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HIGHLIGHTS OF 2020 FROM GU CONNECT

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INTRODUCTION

Although we largely switched to 'virtual mode' in 2020, the year offered a number of new trials and practice-changing developments; herein we present those most relevant to GU malignancies. In 2020 we learned that:

- Existing treatments and protocols can be adapted to work in the context of the COVID-19 era
- The era of targeted therapy for prostate cancer is here
  - The final analysis of the PROFOUND trial reported demonstrating an overall survival (OS) advantage for patients treated with olaparib
  - There is a radiographic progression-free survival (rPFS) benefit of adding ipatasertib (IPAT) in the IPATential150 trial for patients with phosphatase and tensin homologue (PTEN) loss
- There is a clear benefit in terms of OS for patients treated with new hormonal agents in the non-metastatic castration-resistant prostate cancer (nmCRPC) setting
- In metastatic bladder cancer, the new gold standard is maintenance with avelumab after 1st-line standard chemotherapy
- Cabozantinib plus nivolumab (CABO+NIVO) is a new alternative for 1st line treatment in metastatic clear cell renal cell carcinoma

COVID-19 GUIDANCE

COVID-19 AND PROSTATE CANCER

- The **COVID-19 pandemic** has **posed an unprecedented challenge to healthcare**[1]
- During the **COVID-19 global pandemic, cancer patients and physicians must carefully weigh the potential benefit of routine cancer care vs the high morbidity and mortality of COVID-19**[1]
- **Guideline committees have responded rapidly** with a framework of guiding principles to help manage prostate cancer during the COVID-19 pandemic:
  - Management of Prostate Cancer During the COVID-19 Pandemic: Recommendations of the NCCN[2]
  - EAU Guidelines Office Rapid Reaction Group: An organisation-wide collaborative effort to adapt the EAU guidelines recommendations to the COVID-19 era[3]
  - Genitourinary Cancer Management During COVID-19 Pandemic: Dana-Farber/Brigham and Women's Cancer Center Proposed Clinical Guidelines (May 1 2020 version 2.0)[4]

EAU, European Association of Urology; NCCN, National Comprehensive Cancer Network

1. Ribal M, et al. Eur Urol. 2020;78:21-8; 2. www.nccn.org/covid-19/pdf/NCCN_PCa_COVID_guidelines.pdf. Accessed 5 January 2021; 3. https://uroweb.org/wp-content/uploads/EAU-Guidelines-Office-Rapid-Reaction-Group-An-organisation-wide-collaborative-effort-to-adapt-the-EAU-guidelines-recommendations-to-the-COVID-19-era.pdf. Accessed 5 January 2021;
4. www.dana-farber.org/uploadedFiles/Pages/COVID-19_Facts_and_Resources/gu-cancer-covid-19-guidelines.pdf. Accessed 5 January 2021

COVID-19: GENERAL RECOMMENDATIONS FOR GU MALIGNANCIES

- Agents that reduce the incidence of skeletal-related events (such as bisphosphonates) are probably best **postponed**[1]
- For curative treatments, use of growth factors and prophylactic antibiotics should be considered to avoid hospitalisation[1]
- Immunosuppressive agents such as **steroids should be avoided** or reduced if possible.
- For Intermediate and poor risk mRCC start 1st line therapy.
- In metastatic disease, **START** androgen deprivation therapy (ADT)[2]
- If needed, ADT can be delayed in patients receiving treatment with abiraterone[2]
  - Also applies to enzalutamide, apalutamide, and darolutamide, but is not as strongly recommended
- If possible, choose new hormonal agents for metastatic disease instead chemotherapy [2]

1. Gillessen S, et al. Eur Urol. 2020 77:667-8;
2. www.dana-farber.org/uploadedFiles/Pages/COVID-19_Facts_and_Resources/gu-cancer-covid-19-guidelines.pdf. Accessed 5 January 2021

RECOMMENDATIONS FOR RADIOTHERAPY IN PROSTATE CANCER

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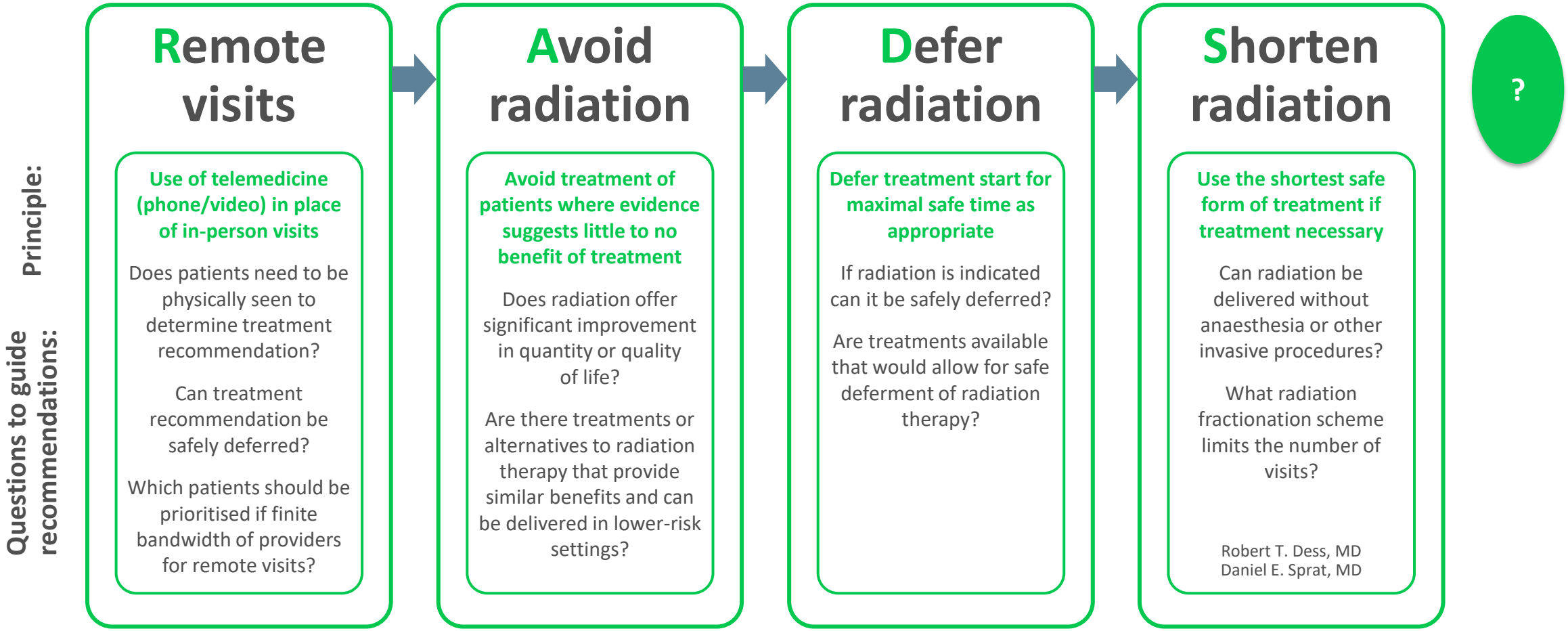

Zaorsky NG, et al. Adv Radiat Oncol. 2020;5:26-32

TREATING METASTATIC PROSTATE CANCER DURING THE PANDEMIC

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METASTATIC CASTRATION-SENSITIVE PROSTATE CANCER

- Docetaxel can be delayed for up to 120 days after starting ADT
- Use new hormonal agents if possible, even in patients fit for chemotherapy
- Potent AR inhibitors preferable to use than abiraterone due to less intensive monitoring visits being required

METASTATIC CASTRATION-RESISTANT PROSTATE CANCER

- Do not delay treatments, if possible
- New hormonal agents preferred vs chemotherapy in patients with risk of severe complications from COVID-19 infection
- Be careful in patients with high risk of rapid progression
- Radium-223 can be administered and is unlikely to be immunosuppressive, but doses can be safely delayed as needed for concerns regarding COVID-19 exposures

ADT, androgen deprivation therapy

www.dana-farber.org/uploadedFiles/Pages/COVID-19_Facts_and_Resources/gu-cancer-covid-19-guidelines.pdf. Accessed 5 January 2021

PROSTATE CANCER
2020 HIGHLIGHTS

KEY APPROVALS

FDA APPROVALS

istant prostate cancer

FDA grants accelerated approval to rucaparib for BRCA-mutated metastatic castration-resistant prostate cancer

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On May 15, 2020, the Food and Drug Administration granted accelerated approval to rucaparib (RUBRACA, Clovis Oncology, Inc.) for patients with deleterious *BRCA* mutation (germline and/or somatic)-associated metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor-directed therapy and a taxane-based chemotherapy.

Efficacy was investigated in TRITON2 (NCT02952534), an ongoing, multi-center, single arm clinical trial in 115 patients with *BRCA*-mutated (germline and/or somatic) mCRPC who had been treated with androgen receptor-directed therapy and taxane-based chemotherapy. Patients received rucaparib 600 mg orally twice daily and concomitant GnRH analog or had prior bilateral orchiectomy.

Objective response rate (ORR) and duration of response (DOR) were assessed in 62 patients with measurable disease. The confirmed ORR was 44% (95% CI: 31, 57). Median DOR was not evaluable (NE; 95% CI: 6.4, NE). The range for the DOR was 1.7-24+ months. Fifteen of the 27 (56%) patients with confirmed objective responses had a DOR of ≥6 months.

The most common adverse reactions (≥ 20%) among all 115 patients with *BRCA*-mutated mCRPC were fatigue, nausea, anemia, increased ALT/AST, decreased appetite, rash, constipation, thrombocytopenia, vomiting, and diarrhea.

The recommended rucaparib dose is 600 mg orally twice daily with or without food. Patients receiving rucaparib for mCRPC should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had bilateral orchiectomy.

ıpproves olaparib for HRR gene-mutated metastatic castration-resistant prostate cancer

FDA approves olaparib for HRR gene-mutated metastatic castration-resistant prostate cancer

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On May 19, 2020, the Food and Drug Administration approved olaparib (LYNPARZA, AstraZeneca Pharmaceuticals, LP) for adult patients with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (mCRPC), who have progressed following prior treatment with enzalutamide or abiraterone.

Today, the FDA also approved FoundationOne CDx (Foundation Medicine, Inc.) for selection of patients with mCRPC carrying HRR gene alterations and BRACAnalysis CDx test (Myriad Genetic Laboratories, Inc.) for selection of patients with mCRPC carrying germline *BRCA1/2* alterations as companion diagnostic devices for treatment with olaparib.

Efficacy was investigated in PROfound (NCT02987543), an open-label, multicenter trial randomizing (2:1) 256 patients to olaparib 300 mg twice daily and 131 patients to investigator's choice of enzalutamide or abiraterone acetate. All patients received a GnRH analog or had prior bilateral orchiectomy. Patients were divided into two cohorts based on their HRR gene mutation status. Patients with mutations in either *BRCA1*, *BRCA2*, or *ATM* were randomized in Cohort A (N=245); patients with mutations among 12 other genes involved in the HRR pathway were randomized in Cohort B (N=142); those with co-mutations (Cohort A gene and a Cohort B gene) were assigned to Cohort A.

The major efficacy outcome of the trial was radiological progression-free survival (rPFS) (Cohort A). Additional efficacy outcomes included confirmed objective response rate (ORR) (Cohort A) in patients with measurable disease, rPFS (combined Cohorts A+B), and overall survival (OS) (Cohort A).

ed PET Imaging Drug for Men with Prostate Cancer

FDA NEWS RELEASE

FDA Approves First PSMA-Targeted PET Imaging Drug for Men with Prostate Cancer

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For Immediate Release: December 01, 2020

Español

Today, the U.S. Food and Drug Administration approved Gallium 68 PSMA-11 (Ga 68 PSMA-11) – the first drug for positron emission tomography (PET) imaging of prostate-specific membrane antigen (PSMA) positive lesions in men with prostate cancer.

Ga 68 PSMA-11 is indicated for patients with suspected prostate cancer metastasis (when cancer cells spread from the place where they first formed to another part of the body) who are potentially curable by surgery or radiation therapy. Ga 68 PSMA-11 is also indicated for patients with suspected prostate cancer recurrence based on elevated serum prostate-specific antigen (PSA) levels. Ga 68 PSMA-11 is a radioactive diagnostic agent that is administered in the form of an intravenous injection.

"Ga 68 PSMA-11 is an important tool that can aid health care providers in assessing prostate cancer," said Alex Gorovets, M.D., acting deputy director of the Office of Specialty Medicine in FDA's Center for Drug Evaluation and Research. "With this first approval of a PSMA-targeted PET imaging drug for men with prostate cancer, providers now have a new imaging approach to detect whether or not the cancer has spread to other parts of the body."

www.fda.gov/drugs/. Accessed 5 January 2021

PROSTATE CANCER
KEY CLINICAL TRIALS
IN 2020

IPATential150: PHASE 3 STUDY OF IPATASERTIB PLUS ABIRATERONE VS PLACEBO PLUS ABIRATERONE IN mCRPC

de Bono J, et al.

ESMO 2020. Abstract #LBA4. Oral presentation

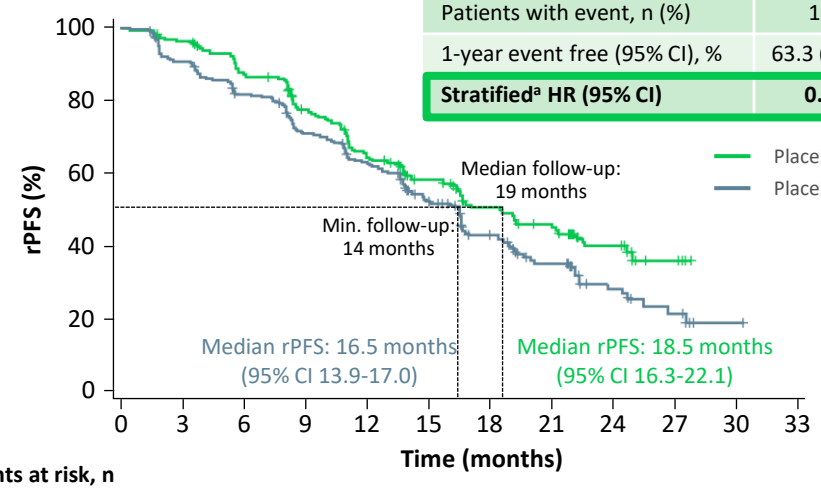
mCRPC, metastatic castration-resistant prostate cancer

IPATential150: RESULTS

- IPAT significantly improved rPFS vs placebo for patients with PTEN-loss mCRPC, but not in the intention-to-treat (ITT) population
  - This effect was consistent across all pre-specified subgroups

rPFS in the PTEN-loss (by IHC) population

	Placebo + AAP (N=261)	IPAT + AAP (N=260)
Patients with event, n (%)	154 (59)	124 (48)
1-year event free (95% CI), %	63.3 (57.3-69.3)	64.4 (58.3-70.5)
Stratified[a] HR (95% CI)	**0.77 (0.61-0.98); p=0.0335[b]**	

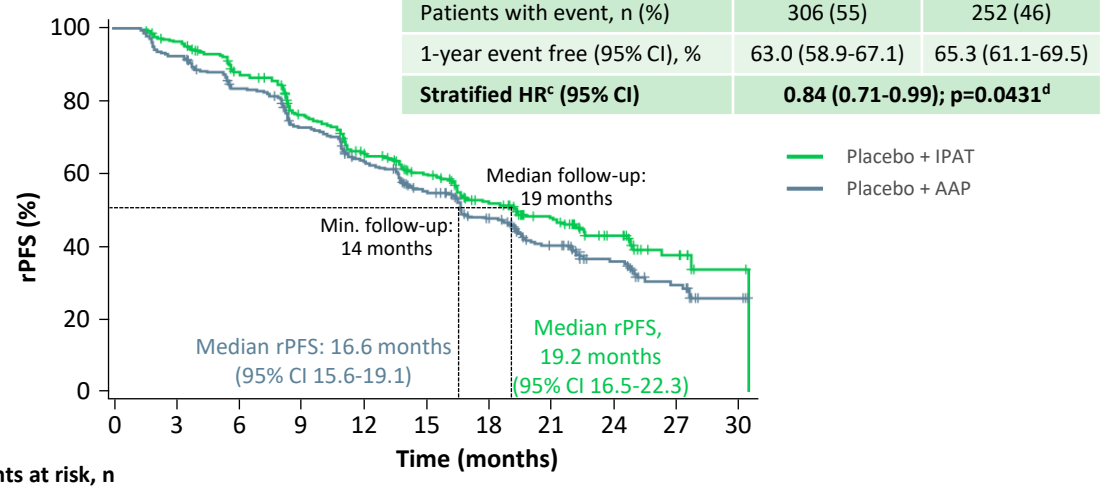


Patients at risk, n

Placebo + AAP	261	233	206	175	151	105	71	41	22	10	3
IPAT + AAP	260	238	211	182	149	113	72	48	25	12	

rPFS in the ITT population

	Placebo + AAP (N=261)	IPAT + AA (N=260)
Patients with event, n (%)	306 (55)	252 (46)
1-year event free (95% CI), %	63.0 (58.9-67.1)	65.3 (61.1-69.5)
Stratified HR[c] (95% CI)	**0.84 (0.71-0.99); p=0.0431[d]**	



Patients at risk, n

Placebo + AAP	554	501	443	377	322	237	165	98	60	29	5
IPAT + AAP	547	495	436	368	310	239	158	103	53	26	2

Data cut-off date: 16 March 2020; [a] Stratified for prior taxane-based therapy and PSA-only progression factor; [b] Statistically significant at α=0.05 level;
[c] Stratified for prior taxane-based therapy, PSA-only progression factor, and tumour PTEN loss status (by IHC); [d] Did not meet statistical significance α=0.01 level

AAP, abiraterone acetate + prednisone; CI, confidence interval; HR, hazard ratio; IHC, immunohistochemistry; IPAT, ipatasertib; mCRPC, metastatic castration-resistant prostate cancer; PSA, prostate-specific antigen; PTEN, phosphatase and tensin homologue; rPFS, radiographic progression-free survival

de Bono J, et al. ESMO 2020. Abstract #LBA4. Oral presentation

IPATential150: CONCLUSIONS

- **IPAT+AAP demonstrated a significantly superior rPFS and antitumour activity** vs placebo+AAP in patients with PTEN-loss mCRPC
  - Improvement of rPFS in the ITT population was not statistically significant
- **The safety profile of IPAT+AAP was in line with known and potential risks** observed in clinical studies
- While initial data are encouraging, overall survival (OS) benefit and additional secondary endpoints are not yet mature. The trial will continue until the next planned analysis and data will be shared with health authorities

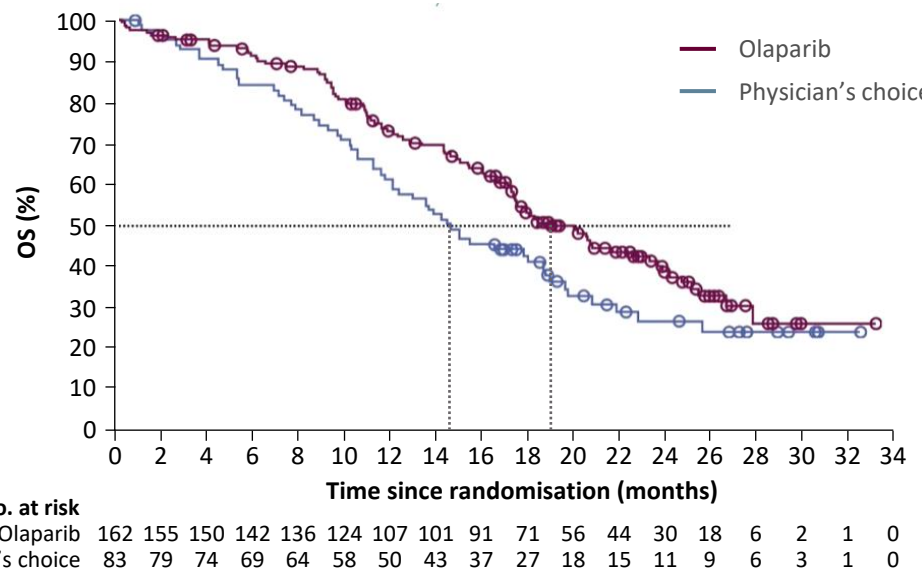
AAP, abiraterone acetate + prednisone; IPAT, ipaterasib; ITT, intention-to-treat; mCRPC, metastatic castration-resistant prostate cancer; rPFS, radiographic progression-free survival; PTEN, phosphatase and tensin homologue

de Bono J, et al. ESMO 2020. Abstract #LBA4. Oral presentation

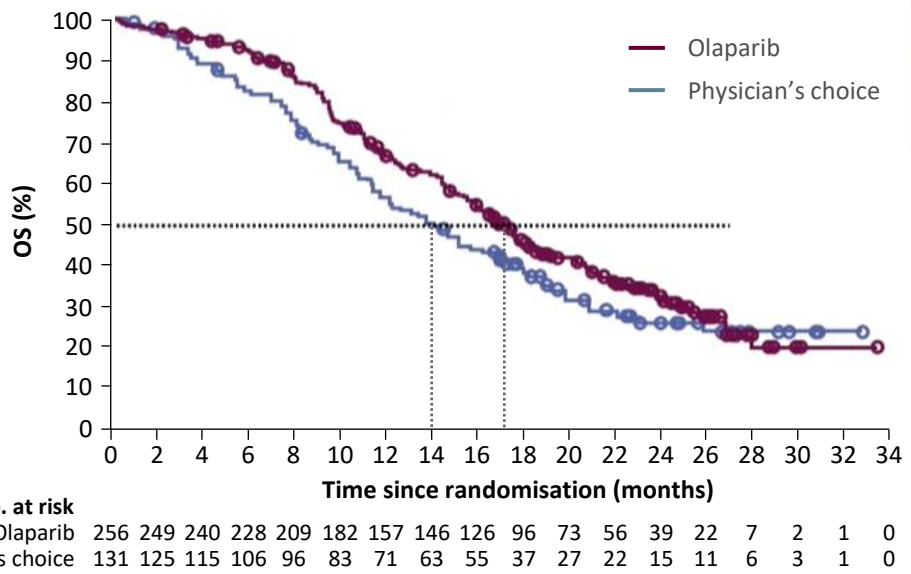
OTHER INTERESTING DATA

PROfound: OVERALL SURVIVAL RESULTS

OS IN COHORT A



OS IN OVERALL POPULATION



	Cohort A	
	Olaparib (N=162)	Physician's choice (N=83)
Median OS, months	19.1	14.7
HR (95% CI)	0.69 (0.50-0.97); p=0.0175	
Median follow-up, months	21.9	21.0

	Overall population	
	Olaparib (N=256)	Physician's choice (N=131)
Median OS, months	17.3	14.0
HR (95% CI)	0.79 (0.61-1.03); p=0.0515	
Median follow-up, months	20.7	20.5

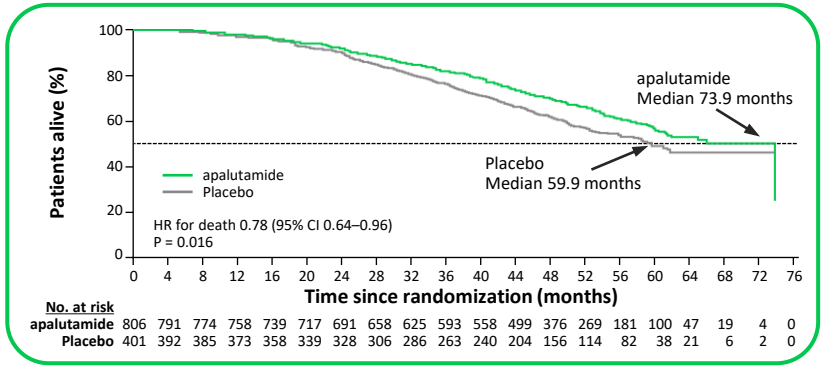
- Patients randomised between April 2017 and November 2018; data cut-off for final OS: 20 March 2020
- Among patients with disease progression in the physician's choice arm , 67% in cohort A and 66% in the overall population crossed over to olaparib
- Longer follow-up yielded no new safety signals

CI, confidence interval; HR, hazard ratio; OS, overall survival

de Bono J, et al. ESMO 2020. Abstract #610O. Oral presentation by Mateo, J

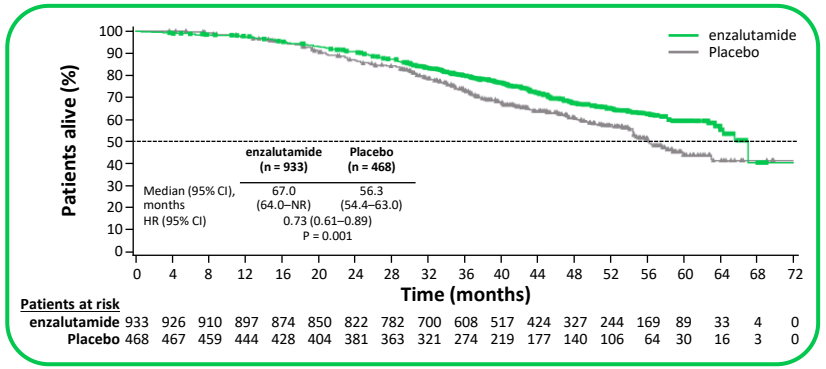
FINAL OS ANALYSES: NEXT GENERATION ARIs IN nmCRPC

SPARTAN[1]
apalutamide



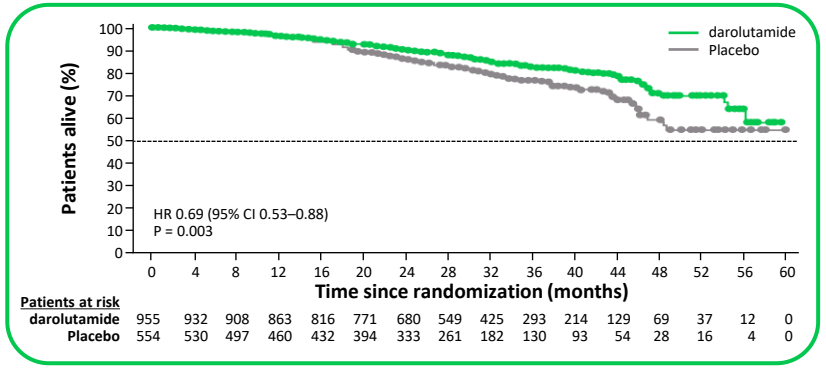
- 22% reduction in risk of death
  HR 0.78 (95% CI 0.64-0.96); p=0.016
- 84% of placebo patients received subsequent life-prolonging therapy

PROSPER[2]
enzalutamide



- 27% reduction in risk of death
  HR 0.73 (95% CI 0.61-0.89); p=0.001
- 65% of placebo patients received subsequent antineoplastic therapy

ARAMIS[3]
darolutamide



- 31% reduction in risk of death
  HR 0.69 (95% CI 0.53-0.88); p=0.003
- 55% of placebo patients received subsequent life-prolonging therapy

CI, confidence interval; HR, hazard ratio; ITT, intention to treat; NR, not reached

1. Smith MR, et al. Eur Urol. 2021;79:150-8; 2. Sternberg CN, et al. N Engl J Med. 2020;382:2197-206; 3. Fizazi K, et al. N Engl J Med. 2020;383:1040-9

TheraP: RESULTS

- TheraP is the first randomised Phase 2 study comparing Lu-PSMA to cabazitaxel in men with mCRPC after docetaxel

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)[a], HR (95% CI)	0.69 (0.50-0.95) P=0.02[b]	

[a]Based on 157 of the required 170 events
[b]p<0.0027 required to trigger rejection of H_0 prior to planned primary analysis

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
Thrombocytopenia	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

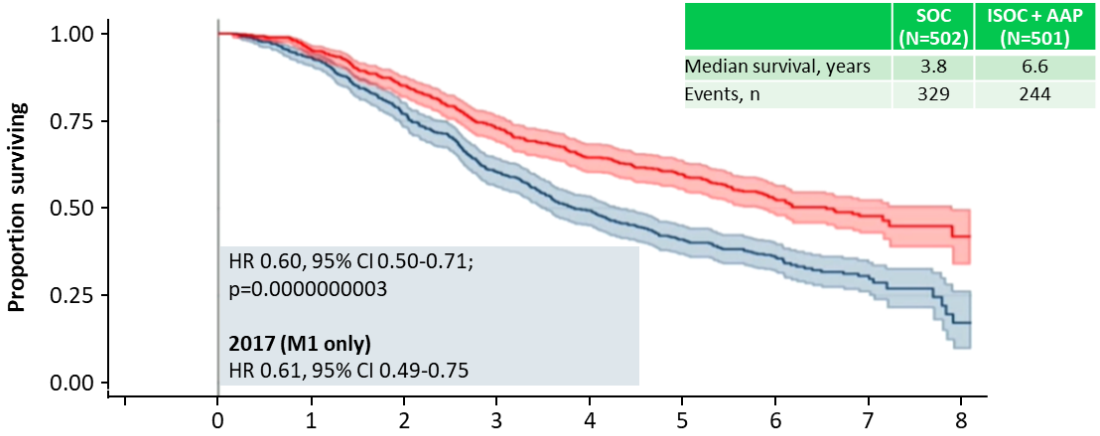
- Lu-PSMA may represent a favourable treatment option compared to cabazitaxel in a selected population with high PSMA expression
- Data from TheraP should be considered alongside that from the Phase 3 VISION trial (NCT03511664) when available

AE, adverse event; CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; Lu-PSMA, ^{177}Lutetium-PSMA-617; mCRPC, metastatic castration-resistant prostate cancer; PFS, progression-free survival; PSMA, prostate-specific membrane antigen; PSA50-RR, prostate-specific antigen ≥50% response rate

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

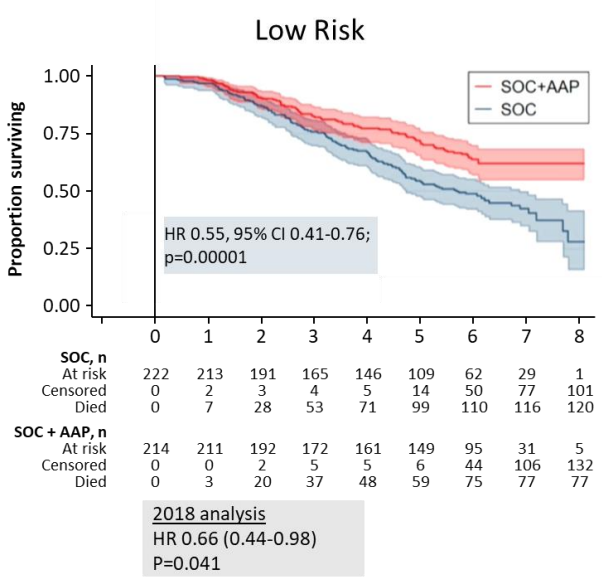
STAMPEDE: LONG-TERM OUTCOMES IN THE SUBSET OF M1 PATIENTS

OS: TOTAL M1 POPULATION

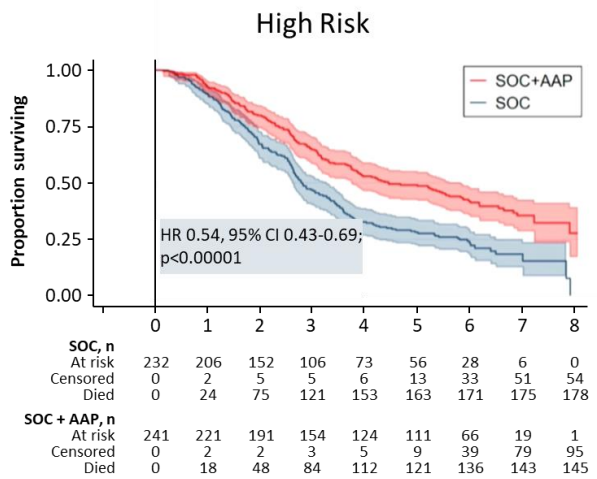


	SOC (N=502)	ISOC + AAP (N=501)
Median survival, years	3.8	6.6
Events, n	329	244

OS BY RISK GROUP (LATITUDE)



2018 analysis
HR 0.66 (0.44-0.98)
P=0.041



2018 analysis
HR 0.54 (0.41-0.70)
P<0.001

- The **results are unchanged** in M1 patients **from the initial analysis in 2017; highly significant OS benefit was observed** in M1 patients receiving ADT+AAP
- **OS benefit** by LATITUDE risk burden was similar **for both low- and high-risk subgroups**
- Toxicity at 4 years post-randomisation was similar between treatment arms: 16% of patients in each group reporting Grade ≥3 toxicity

AAP, abiraterone acetate + prednisolone; CI, confidence interval; HR, hazard ratio; M1, metastatic disease; OS, overall survival; SOC, standard of care

James ND, et al. N Engl J Med. 2017;377:338-51; James N, et al. ESMO 2020. Abstract #611O. Oral presentation

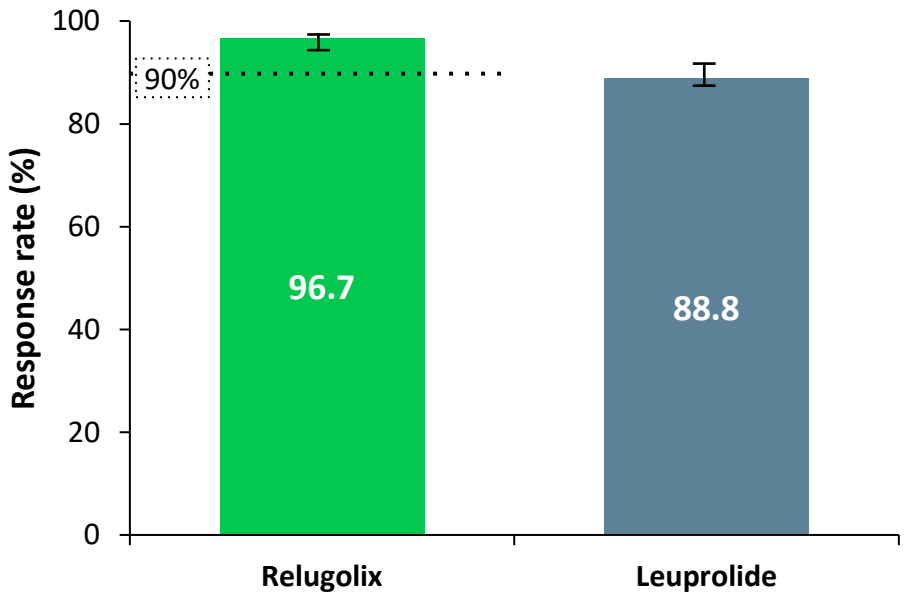
HERO PHASE 3 TRIAL: RESULTS COMPARING RELUGOLIX, AN ORAL GnRH RECEPTOR ANTAGONIST, VS LEUPROLIDE ACETATE FOR ADVANCED PROSTATE CANCER

Shore N, et al.

ASCO 2020. Abstract #5602. Oral presentation

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: 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 vs 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 comorbidities
- 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

OTHER GU CANCERS
2020 HIGHLIGHTS

KEY APPROVALS

FDA APPROVALS

ves avelumab for urothelial carcinoma maintenance treatment

FDA approves avelumab for urothelial carcinoma maintenance treatment

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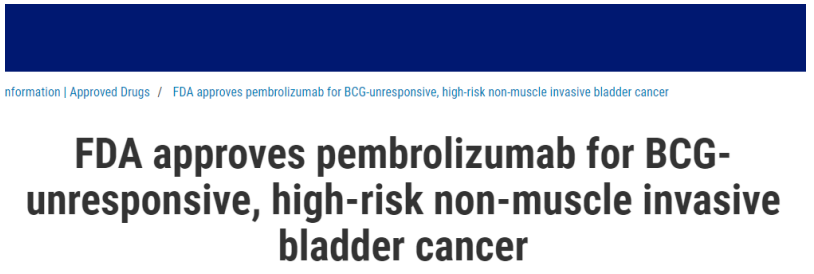
On June 30, 2020, the Food and Drug Administration approved avelumab (BAVENCIO, EMD Serono, Inc.) for maintenance treatment of patients with locally advanced or metastatic urothelial carcinoma (UC) that has not progressed with first-line platinum-containing chemotherapy.

Efficacy of avelumab for maintenance treatment of UC was investigated in the JAVELIN Bladder 100 trial (NCT02603432), a randomized, multi-center, open-label trial that enrolled 700 patients with unresectable, locally advanced or metastatic urothelial carcinoma that had not progressed with four to six cycles of first-line platinum-containing chemotherapy. Patients were randomized (1:1) to receive either avelumab intravenously every 2 weeks plus best supportive care (BSC) or BSC alone. Treatment was initiated within 4-10 weeks after last chemotherapy dose.

The main efficacy outcome measures were overall survival (OS) in all patients and in patients with PD-L1-positive tumors. The median OS in all patients was 21.4 months in the avelumab arm and 14.3 months in the BSC alone arm (HR: 0.69; 95%CI: 0.56, 0.86; p=0.001). Among patients with PD-L1-positive tumors (51%), the HR for OS was 0.56 (95% CI: 0.40, 0.79; p<0.001). In an exploratory analysis of patients with PD- L1- negative tumors (39%), the OS hazard ratio was 0.85 (95% CI: 0.62, 1.18).

The most common adverse reactions in > 20% of patients who received avelumab were fatigue, musculoskeletal pain, urinary tract infection, and rash. One patient died from sepsis and 28% of patients had serious adverse reactions.

The recommended avelumab dose is 800 mg administered as an intravenous infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity.



nformation | Approved Drugs / FDA approves pembrolizumab for BCG-unresponsive, high-risk non-muscle invasive bladder cancer

FDA approves pembrolizumab for BCG-unresponsive, high-risk non-muscle invasive bladder cancer

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On January 8, 2020, the Food and Drug Administration approved pembrolizumab (KEYTRUDA, Merck & Co. Inc.) for the treatment of patients with Bacillus Calmette-Guerin (BCG)-unresponsive, high-risk, non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy.

Efficacy was investigated in KEYNOTE-057 (NCT, a multicenter, single-arm trial that enrolled 148 patients with high-risk NMIBC, 96 of whom had BCG-unresponsive CIS with or without papillary tumors. Patients received pembrolizumab 200 mg every 3 weeks until unacceptable toxicity, persistent or recurrent high-risk NMIBC or progressive disease, or up to 24 months of therapy without disease progression.

The major efficacy outcome measures were complete response (as defined by negative results for cystoscopy [with TURBT/biopsies as applicable], urine cytology, and computed tomography urography [CTU] imaging) and duration of response. The complete response rate in the 96 patients with high-risk BCG-unresponsive NMIBC with CIS was 41% (95% CI: 31, 51) and median response duration was 16.2 months (0.0+, 30.4+). Forty-six percent (46%) of responding patients experienced a complete response lasting at least 12 months.

The most common adverse reactions (incidence ≥10%) in patients who received pembrolizumab in KEYNOTE-057 were fatigue, diarrhea, rash, pruritis, musculoskeletal pain, hematuria, cough, arthralgia, nausea, constipation, urinary tract infection, peripheral edema, hypothyroidism, and nasopharyngitis

www.fda.gov/drugs/. Accessed 5 January 2021

KEY CLINICAL TRIALS IN UROTHELIAL CARCINOMA

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

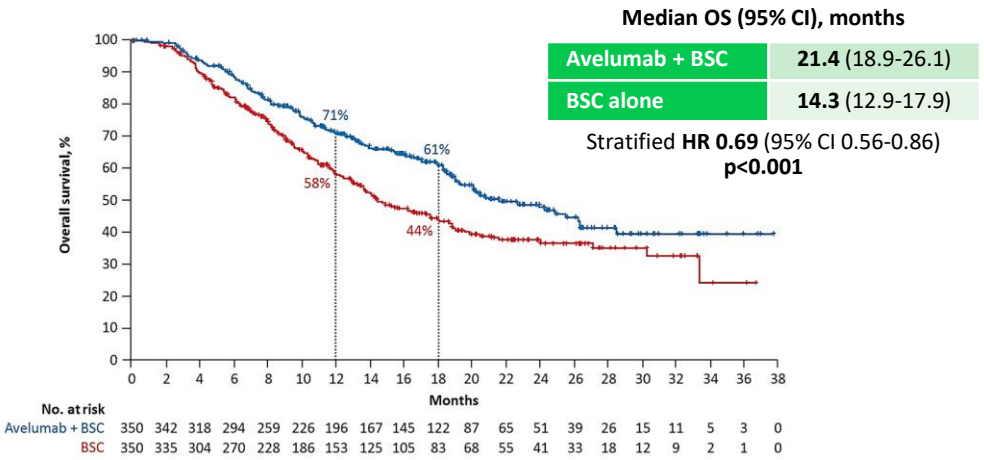
Powles T, et al.

ASCO 2020. Abstract #LBA1. Oral presentation

BSC, best supportive care; UC, urothelial carcinoma

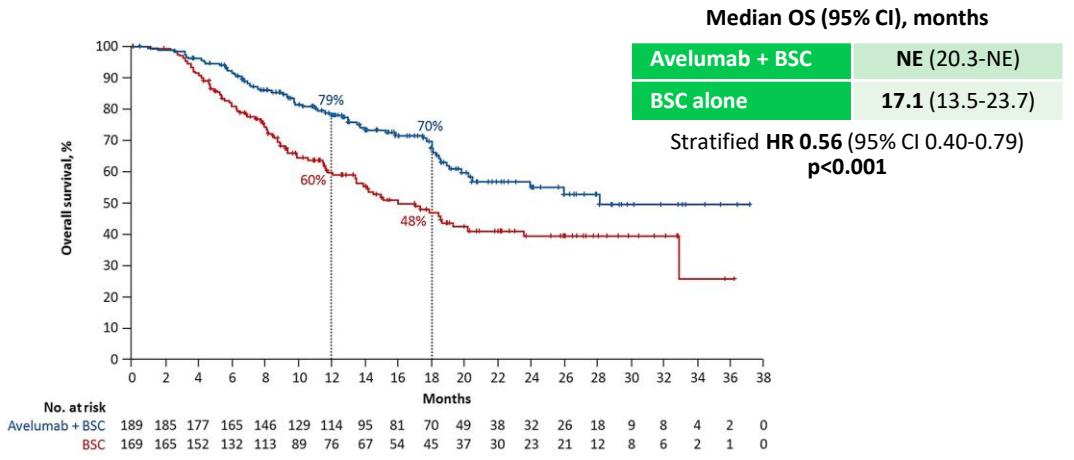
JAVELIN 100: RESULTS

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^{+} 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: CONCLUSIONS

- **JAVELIN 100** demonstrated **significantly longer OS with** first line **maintenance avelumab+BSC** vs 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 chemotherapy should be considered a **SOC**

Take-home messages:

- Maintenance avelumab after platinum-based chemotherapy in patients who achieve a complete response, partial response, or stable disease is a new SOC for patients with advanced UC

BSC, best supportive care; OS, overall survival; PD-L1, programmed death ligand-1; SOC, standard of care; UC, urothelial carcinoma

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

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

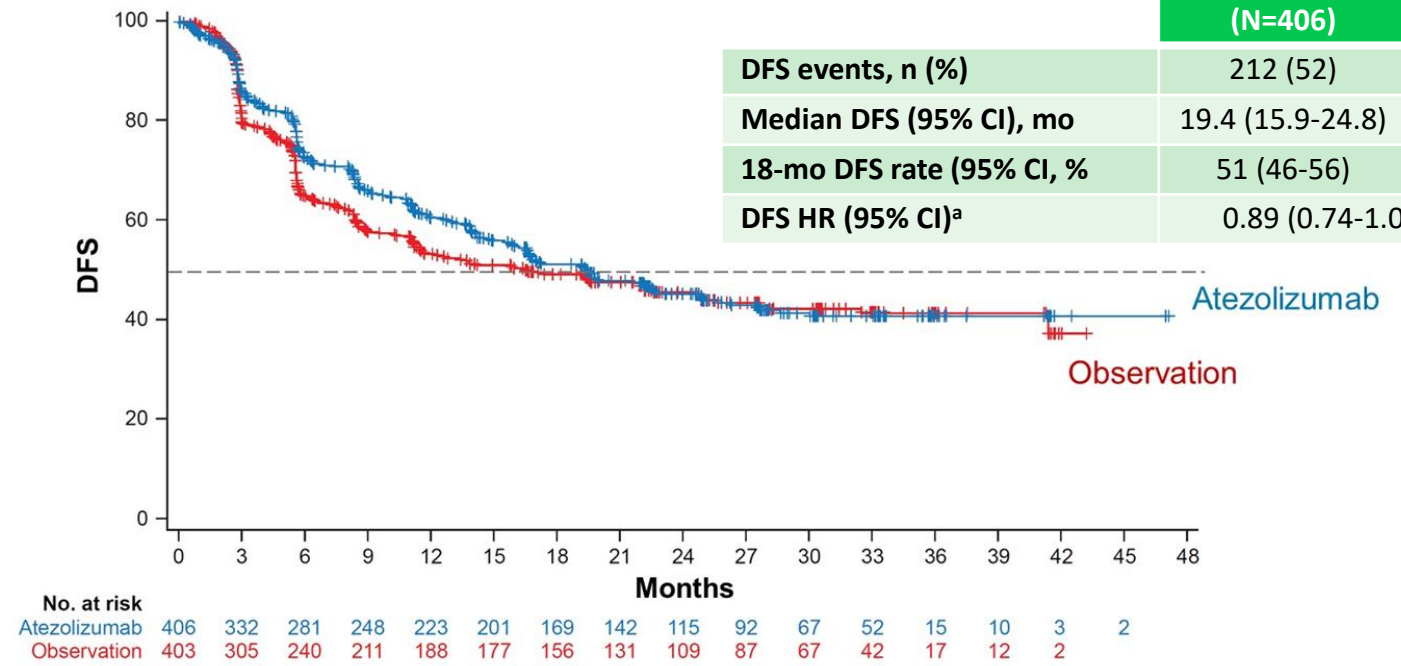
Hussain M, et al.

ASCO 2020. Abstract #5000. Oral presentation

MIUC, muscle-invasive urothelial carcinoma

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 cut-off: 30 November 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: 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:

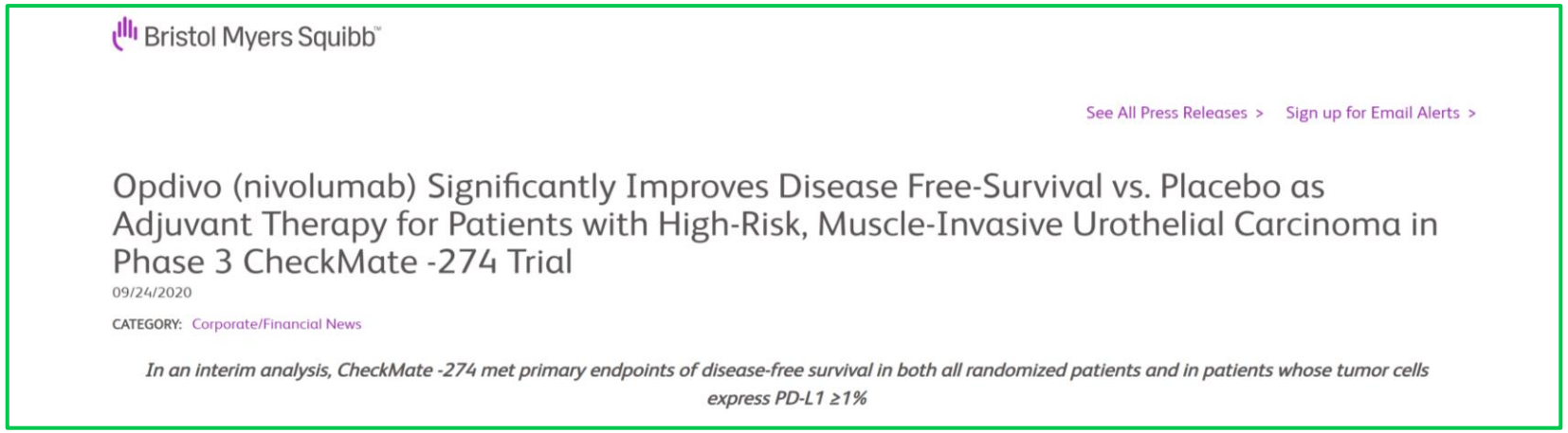
- Based on the data from IMvigor0101, for patients who have had neoadjuvant chemotherapy and radical surgery, observation remains the SOC
- Patients with high-risk features post surgery who did not receive neoadjuvant chemotherapy should receive adjuvant chemotherapy (if they are platinum-eligible)
-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

AE, adverse event; DFS, disease-free survival; MIUC, muscle-invasive urothelial carcinoma; OS, overall survival; SOC, standard of care

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

CHECKMATE-274: MET PRIMARY ENDPOINT

- Randomised multicentre Phase 3 trial comparing NIVO vs placebo after surgery in patients with high-risk MIUC
- 709 patients randomised 1:1 to receive NIVO vs placebo for up to 1 year
- **Primary endpoint:** DFS in ITT and PD-L1 ≥1%
- **Key secondary endpoints:** OS, non urothelial tract recurrence-free survival, and disease-specific survival



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Opdivo (nivolumab) Significantly Improves Disease Free-Survival vs. Placebo as Adjuvant Therapy for Patients with High-Risk, Muscle-Invasive Urothelial Carcinoma in Phase 3 CheckMate -274 Trial

09/24/2020

CATEGORY: Corporate/Financial News

In an interim analysis, CheckMate -274 met primary endpoints of disease-free survival in both all randomized patients and in patients whose tumor cells express PD-L1 ≥1%

DFS, disease-free survival; ITT, intention-to-treat; MIUC, muscle-invasive urothelial carcinoma; NIVO, nivolumab; OS, overall survival; PD-L1, programmed death ligand-1

www.businesswire.com/news/home/20200924005649/en/Opdivo-nivolumab-Significantly-Improves-Disease-Free-Survival-vs. Accessed 5 January 2021

KEY CLINICAL TRIALS IN RENAL CELL CARCINOMA

NIVOLUMAB + CABOZANTINIB VS SUNITINIB IN FIRST-LINE TREATMENT FOR ADVANCED RENAL CELL CARCINOMA: FIRST RESULTS FROM THE RANDOMIZED PHASE 3 CHECKMATE 9ER TRIAL

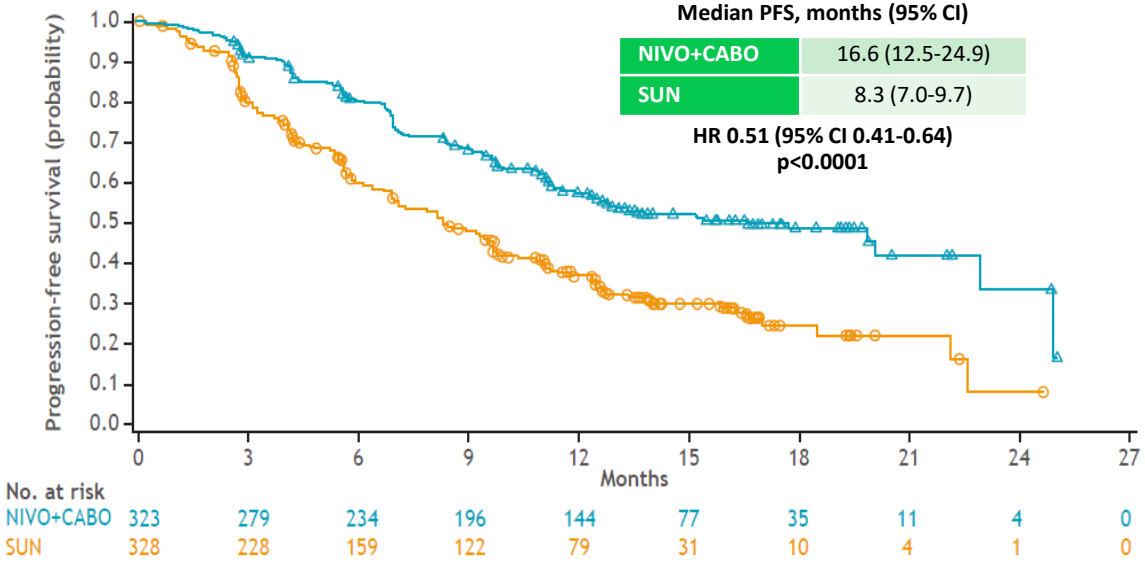
Choueiri T, et al.

ESMO 2020. Abstract #6960_PR. Oral presentation

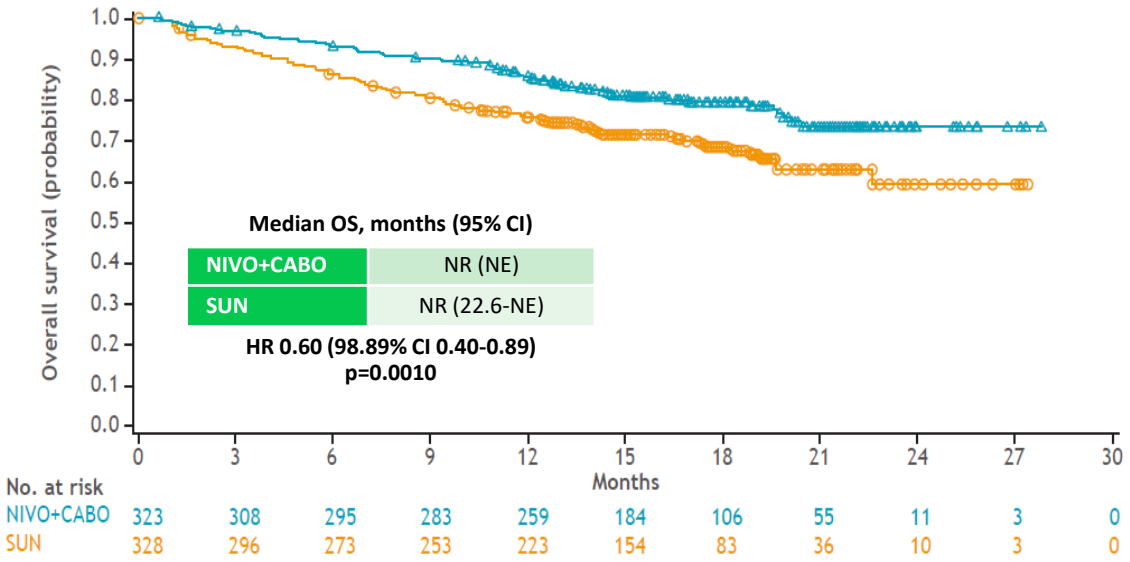
CHECKMATE 9ER

- A Phase 3 trial of NIVO+CABO vs sunitinib (SUN) for the first-line treatment of patients with clear cell advanced renal cell carcinoma (aRCC)

PFS PER BLINDED INDEPENDENT CENTRAL REVIEW



OS



Minimum study follow up: 10.6 months

	NIVO+CABO (N=320)		SUN (N=320)	
Events, %[a]	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**
All-cause AEs	100	75	99	71
Treatment-related AEs	97	61	93	51

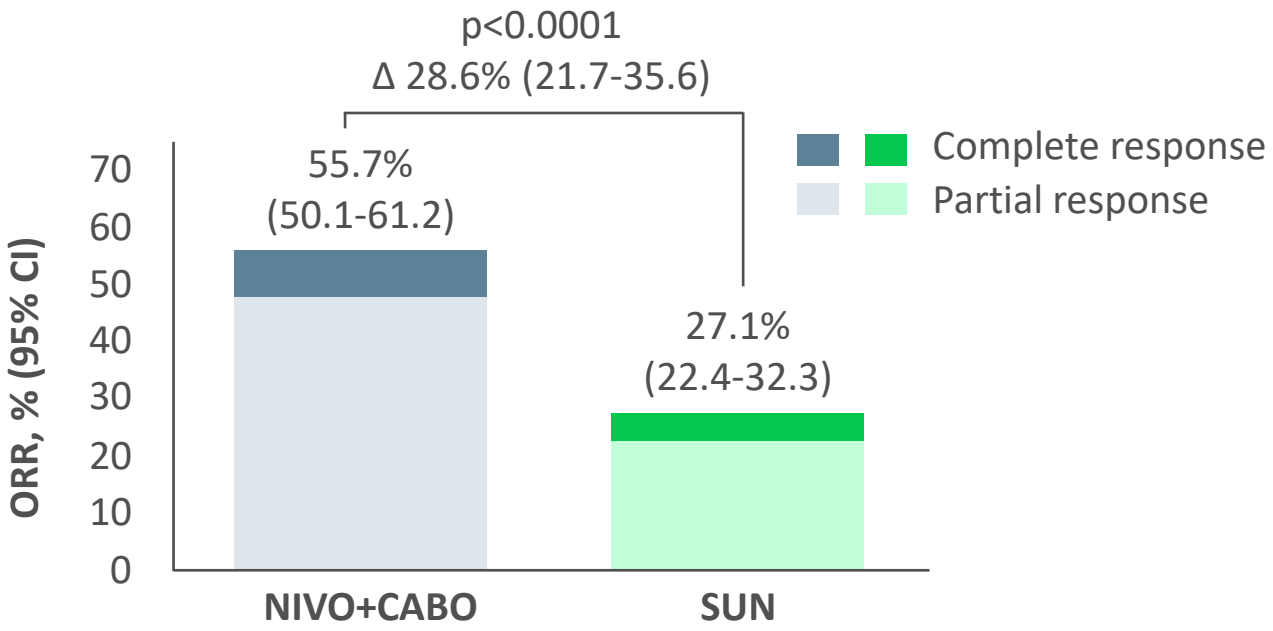
[a] Includes events that occurred on therapy or within 30 days after the end of the treatment period of all treated patients.

AE, adverse event; CABO, cabozantinib; CI, confidence interval; HR, hazard ratio; NE, not estimable; NIVO, nivolumab; NR, not reached; OS, overall survival; PFS, progression-free survival; SUN, sunitinib

Choueiri T, et al. ESMO 2020. Abstract #6960_PR. Oral presentation

CHECKMATE 9ER

OBJECTIVE RESPONSE AND BEST OVERALL RESPONSE (BICR)



Outcome, %	NIVO+CABO (N=323)	SUN (N=328)
Complete response	8.0	4.6
Partial response	47.7	22.6
Stable disease	32.2	42.1
Progressive disease	5.6	13.7
NE/not assessed[a]	6.5	17.1
Median time to response (range), months[b]	2.8 (1.0-19.4)	4.2 (1.7-12.3)
Median duration of response (95% CI), months	20.2 (17.3-NE)	11.5 (8.3-18.4)

- ORR favoured NIVO+CABO over SUN across subgroups including by IMDC risk status, tumour PD-L1 expression (≥1% vs <1%), and bone metastases

BICR-assessed ORR and BOR by RECIST v1.1

[a] Includes patients who were never treated, those who discontinued/died before disease assessment, those without measurable disease at baseline per BICR, or other reason not reported/specified; [b] Median time to and duration of response were calculated for patients who had a complete or partial response (n=180 with NIVO+CABO; n=89 patients with SUN)

BICR, blinded independent central review; BOR, best overall response; CABO, cabozantinib; CI, confidence interval; IMDC, International Metastatic RCC Database Consortium; NE, not evaluable; NIVO, nivolumab; ORR, objective response rate; PD-L1, programmed death ligand-1; RECIST, Response Evaluation Criteria in Solid Tumours; SUN, sunitinib

Choueiri T, et al. ESMO 2020. Abstract #6960_PR. Oral presentation

CHECKMATE 9ER: CONCLUSIONS

- The Phase 3 CheckMate 9ER trial met all efficacy endpoints, demonstrating superiority of 1st-line NIVO+CABO vs SUN in:
  - PFS: risk of disease progression or death reduced by 49%
  - OS: risk of death reduced by 40%
  - ORR: absolute increased by 29%
- NIVO+CABO showed consistent PFS, OS, and ORR benefits vs SUN across key baseline characteristics including IMDC risk status, tumour programmed death ligand-1 (PD-L1) expression, and bone metastases
- NIVO+CABO was generally well tolerated with a low rate of treatment-related discontinuations
- Patients had significantly better quality of life with NIVO+CABO vs SUN
- These results support NIVO+CABO as a potential 1st-line option for patients with aRCC

aRCC, advanced renal cell carcinoma; CABO, cabozantinib; IMDC, International Metastatic RCC Database Consortium; NIVO, nivolumab; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; SUN, sunitinib

Choueiri T, et al. ASCO 2020. Abstract #6960_PR. Oral presentation

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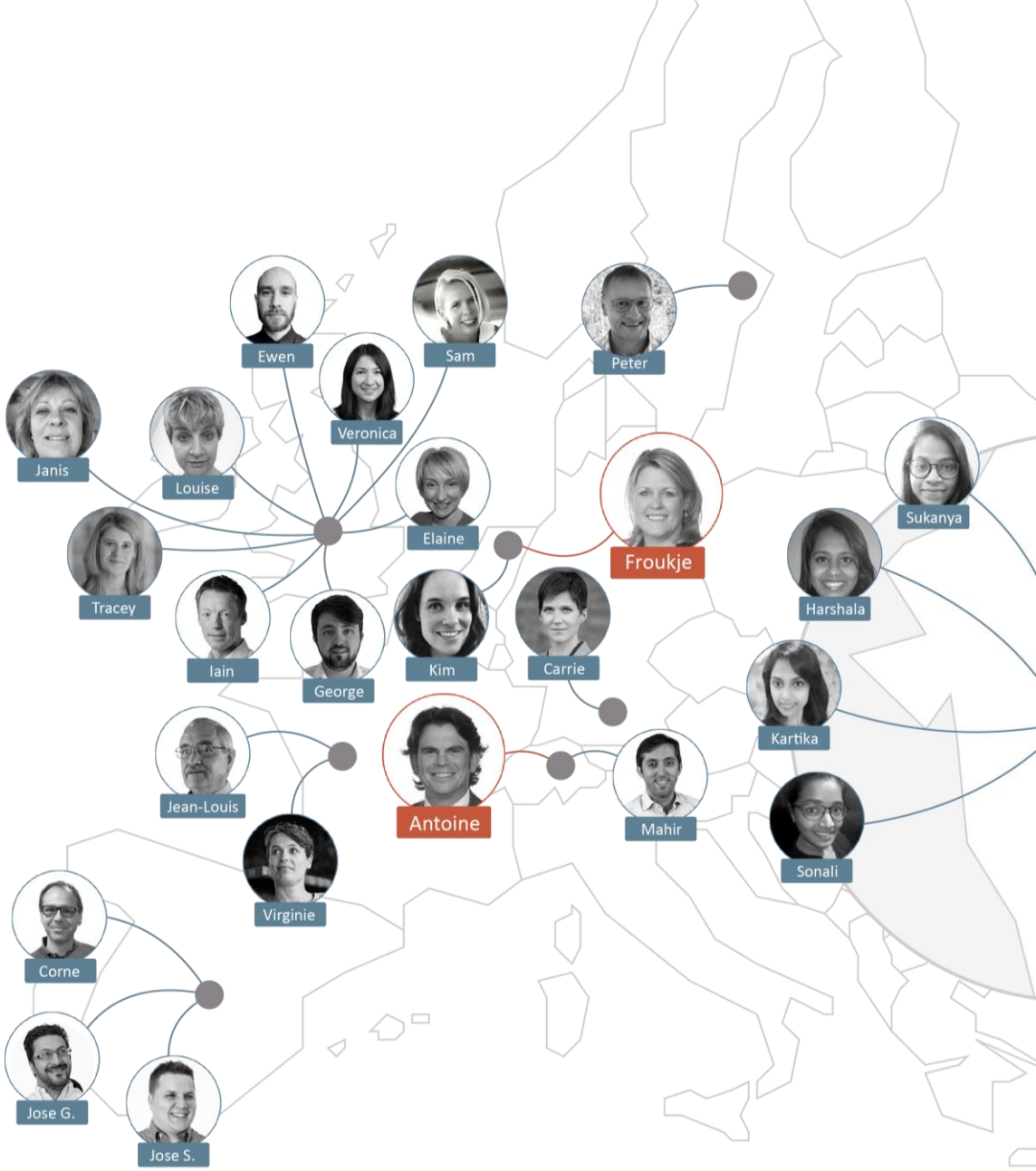

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