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MEETING SUMMARY
ESMO 2021, VIRTUAL MEETING

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PROSTATE CANCER HIGHLIGHTS FROM GU CONNECT

SEPTEMBER 2021

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PRACTICE-CHANGING DATA ESMO 2021

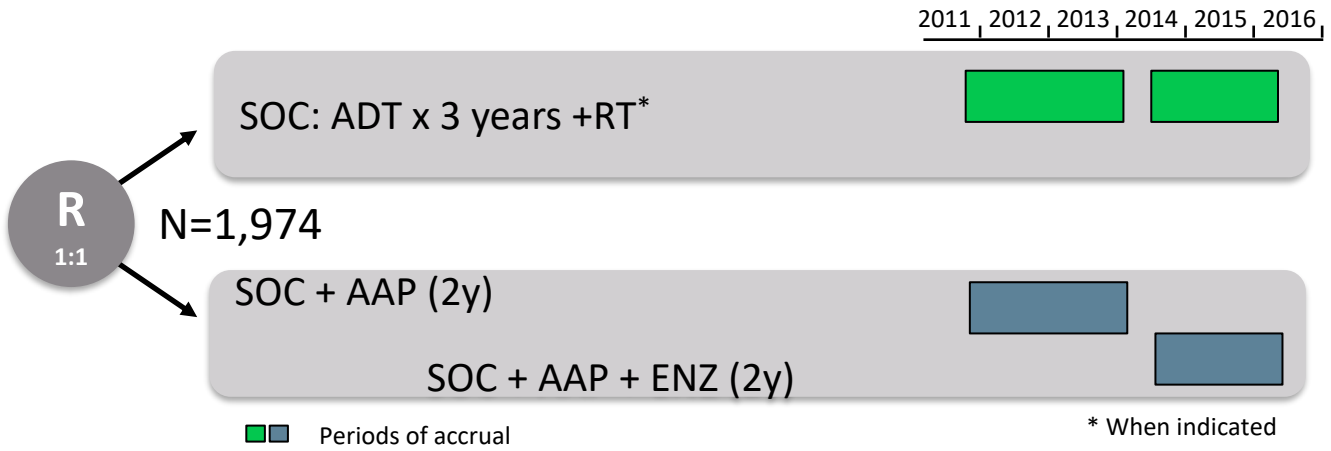
ABIRATERONE ACETATE PLUS PREDNISOLONE WITHOUT ENZALUTAMIDE ADDED TO ADT COMPARED TO ADT ALONE FOR MEN WITH HIGH-RISK M0 PCa: COMBINED ANALYSIS FROM TWO COMPARISONS IN THE STAMPEDE PLATFORM PROTOCOL

Attard G, et al. ESMO 2021, Abstract #LBA4_PR

ADT, androgen deprivation therapy; M0, non-metastatic; Pca, prostate cancer

STAMPEDE: BACKGROUND AND STUDY DESIGN

- Patients with **high-risk non-metastatic prostate cancer** (M0 PCa) are treated with androgen deprivation therapy (ADT) and local radiotherapy (RT), where indicated
- **Intensifying hormone treatment** with abiraterone acetate plus prednisone (AAP), enzalutamide (ENZ) or apalutamide (APA) **continuous to progression improves outcomes of metastatic PCa** but its efficacy in M0 PCa starting ADT is unknown
- This analysis of **STAMPEDE evaluated** whether there is a benefit for abiraterone acetate and prednisone **(AAP) in high-risk M0 PCa patients**



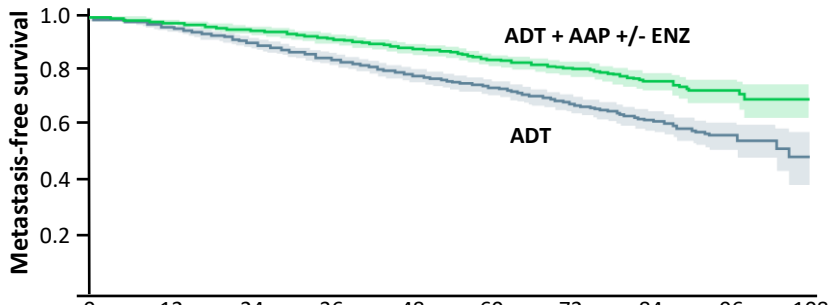
Primary endpoint: metastasis-free survival (MFS)
Secondary endpoint: Overall survival (OS)

AAP, abiraterone and prednisone; ADT, androgen deprivation therapy; APA, apalutamide; ENZ, enzalutamide; M0, non-metastatic; M1, metastatic; MFS, metastasis-free survival; OS, overall survival; PCa, prostate cancer; RT, radiotherapy; SOC, standard of care

Attard G, et al. Abstract #LBA4_PR. ESMO 2021. Oral presentation

STAMPEDE: RESULTS

Metastasis-free survival



ADT										
At-risk	988	950	894	836	767	550	329	172	53	9
Censored	0	8	11	14	26	201	387	522	632	673
Event	0	30	83	138	195	237	272	294	303	306
ADT + AAP +/- ENZ										
At-risk	986	948	917	884	839	622	369	198	71	14
Censored	0	21	28	31	45	225	460	615	737	792
Event	0	17	41	71	102	139	157	173	178	180

Kaplan–Meier estimates with 95% CI in lighter shade

Events
180 ADT + AAP +/- ENZ
306 ADT

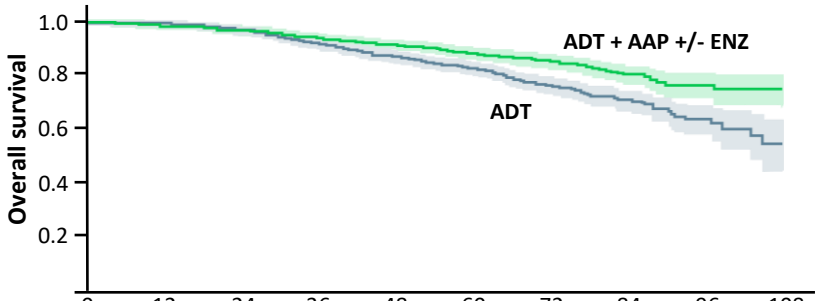
HR: 0.53
95% CI: 0.44-0.64
p value: 2.9×10^{-11}

6-year MFS improved from 69% to 82%

- **OS: treatment effect was consistent** between AAP and AAP + ENZ randomisation periods:
  - **ADT + AAP:** HR 0.63 (95% CI: 0.48-0.82), p=0.0005
  - **ADT + AAP + ENZ:** HR 0.54 (95% CI: 0.39-0.76), p=0.00043
    - Interaction between comparisons p=0.5

- **MFS: treatment effect was consistent** in major subgroups and between AAP and AAP + ENZ randomisation periods:
  - **ADT + AAP:** HR 0.54 (95% CI: 0.43-0.68), p=3.2×10^{-7}
  - **ADT + AAP + ENZ:** HR 0.53 (95% CI: 0.39-0.71), p=2.1×10^{-5}
    - Interaction HR 1.02 (95% CI: 0.70-1.50), p=0.908

Overall survival



ADT										
At-risk	988	974	947	901	837	610	368	200	63	10
Censored	0	8	11	14	28	616	421	568	693	742
Event	0	6	30	73	123	162	199	220	232	236
ADT + AAP +/- ENZ										
At-risk	986	956	928	899	861	645	386	205	74	16
Censored	0	21	29	32	46	234	477	641	766	823
Event	0	9	29	55	79	107	123	140	146	147

Kaplan–Meier estimates with 95% CI in lighter shade

Events
147 ADT + AAP +/- ENZ
236 ADT

HR: 0.60
95% CI: 0.48-0.73
p value: 9.3×10^{-7}

6-year survival improved from 77% to 86%

Non-proportional hazards p=0.1

AAP, abiraterone and prednisone; ADT, androgen deprivation therapy; APA, apalutamide; CI, confidence interval; ENZ, enzalutamide; HR, hazard ratio; M0, non-metastatic; M1, metastatic; MFS, metastasis-free survival; OS, overall survival; PCa, prostate cancer; RT, radiotherapy; SOC, standard of care

Attard G, et al. Abstract #LBA4_PR. ESMO 2021. Oral presentation; Efstathiou, E. Discussant Abstract #LBA4_PR. ESMO 2021

STAMPEDE: SUMMARY

- **2 years of AAP-based therapy** significantly improved MFS and OS of high-risk M0 PCa patients starting ADT and **should be considered a new standard of** care
- Adding ENZA to AAP increased toxicity but has **no apparent effect on efficacy**

Clinical Perspective

- Addressed an unmet need for high-risk M0 PCa patients
- MFS and OS results are clinically meaningful
- First report of enhanced androgen signalling inhibition in M0 HSPC
  - No knowledge of effect of other androgen receptor inhibitors: enzalutamide, apalutamide or darolutamide
- No quality of life data or long-term adverse event data at this stage

AAP, abiraterone and prednisone; ADT, androgen deprivation therapy; ENZA, enzalutamide; HSPC, hormone-sensitive prostate cancer; M0, non-metastatic; M1, metastatic; MFS, metastasis-free survival; OS, overall survival; PCa, prostate cancer

Attard G, et al. Abstract #LBA4_PR. ESMO 2021. Oral presentation; Efstathiou, E. Discussant Abstract #LBA4_PR. ESMO 2021

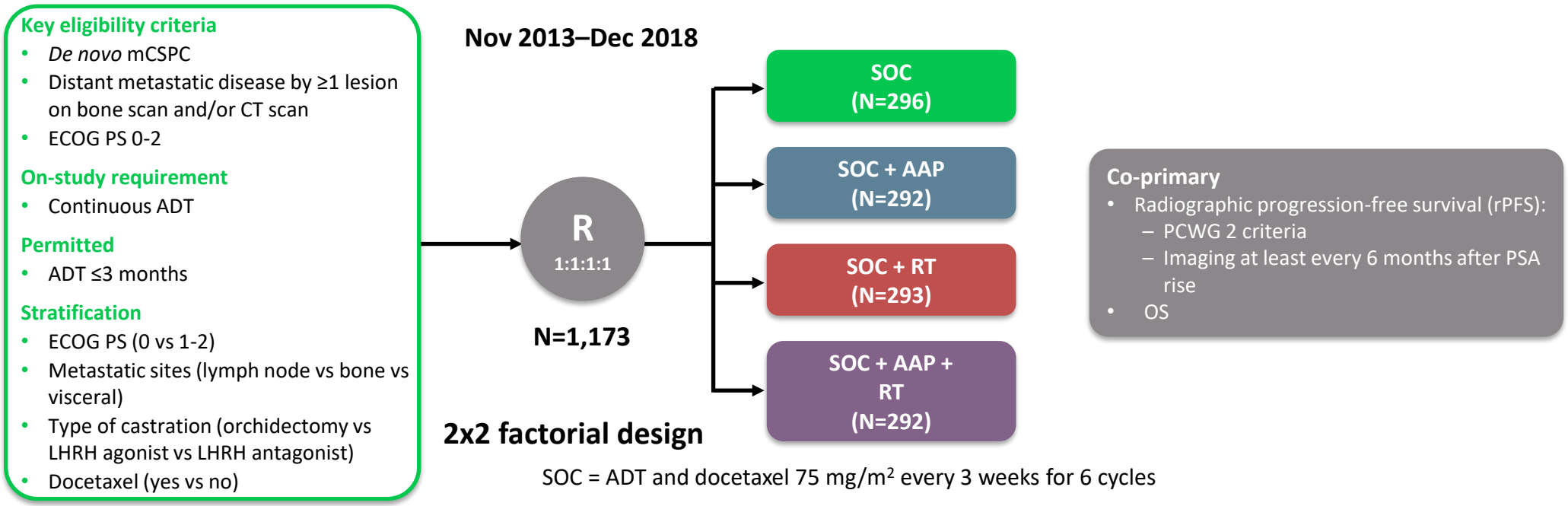
A PHASE 3 TRIAL WITH A 2X2 FACTORIAL DESIGN IN MEN WITH *DE NOVO* mCSPC: OVERALL SURVIVAL WITH ABIRATERONE PLUS PREDNISONE IN PEACE-1

Fizazi K, et al. ESMO 2021, Abstract #LBA5_PR

mCSPC, metastatic castration-sensitive prostate cancer

PEACE-1: BACKGROUND AND STUDY DESIGN

- ADT was SOC for men **with metastatic castration-sensitive prostate cancer** (mCSPC) for many years
- Since 2015, **combining ADT with either docetaxel, novel hormonal therapies, or RT** to the primary tumor (for those with low-burden metastases) was shown to improve OS and **is now the new SOC**
- **PEACE-1** evaluates whether combining these new treatments on top of ADT leads to improved outcomes



SOC = ADT and docetaxel 75 mg/m^2 every 3 weeks for 6 cycles

AAP, abiraterone and prednisone; ADT, androgen deprivation therapy; ECOG PS, Eastern Cooperative Oncology Group performance status; LHRH, luteinising hormone releasing hormone; mCSPC, metastatic castration-sensitive prostate cancer; OS, overall survival; PCWG 2, Prostate Cancer Working Group 2; PSA, prostate specific antigen; rPFS, radiographic progression-free survival; RT, radiotherapy; SOC, standard of care

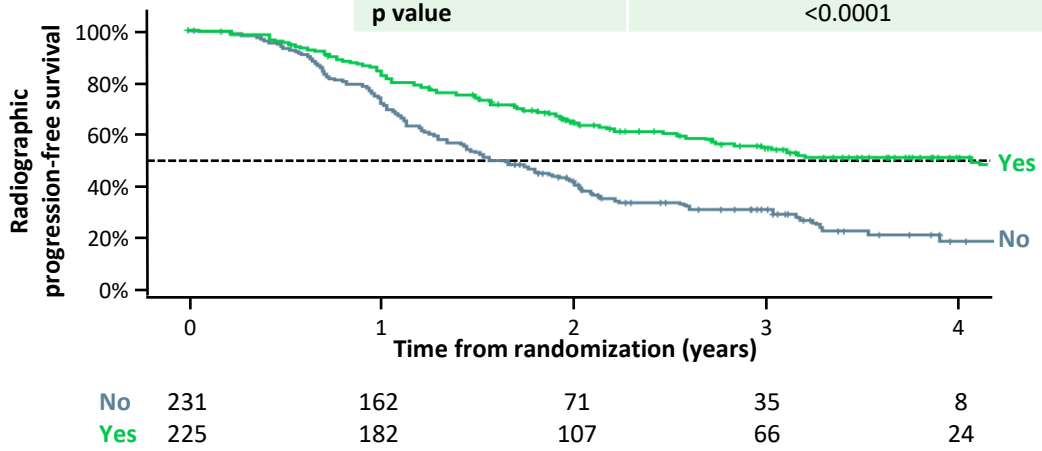
Fizazi K, et al. Abstract #LBA5_PR. ESMO 2021. Oral presentation

PEACE-1: RESULTS

- Previous results from PEACE-1, showed that **AAP + ADT + docetaxel significantly improved rPFS** in men with mCSPC (HR 0.50; (95% CI: 0.40-0.62), p<0.0001)[1]
- Low and high volume disease data were presented at ESMO[2]

High volume

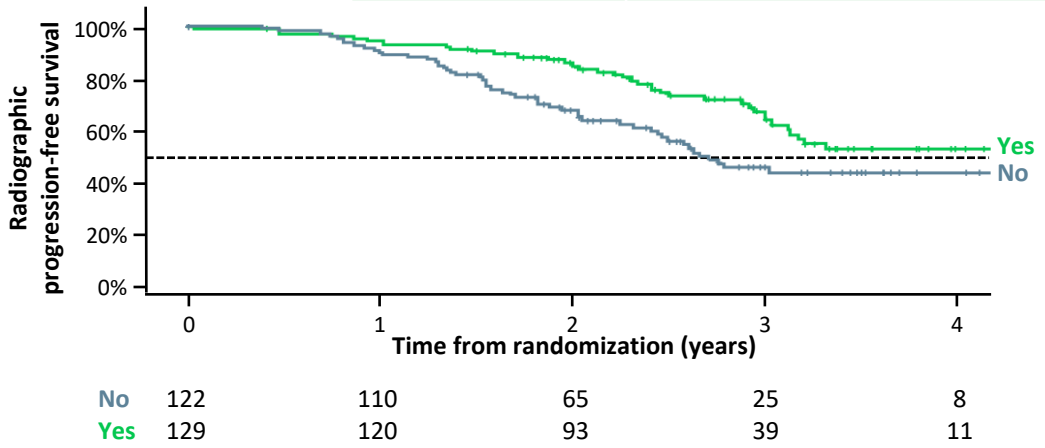
	SOC + AAP (N=225)	SOC (N=231)
Median, y (95% CI)	4.1 (2.7-NE)	1.6 (1.4-2.0)
Events	97	156
HR (95% CI)[a]	0.47 (0.36-0.60)	
p value	<0.0001	



No	231	162	71	35	8
Yes	225	182	107	66	24

Low volume

	SOC + AAP (N=129)	SOC (N=122)
Median, y (95% CI)	NE (3.1-NE)	1.6 (1.4-2.0)
Events	41	55
HR (95% CI)[a]	0.58 (0.39-0.87)	
p value	0.006	



No	122	110	65	25	8
Yes	129	120	93	39	11

[a]Adjusted on stratification parameters (RXT, PS, type of castration, metastatic burden)

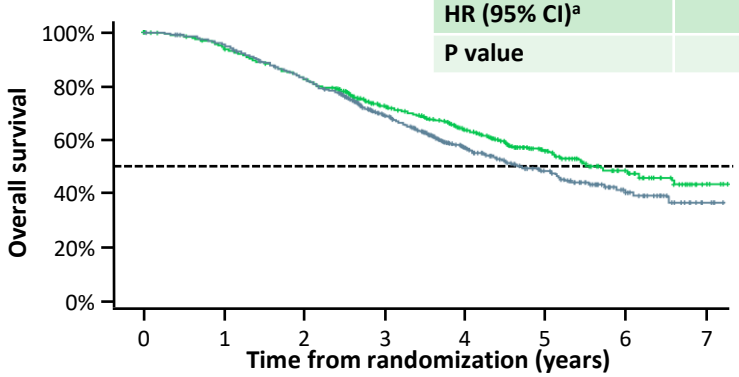
AAP, abiraterone and prednisone; ADT, androgen deprivation therapy; CI, confidence interval; HR, hazard ratio; mCSPC, metastatic castration sensitive prostate cancer; NE, not estimable; rPFS, radiographic progression-free survival; RXT, radiotherapy to primary tumour; SOC, standard of care

1. Fizazi K, et al. Abstract #5000. ASCO 2021; 2. Fizazi K, et al. Abstract #LBA5_PR. ESMO 2021. Oral presentation

PEACE-1: RESULTS

OS in the overall population

	SOC + AAP (N=583)	SOC (N=589)
Median, y (95% CI)	5.7 (5.1-NE)	4.7 (4.3-5.3)
Events	228	268
HR (95% CI)[a]	0.82 (0.69-0.98)	
P value	0.030	

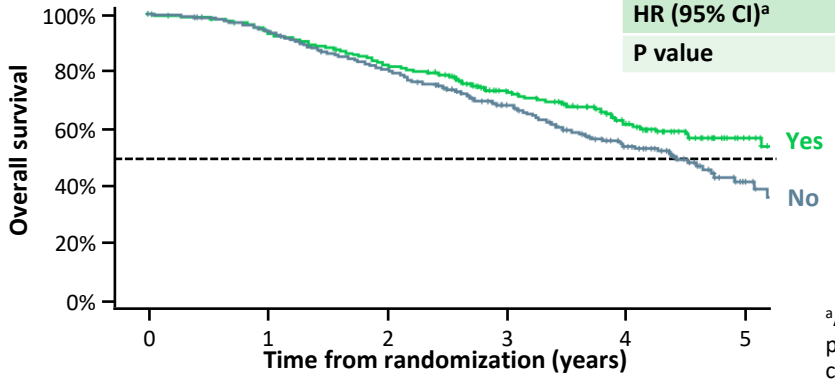


No	589	556	480	334	207	101	37	4
Yes	583	541	470	340	230	111	47	6

[a]Adjusted on stratification parameters (RXT, PS, type of castration, metastatic burden, doxetaxel)

OS with AAP in the ADT + docetaxel (+/- RXT) population

	SOC + AAP (N=355)	SOC (N=355)
Median, y (95% CI)	NE (4.5-NE)	4.4 (3.8-4.9)
Events	121	151
HR (95% CI)[a]	0.75 (0.59-0.95)	
P value	0.017	



No	355	329	281	172	78	18
Yes	355	328	287	183	98	25

[a]Adjusted on stratification parameters (RXT, PS, type of castration, metastatic burden)

- **OS effect seen across subgroups**, including those with **high volume disease** (HR 0.72, 95% CI 0.55-0.95) and **low volume disease** (HR 0.83, 95% CI 0.50-1.38; data immature)
- Combination of **AAP + ADT + docetaxel was well tolerated**
  - No difference in rates of grade 3 to 5 neutropenia or febrile neutropenia
  - Grade 3 to 5 liver toxicity (6% vs 1%) and hypertension (22% vs 13%) with SOC + AAP compared to SOC alone

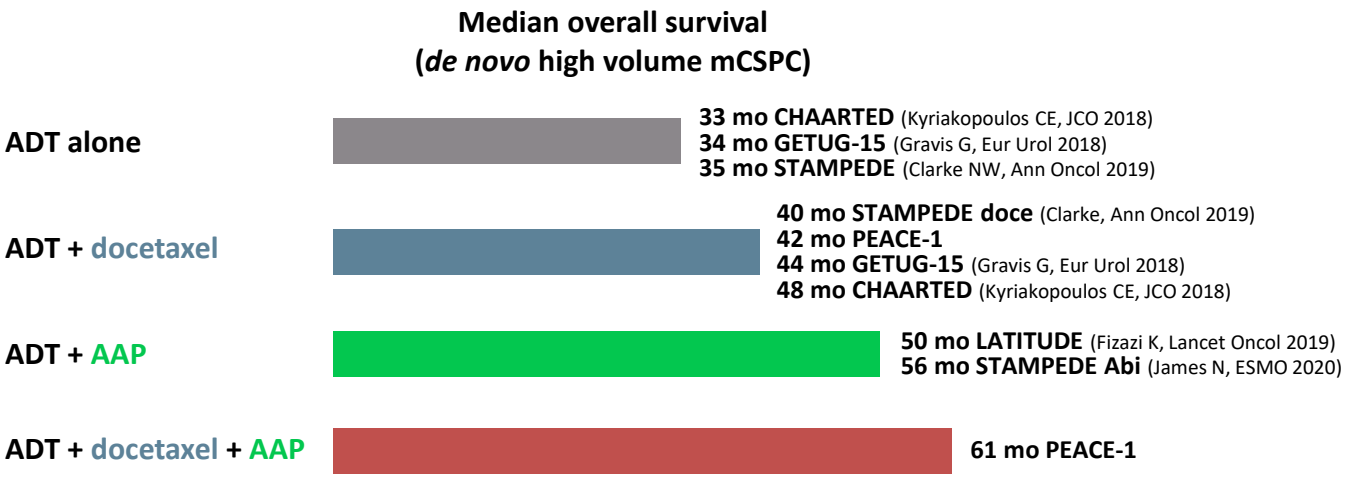
AAP, abiraterone and prednisone; ADT, androgen deprivation therapy; CI, confidence interval; HR, hazard ratio; OS, overall survival; RXT, radiotherapy to primary tumour; SOC, standard of care

Fizazi K, et al. Abstract #LBA5_PR. ESMO 2021. Oral presentation

PEACE-1: SUMMARY

- **Adding AAP to ADT plus docetaxel improves both rPFS and OS** in mCSPC men, even when 84% of mCRPC men from the control arm receive an androgen signalling inhibitor
- Toxicity was as expected – **no safety concerns** from combination treatment

PEACE-1 OS results in the context of recent data



Clinical Perspective

- Benefit of a median **lifetime gain of more than 1.5 years** for mCSPC men with high volume disease (5.1 vs 3.5 years)

AAP, abiraterone and prednisone; ADT, androgen deprivation therapy; mCRPC, metastatic castration-resistant prostate cancer; mCSPC, metastatic castration-sensitive prostate cancer; mo, months; OS, overall survival; rPFS, radiographic progression free survival

Fizazi K, et al. Abstract #LBA5_PR. ESMO 2021. Oral presentation

OTHER NOTEWORTHY PRESENTATIONS ESMO 2021

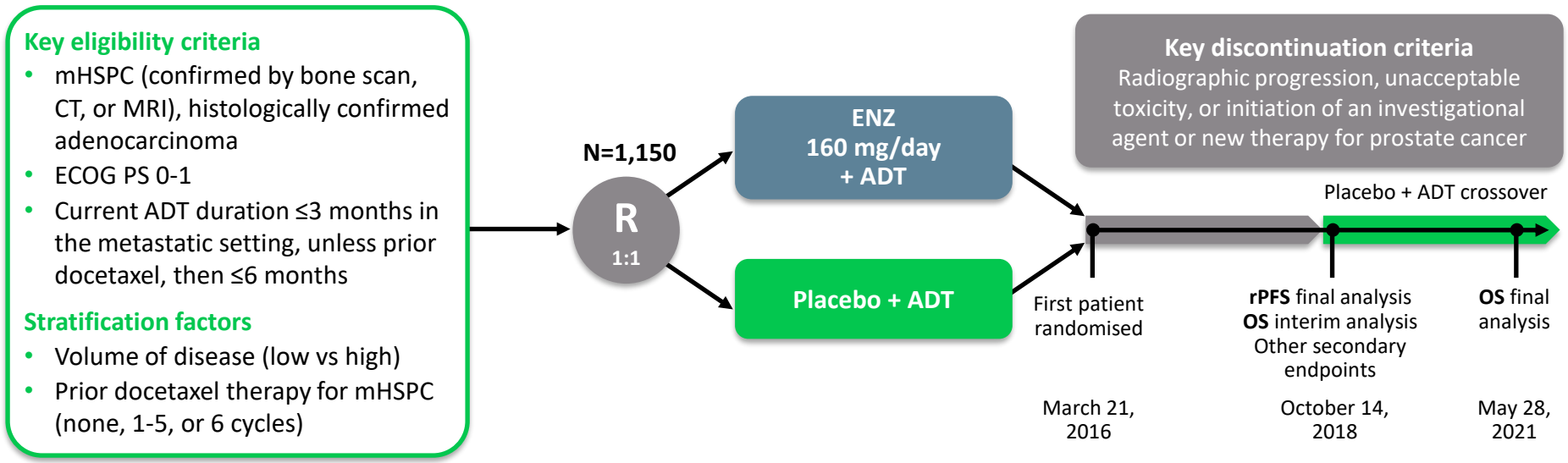
FINAL OS ANALYSIS FROM ARCHES: A PHASE 3, RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF ENZ + ADT IN MEN WITH mHSPC

Armstrong A, et al. ESMO 2021, Abstract #LBA25

ADT, androgen deprivation therapy; ENZ, enzalutamide; mHSPC, metastatic hormone-sensitive prostate cancer; OS, overall survival

ARCHES: BACKGROUND AND STUDY DESIGN

- The **primary analysis** of **ARCHES showed** that **addition of ENZ to ADT reduced risk of rPFS** and improved secondary outcomes in men with mCSPC[1]
- This approach, along with the use of abiraterone, apalutamide, or docetaxel, has **now become SOC** in this disease space
- OS was immature at the previous analysis; **final OS analysis is reported here**[2]

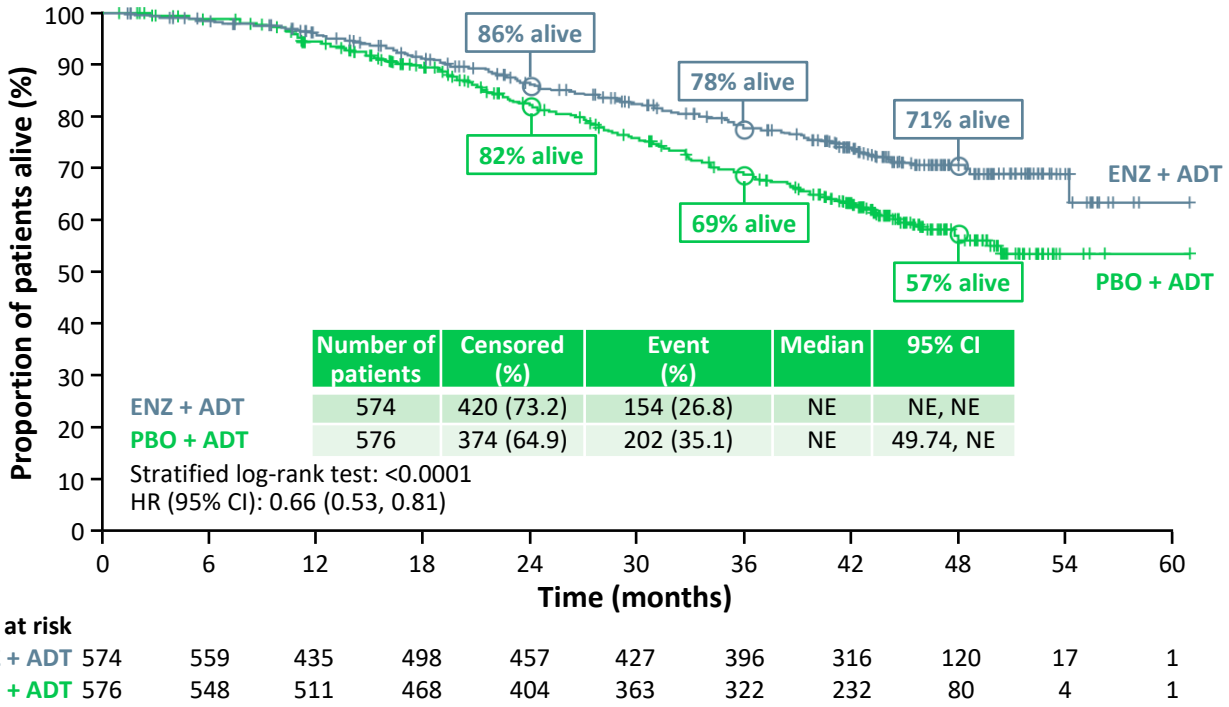


ADT, androgen deprivation therapy; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; ENZ, enzalutamide; mHSPC, metastatic castration-sensitive prostate cancer; MRI, magnetic resonance imaging; OS, overall survival; rPFS, radiographic progression-free survival; SOC, standard of care

1. Armstrong A, et al. J Clin Oncol 2019; 37: 2974-2986; 2. Armstrong A, et al. Abstract #LBA25. ESMO 2021. Oral presentation

ARCHES: OVERALL SURVIVAL RESULTS

- **ENZ + ADT significantly improved OS** by 34% vs placebo + ADT



	Number of patients	Censored (%)	Event (%)	Median	95% CI
ENZ + ADT	574	420 (73.2)	154 (26.8)	NE	NE, NE
PBO + ADT	576	374 (64.9)	202 (35.1)	NE	49.74, NE

Patients at risk

ENZ + ADT	574	559	435	498	457	427	396	316	120	17	1
PBO + ADT	576	548	511	468	404	363	322	232	80	4	1

- As of May 28, 2021: 356 deaths (ENZ + ADT, 154; placebo + ADT, 202)
- Median follow-up time: 44.6 mo
- Median treatment duration:
  - ENZ + ADT: 40.2 mo
  - Placebo + ADT: 13.8 mo
  - Placebo + ADT crossover: 23.9 mo

- **Conclusion: ENZ + ADT significantly prolongs survival in men with mHSPC** and, together with the acceptable safety profile, supports the clinical benefit of ENZ + ADT in men with mHSPC

ADT, androgen deprivation therapy; CI, confidence interval; ENZ, enzalutamide; HR, hazard ratio; ITT, intent-to-treat; mo, months; NE, not evaluable; PBO, placebo

Armstrong A, et al. Abstract #LBA25. ESMO 2021. Oral presentation

DAROLUTAMIDE MAINTENANCE IN mCRPC PREVIOUSLY TREATED WITH NHA AND NON-PROGRESSIVE DISEASE AFTER SUBSEQUENT TREATMENT WITH A TAXANE: A RANDOMISED DOUBLE-BLIND PLACEBO-CONTROLLED PHASE 2 TRIAL (SAKK 08/16)

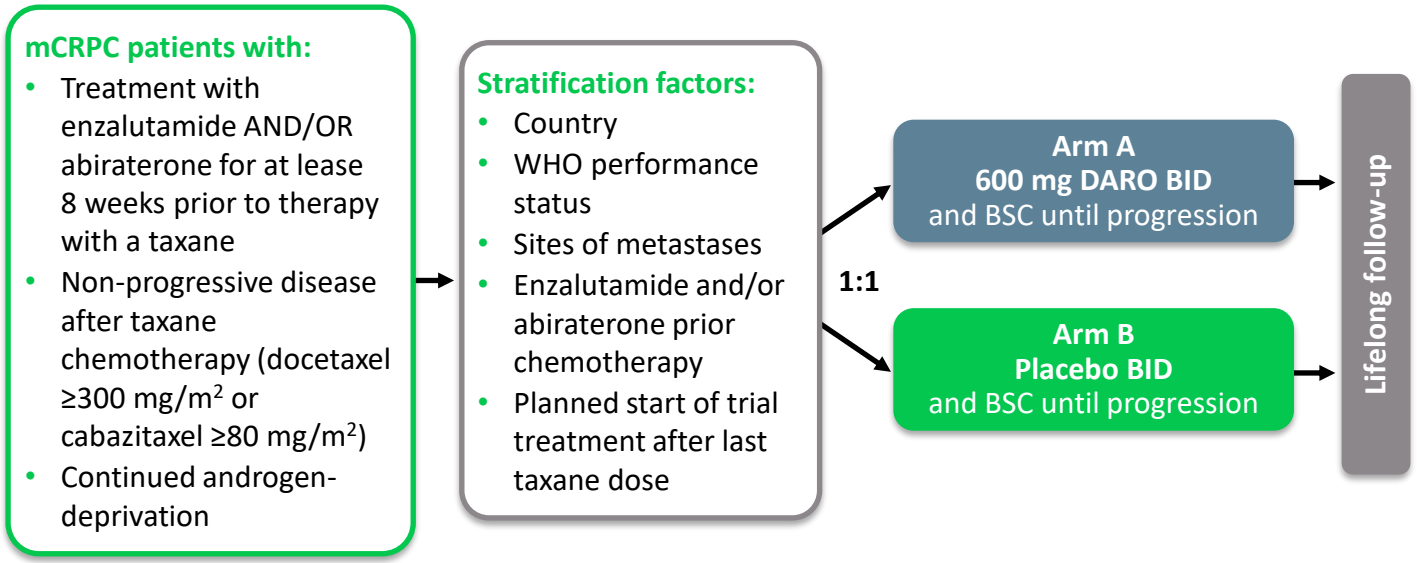
Cathomas R, et al. ESMO 2021, Abstract #LBA26

mCRPC, metastatic castration resistant prostate cancer; NHA, novel hormonal agents

SAKK 08/16: BACKGROUND AND STUDY DESIGN

- **Proof-of-concept study** to assess the impact of maintenance therapy with DARO on rPFS of mCRPC patients treated with NHAs who have non-progressive disease under chemotherapy with a taxane

International multicentre randomised Phase 2 study: placebo-controlled, double-blind



Primary endpoint: rPFS at 12 weeks after treatment start

Secondary endpoints:

- rPFS
- Time to PSA progression; Time to symptomatic/clinical progression
- Event-free survival
- OS
- PSA response
- Adverse events; Fatigue

Start of trial treatment within 2-8 weeks after last taxane dose

BID, twice daily; BSC, best supportive care; DARO. darolutamide; mCRPC, metastatic castration resistant prostate cancer; NHA, novel hormonal therapies; OS, overall survival; PSA, prostate specific antigen; rPFS, radiographic progression-free survival; WHO, world health organisation

Cathomas R, et al. Abstract #LBA26. ESMO 2021. Oral presentation

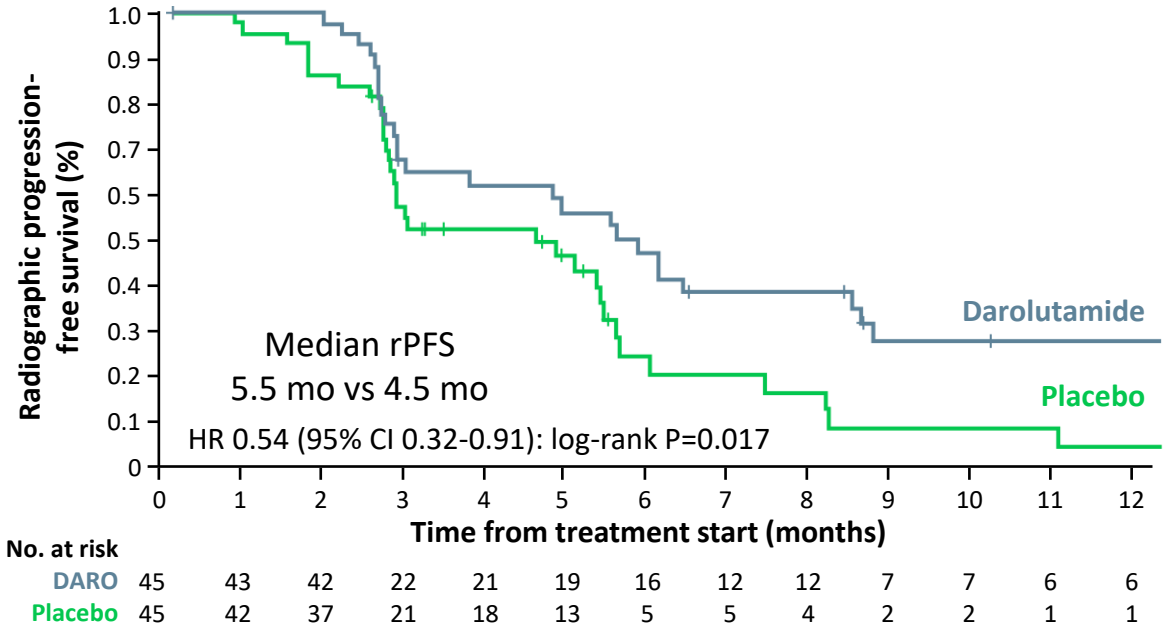
SAKK 08/16: RESULTS

PRIMARY ENDPOINT: rPFS AT 12 WEEKS

	Arm A (N=45): DARO	Arm B (N=45): Placebo
rPFS at 12 weeks	64.7%	52.2%
95% CI	47.6%, 77.5%	36.1%, 66.1%

	Result
Est. difference in rPFS at 12 weeks	12.5%
One-sided 85% CI (lower bound)	1.1%
p value (one-sided)	0.127

SECONDARY ENDPOINT: rPFS



- **Study met it's primary endpoint of rPFS at 12 weeks**
- **Treatment-related AEs were mild and similar in both arms** (DARO vs placebo):
  - grade 1: 26% vs 22%, grade 2: 13% vs 15%, grade 3: 2% vs 2%
  - Fatigue grade 1 or 2 was less common in DARO arm (11% vs 20%)
- **Switch maintenance with DARO after prior taxane** and at least one NHA **results in a statistically significant prolongation of rPFS**. Prior response to NHA might predict benefit from maintenance treatment after NHA and taxane

CI, confidence interval; DARO, darolutamide; HR, hazard ratio; mo, months; NHA, novel hormonal therapies; rPFS, radiographic progression free survival
Cathomas R, et al. Abstract #LBA26. ESMO 2021. Oral presentation

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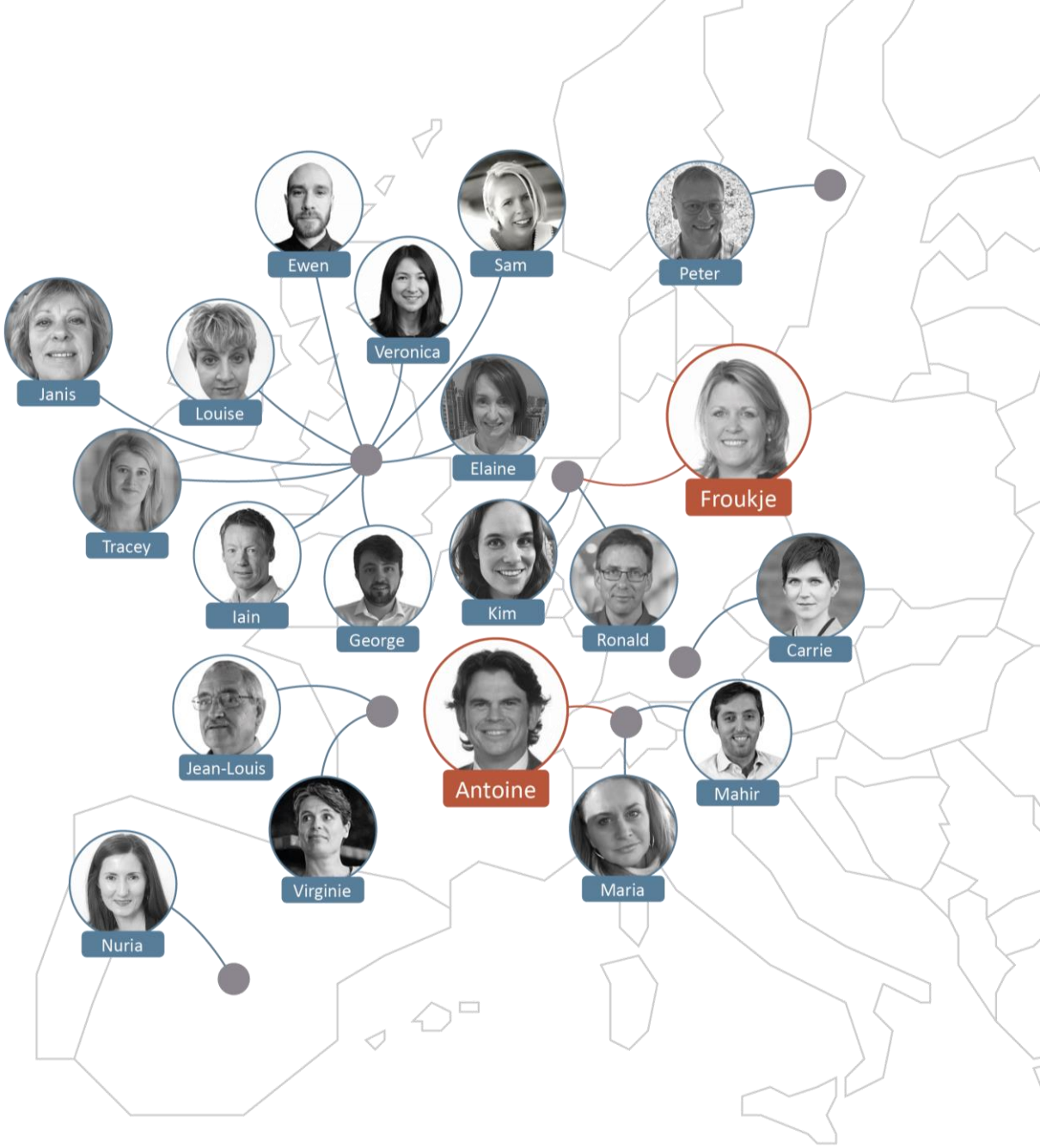

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