA only **CABA→A** **RT** ART→CA BA	Ref **0.60 [0.42; 0.84]** 0.88 [0.68; 1.14]	0.012

Delanoy N et al. J Clin Oncol 2017;35 (suppl 6S):abstract 267 (poster presentation)

FLAC - Conclusions

- This large retrospective cohort suggests that patients receiving 3 life-extending therapies (DOC, CABA and a novel AR-targeted agent) have a longer OS benefit than DOC→CABA only

Delanoy N et al. J Clin Oncol 2017; 35 (suppl 6S); abstract 267 (poster)

CATS International Database (HEGP)

- Retrospective analysis of 560 consecutive patients treated with DOC, CABA and one ART in 31 centers in 7 countries (France, Austria, Greece, Italy, Israel, Spain, UK)

560 mCRPC pts treated with DOC, CABA and ART

DOC → CABA →ART (N=129)

DOC → ART → CABA (N=390)

ART → DOC → CABA (N=41)

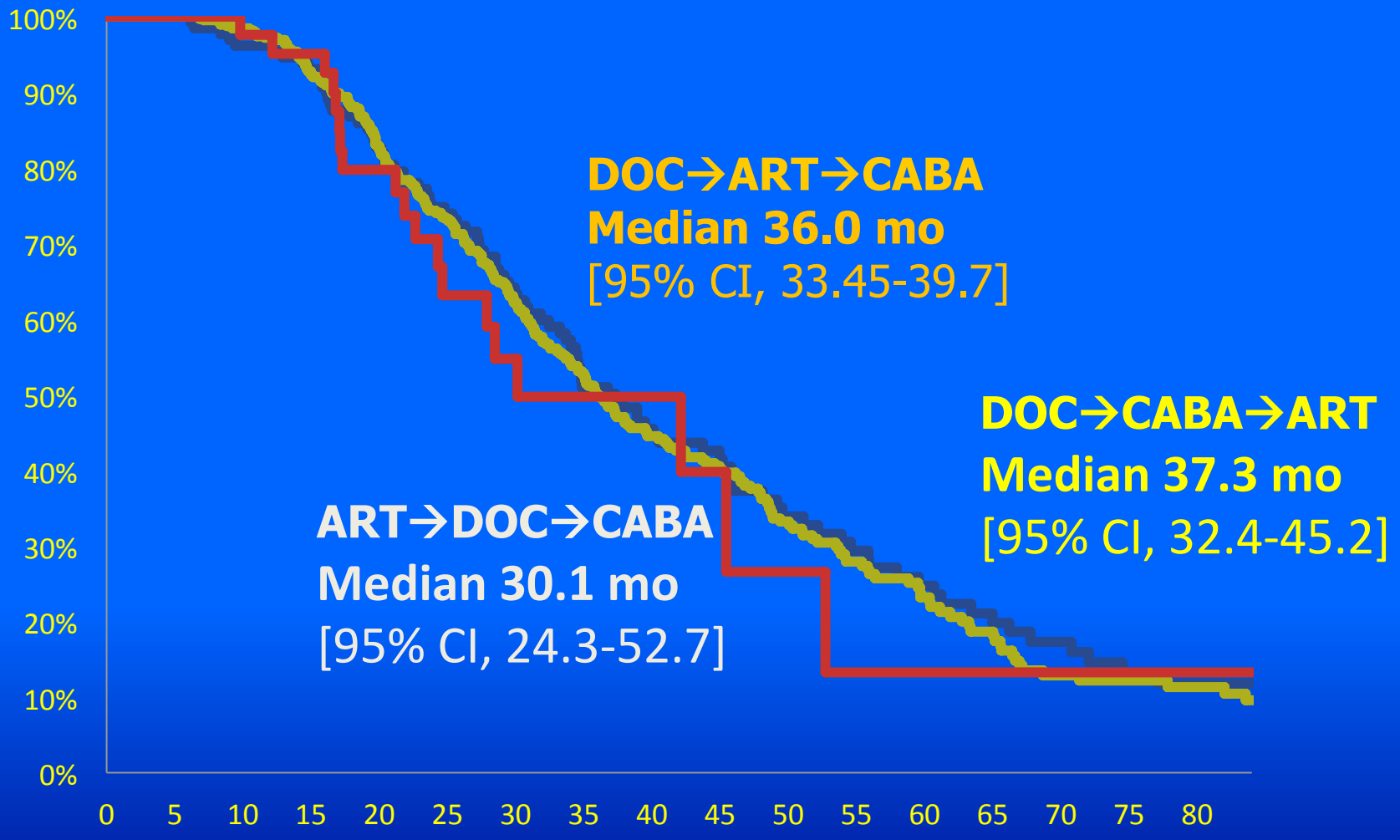
Angelergues A et al. Ann Oncol 2016;27 (suppl 6):abstract 744P (poster presentation)

CATS - Patient Profile at Sequence

	DOC→CABA→ART (N=129)	DOC→ART→CABA (N=390)	ART→DOC→CABA (N=41)
Gleason 8–10 at diagnosis	**63.8 %**	49.1 %	45.9 %
M1 at diagnosis	**61.7 %**	44.7 %	**57.5 %**
Patients characteristics at DOC initiation			
Median age, yrs	67	66	66
Duration of response to first ADT ≤12 mo	27%	19%	27 %
ECOG PS 2+	4.3 %	5.5 %	3.6 %
Pain	**47.6%**	41.2 %	40.5 %
Visceral mets	**14.1 %**	7.2%	5.3%
High-volume disease (as per CHAARTED)	62.5%	58.2%	56.0%
PSA level, ng/ml	**46.4**	**46.0**	32.4
Alkaline phosphatase	103	101	98
Hemoglobin, median	13.2	12.9	13.4
Treatment modalities			
Median number of DOC cycles	6	6	6
Median number of CABA cycles	7	6	5
Median duration of ART, mo	4.6	6.0	7.0

Angelergues A et al. Ann Oncol 2016;27 (suppl 6):abstract 744P (poster presentation)

CATS – OS from First Life-Extending Therapy Initiation by Sequence



Angelergues A et al. Ann Oncol 2016;27 (suppl 6):abstract 744P (poster presentation)

CATS - Factors Influencing Survival (Multivariate Analysis)

Criterion at sequence initiation		HR [95% CI]	*P* value
Baseline PSA >44 ng/ml (median)	No	Ref	0.005
	Yes	1.526 [1.135; 2.051]	
Performance status (ECOG)	0-1	Ref	0.006
	≥ 2	2.258 [1.27; 4.014]	
High-volume disease*	No	Ref	0.022
	Yes	1.998 [1.104; 3.614]	
Pain	No	Ref	0.012
	Yes	1.479 [1.091; 2.005]	

**Visceral metastases and/or ≥4 bone metastases (with ≥1 beyond pelvis and vertebral column)*

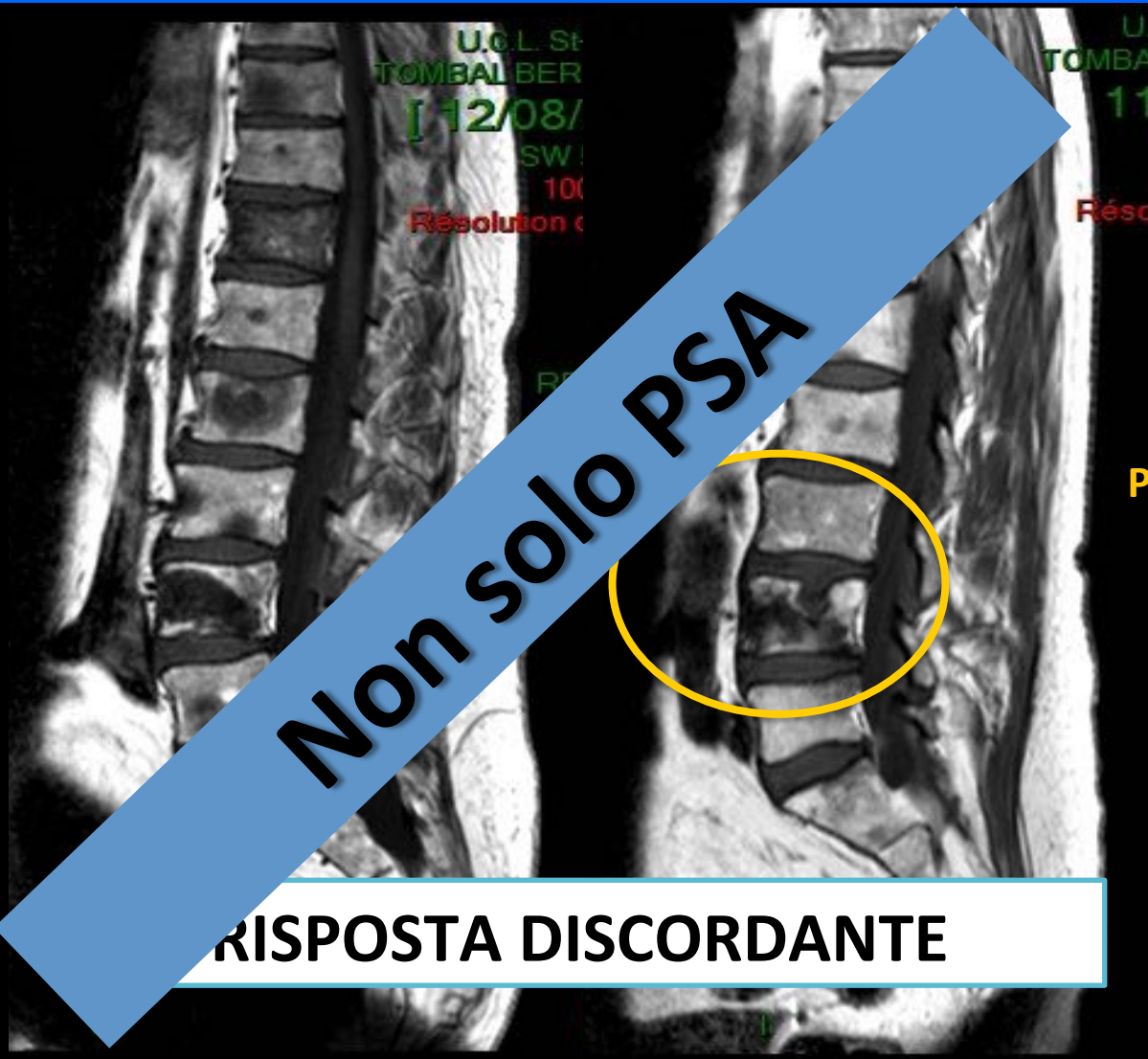
Angelergues A et al. Ann Oncol 2016;27 (suppl 6):abstract 744P (poster presentation)

Quindi ….Come scegliere la I-II-III linea….?

- Non esistono studi head to head
- Tutti i dati provengono da analisi retrospettive
- In alcuni casi le sequenze sono ricavate dai trials registrativi
- Nessun dato circa la capacità da parte della chemioterapia di revertire le resistenze ARV7 correlate
- Necessità di ottimizzare la gestione del Paziente DMT
- Ricorrere sempre ad una valutazione biochimica e strumentale anche in fase avanzata con frequenza regolare

65 aa, in trattamento con LHRH per M1 Pca
importante rivalutare il Paziente

08/2010
PSA 42 ng/ml



11/2010
PSA 1.5 ng/ml

Grazie per l'attenzione!!!!
e…..
soprattutto molto DMT