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MEETING SUMMARY
ASCO 2020, VIRTUAL MEETING

Sandy Srinivas, MD
Stanford University Medical Center, California, USA

HIGHLIGHTS FROM GU CONNECT
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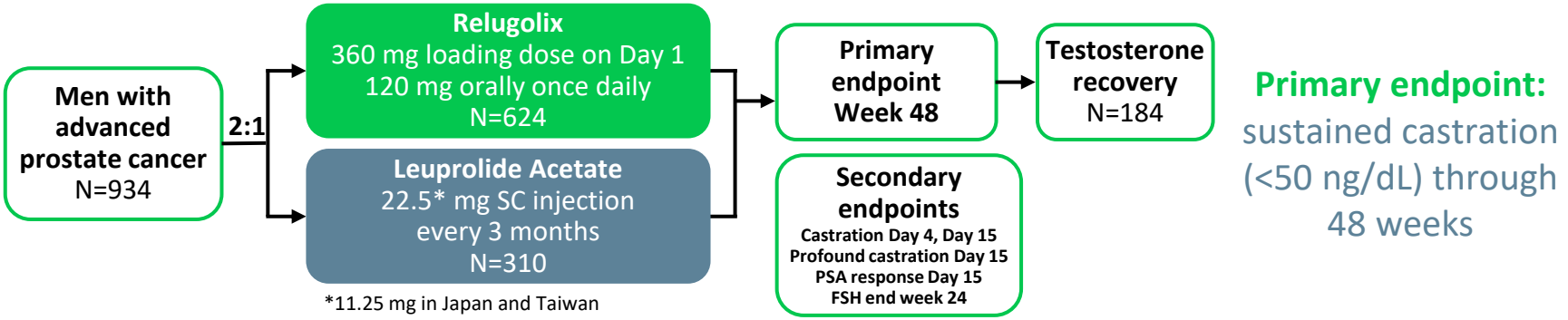
HERO PHASE 3 TRIAL: RESULTS COMPARING RELUGOLIX, AN ORAL GnRH RECEPTOR ANTAGONIST, VERSUS LEUPROLIDE ACETATE FOR ADVANCED PROSTATE CANCER

Shore N, et al.
ASCO 2020. Abstract #5602. Oral presentation

HERO STUDY: BACKGROUND

- Androgen deprivation therapy **(ADT)** is the **mainstay of treatment for advanced or metastatic prostate cancer**[1]
- Gonadotropin-releasing hormone **(GnRH) agonists**, such as leuprolide acetate, **are the most commonly used ADT for medical castration**. However **they cause an initial testosterone surge** with a delayed onset of castration and require depot injection[2]
- **Relugolix is an oral, GnRH receptor antagonist** in development for the treatment of men with advanced prostate cancer[3,4]
- **HERO, a global, pivotal, phase 3 trial**



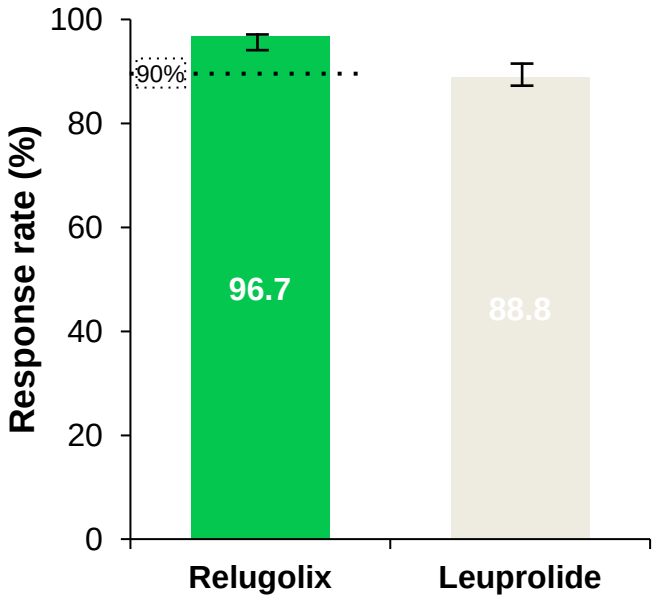
Primary endpoint: sustained castration (<50 ng/dL) through 48 weeks

ADT, androgen deprivation therapy; FSH, follicle stimulating hormone; GnRH, gonadotropin-releasing hormone; PSA, prostate specific antigen; SC subcutaneous

1. Schröder F, et al. BJU Int 2012; 109(Suppl 6):1-12. 2. Shore N, et al. Prostatic Dis 2013; 16: 7-15; 3. Shore N, et al. ASCO 2020. Abstract #5602. Oral Presentation; 4. Shore N, et al. N Engl J Med 2020. DOI: 10.1056/NEJMoa2004325

HERO STUDY: RESULTS

PRIMARY ENDPOINT



. . . **Primary endpoint success criterion:**
Relugolix lower bound of 95% CI ≥90%

Difference between treatments demonstrated non-inferiority and superiority of relugolix to leuprolide [7.9 %; 95% CI: 4.1-11.8%, p<0.001]

SECONDARY ENDPOINTS

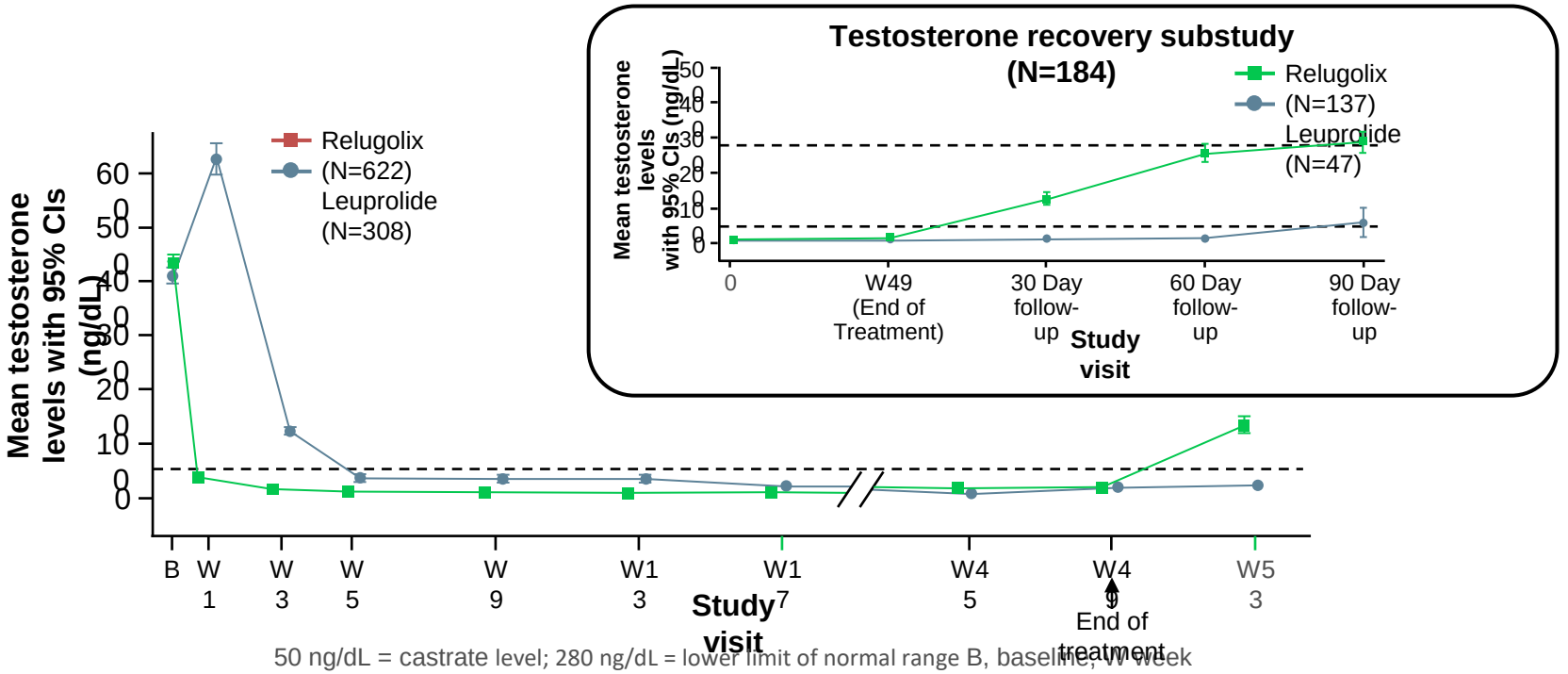
Secondary Endpoints	Relugolix (N=622) %	Leuprolide (N=308) %	P-value
Cumulative probability of testosterone suppression to <50 ng/dL at Day 4	56.0	0	<0.001
Cumulative probability of testosterone suppression to <50 ng/dL at Day 15	98.7	12.0	<0.001
Proportion of patients with PSA response at Day 15 followed with confirmation at Day 29	79.4	19.8	<0.001
Cumulative probability of profound testosterone suppression to <20 ng/dL at Day 15	78.4	1.0	<0.001
Mean of FSH level at end of week 24, IU/L	1.72	5.95	<0.001

CI, confidence interval; FSH, follicle stimulating hormone; IU, international unit; PSA, prostate specific antigen

Shore N, et al. ASCO 2020. Abstract #5602. Oral Presentation; Shore N, et al. N Engl J Med 2020. DOI: 10.1056/NEJMoa2004325

HERO STUDY: RESULTS

TIME COURSE OF TESTOSTERONE



50 ng/dL = castrate level; 280 ng/dL = lower limit of normal range B, baseline; W week

SAFETY SUMMARY

- Safety and tolerability profiles of relugolix and leuprolide were similar
- MACE were experienced by 2.9% relugolix group versus 6.2% leuprolide group

CI, confidence interval; MACE, major cardiovascular adverse events

Shore N, et al. ASCO 2020. Abstract #5602. Oral Presentation; Shore N, et al. N Engl J Med 2020. DOI: 10.1056/NEJMoa2004325

HERO STUDY: CONCLUSIONS

- Relugolix achieved castration as early as Day 4
- Compared to leuprolide, **relugolix achieved superiority** for:
  - **Sustained castration** rates
  - **Castration** (<50 ng/dL) and **profound castration** (<20 ng/dL) by Day 15
  - **PSA response** (decrease of >50%) by Day 15
- **Testosterone recovery within normal range** (54% vs 3%) at 90 days
- Relugolix treatment was **well tolerated**
  - **54% reduction in the risk of MACE** with relugolix treatment compared with leuprolide

Take home messages:

- As an oral agent, relugolix offers an option for men who want to avoid an injection
- It offers rapid testosterone recovery and may be best suited for men wanting intermittent ADT as well as men with cardiac co-morbidities
- The compliance of taking an oral agent everyday needs to be considered

MACE, major cardiovascular adverse events; PSA, prostate specific antigen

Shore N, et al. ASCO 2020. Abstract #5602. Oral Presentation; Shore N, et al. N Engl J Med 2020. DOI: 10.1056/NEJMoa2004325

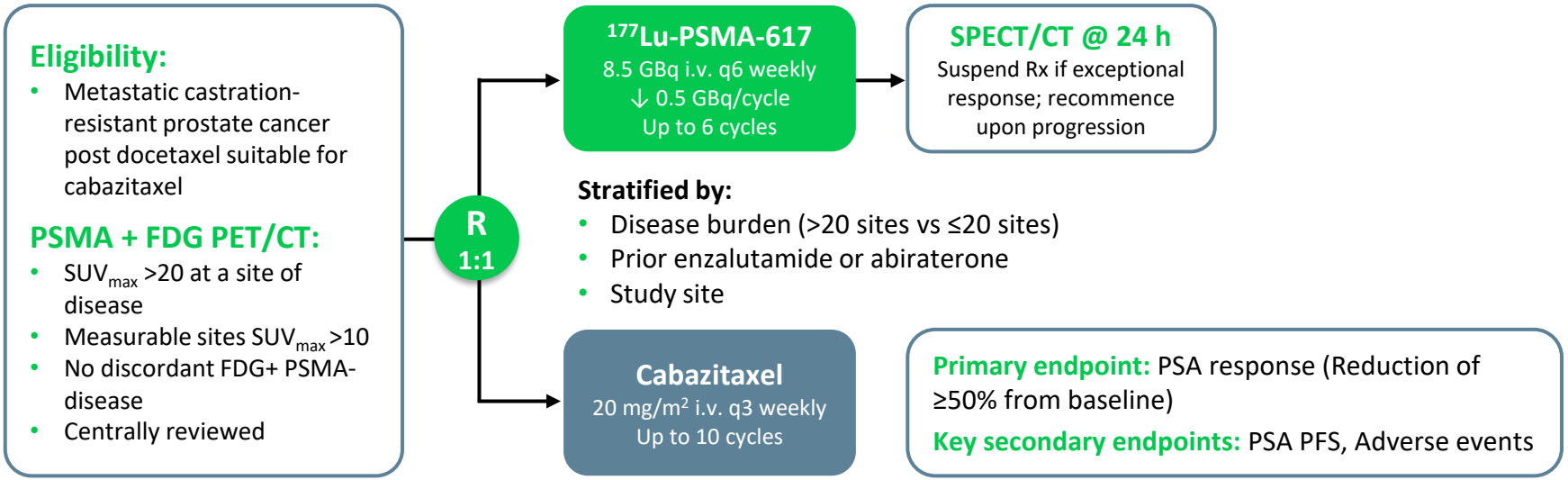
TheraP: A RANDOMISED PHASE 2 TRIAL OF ^{177}LU-PSMA-617 THERANOSTIC VERSUS CABAZITAXEL IN mCRPC PROGRESSING AFTER DOCETAXEL: INITIAL RESULTS (ANZUP PROTOCOL 1603)

Hofman M, et al.
ASCO 2020. Abstract #5500. Oral presentation

mCRPC, metastatic castration resistant prostate cancer

TheraP: OVERVIEW

- ^{177}Lu-PSMA-617 **(Lu-PSMA)** is a radiolabelled small molecule that delivers **therapeutic β-radiation to PSMA-expressing tumours**
- Encouraging efficacy and safety of Lu-PSMA has been observed in prior trials of mCRPC
- **TheraP is the first randomised study comparing Lu-PSMA to cabazitaxel in men with mCRPC after docetaxel**



FDG, Fluorodeoxyglucose; LuPSMA, 177Lu-PSMA-617; i.v., intravenous; mCRPC, metastatic castration resistant prostate cancer; PET/CT, Positron emission tomography-computed tomography; PFS, progression free survival; PSA, prostate specific antigen; PSMA, prostate specific membrane antigen; Rx, treatment; SUV, standardised uptake value. Hofman M, et al. ASCO 2020. Abstract #5500. Oral presentation

TheraP: RESULTS

PATIENT CHARACTERISTICS

Key Patient Characteristics	Cabazitaxel N=101	Lu-PSMA (N=99)
Median Age, years (IQR)	72 (67-77)	72 (67-77)
Prior enza/abi	91%	91%
Disease burden (>20 sites)	79%	77%
Median PSA (IQR)	110 (64-245)	94 (44-219)
Median follow-up of 13.3 months (IQR: 9.5-17.7 months)		

EFFICACY ENDPOINTS

Efficacy Endpoints (ITT)	Cabazitaxel N=101	Lu-PSMA (N=98)
PSA50-RR	37% (27-46)	66% (56-75)
PSA50-RR, absolute difference (95% CI)	29% (16-42) P<0.0001	
PSA PFS (preliminary)*, HR (95% CI)	0.69 (0.50-0.95) P=0.02#	

*Based on 157 of the required 170 events
#p<0.0027 required to trigger rejection of H_0 prior to planned primary analysis

- Efficacy results were similar when restricted to per protocol treated men

Abi, abiraterone; CI, confidence interval; enza, enzalutamide; HR, hazard ratio; IQR, inter-quartile range; ITT, intention-to-treat; Lu-PSMA, ^{177}Lutetium-PSMA-617; PFS, progression free survival; PSA, prostate specific antigen; PSA50-RR, PSA ≥50% response
Hofman M, et al. ASCO 2020. Abstract #5500. Oral presentation

TheraP: RESULTS

SELECTED AEs BY WORSE GRADE

Term	Cabazitaxel (N=85)		Lu-PSMA (N=98)	
	G1-2 %	G3-4 %	G1-2 %	G3-4 %
Neutropenia (+/- fever)	5	**13**	6	4
Thrombocytopaenia	4	0	**17**	**11**
Dry mouth	21	0	59	0
Diarrhoea	**52**	**5**	18	1
Dry eye	4	0	**30**	0
Dysgeusia	**27**	0	12	0
Neuropathy (motor or sensory)	**26**	1	10	0
Fatigue	72	4	70	5
Nausea	34	0	39	1
Anaemia	12	8	18	8
Vomiting	12	2	12	1
TOTAL (all AEs)	**40**	**54**	**53**	**35**

Discontinuations for toxicity occurred in 1/98 (1%) Lu-PSMA vs 3/85 (4%) cabazitaxel-treated
There were no Lu-PSMA related deaths; 5 G5 AEs for cabazitaxel and 11 G5 AEs for Lu-PSMA

AE, adverse event; G, grade; Lu-PSMA, 177Lutetium-PSMA-617

Hofman M, et al. ASCO 2020. Abstract #5500. Oral presentation

TheraP: CONCLUSIONS

- **Lu-PSMA** demonstrated a **greater PSA50 response compared to cabazitaxel** in men with mCRPC after docetaxel
- Lu-PSMA may represent a favourable treatment option compared to cabazitaxel in a selected population with high PSMA expression
- **PFS data is immature** at the time of this analysis **but initial data is favourable**
- Improvement in **overall survival is yet to be confirmed** from this trial and the ongoing VISION trial
- **Relatively fewer G3-4 AEs** were experienced by patients treated **with Lu-PSMA** compared to those receiving cabazitaxel

Take home messages:

- Data from TheraP should be considered alongside that from the phase 3 VISION trial (NCT 03511664) when available and may be helpful for physicians to sequence therapy once Lu-PSMA is approved

AE, adverse event; Lu-PSMA, ^{177}Lutetium-PSMA-617; mCRPC, metastatic castration resistant prostate cancer; PFS, progression free survival; PSA50, PSA ≥ 50% response

Hofman M, et al. ASCO 2020. Abstract #5500. Oral presentation

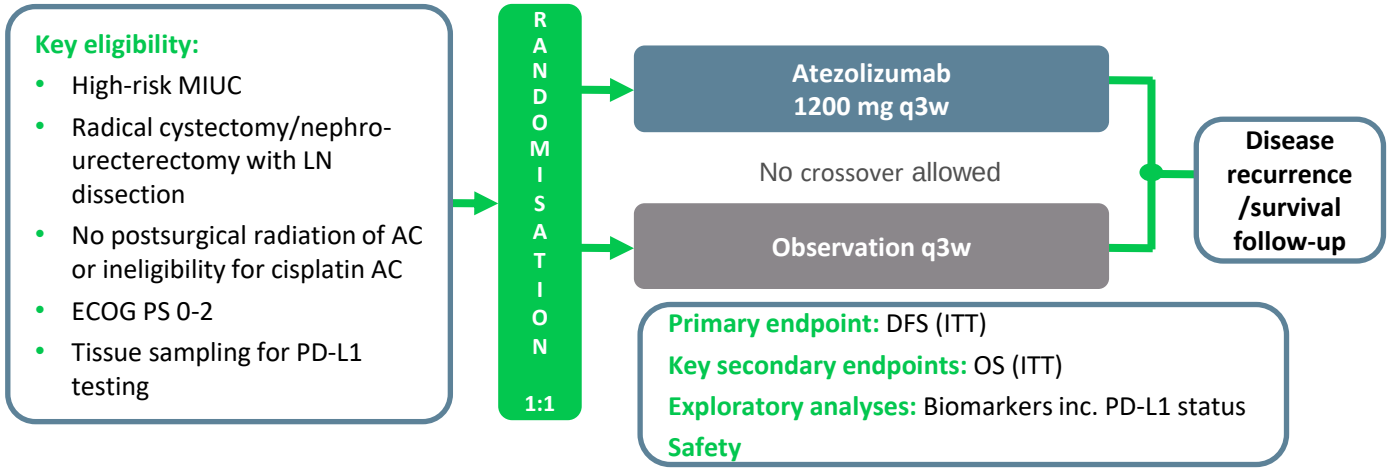
IMvigor010: PRIMARY ANALYSIS FROM A PHASE 3 RANDOMISED STUDY OF ADJUVANT ATEZOLIZUMAB VERSUS OBSERVATION IN HIGH-RISK MIUC

Hussain M, et al.
ASCO 2020. Abstract #5000. Oral presentation

MIUC, muscle-invasive urothelial carcinoma

IMvigor010: OVERVIEW

- **Radical cystectomy is the mainstay treatment for** muscle-invasive urothelial carcinoma (**MIUC**) (+/- cisplatin-based neoadjuvant chemotherapy (NAC)) but there is no conclusive evidence to support the use of adjuvant chemotherapy
- **IMvigor010 investigated** the immune checkpoint inhibitor **atezolizumab as adjuvant immunotherapy following cystectomy**



Baseline Characteristics

- In atezolizumab and observation arms, respectively: 48% of patients and 47% had NAC, 7% and 6% had UTUC as primary disease

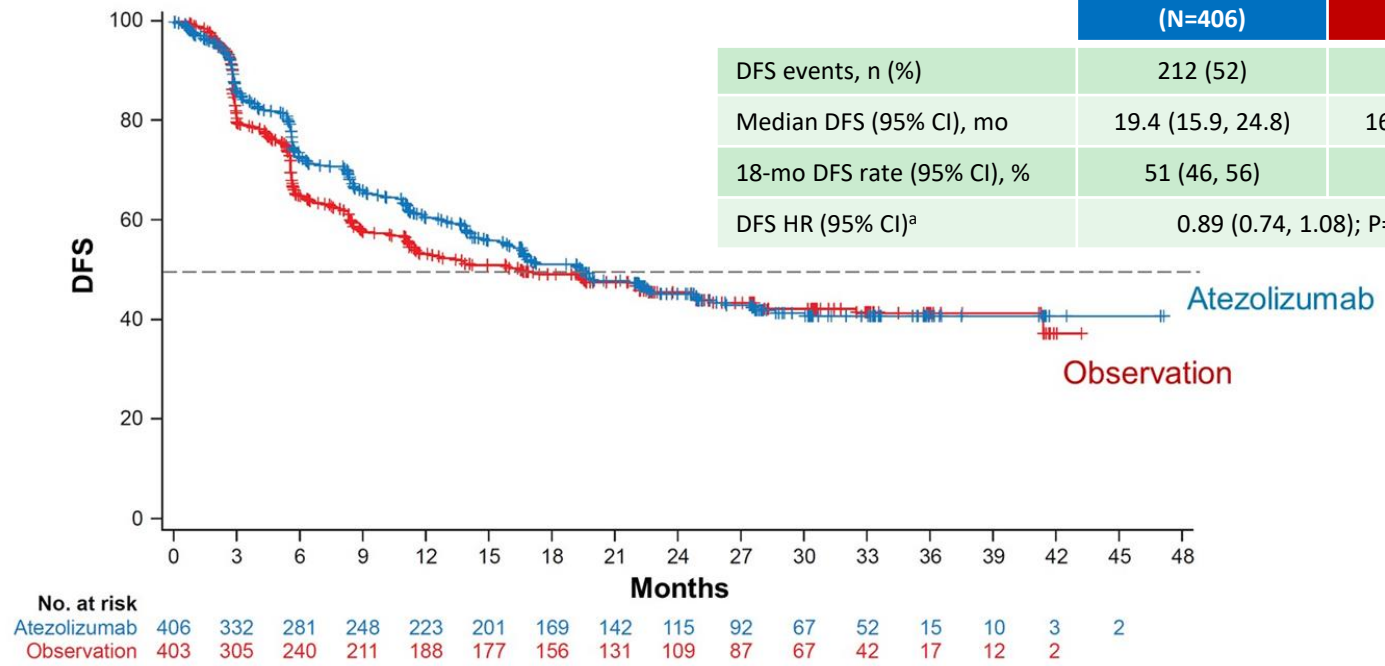
AC, adjuvant chemotherapy; DFS, disease free survival; ECOG PS, Eastern Cooperative Oncology Group performance status; ITT, intention to treat; LN, lymph nodes; MIUC, muscle invasive urothelial carcinoma; NAC, neoadjuvant chemotherapy; OS, overall survival; PD-L1, programmed death ligand-1; Q3W, every 3 weeks; UTUC, upper tract urothelial carcinoma

Hussain M, et al. ASCO 2020. Abstract #5000. Oral presentation

IMvigor010: RESULTS

PRIMARY ENDPOINT: DFS (ITT POPULATION)

	Atezolizumab (N=406)	Observation (N=403)
DFS events, n (%)	212 (52)	208 (52)
Median DFS (95% CI), mo	19.4 (15.9, 24.8)	16.6 (11.2, 24.8)
18-mo DFS rate (95% CI), %	51 (46, 56)	49 (44, 54)
DFS HR (95% CI)[a]	0.89 (0.74, 1.08); P=0.2446[b]	



Data cutoff: November 30, 2019. Median follow-up: 21.9 months; [a]Stratified by post-resection tumour stage, nodal status and PD-L1 status; [b]2-sided

- Baseline prognostic/clinical factors did not influence DFS treatment benefit:
  - PD-L1 IC 0/1 (n= 417): HR 0.81 (95% CI, 0.63-1.05)
  - PD-L1 IC 2/3 (n= 392): HR 1.01 (95% CI, 0.75-1.35)

CI, confidence interval; DFS, disease free survival; HR, hazard ratio; ITT, intent-to-treat; mo, month; PD-L1, programmed death ligand-1

Hussain M, et al. ASCO 2020. Abstract #5000. Oral presentation

IMvigor010: RESULTS

SECONDARY ENDPOINTS

Interim Overall Survival Analysis	Atezolizumab N=406	Observation N=403
OS events, n (%)	118 (29)	124 (31)
Median OS (95% CI), mo	NR	NR
18-mo OS rate (95% CI), %	79 (75, 83)	73 (69, 78)
OS HR (95% CI)	0.85 (0.66, 1.09)	

Safety	Atezolizumab N=390
Treatment-related AE	276 (71%)
Treatment related grade 3-4 AEs	63 (16%)
Treatment related grade 5 AE	1 (<1%)
Treatment related SAE	41 (11%)
AE leading to discontinuation of atezolizumab	61 (16%)

- Skin and gastrointestinal toxicities most commonly led to treatment discontinuation

AE, adverse event; CI, confidence interval; HR, hazard ratio; OS, overall survival; SAE, serious adverse event

Hussain M, et al. ASCO 2020. Abstract #5000. Oral presentation

IMvigor010: CONCLUSION

- **IMvigor010** is the first phase 3 study of a checkpoint inhibitor in MIUC
- The **primary endpoint of DFS was not met**
  - No pre-specified subgroups showed a treatment benefit with atezolizumab
  - OS follow up is ongoing
- **Safety profile of atezolizumab was consistent with other studies**
  - Higher frequency of treatment discontinuations due to AEs was observed

Take home messages:

- Based on the data from IMvigor0101, for patients who have had NAC and radical surgery, observation remains the standard of care
- Patients with high risk features post surgery who did not receive NAC should receive adjuvant chemotherapy (if they are platinum eligible)
- Await results from AMBASSADOR and CHECKMATE 274 trials

AE, adverse event; DFS, disease free survival; MIUC, muscle invasive urothelial carcinoma; NAC, neo-adjuvant chemotherapy; OS, overall survival

Hussain M, et al. ASCO 2020. Abstract #5000. Oral presentation

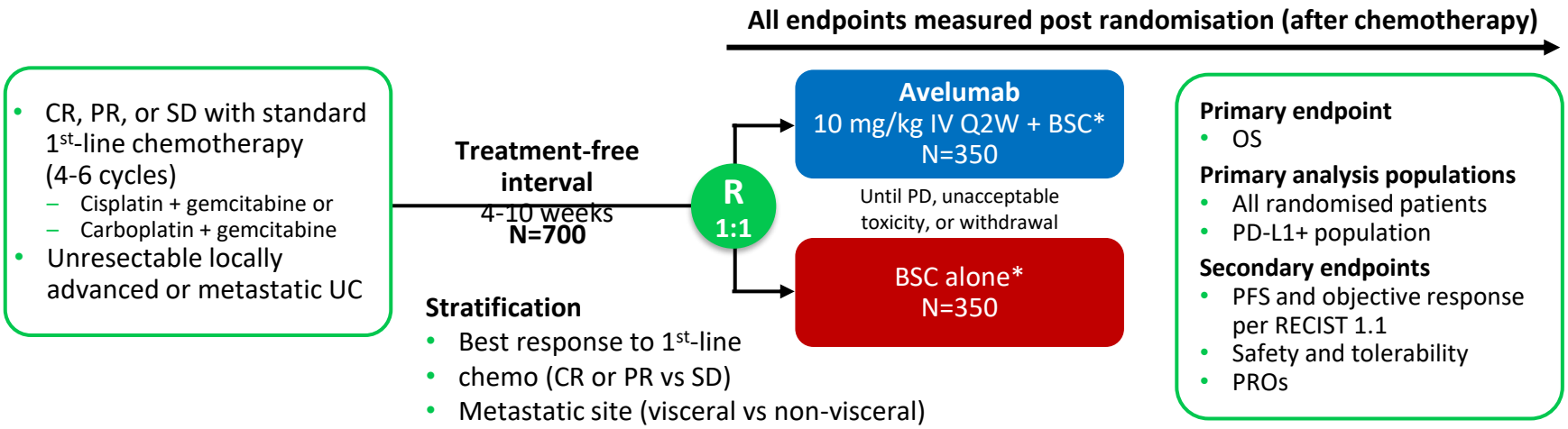
MAINTENANCE AVELUMAB + BSC VERSUS BSC ALONE AFTER PLATINUM-BASED FIRST-LINE CHEMOTHERAPY IN ADVANCED UC: JAVELIN BLADDER 100 PHASE 3 INTERIM ANALYSIS

Powles T, et al.
ASCO 2020. Abstract #LBA1. Oral presentation

BSC, best supportive care; UC, urothelial carcinoma

JAVELIN 100: OVERVIEW

- **Platinum chemotherapy (CT) is the standard of care for patients** with metastatic urothelial carcinoma (UC) in the 1st line setting however progression-free survival and overall survival benefits are short lived due to emergence of CT resistance
- **JAVELIN 100** assessed patients with locally advanced or metastatic UC following 1st line chemotherapy, who have not progressed and randomised to either standard of care or avelumab (anti-PD-L1)



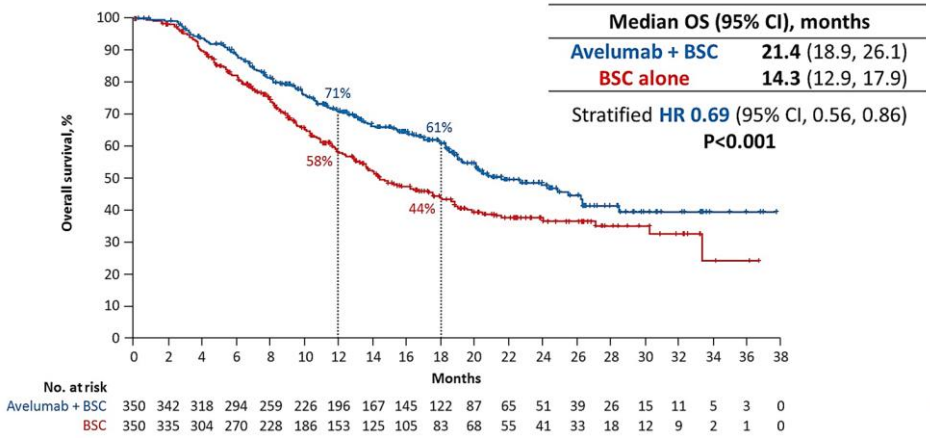
*BSC was administered per local practice based on patient needs and clinical judgement; other systemic anti-tumour therapy was not permitted but palliative local radiotherapy for isolated lesions was acceptable

BSC, best supportive care; CR, complete response; CT, chemotherapy; IV, intravenous; OS, overall survival; PD-L1, programmed death ligand-1; PFS, progression free survival; PR, partial response; PRO, patient reported outcomes; Q2W, every 2 weeks; R, randomisation; RECIST 1.1; Response Evaluation Criteria in Solid Tumours version 1.1; SD, stable disease; UC, urothelial carcinoma

Powles T, et al. ASCO 2020. Abstract #LBA1. Oral presentation

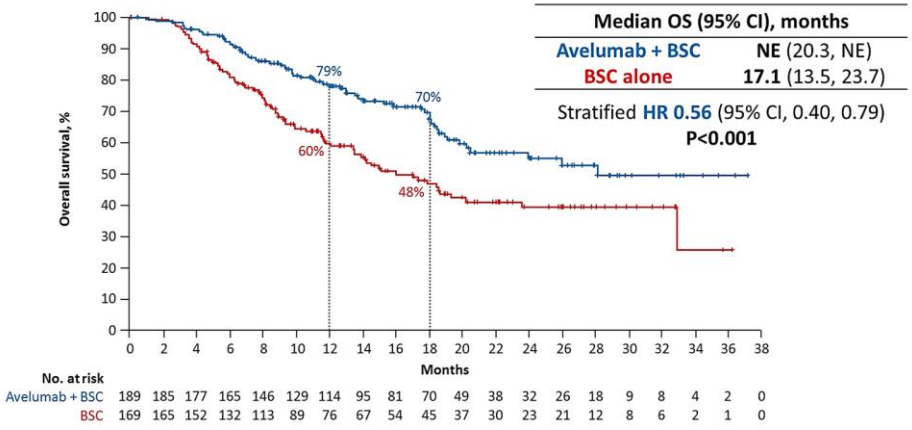
JAVELIN 100: RESULTS

OS IN THE OVERALL POPULATION



- OS was longer with avelumab vs BSC across all pre-specified subgroups

OS IN THE PD-L1+ POPULATION



- 358 patients (51%) had a PD-L1 positive tumour
- PD-L1+ status was defined as PD-L1 expression in ≥25% of tumour cells or 100% of tumour-associated immune cells if the percentage of immune cells was >1% or ≤1%, respectively (SP263 assay)

BSC, best supportive care; CI, confidence interval; HR, hazard ratio; OS, overall survival; PD-L1, programmed death ligand-1

Powles T, et al. ASCO 2020. Abstract #LBA1. Oral presentation

JAVELIN 100: RESULTS

SECONDARY ENDPOINTS

PFS by independent radiology review	Avelumab+BCS N=350	BSC alone N=350
Median PFS - overall population Months (95% CI)	3.7 (3.5-5.5)	2.0 (1.9-2.7)
Stratified HR (95% CI), p-value	0.62 (0.52-0.75) P<0.001	
Median PFS – PD-L1+ population Months (95% CI)	5.7 (3.7-7.4)	2.1 (1.9-3.5)
Stratified HR (95% CI), p-value	0.56 (0.43-0.73) P<0.001	

	Avelumab+BCS N=344		BSC alone N=345	
	Any grade	grade ≥ 3	Any grade	grade ≥ 3
Any TEAE (any grade ≥10%)	98%	47.4%	77.7%	25.2%
Most frequent grade ≥ 3 AEs (≥5% in either arm)				
UTI	17.2%	**4.4%**	10.4%	**2.6%**
Anaemia	11.3%	**3.8%**	6.7%	**2.9%**
Haematuria	10.5%	**1.7%**	10.7%	**1.4%**
Fatigue	17.7%	**1.7%**	7.0%	**0.6%**
Back Pain	16.0%	**1.2%**	9.9%	**2.3%**

- TEAEs led to discontinuation of avelumab in 11.9%
- Death was attributed to study treatment toxicity in 2 patients (0.6%) in avelumab + BSC arm
- No grade 4/5 irAEs occurred

AE, adverse event; BSC, best supportive care; CI, confidence interval; HR, hazard ratio; irAEs, immune response adverse events; PD-L1, programmed death ligand-1; PFS, progression free survival; TEAE, treatment emergent adverse events; UTI, urinary tract infection

Powles T, et al. ASCO 2020. Abstract #LBA1. Oral presentation

JAVELIN 100: CONCLUSIONS

- **JAVELIN 100** demonstrated **significantly longer OS with** first line **maintenance avelumab + BSC** compared to BSC alone, in both the overall and PD-L1 populations
  - OS benefits were seen across all pre-specified subgroups
- The **safety profile of avelumab** was **consistent with** that observed in **previous studies** of monotherapy
- **Avelumab 1st line maintenance in patients with advanced UC** whose disease has not progressed with platinum based CT should be considered a **new standard of care**

Take home messages:

- Maintenance avelumab after platinum based CT in patients who achieve a CR, PR, or SD is a new standard of care for patients with front line metastatic urothelial cancer

BSC, best supportive care; CT, chemotherapy; PD-L1, programmed death ligand-1; OS, overall survival; TEAE, treatment emergent adverse events; UC, urothelial carcinoma

Powles T, et al. ASCO 2020. Abstract #LBA1. Oral presentation

OTHER INTERESTING DATA

OS ANALYSES OF NEXT GENERATION ANDROGEN RECEPTOR INHIBITORS IN nmCRPC

SPARTAN study. Small E, et al. ASCO 2020. Abs# 5516
ARAMIS study. Fizazi K, et al. ASCO 2020. Abs# 5514
PROSPER study. Sternberg C, et al. ASCO 2020. Abs# 5515

OS, overall survival; nmCRPC, non-metastatic castration resistant prostate cancer

BACKGROUND

- nmCRPC is defined as rising PSA despite continuing ADT and no detected metastases[1]
- nmCRPC patients are high risk for progression and cancer related mortality[1]
- Next generation androgen receptor inhibitors have previously demonstrated significant improvements in metastasis-free survival in nmCRPC:

Androgen receptor inhibitor	Study
Apalutamide	SPARTAN[2]
Darolutamide	ARAMIS[3]
Enzalutamide	PROSPER[4]

- Final overall survival results for SPARTAN, ARAMIS and PROSPER are reported here

ADT, androgen deprivation therapy; nmCRPC, non-metastatic castration-resistant prostate cancer; PSA, prostate specific antigen

1. Fizazi K, et al. ASCO 2020. Abstract #5514; 2. Smith, et al. N Engl J Med 2018; 378:1408-18; 3. Fizazi, K et al. N Engl J Med 2019; 380: 1235-1246; 4.Hussain, et al. N Engl J Med 2018; 378: 2465-74

RESULTS

OVERALL SURVIVAL

- **Apalutamide, darolutamide and enzalutamide** demonstrated a significant **benefit in OS** compared to placebo in patients with nmCRPC

	SPARTAN[1]		ARAMIS[2]		PROSPER[3]	
	APA + ADT N=806	PBO + ADT N=401	DARO + ADT N=955	PBO + ADT N=554	ENZA + ADT N=933	PBO + ADT N=468
Median OS (months)	73.9	59.9	NR	NR	67.0	56.3
HR, (95% CI), P-value	0.78 (0.64-0.96) P=0.0161		0.69 (0.53-0.88) P=0.003		0.73 (0.61-0.89) P=0.001	

NOTE: Due to differences in study design the data presented here is for reference purposes only and cannot be directly compared

SAFETY

- The **safety profile of apalutamide, darolutamide and enzalutamide** at the final study analyses was consistent with that reported for the primary analyses

ADT, androgen deprivation therapy; APA, apalutamide; CI, confidence interval; DARO, darolutamide; ENZA, enzalutamide; HR, hazard ratio; nmCRPC, non-metastatic castration resistant prostate cancer; NR, not reached; OS, overall survival; PBO, placebo

1.Small E, et al. ASCO 2020. Abs# 5516; 2.Fizazi K, et al. ASCO 2020. Abstract #5514; 3. Sternberg C, et al. ASCO 2020. Abs# 5515

CONCLUSIONS

- The benefit of the next generation androgen receptor inhibitors previously observed in the primary analysis of the SPARTAN, ARAMIS and PROSPER trials is confirmed in the final OS analyses

OS, overall survival

1.Small E, et al. ASCO 2020. Abs# 5516; 2.Fizazi K, et al. ASCO 2020. Abstract #5514; 3. Sternberg C, et al. ASCO 2020. Abs# 5515

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GU CONNECT
Bodenackerstrasse 17
4103 Bottmingen
SWITZERLAND

Dr. Froukje Sosef MD

+31 6 2324 3636

froukje.sosef@cor2ed.com

Dr. Antoine Lacombe Pharm D, MBA

+41 79 529 42 79

antoine.lacombe@cor2ed.com

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