Efficacy and safety of apalutamide in metastatic castration sensitive prostate cancer patients with a prior history of cardiovascular or metabolic risk factors – a post-hoc analysis of the TITAN study

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CONCLUSIONS

- A large majority (~70%) of patients enrolled in TITAN reflected a patient population with a considerable CV and metabolic risk profile and were receiving concomitant meds for these conditions, in line with that commonly seen in the real world
- Addition of apalutamide to ADT resulted in a significant improvement in both rPFS and OS and achievement of PSA90 or PSA<0.2ng/ml regardless of prior history of CV and metabolic baseline risk factors or use of associated concomitant medications for these conditions
- TEAE's of any grade and Gr/3/4 were similar between subjects with and without CV and metabolic risk.
- Incidence of falls, IHD and Ischemic CV disorders and TEAE's associated with long term use of ADT were relatively infrequent, although rates were slightly higher in patients with history of CV and metabolic risk factors in both the APA and PBO arms, possibly due to the older age of this cohort

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INTRODUCTION

- TITAN, a phase III, randomized, placebo- controlled study, demonstrated improved radiographic progression-free survival (rPFS) and Overall Survival (OS) with apalutamide (APA) added to ADT versus ADT + placebo (PBO) in a patient population with mCSPC. [1, 2, 3]
- Patients with cardiovascular issues (CV), such as myocardial infarction, symptomatic congestive heart failure, or thromboembolic events occurring ≤6 months of randomization were excluded from the TITAN trial. However, patients with events occurring > 6 months prior or non-excluded CV conditions like ischemic heart disease without myocardial infarction were allowed to enrol.
- Considering the demographics of prostate cancer and given prolonged ADT use may worsen existing co-morbid conditions, we conducted a post-hoc analysis to assess the efficacy and safety of APA+ADT vs PBO+ADT in patients with or without ≥ 1 risk factor or a history of CV or metabolic risk factors at baseline.
- Given polypharmacy and concern for potential drug-drug interactions on the efficacy and safety with ARPI's in patients with advanced prostate cancer[4] , an additional analysis was performed in patients who were receiving associated concomitant medications for CV and metabolic conditions or risk factors at baseline.

1. Chi KN, Agarwal N, Bjartell A, et al. Apalutamide for metastatic, castration-sensitive prostate cancer. N Engl J Med. 2019;381:13-24.
2. Chi KN, Chowdhury S, Bjartell A, et al. Apalutamide in patients withmetastatic castration-sensitive prostate cancer: final survival analysis of the randomized, double-blind, phase III TITAN study. J Clin Oncol. 2021;39:2294-2303.
3. Clinical Trial Registration number: NCT02489318
4. Appikkuttan S, Ko, G, Chunmay R, et al. Drug-drug interaction potential among patients with nonmetastatic castration-resistant prostate cancer (nmCRPC) treated with novel androgen receptor inhibitors. Expert Rev Anticancer Ther. 2024 May;24(5):325-333. doi: 10.1080/14737140.2024.2328778. Epub 2024 Mar 12.

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METHODS

- CV and metabolic risk factors were categorized using MeDRA terminology and included CV ischemia, CV failure, CV arrhythmia, diabetes, hyperlipidemia, HT and obesity.
- Use of associated concomitant medications (con meds) were identified at study entry.
- rPFS was assessed using the first interim analysis cutoff that was prespecified to be final (median f/u 22.7 mo).
- OS and other clinical end-points were assessed at the final analysis (median f/u 44 mo).
  - PBO arm included patients who crossed over to receive APA after the first I.A.
- The proportion of patients who achieved a decline in PSA level >90% (PSA90) or PSA nadir of <0.2ng/ml from baseline was assessed according to Prostate Cancer Working Group 2 (PCWG2) recommendations
- TEAEs, TEAE's of Special Interest and TEAE's associated with long term use of ADT were also analysed in patients across these three cohorts

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RESULTS

Demographics (Table 1 and Supplementary Table)

- In TITAN, 72% and 69% patients in the APA and PBO arms had a prior history of CV or metabolic risk factors
- Patient demographics were well matched across the APA and PBO arms
- The median age of patients with history of CV or metabolic risk factors was 3-4 years older than those without these risk factors in both APA and PBO arms. There was a higher percentage of patients aged over 75 in both APA and PBO arms.
- The median weight of patients with a history of CV or metabolic risk factors was 8kg higher than those without these risk factors in both APA and PBO arms.
- Approximately 95% of patients with prior CV or metabolic risk were also receiving one or more associated concomitant medications for these conditions.
- Common concomitant medications included:
  - Anti-hypertension medications in ~ 60%
  - Statins in ~30%, beta blockers in ~30%, channel calcium blockers in ~25%
  - Anti-thrombotic agents in ~20% including direct factor Xa inhibitors in ~5%

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Table 1: Patient Demographics were well matched - 70% of patients had history of CV and metabolic risk factors

	With history of CV/metabolic risk		with history of CV/metabolic risk and con meds		No history of CV /metabolic risk	
	APA+ADT	PBO+ADT	APA+ADT	PBO+ADT	APA+ADT	PBO+ADT
Sub-group prevalence n (% of ITT population)	378 (72)	364 (69)	358 (68)	347 (66)	146 (28)	163 (31)
Median (Q1-Q3) Age in Years	69 (65-75)	70 (63-74)	69 (65-75)	70 (63-74)	66 (61-73)	66 (60-71)
<65 n (%)	94 (25)	109 (30)	89 (25)	103 (30)	55 (37)	73 (45)
>=75 n (%)	103 (27)	88 (24)	99 (27)	85 (24)	30 (20)	25 (15)
Median Baseline Weight (Q1-Q3) in kg	79.1 (70-90)	80.3 (70-92)	80 (71-91)	81.2 (70-92)	72.8 (65-80)	70 (62-79)
Patients receiving ACE inhibitors and angiotensin ii antagonists	226 (59.8)	210 (57.7)	226 (63.1))	209 (60.2)	12 (8.2)	14 (8.6)
Patients receiving Statins n (%)	125 (33.1)	92 (25.3)	123 (34.4)	90 (25.9)	11 (7.5)	8 (4.9)
Patients receiving direct factor Xa inhibitors n(%)	22 (5.8)	18 (4.9)	22 (6.1)	18 (5.2)	2 (1.4)	3 (1.8)
Median Time from initial diagnosis to randomization in months (Q1-Q3)	4.29 (2.4-9.0)	4.04 (2.4-7.1)	4.4 (2.4 - 9.0)	4.07 (2.4-7.3)	3.78 (2.1-6.7)	3.94 (2.3 - 5.9)
Gleason score at initial diagnosis						
N	378	364	358	347	147	163
<8	138 (37)	123 (34)	130 (36)	118 (34)	36 (24)	46 (28)
≧8	240 (63)	241 (66)	228 (64)	229 (66)	111 (76)	117 (72)
ECOG Performance Status n(%)						
0	240 (64)	230 (63)	227 (63)	219 (63)	88 (60)	118 (72)
1	138 (37)	133 (37)	131 (37)	127 (37)	59 (40)	45 (28)
Metastasis stage at diagnosis n (%)						
M0	73 (19)	49 (14)	73 (20)	48 (14)	12 (8)	10 (6)
M1	287 (76)	294 (81)	269 (75)	278 (80)	124 (84)	147 (90)
MX	18 (5)	21 (6)	16 (5)	21 (6)	11 (8)	6 (4)
Volume of disease n (%)						
High volume	221 (59)	229 (63)	206 (58)	220 (63)	104 (71)	106 (65)
Low volume	157 (41)	135 (37)	152 (42)	127 (37)	43 (29)	57 (35)
Median Baseline PSA ng/L (Q1-Q3)	5.7 (1.2-22.9)	4.2 (0.9-28.7)	5.4 (1.1 - 21.9)	4.3 (1.1- 27.0)	8.3 (1.1 - 51.1)	2.9 (0.7-23.3)

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Supplementary Table

Analysis of subjects with medical history of cardiovascular or metabolic risk factors enrolled in TITAN

	Apalutamide	Placebo
Safety Population n	524	527
Subjects with no medical history of CV or metabolic events n (%)	147 (27.9)	163 (30.9)
Subjects with a history of cardiac disorders, diabetes, hypertension, hyperchol/lipidaemia, stroke, PE, or TIA or baseline obesity n (%)	378 (72.1)	364 (69.1)
Subjects with a history of cardiac disorders, diabetes, hypertension, hyperchol/lipidaemia, stroke, PE, or TIA or baseline obesity with concomitant medication for disease at baseline n (%)	358 (68.3)	347 (65.8)
Subjects with a history of hypertension n (%)	299 (57.1)	275 (52.2)
Subjects with a history of hyperchol/lipidaemia n (%)	98 (18.7)	90 (17.1)
Subjects with a history of diabetes n (%)	77 (14.7)	81 (15.4)
Subjects with a history of cardiac disorders n (%)	130 (24.8)	122 (23.1)
Subjects with a history of CV ischaemic n (%)	81 (15.5)	91 (17.3)
Subjects with a history of CV failure n (%)	56 (10.7)	52 (9.9)
Subjects with a history of CV arrhythmia n (%)	48 (9.2)	31 (5.9)
Subjects with a history of stroke, PE, or TIA n (%)	19 (3.6)	25 (4.7)

Note: Percent is based on the Safety population; groups are not mutually exclusive

Subsequent Efficacy and safety analyses were performed on the following populations:

- Subjects with a history of cardiac disorders, diabetes, hypertension, hyperchol/lipidaemia, stroke, PE, or TIA or baseline obesity
- Subjects with a history of cardiac disorders, diabetes, hypertension, hyperchol/lipidaemia, stroke, PE, or TIA or baseline obesity with concomitant medication for disease at baseline
- Subjects with no medical history of CV or metabolic events

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RESULTS

PSA Response – PSA90 or PSA <0.2ng/ml by PCWG2 criteria

- Achievement of PSA90 or PSA<0.2ng/ml favoured the APA+ADT arm vs PBO+ADT in all 3 patient cohorts (**Figure 1**)
- Across all three cohorts, >80% of patients treated with APA+ADT achieved this threshold, approximately double the proportion of that treated with PBO +ADT
- Both the proportion and the magnitude of benefit of APA+ADT was similar regardless of prior history of CV or metabolic risk

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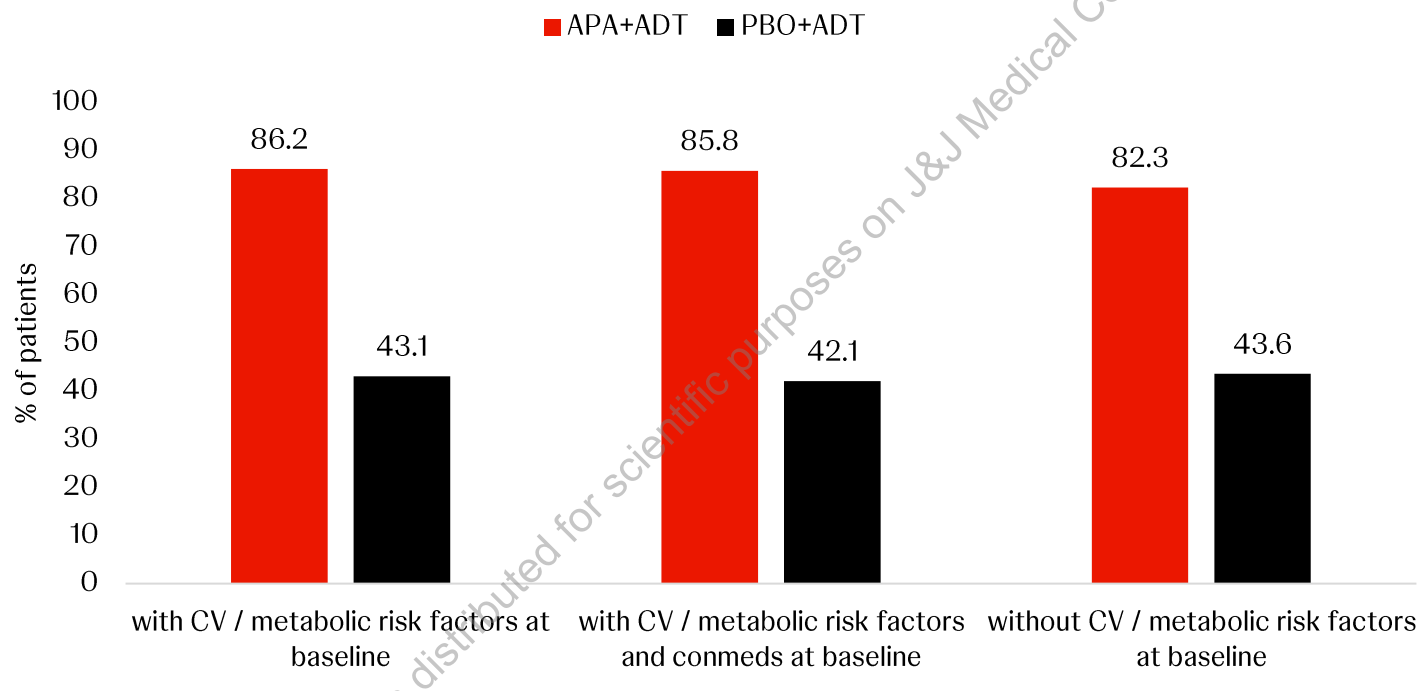
Figure 1: Percentage of patients achieving PSA90 or PSA<0.2ng/ml was similar in those with and without baseline CV or metabolic risk factors or conmeds and approximately double in the APA vs PBO group



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RESULTS

Radiographic Progression Free Survival

- Median rPFS was superior in favour of APA+ADT vs PBO +ADT regardless of prior history of CV or metabolic risk factors or use of associated concomitant medications (**Figure 2**)
- The magnitude of treatment effect of APA vs PBO was similar across all 3 patient cohorts:
  - Patients with prior history of CV or metabolic risk factors: HR (95% CI) 0.49 (0.38, 0.63) p<0.0001
  - Patients with prior history of CV or metabolic risk factors + concomitant medications: HR (95% CI) 0.47 (0.36, 0.62) p<0.0001
  - Patients without prior history of CV or metabolic risk factors: HR (95% CI) 0.48 (0.33, 0.70) p 0.0001

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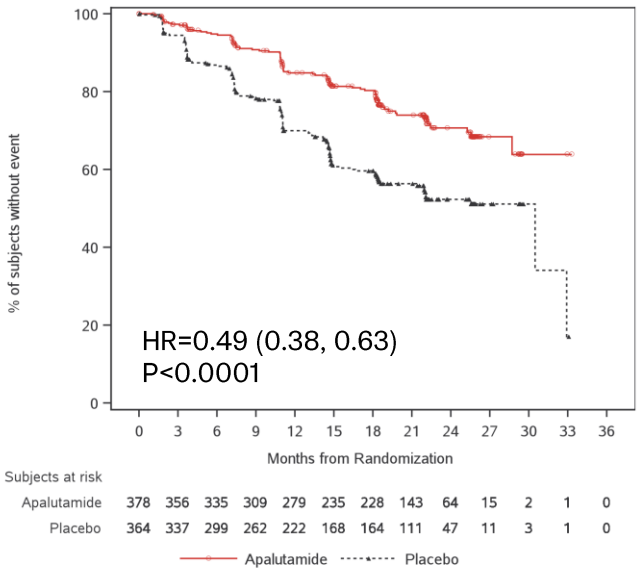
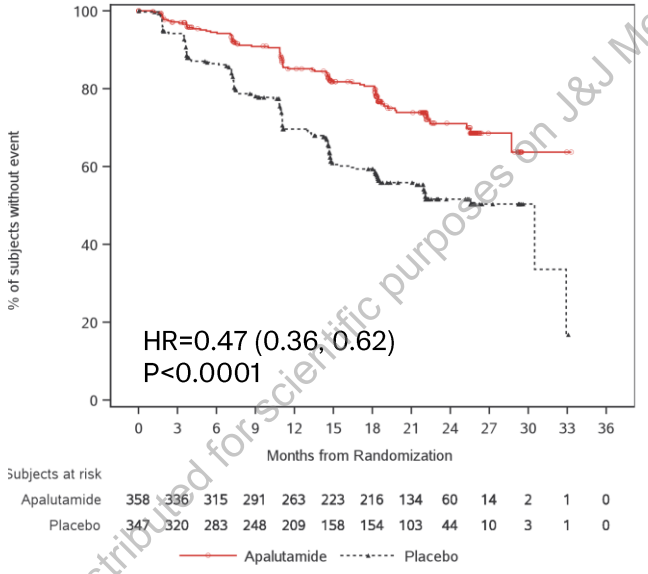
Figure 2 – Treatment effect of APA on rPFS was similar in those with and without baseline CV or metabolic risk factors +/- concomitant medications

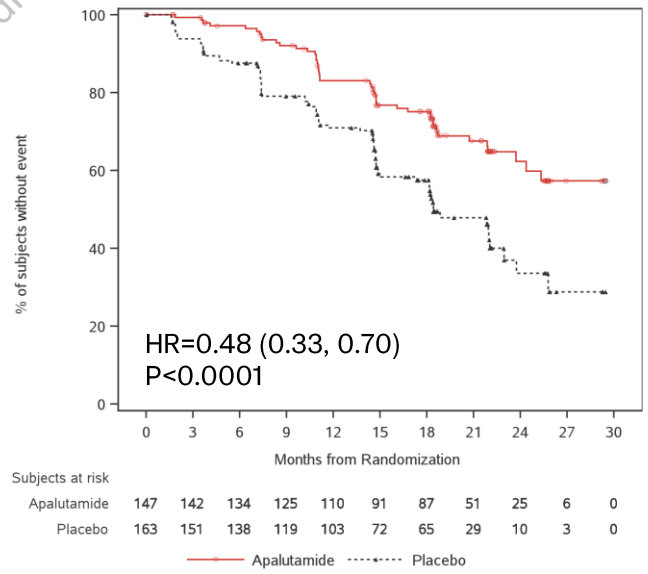
a) With history of CV/metabolic risk factors



b) With history of CV/metabolic risk and con meds



c) no history of CV/metabolic risk factors



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RESULTS

Overall Survival

- Median Overall Survival was superior in favour of APA+ADT vs PBO +ADT regardless of prior history of CV or metabolic risk factors or use of associated concomitant medications; with curves separating within the first 12 months (**Figure 3**)
  - Patients with prior history of CV or metabolic risk factors: HR (95% CI) 0.63 (0.50, 0.80) p0.001
  - Patients with prior history of CV or metabolic risk factors + concomitant medications: HR (95% CI) 0.61 (0.48, 0.78) p<0.0001
  - Patients without prior history of CV or metabolic risk factors: HR (95% CI) 0.71 (0.49, 1.02) p 0.0604

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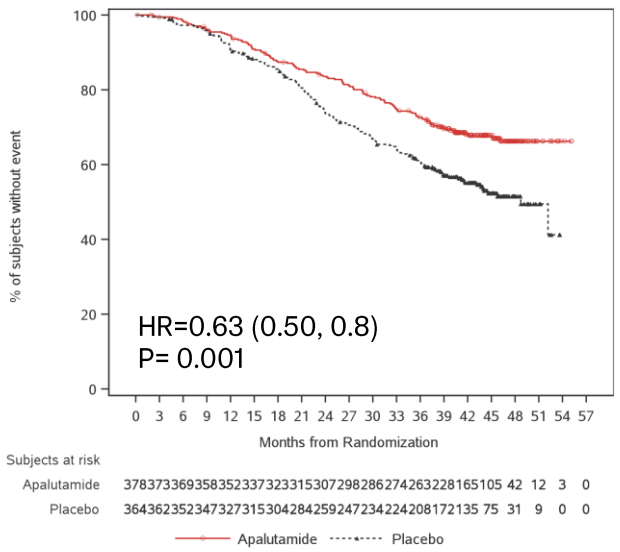
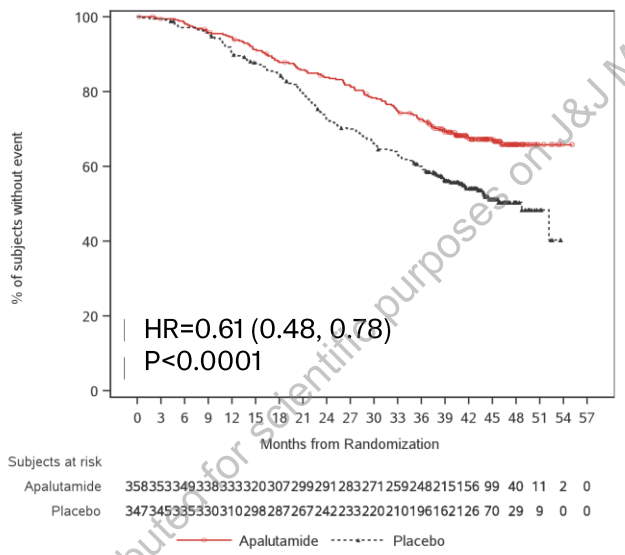
RESULTS

Figure 3 – Treatment effect of APA on Overall Survival was similar in those with and without baseline CV or metabolic risk factors +/- concomitant medications, with curves separating within the first 12 months

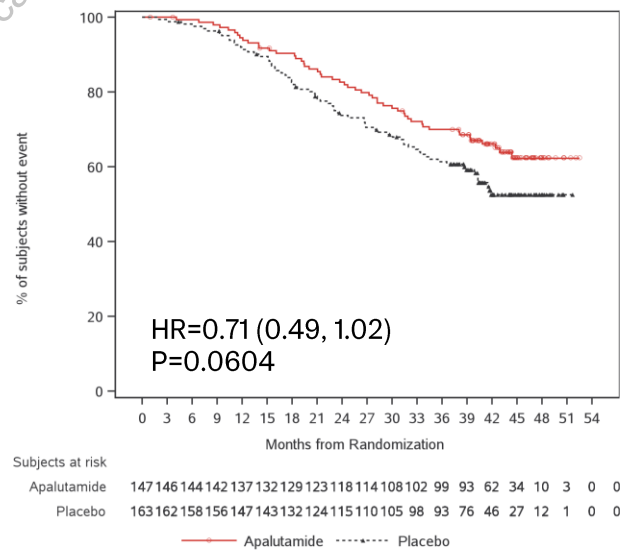
a) With history of CV/metabolic risk factors



b) With history of CV/metabolic risk and con meds



c) no history of CV/metabolic risk



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RESULTS

Safety - TEAEs were similar regardless of CV/metabolic risk. Rates of some TEAE of S.I or TEAE associated with LT ADT use were slightly higher in patients with a history of these risk factors in both the APA and PBO arms (Table 2)

- Incidence of TEAEs, ≧Gr 3 TEAEs and TEAEs leading to death were similar across all 3 cohorts and between both arms
- Incidence of falls, IHD and Ischemic CV disorders were infrequent, rates were slightly higher in those patients with history of CV and metabolic risk factors vs those without in both the APA and PBO arms:
  - Possibly due to the skewed older age of this cohort
- Similarly, TEAE's associated with long term use of ADT such as diabetes and cardiac AEs were also slightly higher in patients with history of these risk factors than those without in both the APA and PBO arms
- Cognitive deficits were infrequently observed across all groups
- The median treatment duration was 19.1 months longer in the APA arm vs the PBO arm. Reported incidence of TEAEs are not treatment exposure adjusted and should be interpreted accordingly

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Efficacy and safety of apalutamide in metastatic castration sensitive prostate cancer patients with a prior history of cardiovascular or metabolic risk factors – a post-hoc analysis of the TITAN study.

Arun Azad, Ding-Wei Ye, Hiroji Uemura, Amitabha Bhaumik, Michael Eisbacher, Anildeep Singh, Sharon McCarthy, Suneel Mundle, Kim N. Chi, Neeraj Agarwal

Table 2: Incidence of TEAEs were similar regardless of CV/metabolic risk. Rates of some TEAE of S.I or TEAE associated with LT ADT use were higher in patients with a history of these risk factors in both the APA and PBO arms. Cognitive deficits were infrequent.

	With history of CV / metabolic risk factors		With history CV/metabolic risk factors + associated con meds		without history of CV / metabolic risk factors	
	APA+ADT n (%)	PBO+ADT n (%)	APA+ADT n (%)	PBO+ADT n (%)	APA+ADT n (%)	PBO+ADT n (%)
n	378	364	358	347	146	163
Number of subjects with TEAEs	368 (97.4)	353 (97.0)	350 (97.8)	337 (97.1)	142 (97.3)	157 (96.3)
Number of subjects with Grade 3-4 TEAEs	183 (48.4)	165 (45.3)	177 (49.4)	161 (46.4)	76 (52.1)	55 (33.7)
Number of subjects with SAEs[b]	117 (31.0)	81 (22.3)	115 (32.1)	80 (23.1)	36 (24.7)	34 (20.9)
Number of subjects with TEAEs leading to treatment discontinuation	48 (12.7)	21 (5.8)	48 (13.4)	20 (5.8)	14 (9.6)	9 (5.5)
Number of subjects with TEAEs leading to death	15 (4.0)	11 (3.0)	15 (4.2)	11 (3.2)	5 (3.4)	6 (3.7)
TEAE of Special Interest - by category n (%)						
Skin Rash						
All grades	113 (29.9)	37 (10.2)	104 (29.1)	37 (10.7)	40 (27.4)	12 (7.4)
≧Gr 3	22 (5.8)	5 (1.4)	22 (6.1)	5 (1.4)	11 (7.5)	0
Fall						
All grades	38 (10.1)	30 (8.2)	37 (10.2)	29 (8.4)	11 (7.5)	7 (4.3)
≧Gr 3	6 (1.6)	3 (0.8)	6 (1.7)	3 (0.9)	1 (0.7)	2 (1.2)
Fracture						
All grades	38 (10.1)	17 (4.7)	38 (10.6)	16 (4.6)	16 (11)	9 (5.5)
≧Gr 3	10 (2.6)	4 (1.1)	10 (2.8)	4 (1.2)	8 (5.5)	0
Ischemic Heart Disease						
All grades	26 (6.9)	10 (2.7)	25 (7.0)	5 (1.4)	5 (3.4)	1 (0.6)
≧Gr 3	14 (3.7)	4 (1.0)	14 (4.1)	4 (1.0)	2 (1.4)	0
Ischaemic cerebrovascular disorders						
All grades	13 (3.4)	5 (1.4)	13 (3.6)	5 (1.4)	0	3 (1.8)
≧Gr 3	8 (2.1)	1 (0.3)	8 (2.2)	1 (0.3)	0	0
Seizure						
All grades	1 (0.3)	2 (0.5)	1 (0.3)	2 (0.5)	2 (1.4)	0
≧Gr 3	0	0	0	0	1 (0.7)	0
TEAEs associated with long-term use of ADT By Grouped terms n (%)						
Diabetes						
All grades	32 (8.5)	19 (5.2)	31 (8.7)	19 (5.5)	4 (2.7)	0
≧Gr 3	9 (2.4)	6 (1.6)	9 (2.5)	6 (1.7)	0	0
Arrhythmia & Cardiac Disorders						
All grades	23 (6.1)	15 (4.1)	22 (6.1)	15 (4.3)	7 (4.8)	2 (1.2)
≧Gr 3	9 (2.4)	6 (1.6)	8 (2.2)	6 (1.8)	4 (2.8)	0
Cardiac Failure						
All grades	14 (3.7)	9 (2.5)	14 (3.9)	9 (2.6)	1 (0.7)	1 (0.6)
≧Gr 3	8 (2.1)	3 (0.8)	8 (2.2)	3 (0.9)	0	0
Cognitive Deficits						
All grades	13 (3.4)	6 (1.6)	13 (3.6)	6 (1.7)	3 (2.1)	4 (2.5)
≧Gr 3	1 (0.3)	0	1 (0.3)	0	1 (0.7)	0

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DISCLOSURES:

Prof A Azad is an employee of the PeterMacCallum Cancer Centre, Melbourne Australia

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Prof H Uemura is an employee of Yokohama City University Medical Center, Kanagawa, Japan;

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Other relevant disclosures relevant to this abstract can be found on the ASCO website: https://meetings.asco.org/abstracts-presentations/242386

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