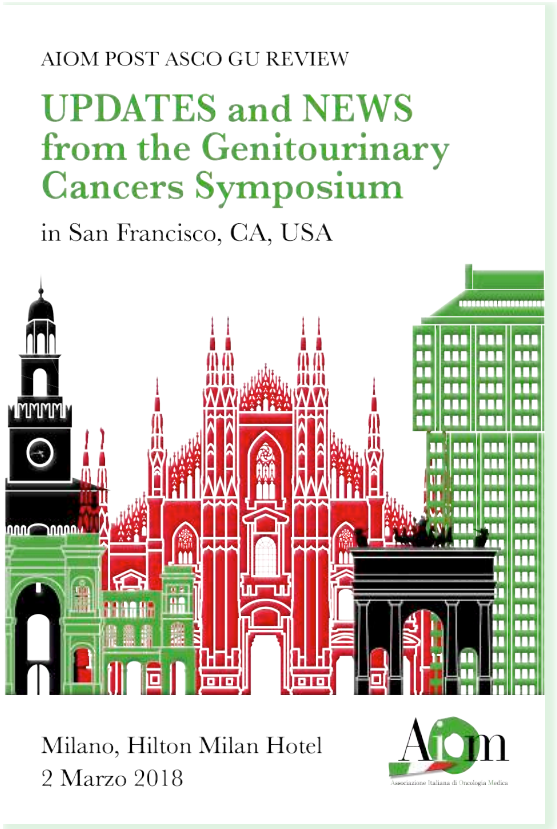


Prostata: Emerging strategies and controversial topics in advanced prostate cancer: POSTERS

Alessandra Mosca

SCDU Oncologia
Direttrice: Prof.ssa A. Gennari
AOU Maggiore della Carità, Novara

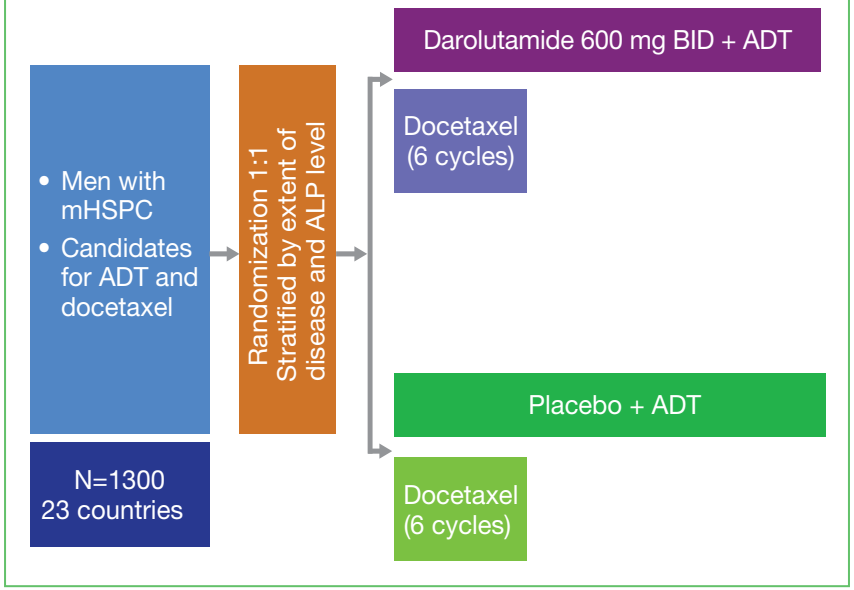
ARASENS: A Phase 3 Trial of Darolutamide in Combination with Docetaxel for Men with Metastatic Hormone-Sensitive Prostate Cancer (mHSPC)

TPS383

Matthew R. Smith[1], Fred Saad[2], Maha Hussain[3], Cora N. Sternberg[4], Karim Fizazi[5], Karin Yamada[6], Christian Kappeler[7], Iris Kuss[8] and Bertrand Tombal[9]

[1]Massachusetts General Hospital Cancer Center and Harvard Medical School, Boston, MA, United States; [2]Centre Hospitalier de l'Université de Montréal / CRCHUM, University of Montreal, Montreal, Canada; [3]Division of Hematology and Oncology, Northwestern University Feinberg School of Medicine, Chicago, IL, United States; [4]Department of Medical Oncology, San Camillo-Forlanini Hospital, Rome, Italy; [5]Gustave Roussy, University of Paris Sud, Villejuif, France; [6]Oncology Department, Bayer HealthCare Pharmaceuticals Inc., Whippany, NJ, United States; [7]Clinical Statistics, Bayer AG, Berlin, Germany; [8]CD Oncology AR Inhib, Bayer AG, Berlin, Germany; [9]Urology Department, Cancer Centre, Catholic University of Louvain (UCL), Brussels, Belgium

Figure 1. ARASENS trial design



Endpoints and assessments

- *Primary:* The primary objective is to demonstrate the superiority of darolutamide compared with placebo, both in combination with ADT + docetaxel.
  - The primary endpoint is OS; timeframe ~70 months.
- *Secondary:* Secondary endpoints include time to CRPC, time to initiation of subsequent antineoplastic therapy, symptomatic skeletal event-free survival (SSE-FS), time to first SSE, time to initiation of opioid use, time to pain progression, and time to worsening of physical disease symptoms.
  - Each of these will be measured at 12-week intervals.
  - Safety will be assessed by frequency and severity of adverse events.

ARASENS trial status

- Currently recruiting patients.
- The first patient first visit was in November 2016, and >300 sites are open for recruitment and enrolling patients.

Australia	France	Poland
Belgium	Germany	Russian Federation
Brazil	Israel	Spain
Bulgaria	Italy	Sweden
Canada	Japan	Taiwan
China	Republic of Korea	United Kingdom
Czech Republic	Mexico	United States
Finland	Netherlands	

Alessandra Mosca, Milano, 2 Marzo 2018

Low Blood–Brain Barrier Penetration of [^{14}C]Darolutamide Compared with [^{14}C]Enzalutamide in Rats Using Whole Body Autoradiography

Steffen Sandmann[1], Dagmar Trummel[1], Dietrich Seidel[1], Hille Gieschen[2] and Christian Zurth[3]

[1]Drug Discovery, Bayer AG, Wuppertal, Germany; [2]Drug Discovery, Bayer AG, Berlin, Germany; [3]Clinical Pharmacokinetics Oncology, Bayer AG, Berlin, Germany.

Darolutamide

Dose, oral Sacrifice time Animal no.	10 mg/kg 1 h 501	Ratio Brain/ Blood	10 mg/kg 8 h 502	Ratio Brain/ Blood
Blood heart	**11.7**		**0.870**	
Brain	0.789	0.067	0.0688	0.079
Hypothalamus	0.757	0.064	0.527	0.061

Enzalutamide

Dose, oral Sacrifice time Animal no.	10 mg/kg 4 h 503	Ratio Brain/ Blood	10 mg/kg 8 h 504	Ratio Brain/ Blood
Blood heart	**4.25**		**4.03**	
Brain	3.08	0.723	3.25	0.807
Hypothalamus	3.08	0.724	3.44	0.854

Table 1. Quantitative tissue distribution of [^{14}C]darolutamide and [^{14}C]enzalutamide in male Wistar rats based on WBA

	Darolutamide [µg-eq/g]		Enzalutamide [µg-eq/g]	
Dose, oral Sacrifice time	10 mg/kg 1 h	10 mg/kg 8 h	10 mg/kg 4 h	10 mg/kg 8 h
Brown adipose tissue	6.89	0.541	15.1	15.4
White adipose tissue	2.76	0.171	15.2	21.0
Epididymides	2.42	0.416	6.32	8.11
Kidneys	17.3	2.66	12.0	12.9
Liver	20.2	2.37	22.2	23.7
Lungs	11.0	0.558	5.50	5.67
Preputial gland	7.60	1.37	9.67	10.3
Prostate	5.75	0.768	5.07	6.35
Seminal vesicles	2.65	0.667	2.35	3.04
Skeletal muscle, dorsal	5.22	0.437	3.91	4.29
Testes	1.66	0.523	3.33	3.56

CONCLUSIONS

blood–brain barrier (BBB) penetration of [^{14}C]darolutamide was 10 times smaller, compared with [^{14}C]enzalutamide.

This may lead to a reduction in the risk of CNS-related AEs with darolutamide compared with enzalutamide; ongoing clinical studies will provide further supporting data (NCT02907372, NCT00579072, NCT03124615).

[^{14}C]Darolutamide was rapidly eliminated from all tissues including the brain, and was almost undetectable at 8 hours post-dose. By contrast, [^{14}C]enzalutamide concentration remained constant in all tissues.

↳ equal efficacy???

Alessandra Mosca, Milano, 2 Marzo 2018

Hepatic effects assessed by review of safety data in enzalutamide castration-resistant prostate cancer trials

Poster J19

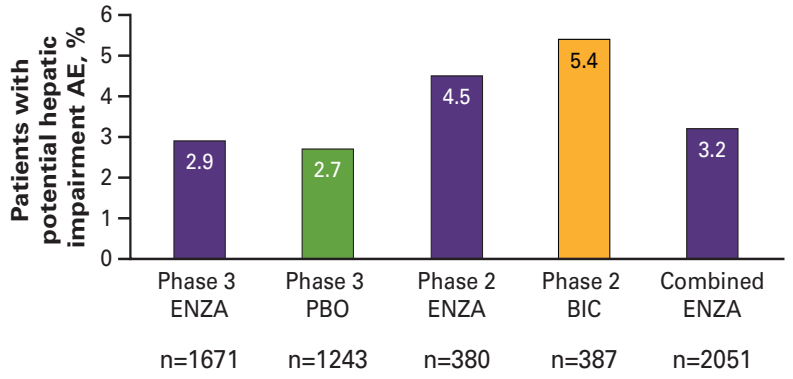
Tomasz M. Beer,[1,*] Simon Chowdhury,[2] Fred Saad,[3] Neal D. Shore,[4] Celestia S. Higano,[5] Peter Iversen,[6] Karim Fizazi,[7] Kurt Miller,[8] Axel Heidenreich,[9] Choung Soo Kim,[10] De Phung,[11] Jeffrey Barrus,[12] Natalia Nikolayeva,[11] Andrew Krivoshik,[12] Javier Waksman,[13] Bertrand Tombal[14]

Table 1. Studies included for treatment group comparisons

Study	Phase	Comparator	Patient population	Treatment randomization (enzalutamide: comparator)	Treatment dosage	Treated patients, n	Total treatment exposure, patient-years
AFFIRM (NCT00974311)[1]	3	PBO	Post-chemotherapy (docetaxel) mCRPC	2:1	ENZA: 160 mg/day PBO: matched capsules	ENZA: 800 PBO: 399	ENZA: 677 PBO: 172
PREVAIL (NCT0121299)[2]	3	PBO	Chemotherapy-naïve mCRPC	1:1	ENZA: 160 mg/day PBO: matched capsules	ENZA: 871 PBO: 844	ENZA: 1294 PBO: 560
TERRAIN (NCT01288911)[3]	2	BIC	Chemotherapy-naïve mCRPC	1:1	ENZA: 160 mg/day BIC: 50 mg/day	ENZA: 183 BIC: 189	ENZA: 219 BIC: 144
STRIVE (NCT01664923)[4]	2	BIC	Chemotherapy-naïve nmCRPC/mCRPC	1:1	ENZA: 160 mg/day BIC: 50 mg/day	ENZA: 197 BIC: 198	ENZA: 248 BIC: 182

BIC=bicalutamide; ENZA=enzalutamide; mCRPC=metastatic castration-resistant prostate cancer; nmCRPC=non-metastatic castration-resistant prostate cancer; PBO=placebo.

Figure 1. Incidence of potential hepatic-related AEs



AE=adverse event; BIC=bicalutamide; ENZA=enzalutamide; PBO=placebo.

CONCLUSIONS

- In Phase 3 and Phase 2 trials, the rate of potential hepatic-related AEs were generally low and comparable in the enzalutamide groups versus placebo and bicalutamide groups, respectively, despite the longer exposure with enzalutamide. The exposure-adjusted rates were lower for the enzalutamide groups.
- The incidences of grade ⩾3 potential hepatic-related AEs were low and generally similar between the enzalutamide and placebo groups in the Phase 3 trials, and slightly lower in the bicalutamide group compared with enzalutamide in Phase 2 trials.
- The observed frequencies of hepatic events/laboratory abnormalities were generally low across all groups, and the aggregate analyses of liver laboratory data did not reveal a consistent pattern of treatment differences in liver chemistry tests in the Phase 3 and Phase 2 trials.
- Taken together, data from this combined analysis of CRPC trials indicate that, after adjustment for exposure, hepatic toxicity with enzalutamide is no greater than the comparators.

Alessandra Mosca, Milano, 2 Marzo 2018

Visceral metastases on abiraterone vs placebo: a post-hoc analysis of mode of radiographic progression in COU-AA-302.

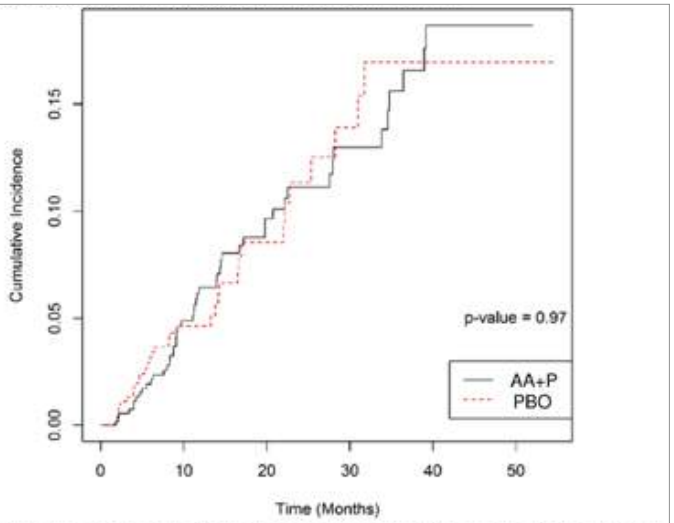
Benjamin A. Teply[1*], Fang Qiu[1], Emmanuel S. Antonarakis[2], Michael A. Carducci[2], Samuel R. Denmeade[2]

[1] University of Nebraska Medical Center, Omaha, NE, USA; *ben.teply@unmc.edu
[2] Johns Hopkins University, Baltimore, MD, USA.

Hypothesis: We hypothesized that the rate of development of visceral disease was increased with AA+P compared to other treatments without potent androgen signaling inhibition.

Methods

In order to test our hypothesis, we examined incidence of the development visceral disease among patients treated in the COU-AA-302 trial [2]. We performed a post-hoc analysis among patients with mCRPC treated on the phase 3 trial of abiraterone acetate plus prednisone (AA+P) vs placebo plus prednisone (PBO) in the pre-chemotherapy setting.



Univariate log-rank testing showed no evidence of a difference in time to visceral metastases between AA+P and PBO groups.

Results (cont.)

Cox regression identified baseline LDH and baseline presence of both bone and soft tissue metastases as independent risk factors for development of visceral disease. Treatment group (AA+P vs PBO) was not an independent risk factor.

Variable	Hazard Ratio (95% CI)	p-value
Treatment group, AA+P vs PBO	0.76 (0.47 – 1.21)	0.24
Bone metastases, present vs not	1.92 (1.04 – 3.54)	0.04
Soft tissue metastases, present vs not	3.25 (1.93 – 5.48)	<0.0001
LDH	1.006 (1.004 – 1.007)	<0.0001

Conclusions

Treatment with AA+P was not associated with an increased risk of development of visceral metastatic disease at the time of progression compared with PBO.

Abiraterone is being testing and used in earlier disease states, including castration-naïve non-metastatic and metastatic disease [8]. This data alleviates potential concerns regarding abiraterone driving prostate cancer to an aggressive phenotype at the time of progression.

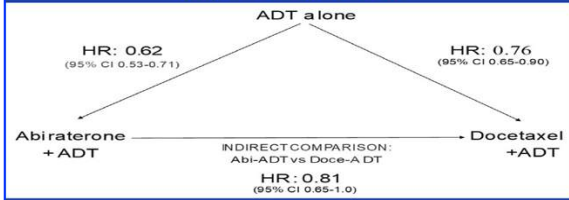
A. Mosca,
Milano, 2 Marzo 2018

Abiraterone Acetate (AA) or Docetaxel (D) in Metastatic Castration-sensitive Prostate Cancer (mCSPC): A Systematic Review and Network Meta-Analysis of Randomized Clinical Trials

Irbaz Bin Riaz, Abdulaali Mutairi, Saad Ullah Malik, Zeeshan Ali, Abdullah Alhifany, Sandipan Bhattacharjee, Ivo Abraham, Manish Kohli

- Five clinical trials were included in this analysis.
- Two trials (LATITUDE, STAMPEDE) compared AA to ADT.
- Three trials (CHAARTED,STAMPEDE, GETUG-AFU 15 study) compared D to ADT.
- Results from both fixed effect and random effect network meta-analyses for the primary outcome (OS) revealed no statistical significance between AA and D (HR 0.81,95%CI 0.65-1.01; HR 0.81, 95%CI 0.40-1.82) respectively.

Schematic diagram of indirect treatment comparison derivation



Results from Fixed effect NMA For Metastasized Prostate Cancer

	HR	Lower CrI	Upper CrI
Docetaxel+ ADT vs ADT	0.7613	0.6479	0.8957
Abiraterone+ ADT vs ADT	0.6166	0.533	0.7144
Abiraterone+ADT vs Docetaxel+ ADT	0.8102	0.6509	1.008

Results from Random effect NMA For Metastasized Prostate Cancer

	HR	Lower CrI	Upper CrI
Docetaxel+ ADT vs ADT	0.7666	0.4778	1.307
Abiraterone+ ADT vs ADT	0.6242	0.3764	1.209
Abiraterone+ADT vs Docetaxel+ ADT	0.8137	0.401	1.816

Results(AEs)

- AA had statistically significant fewer events of anemia (OR 0.14,95%CI 0.08-0.23), neutropenia (OR 0.06,95%CI 0.03-0.12),nausea (OR 0.09,95%CI 0.02-0.24), diarrhea (OR 0.06,95%CI 0.02-0.15), constipation (OR 0.25,95%CI 0.11-0.53), and fatigue (OR 0.12,95%CI 0.07-0.20).
- AA had statistically significant more events of hot flashes (OR 3.85, 95% CI2.33-6.25).
- For other adverse events, both drugs were statistically similar.

A. Mosca,
Milano, 2 Marzo 2018

Conclusion

- There is no difference in OS using AA for longer periods in CSPC than a regimen of a limited number of cycles of D.
- There are significant differences in side effect profile of these drugs.
- Factors such as side effect profile, patient and physician preference, cost and convenience of therapy are important in making the choice.
- There is high likelihood that Abi-ADT may be a superior approach.
- Currently, both approaches are acceptable in the absence of head to head comparison.

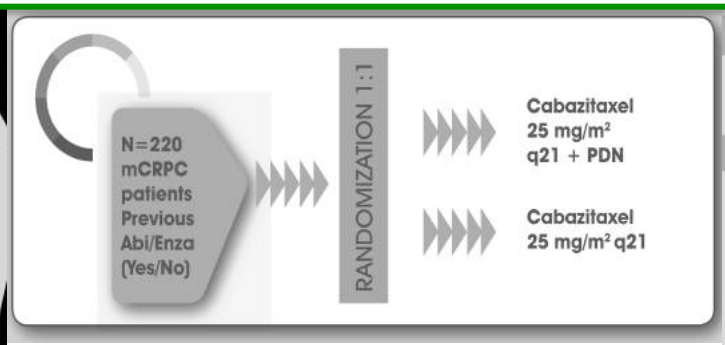
Future Prospects

- Further analyses are needed to determine cost effectiveness of AA vs D under consideration of comparative efficacy and safety.
- Direct comparison of Abi-D and Abi-ADT may be possible in future.
- AR-V7 may be helpful in guiding treatment decisions.
- Results from ongoing trials of enzalutamide in front line treatment of mCSPC are awaited.

A Randomized Phase II study comparing cabazitaxel/prednisone to cabazitaxel alone for second-line chemotherapy in men with metastatic castration resistant prostate cancer (mCRPC): CABACARE

ABSTRACT TPS387

Authors:
C. Buonerba[1,3], D. Bosso[2], S. De Placido[1], G. Di Lorenzo[1]



Primary Objective

To evaluate whether cabazitaxel alone is non inferior in terms of PFS to cabazitaxel plus daily prednisone in patients with castration resistant prostate cancer

Secondary Objectives

- Safety
- Health-Related Quality of Life HRQL and pain
- Objective Response Rate according to RECIST 1.1
- Biochemical (PSA) response (decrease ≥50%, waterfall plot)
- Time to biochemical (PSA) Progression (TTPP)
- Time to radiological Progression (rTTP)
- Overall survival (OS)
- Association of OS, PFS and response rate with AR-V7 and RB status in CTC by the use of Adna test
- Time to SRE.

GOIM
GRUPPO ONCOLOGICO DELL'ITALIA MERIDIONALE

Impact of cabazitaxel on metastatic bone disease in patients with castration resistant prostate cancer previously treated with docetaxel: *CABONE Study*

Abstract TPS405

Authors: Daniele Santini[1], Gaetano Facchini[2], Francesco Bertoldo[3], Franco Morelli[4], Evaristo Maiello[4]

Primary Objective

Bone (Skeletal) Progression Free Survival according to PCWG2 criteria.

Secondary Objectives

- Time to Skeletal Related Events
- Time to Bone Pain Progression
- Bone Pain Response
- Time to opiate use for cancer-related pain
- Time to deterioration in ECOG Performance Status
- Evaluation of Quality of Life and Functional status
- Safety and centralized bone turnover markers: Alkaline Phosphatase, Bone ALP, LDH, Serum CTx, iPTH, 1.25 (OH)2 D3

CaBone is a single arm, prospective, open label, multi center, phase II, independent GOIM – Gruppo Oncologico dell'Italia Meridionale – cooperative study of cabazitaxel 25 mg/m² q21 plus daily PDN (10 mg) in mCRPC patients with bone metastases without visceral disease progressed during or after docetaxel treatment.

Alessandra Mosca, Milano, 2 Marzo 2018

First Interim Results of the Radium-223 (Ra-223) REASSURE Observational Study in Metastatic Castration-Resistant Prostate Cancer (mCRPC): Safety and Baseline (BL) Characteristics of US Patients (Pts) by Prior/Concomitant Treatment (Tx)

Abstract 233

Lauren C. Harshman,[1] Oliver Sartor,[2] Timothy Richardson,[3] John Sylvester,[4] Daniel Y. Song,[5] Constantine Mantz,[6] Robert Brookland,[7] Mark Perlmutter,[8] Robert Given,[9] Ján Kalinovský,[10] Svetlana Babajanyan,[11] Yoriko De Sanctis,[11] Celestia S. Higano[12]

[1]Dana-Farber Cancer Center, Boston, MA, USA; [2]Tulane University School of Medicine, New Orleans, LA, USA; [3]Wichita Urology, Wichita, KS, USA; [4]21st Century Oncology, Lakewood Ranch, FL, USA; [5]Johns Hopkins University, Baltimore, MD, USA; [6]21st Century Oncology, Fort Myers, FL, USA; [7]Chesapeake Urology, Towson, MD, USA; [8]Jersey Shore Medical Center, Neptune, NJ, USA; [9]Urology of Virginia, Virginia Beach, VA, USA; [10]Bayer, Basel, Switzerland; [11]Bayer, Whippany, NJ, USA; [12]University of Washington and Fred Hutchinson Cancer Research Center, Seattle, WA, USA

Table 2. Most common drug-related TEAEs (updated analysis n=244)*

MedDRA PT†	Any grade	Grade 1–2	Grade 3–4
Anemia	26 (11)	13 (5)	13 (5)
Diarrhea	23 (9)	22 (9)	1 (<1)
Nausea	17 (7)	17 (7)	0
Fatigue	21 (9)	19 (8)	2(<1)

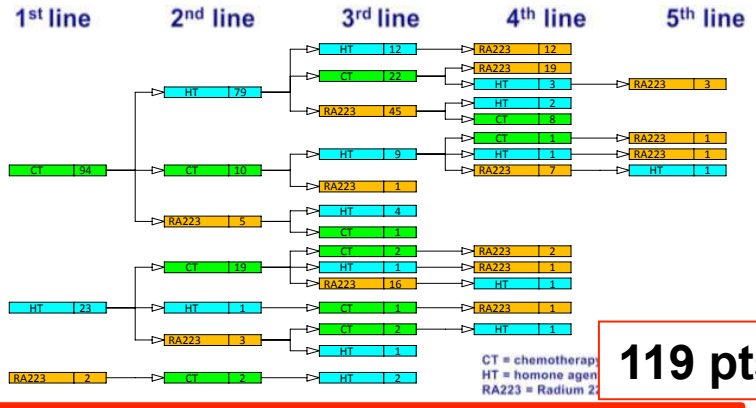
Conclusions

- To date, the interim analysis and extended safety update of REASSURE has not revealed any new safety findings.
- Most patients complete 5–6 Ra-223 doses in routine US clinical practice.
- Patients with prior treatment lines had lower Ra-223 treatment completion and higher incidence of adverse events, likely reflecting greater disease burden, as evidenced by higher median baseline PSA.

322 Sequencing Radium 223 (RA223) for metastatic castration-resistant prostate cancer (mCRPC) patients (pts) in the daily practice: preliminary results from a retrospective study in Italian Centers.

O. Caffo[1] – V. Frantellizzi[2] – L. Galli[3] – F. Monari[4] – G. Facchini[5] – S. Baldari[6] – M. Tucci[7] – F. Alongi[8] – R. Bortolus[9] – S. Agostini[10] – E. Biasco[3] – S. Fanti[11] S. Rossetti[5]– S. Pignata[6]– C. Zichi[7] – M. Salgarello[12] – E. Borsatti[13] – E. Cortesi[2] – A. Sbrana[3] – G. Devincentis[2]

TREATMENTS SEQUENCES (with pts number)



119 pts

# RA223	2	8	62	42	5

Skeletal metastatic burden at RA223 start

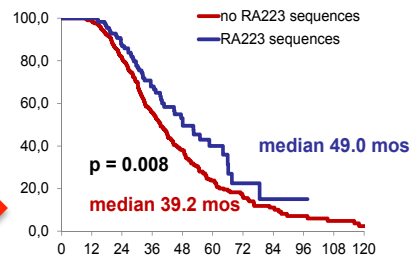
< 3 bone mets	3.3%
3-10 bone mets	18.5%
> 10 bone mets	52.9%
superscan	21.0%
not reported	4.2%

Outcomes

Biochemical and objective response rates

PSA reduction > 50%	7.2%
Objective partial response	11.3%
Objective stable disease	24.5%

Overall survival from 1st treatment line for mCRPC*

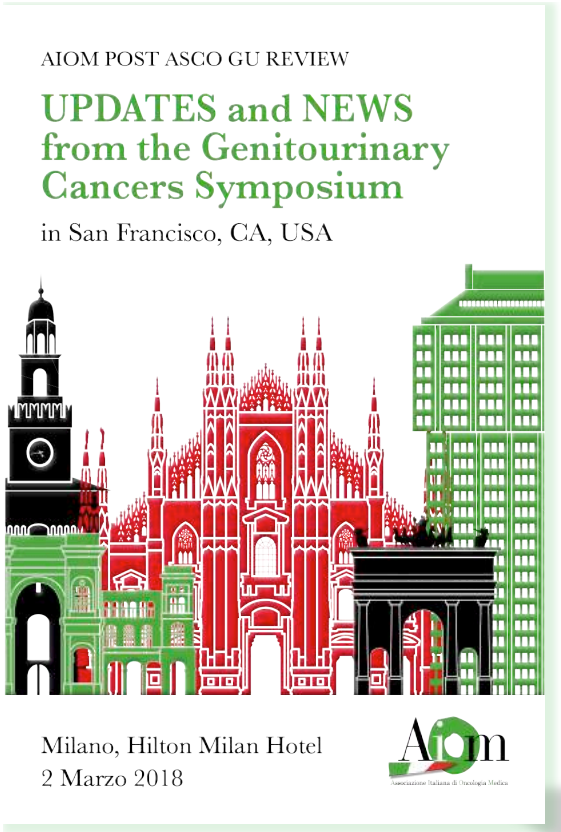


*contemporary series of 405 pts w/o visceral mets treated with 2 ADs after DOC

CONCLUSIONS

Despite the limitations of its retrospective nature, this preliminary data suggests that treatment sequencing of ADs that includes RA223 offers a survival advantage in mCRPC.

Alessandra Mosca, Milano, 2 Marzo 2018



Thank you!

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