2021 ESMO congress

ONCO NOUVELLE-AQUITAINE
Réseau Régional de Cancérologie

ACTUALITES EN ONCOLOGIE UROLOGIQUE

Jeudi 14 octobre 2021

Domaine de la Tuilerie

BOUCHAERT Patrick

PLAN

- CARCINOME UROTHELIAL
  - Chimiothérapie péri-opératoire : Etude VESPER
- CARCINOME A CELLULES RENALES METASTATIQUE
  - Pauses thérapeutiques avec les ITK en 1ère ligne : Etude STAR
  - Adaptation posologique de l'IPILIMUMAB en 1ère ligne : Etude PRISM
- CANCER DE PROSTATE
  - ABIRATERONE en plus du DOCETAXEL en hormono-sensible métastatique : Etude PEACE-1
  - ABIRATERONE en hormono-sensible M0 à haut risque : Etude STAMPEDE

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DOSE DENSE METHOTREXATE, VINBLASTINE, DOXIRUBICINE AND CISPLATIN (dd-MVAC) or GEMCITABINE AND CISPLATIN (GC) AS PERI OPERATIVE CHEMOTHERAPY FOR PATIENTS WITH MUSCLE INVASIVE BLADDER CANCER

RESULTS OF THE GETUG/AFU V05 VESPER PHASE III TRIAL

Ch Pfister, G Gravis, A Flechon, C Chevreau, H Mahamedi, B Laguerre, A Guillot, F Joly, M Soulie, Y Allory, V Harter, S Culine for the VESPER trial investigators

TRIAL DESIGN

Inclusion criteria

- Pure or mixed urothelial bladder cancer (neuroendocrine excluded)
- ECOG patient, PS < 2
- All criteria for cisplatin eligibility
- Written informed consent
- ≥ T2, N0 (LN ≤ 10 mm on CT scan), M0 (Neoadjuvant CT)

OR > pT2 or pN+ and M0 (Adjuvant CT)

Chemotherapy

- **4 cycles of GC every 3 weeks**

  Gemcitabine 1250 mg/m^2 d1 and d8, Cisplatin 70 mg/m2 d1

- **6 cycles of dd-MVAC every 2 weeks**

  Methotrexate 30 mg/m^2 d1, Vinblastine 3 mg/m^2 d2,

  Doxorubicin 30 mg/m^2 d2, Cisplatin 70 mg/m^2 d2 + G-CSF support

RESULTS

- From February 2013 to March 2018
- 500 patients included in 28 French cancer centers
- 493 patients available for intent-to-treat analysis
- Adjuvant group n=56 and Neoadjuvant group n=437 (88%)
- Primary End Point : Progression Free Survival (PFS) at 3 years

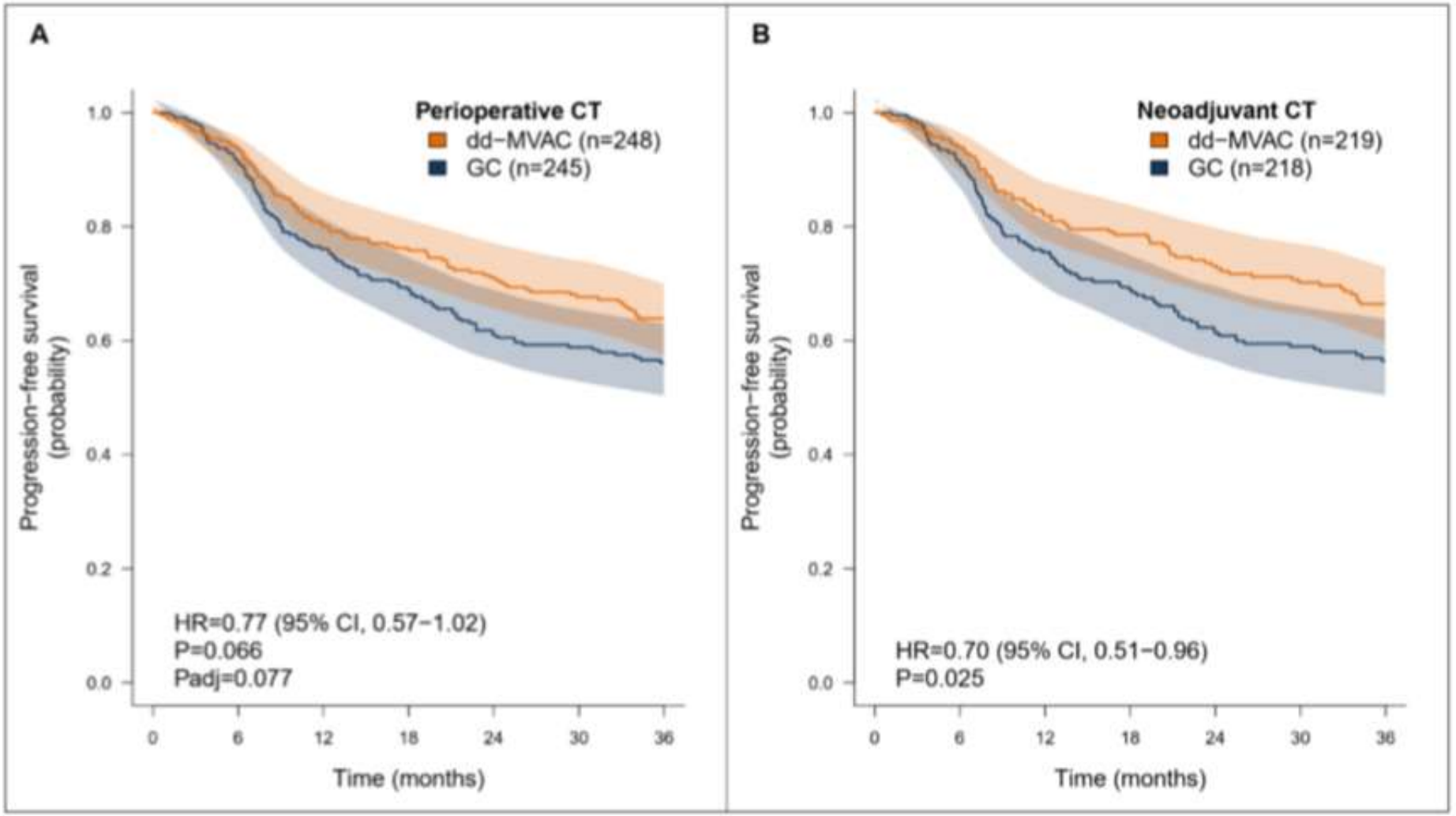
		CC	dd-MVAC
		n = 245	n = 248
Demography			
Age		63 [59 – 69]	63 [58 – 68]
Sex	Male	206 (84%)	202 (81%)
	Female	39 (16%)	46 (19%)
Peri-operative chemotherapy			
	Adjuvant	26 (11%)	30 (12%)
	Neodjuvant	219 (89%)	218 (88%)
Staging at randomization (adjuvant CT only)			
	pT3 N0	3 (12%)	9 (30%)
	pT4 N0	4 (15%)	3 (10%)
	pN+	19 (73%)	18 (60%)
Staging at randomization (neoadjuvant CT only)			
	cT2 N0	207 (95%)	197 (90%)
	cT3 N0	8 (3.7%)	12 (5.5%)
	cT4 N0	4 (1.8%)	9 (4.1%)
Cystectomy (neoadjuvant CT only)			
	Not performed	21 (9.6%)	19 (8.7%)
	Performed	198 (90%)	199 (91%)
Pathological response (neoadjuvant CT +cystectomy performed only)			
	ypT0 N0	71 (36%)	84 (42%)
	ypTis,Ta or T1 and ypN0	27 (14%)	42 (21%)
	ypT2 N0	26 (13%)	28 (14%)
	≥ ypT3 or ypN+	73 (37%)	43 (22%)
	Uncertain staging	1	2

60% des patients du bras ddMVAC ont reçu les 6 cycles prévus
84% des patients du bras CG ont reçu les 4 cycles prévus

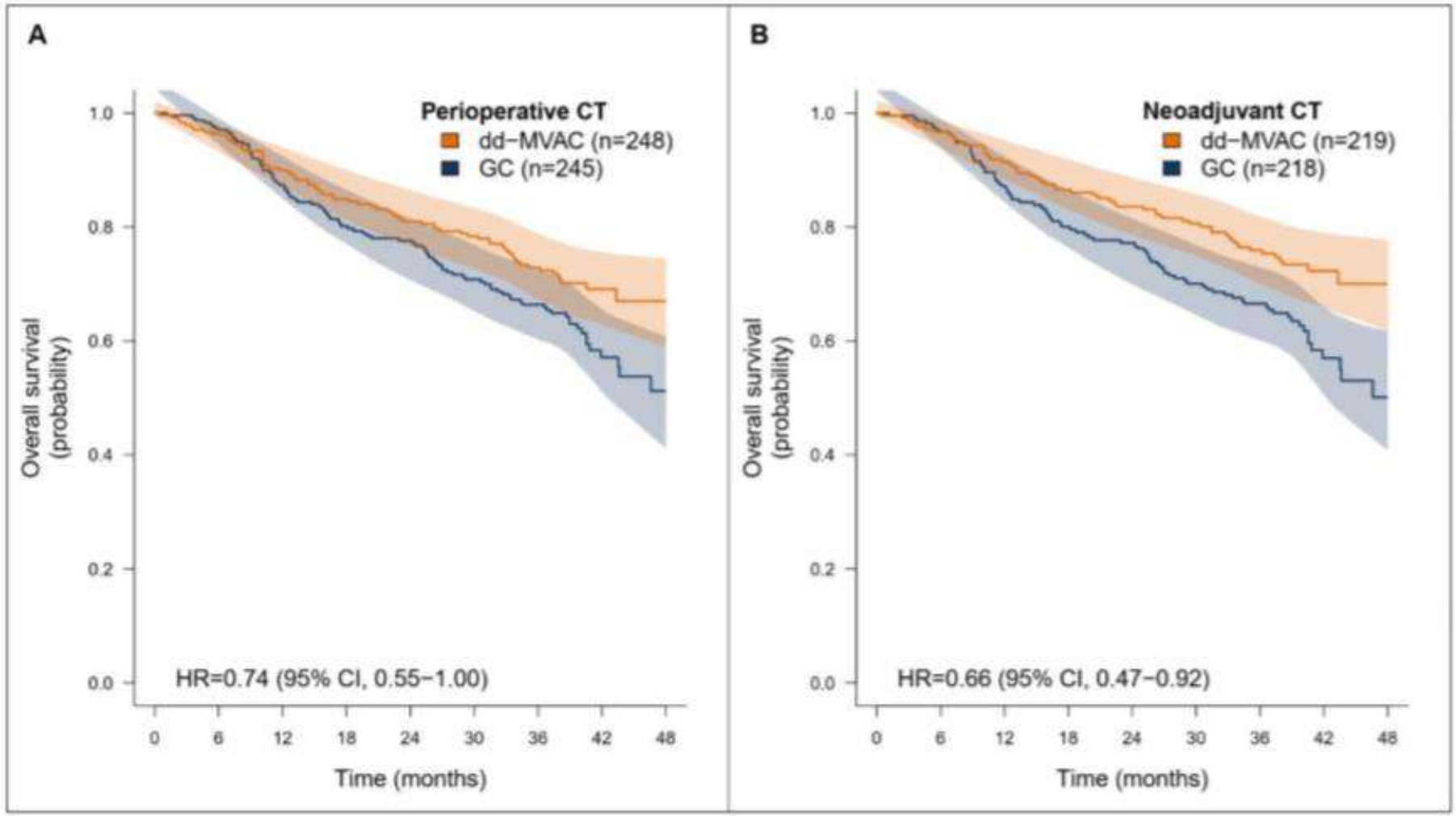
Pathological response (neoadjuvant CT +cystectomy performed only)			
	ypT0 N0	71 (36%)	84 (42%)
	ypTis,Ta or T1 and ypN0	27 (14%)	42 (21%)
	ypT2 N0	26 (13%)	28 (14%)
	≥ ypT3 or ypN+	73 (37%)	43 (22%)
	Uncertain staging	1	2

PROGRESSION FREE SURVIVAL (PFS)

SSP à 3 ans en situation néo-adjuvante : 66% vs 56%



OVERALL SURVIVAL (OS)



TAKE HOME MESSAGES

The VESPER trial is a milestone in the history of chemotherapy for MIBC

Dose dense (dd) MVAC regimen should now become the gold standard for neoadjuvant CT because of a higher local control and a significant improvement in 3-year progression free survival (PFS)

Final data on overall survival (OS) are expected to confirm these results and also design the future trials with optimal chemotherapy combined with immunotherapy

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The University Of Sheffield.

STAR
Planned treatment breaks in locally advanced/metastatic renal cancer

UNIVERSITY OF LEEDS

STAR. A Randomised Multi-Stage Phase II/III Trial of Standard First-line therapy (sunitinib or pazopanib) Comparing Temporary Cessation with Allowing Continuation, in the Treatment of Locally Advanced and/or Metastatic Renal Cancer (RCC).

J. Brown, K.-L. Royle, C. Ralph, D. Meads, A. Martin, H. Howard, C. Linsley, J. Swain, T. Powles, R.Jones, T. Eisen, A. Maraveyas, R. Griffiths, O. Din, V. Goh, T. Wah, P. Selby, J. Hewison, J. Brown, F. Collinson, on behalf of the STAR investigators.

ctru University of Leeds

FUNDED BY NIHR | National Institute for Health Research

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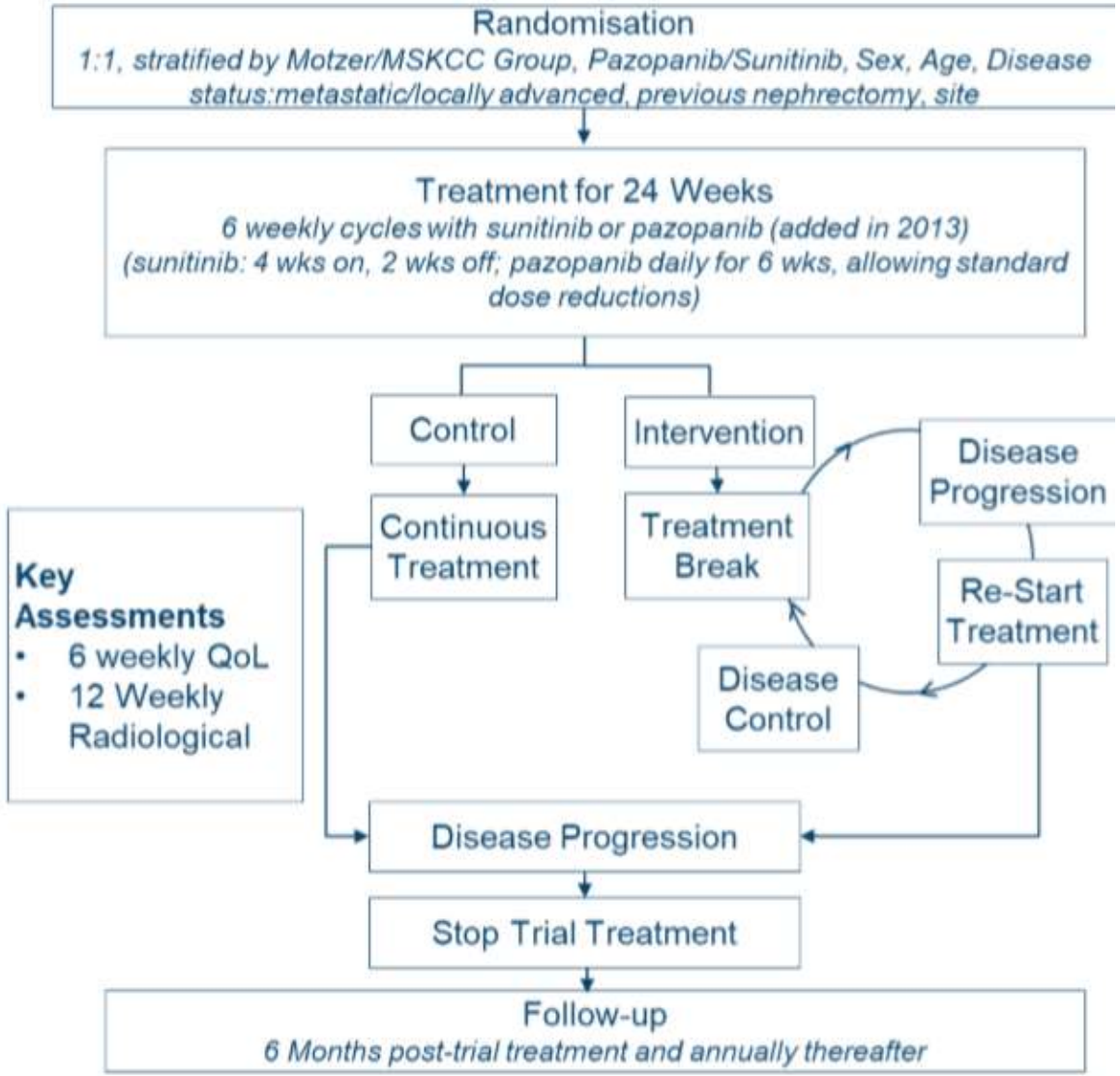
Trial Schema

Co-Primary Outcomes

- Overall Survival
- Quality adjusted life years (QALYs) - calculated using the EQ-5D utility index
- Prespecified that both ITT and PP analyses show non-inferiority

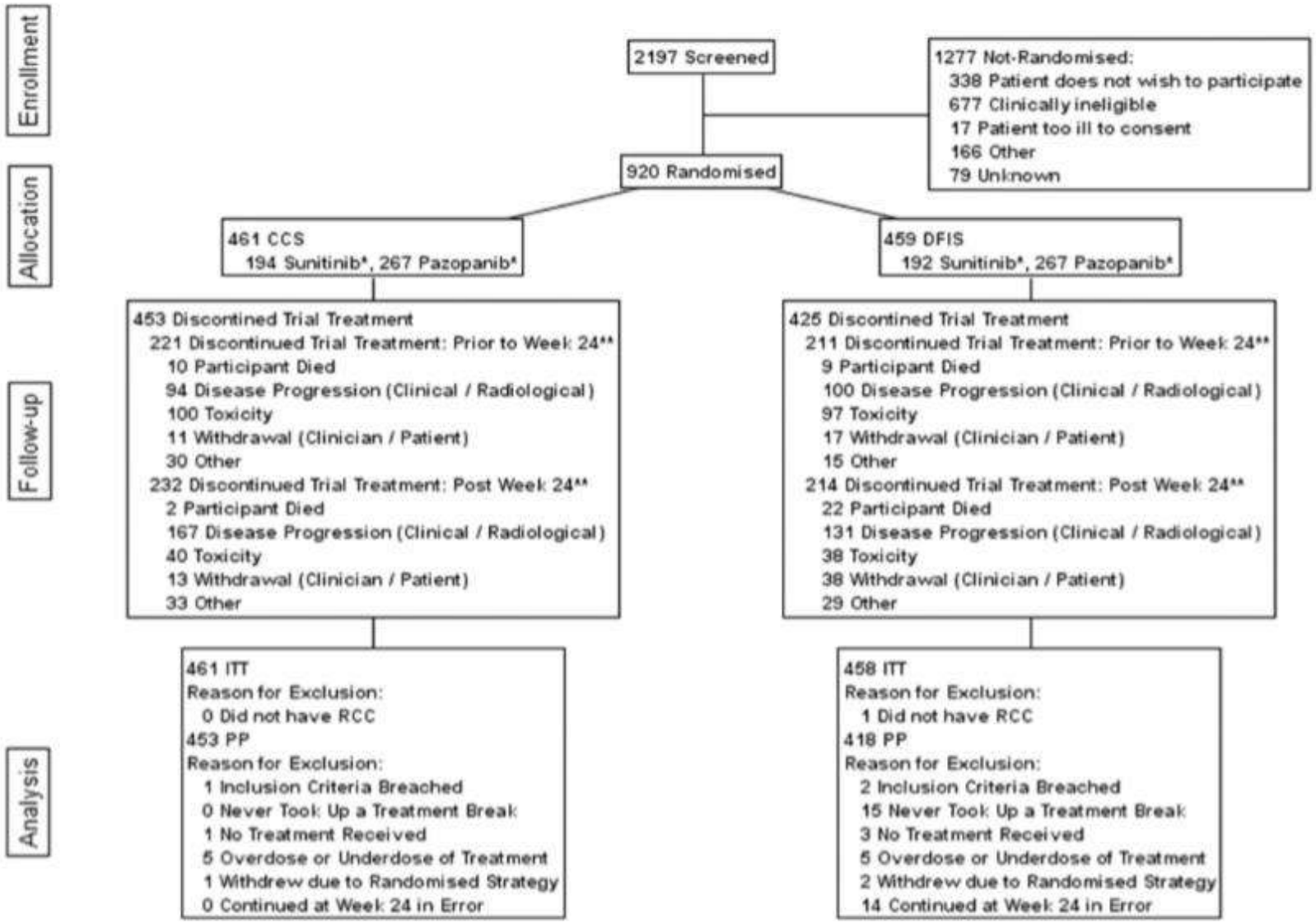
Secondary Outcomes

- Quality of Life (FKSI, FACT-G, EQ5D™, EQ-VAS™) and *cost effectiveness* (health economic analysis)
- *Time to Strategy Failure, Summative Progression-free Interval, Toxicity*, Progression-Free Survival, Time to treatment failure



Participant Flow

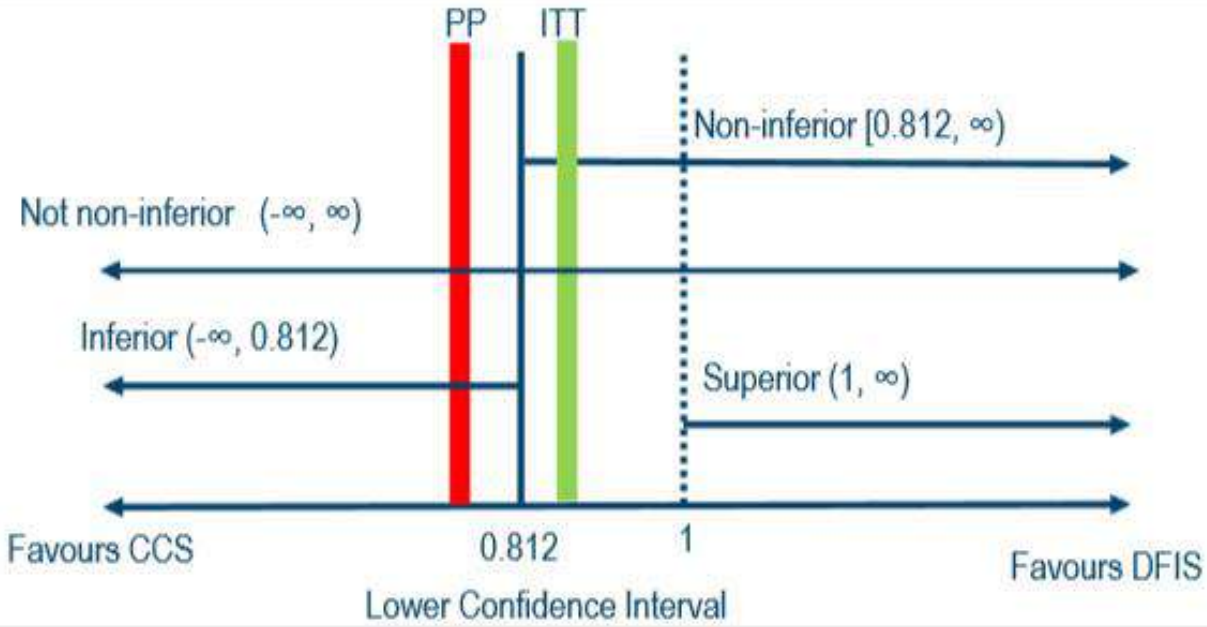
- 60 UK centres were involved in the trial.
- 920 participants were recruited between Jan 12 and Sept 17.
- Median (IQR) follow-up for the ITT Population was 58 (46, 73) months.
- In total 13,147 out of 16,726 (78.6%) of QoL booklets were returned.



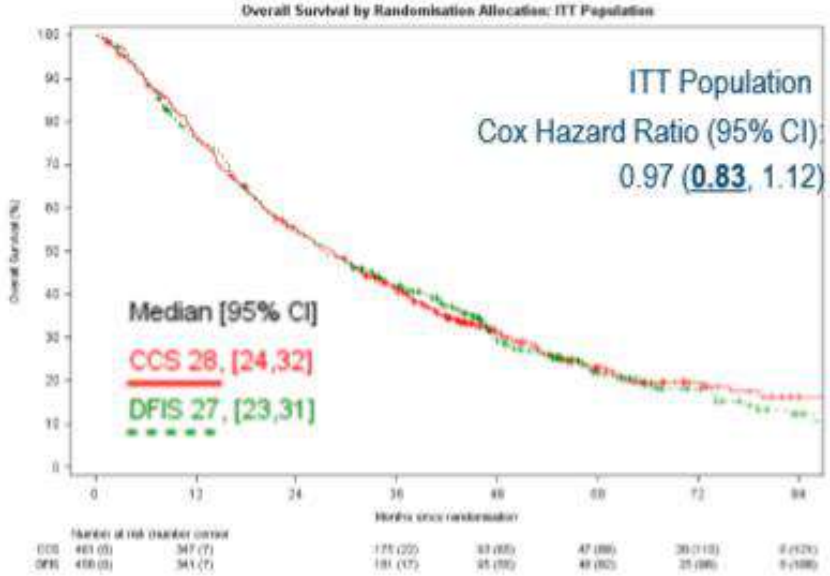
* = TKI patient received, ** = Non-mutually exclusive reasons

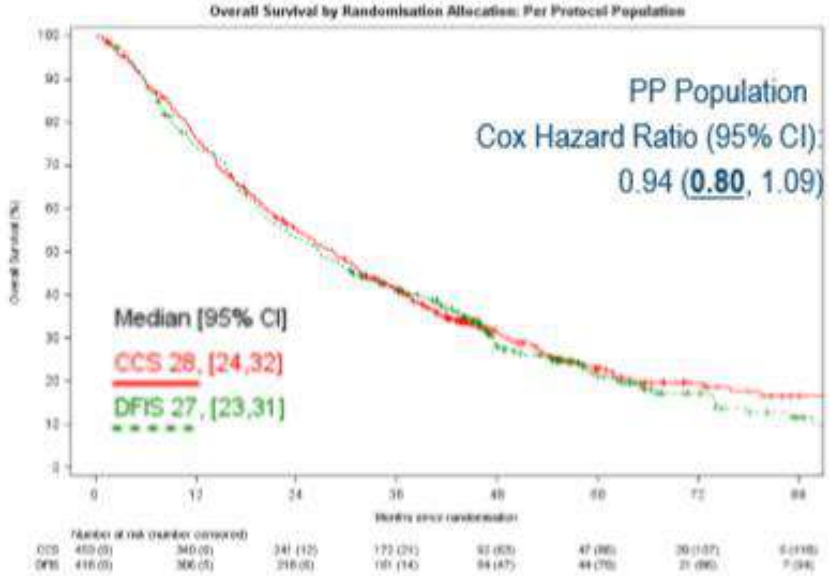
Overall Survival

For non-inferiority to be concluded the lower bound of the 95% confidence interval for the treatment effect from an adjusted Cox proportional hazards model must be above 0.812 in both ITT and PP analysis. This equates to a ≤7.5% difference in OS.



As only the lower bound falls to the right of the boundary only for the ITT analysis, we cannot conclude overall non-inferiority in terms of OS as predefined. However, this analysis had reduced power due to the trial stopping before the required number of events was reached for 80% power.



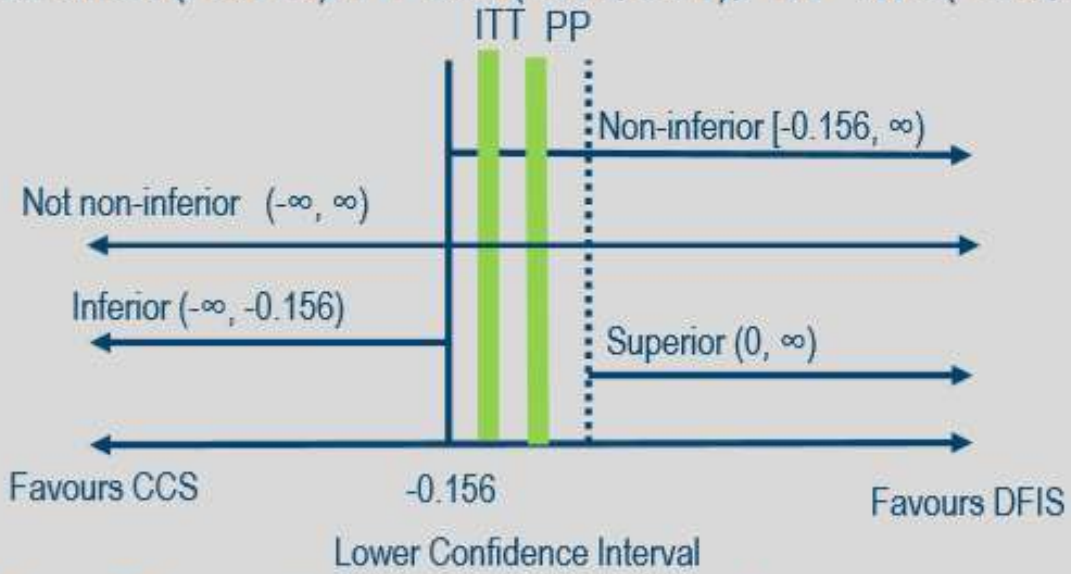


QALYs

Co-Primary Analysis

For non-inferiority to be concluded the lower bound of the 95% confidence interval for the treatment effect from the marginal model derived from an adjusted finite mixture model with two components must be above -0.156 in both ITT and PP analysis. This equates to a ≤10% difference in QALYs.

Treatment effect (95% CI): PP 0.04 (-0.14, 0.21), ITT -0.05 (-0.15, 0.05)



Both ITT and PP populations demonstrate non-inferiority

Cost-Effectiveness Analysis

- At 2 years, DFIS was associated with cost savings (£6,954 and £3,303 per patient in complete case and imputation analyses, respectively)
- Savings driven by reduced treatment costs
- DFIS likely to meet cost-effectiveness at 2 years regardless of analysis

Key Secondary Endpoints – Safety

- On consideration of serious adverse events, deemed to be related to TKI treatment, a smaller proportion of participants in the DFIS arm experienced an event and participants in the DFIS arm accounted for fewer of the overall events compared to the CCS arm.

	CCS N (%)	DFIS N (%)	Total N (%)
Did the participant experience a SAR from week 24 onwards?			
Yes	31 (11.7%)	21 (9.4%)	52 (10.7%)
No	234 (88.3%)	202 (90.6%)	436 (89.3%)
Total	265 (100%)	223 (100%)	488 (100%)

	CCS N (%)	DFIS N (%)	Total
Number of SARs reported from week 24 onwards	36 (61.0%)	23 (39.0%)	59

Conclusions

Treatment breaks were acceptable to patients and clinicians, were not detrimental to overall survival or Quality of Life and had significant cost savings.

- 42.7% of patients in the DFIS arm who continued post week-24 had multiple treatment breaks. Further exploratory analysis will consider the characteristics of patients who benefited from a treatment break.
- Although immunotherapy is now first line therapy for many patients, TKIs remain the most appropriate treatment for some patients in the first-line setting, and many others second-line.

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Nivolumab in combination with alternatively scheduled ipilimumab in first-line treatment of patients with advanced renal cell carcinoma: a randomized phase II trial (PRISM)

Naveen Vasudev[1], Gemma Ainsworth[2], Sarah Brown[2], Lisa Pickering[3], Tom Waddell[4], Kate Fife[5], Richard Griffiths[6], Anand Sharma[7], Eszter Katona[2], Helen Howard[2], Galina Velikova[8], Anthony Maraveyas[9], Janet Brown[10], Balaji Venugopal[11], Poulam Patel[12], Ankit Jain[13], Stefan Symeonides[14], Paul Nathan[7], Fiona Collinson[2], Thomas Powles[15]

[1]St James's University Hospital, Leeds, UK; [2]Clinical Trials Research Unit, University of Leeds, UK; [3]Royal Marsden Hospital, London, UK; [4]Christie Hospital, Manchester, UK; [5]Addenbrooke's Hospital, Cambridge, UK; [6]Clatterbridge Cancer Centre, Liverpool, UK; [7]Mount Vernon Cancer Centre, Middlesex, UK; [8]University of Leeds, Leeds; [9]Castle Hill Hospital, Hull, UK; [10]Weston Park Hospital, Sheffield, UK; [11]Beatson Cancer Centre, Glasgow, UK; [12]Nottingham City Hospital, Nottingham, UK; [13]New Cross Hospital, Wolverhampton, UK; [14]Great Western Hospital, Edinburgh; [15]Barts Cancer Institute, London, UK

Introduction

- Ipilimumab (IPI; CTLA4 targeted antibody) plus Nivolumab (NIVO; PD-1 targeted antibody) is an approved first-line treatment for patients with intermediate/poor-risk aRCC

- IPI+NIVO demonstrated improved ORR and significant OS benefit versus sunitinib amongst patients with intermediate/poor-risk aRCC in the Phase III CheckMate 214 trial[1,2]

  - ❖ 47% of patients experienced a grade 3-4 trAE
  - ❖ 22% patients discontinued treatment due to trAEs

- Dose and frequency of IPI appear related to toxicity[3-6]

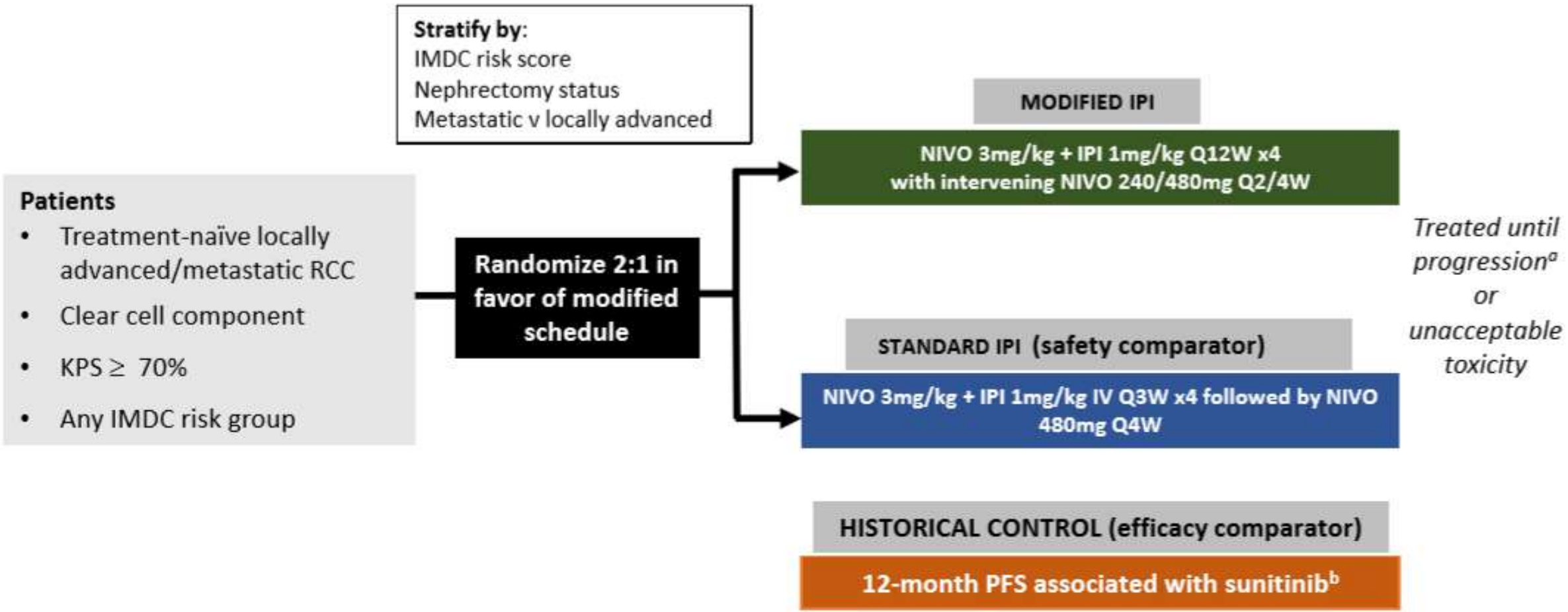
  In NSCLC, Q6W or Q12W IPI (+NIVO) was better tolerated than Q3W dosing[6]

- Optimal scheduling of IPI, in combination with NIVO, is not defined in aRCC

aRCC – advanced renal cell carcinoma; ORR – objective response rate; OS – overall survival; trAE – treatment-related adverse event

1. Motzer RJ, et al. *NEJM* 2018;3781277-1290; 2. Motzer RJ, et al. *J Immunother Cancer* 2020:8:e000891; 3. Ascierto PA et al. *Lancet Oncol* 2017;18:611-622; 4. Hammers H, et al. *J Clin Oncol* 2017;35:3851-3858; 5. Lebbe C, et al. *J Clin Oncol* 2019;37:867-875; 6. Hellmann MD et al. *Lancet Oncol* 2017;18:31-41

PRISM: Study design



[a] patients were allowed to continue treatment beyond RECIST defined progression if clinically stable and tolerating therapy

[b] Motzer RJ et al. *N Eng J Med* 2013;14:141-8

Q2, 3, 4, 12W – every n weeks; KPS – Karnofsky Performance Status; IMDC – International Metastatic RCC Database Consortium

Study endpoints

- **Primary endpoint**: Proportion of patients experiencing at least one CTCAE (v 5.0) grade 3 or 4 treatment-related AE within 12 months of initiating therapy[a]
- **Key secondary endpoint:** Progression-free survival in the modified IPI arm at 12 months, tested against historical progression-free survival associated with sunitinib[b]
- **Additional secondary endpoints:** Treatment tolerability, median PFS, ORR using RECIST v1.1, OS, duration of response, HRQoL

The study was designed to allow formal comparison between treatment arms for the primary endpoint only

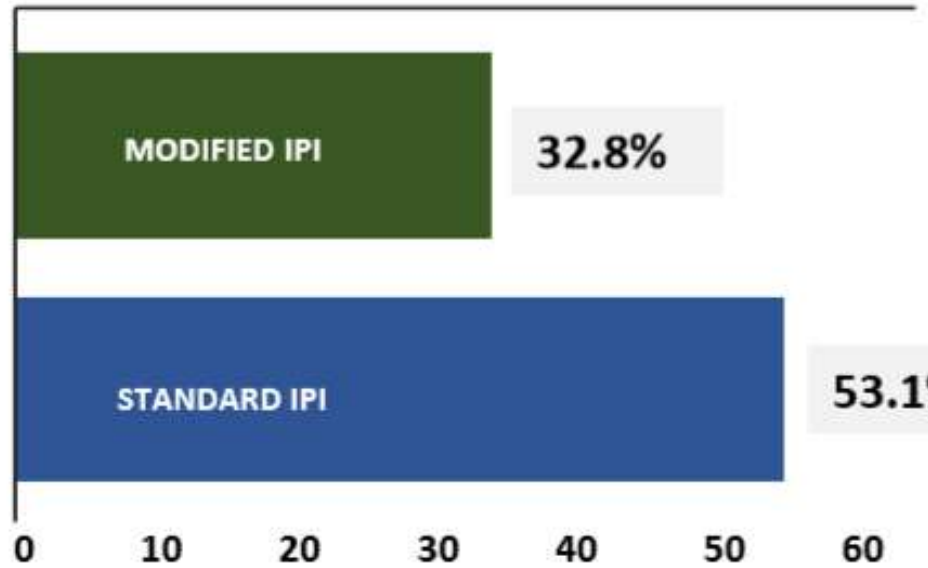
[a] All endpoints were considered amongst patients who received at least one dose of trial therapy (modified intention to treat (mITT) population)
[b] Motzer et al. *N Eng J Med* 2013;14:141-8
HRQoL – Health Related Quality of Life; AE – adverse event; OS – overall survival

Baseline characteristics

	Modified IPI n=128	Standard IPI n=64
Median age (range) (years)	61 (39-81)	65 (28-81)
Male (%)	101 (79)	48 (75)
IMDC prognostic score n (%)		
Favorable (0)	38 (30)	21 (33)
Intermediate (1-2)	67 (52)	32 (50)
Poor (3-6)	23 (18)	11 (17)
Previous nephrectomy n (%)	78 (61)	42 (66)
Most common site of metastasis n (%)		
Lung	89 (72)	51 (81)
Lymph node	39 (31)	21 (33)
Liver	18 (15)	8 (13)
Bone	23 (19)	12 (19)
Median follow-up (IQR) (months)	19.7 (15.9 - 23.6)	

Three patients were randomized but received no study treatment and were excluded from subsequent analyses

Primary endpoint: Proportion of patients with G3/4 trAE within 12m

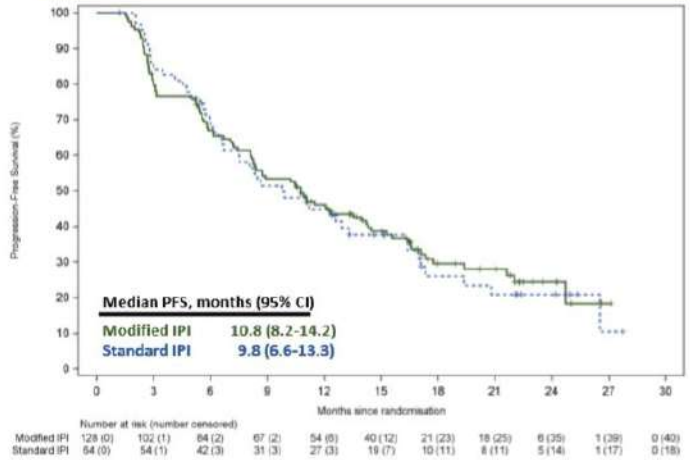


Δ -20.3% (90%CI -32.6, -8.0)

OR 0.43 (90% CI 0.25-0.72); p = 0.0075

trAE – treatment-related adverse event

Progression-free survival: modified ITT



12m PFS rate (90% CI)	
Modified IPI	46.1% (38.6%, 53.2%)
Historical rate	39.7%*

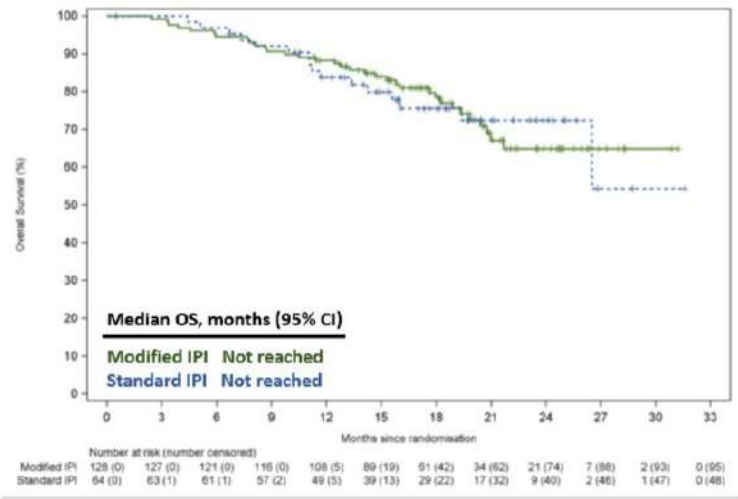
*based on 9m median PFS with sunitinib in COMPARZ trial[3]

The study was not designed to allow formal comparison of PFS between treatment arms, only against historical control.

Modified intention to treat (mITT) population - randomized patients who received at least one dose of trial therapy

[3] Motzer et al. *N Eng J Med* 2013;14:141-8

Overall survival: modified ITT



12m OS rate (95% CI)	
Modified IPI	88.3% (81.2, 92.8)
Standard IPI	83.7% (71.8, 90.1)

Objective response rates

Outcome	modified ITT		Intermediate/Poor risk	
	Modified IPI n=128	Standard IPI n=64	Modified IPI n=90	Standard IPI n=44
ORR (%) (95% CI)	**45.3 (36.7-53.9)**	**35.9 (24.2-47.7)**	**46.7 (36.4-57.0)**	**40.9 (26.4-55.4)**
Best overall response n(%)				
Complete Response	8 (6.3)	1 (1.6)	6 (6.7)	1 (2.3)
Partial Response	50 (39.1)	22 (34.4)	36 (40.0)	17 (38.6)
Stable Disease	40 (31.3)	25 (39.1)	23 (25.6)	17 (38.6)
Progressive Disease	29 (22.7)	15 (23.4)	24 (26.7)	9 (20.5)
Missing	1 (0.8)	1 (1.6)	1 (1.1)	0 (0.0)
Median duration of response (95% CI)	16 (13-NR)	17 (13-NR)	-	-

Investigator-assessed ORR and BOR by RECIST v1.1

Summary

In this cohort of treatment-naive aRCC patients:

- Giving IPI 12-weekly, instead of 3-weekly, led to a significant reduction in the proportion of patients experiencing a grade 3 or 4 trAE (33% v 53%)
- The lower limit of the confidence interval for 12m PFS observed with modified IPI failed to exclude the rate associated with historical control data (sunitinib)
- However, median PFS, ORR, DoR and 12m landmark OS were comparable between treatment arms
- This positive PII trial supports further exploration of different IPI/NIVO regimes

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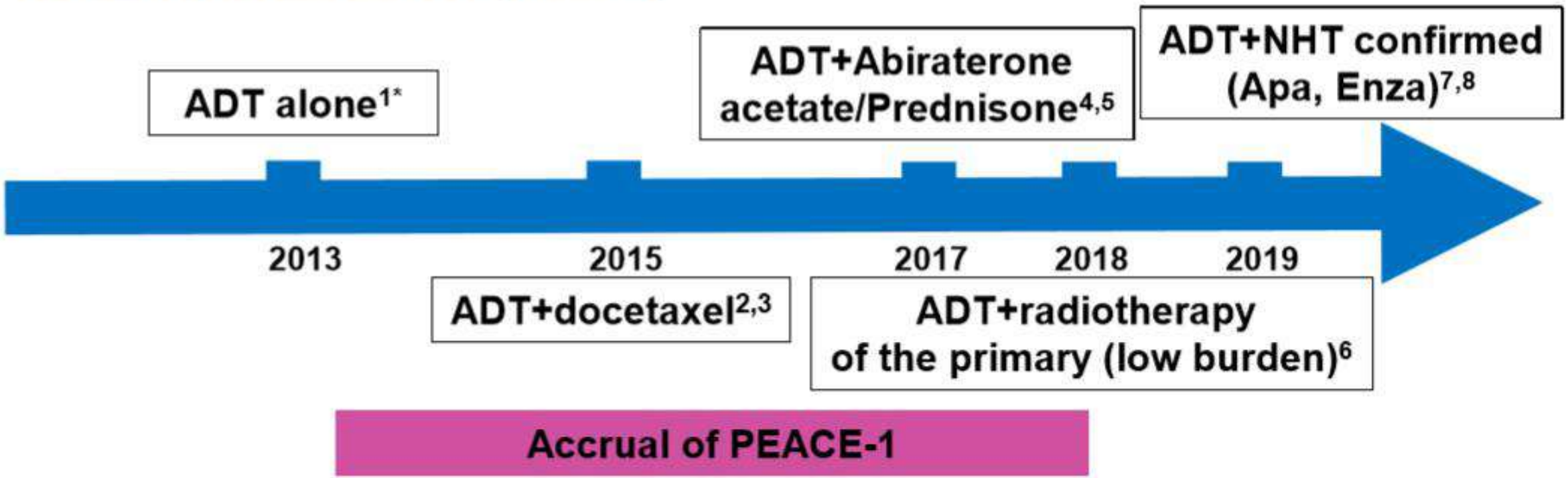
EORTC The future of cancer therapy

A phase 3 trial with a 2x2 factorial design in men with *de novo* metastatic castration-sensitive prostate cancer (mCSPC): Overall survival with abiraterone acetate plus prednisone in PEACE-1

Karim Fizazi, Joan Carles, Stéphanie Foulon, Guilhem Roubaud, Ray McDermott, Aude Fléchon, Bertrand Tombal, Stéphane Supiot, Dominik Berthold, Philippe Ronchin, Gabriel Kacsó, Gwenaëlle Gravis, Fabio Calabro, Jean-François Berdah, Ali Hasbini, Marlon Silva, Antoine Thiery-Vuillemin, Igor Latorzeff, Isabelle Rieger, Alberto Bossi

Background

Very rapidly evolving Standard of Care (SOC) for men with metastatic castration-sensitive prostate cancer (mCSPC)



*ADT: Androgen Deprivation Therapy

[1]Gravis G, Lancet Oncol 2013, [2]Sweeney C, NEJM 2015, [3]James N, Lancet 2016, [4]Fizazi K, NEJM 2017, [5]James N, NEJM 2017, [6]Parker C, Lancet 2018,[7]Davis I, NEJM 2019, [8]Chi K, NEJM 2019

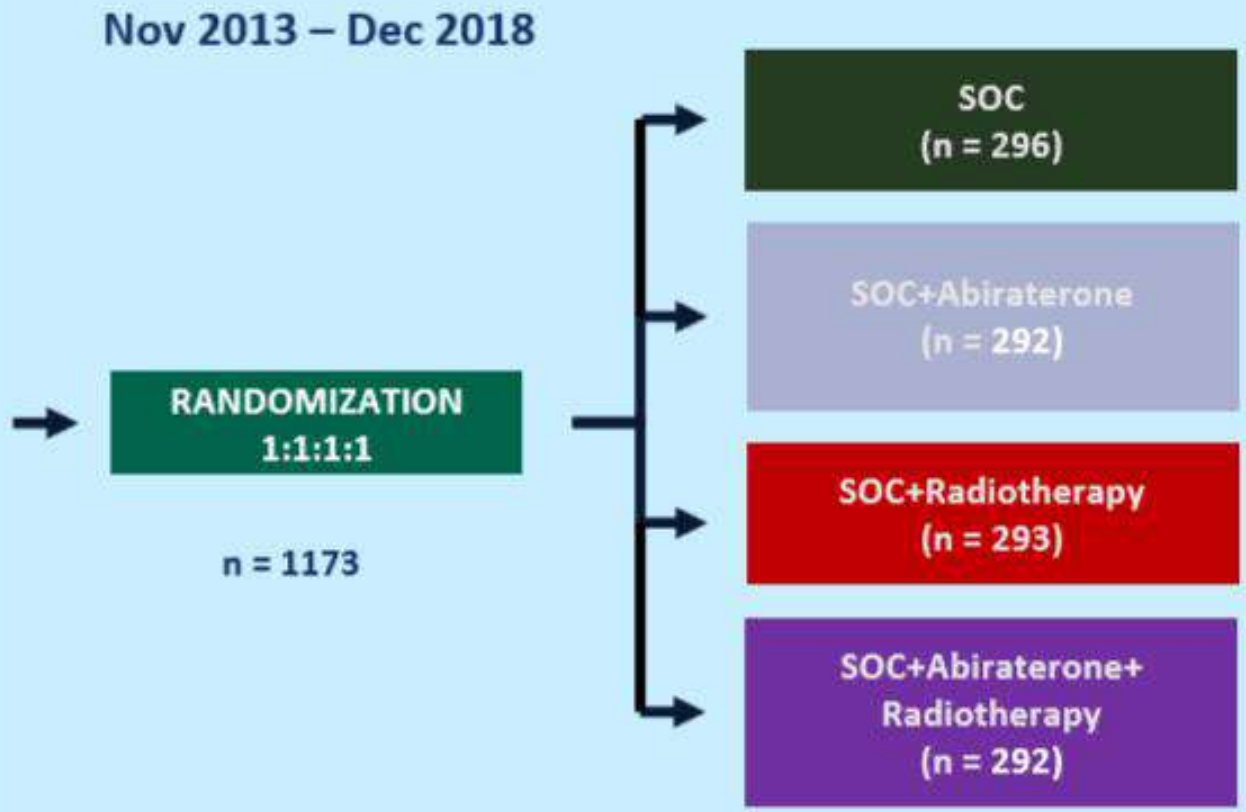
Design of PEACE-1 (2x2)

Key Eligibility Criteria
De novo mCSPC
Distant metastatic disease by ≥ 1 lesion on bone scan and/or CT scan
ECOG PS 0 -2

On-Study Requirement
Continuous ADT

Permitted
ADT ≤ 3 months

Stratification
ECOG PS (0 vs 1-2)
Metastatic sites (LN vs bone vs visceral)
Type of castration (orchidectomy vs LHRH agonist vs LHRH antagonist)
Docetaxel (yes vs no)



ECOG PS, Eastern Cooperative Oncology Group performance status

Treatments

STANDARD treatments

- Androgen Deprivation Therapy (ADT) continuously (LHRH agonist/antagonist or bilateral orchiectomy)
- +/- Docetaxel 75 mg/m^2/3w x 6 (G-CSF recommended)

EXPERIMENTAL treatments

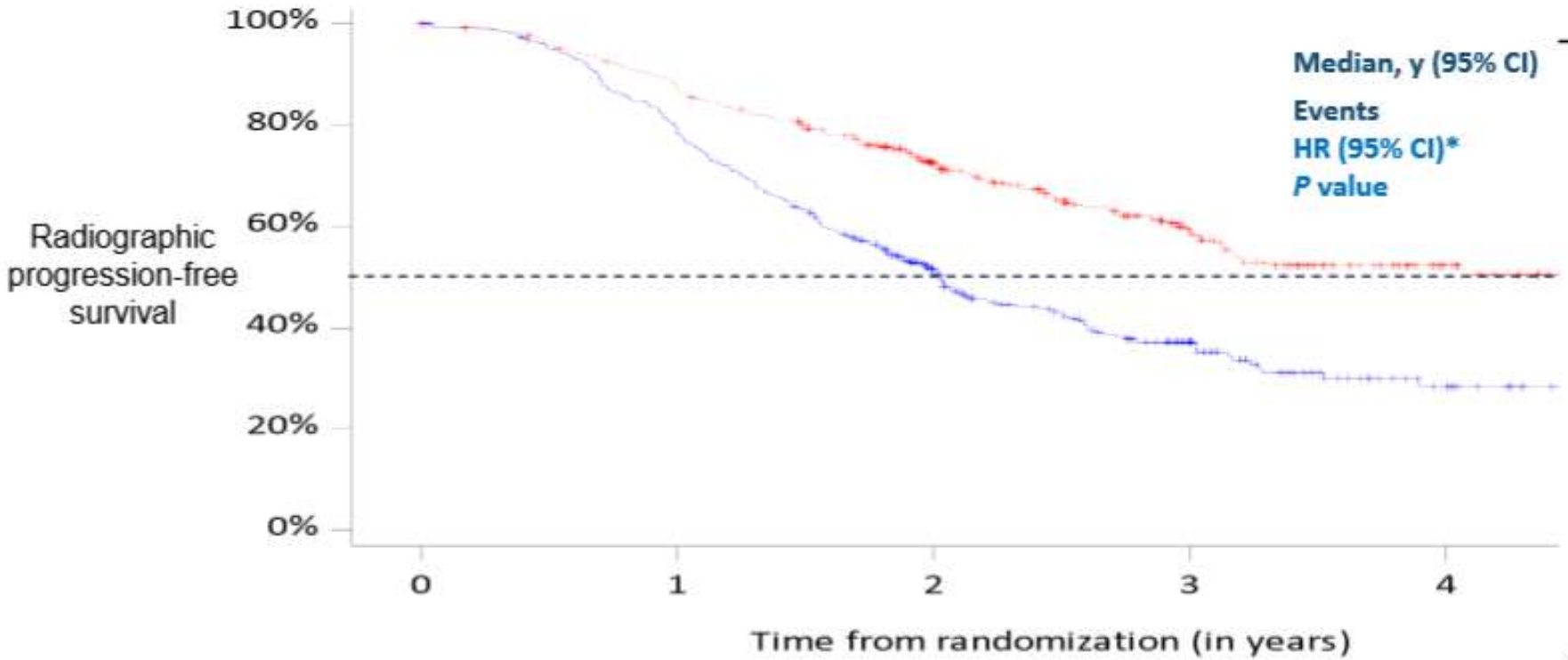
- Abiraterone 1000 mg/d + Prednisone 5 mgx2/d until disease progression or intolerance (concomitant to docetaxel)
- Radiotherapy (RXT) of the prostate 74 Gy in 37 fractions (after docetaxel is completed)

Patient characteristics (ADT+docetaxel population)

		SOC (+/- RXT) + Abiraterone (n = 355)	SOC (+/- RXT) (n = 355)
Median age, year (IQR)		66 (60–70)	66 (59–70)
ECOG PS score, n (%)	0 1-2	250 (70) 105 (30)	246 (69) 109 (31)
Gleason score at initial diagnosis, n (%)	≤ 7 ≥ 8	79 (23) 270 (77)	71 (21) 276 (79)
Median time from diagnosis, month (IQR)		2.2 (1.6-3.0)	2.2 (1.4-2.9)
Metastatic sites, n (%)	Lymph nodes only Bone without visceral Visceral	27 (8) 287 (81) 41 (12)	29 (8) 279 (79) 47 (13)
Disease burden, n (%)	Low High	131 (37) 224 (63)	123 (35) 232 (65)
Median baseline PSA, ng/mL (IQR)		13.7 (2.4-58.9)	12.0 (3.0-59.9)
Docetaxel, n (%)	Yes No	355 (100) 0 (0)	355 (100) 0 (0)

Co-primary endpoint: rPFS with Abiraterone in the ADT+docetaxel (+/- RXT) population

	SOC+Abi (n = 355)	SOC (n = 355)
Median, y (95% CI)	4.5 (3.1-NE)	2.0 (1.8-2.3)
Events	139	211
HR (95% CI)*	0.50 (0.40-0.62)	
P value	< 0.0001	

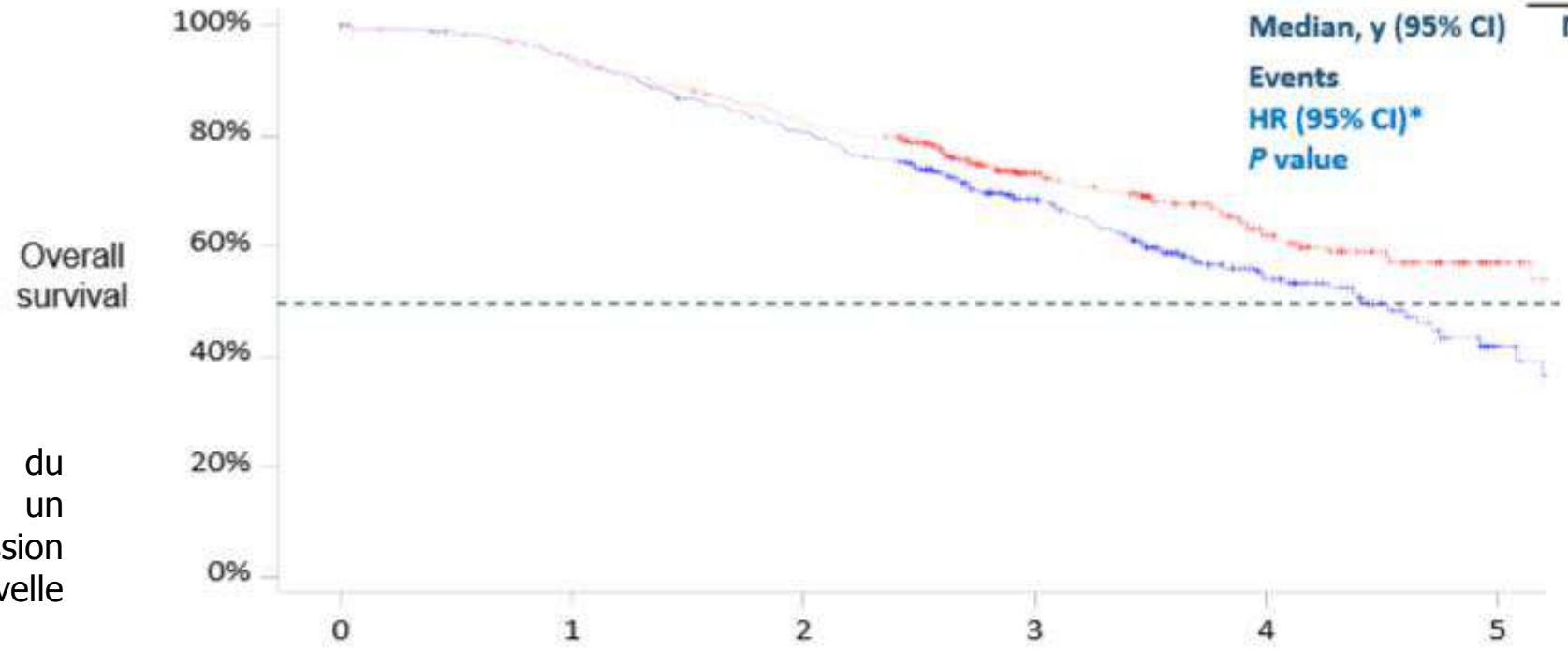


No	355	274	137	61	16
Yes	355	303	200	105	35

*Adjusted on stratification parameters (RXT, PS, type of castration, metastatic burden)

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

	SOC+Abi (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)*	0.75 (0.59-0.95)	
P value	0.017	



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

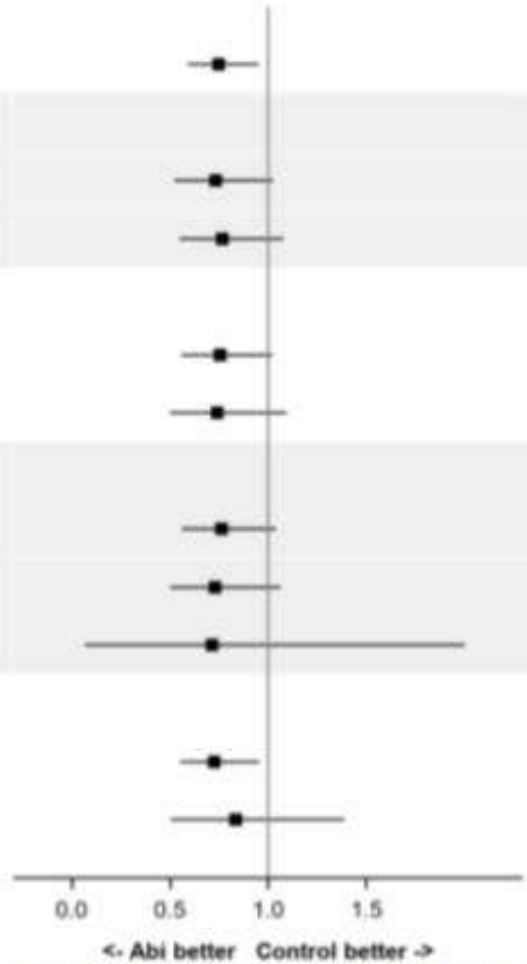
*Adjusted on stratification parameters (RXT, type of castration, PS, metastatic burden)

84% des patients du bras SOC ont reçu un traitement à progression dont 81% une nouvelle hormonothérapie

Suivi médian population ADT + docetaxel (n=710) : 3,8 ans

Subgroup analysis of OS: Abiraterone effect ADT+docetaxel (+/-RXT) population

Subgroup	N Events/N Pts Abi	N Events/N Pts Control	Hazard Ratio	Hazard Ratio	pvalue
Overall	121/355	151/355		0.75 [0.59-0.95]	
Radiotherapy					0.85
No				0.73 [0.52-1.03]	
Yes				0.76 [0.54-1.07]	
Performance Status					0.93
0	76/250	93/246		0.75 [0.56-1.02]	
1-2	45/105	58/109		0.74 [0.50-1.09]	
Type of castration					0.98
LHRH agonist	72/219	88/222		0.76 [0.56-1.04]	
LHRH antagonist	47/134	62/132		0.73 [0.50-1.06]	
Surgical castration	2/ 2	1/ 1		0.71 [0.06-7.91]	
Metastatic burden					0.64
High	92/224	120/232		0.72 [0.55-0.95]	
Low	29/131	31/123		0.83 [0.50-1.38]	



PEACE-1 OS results in the context of recent data

Median Overall Survival
(*de novo* High-Volume mCSPC)

ADT alone

33 m CHAARTED (Kyriakopoulos CE, JCO 2018)
34 m GETUG-15 (Gravis G Eur Urol 2018)
35 m STAMPEDE (Clarke NW, Ann Oncol 2019)

ADT+docetaxel

40 m STAMPEDE doce (Clarke Ann Oncol 2019)
42 m PEACE-1
44 m GETUG-15 (Gravis G Eur Urol 2018)
48 m CHAARTED (Kyriakopoulos CE, JCO 2018)

ADT+abiraterone

50 m LATITUDE (Fizazi K Lancet Oncol 2019)
56 m STAMPEDE Abi (James N ESMO 2020)

ADT+docetaxel+abiraterone

61 m PEACE-1

2021 ESMO congress

Karim Fizazi

Conclusion: Abiraterone in PEACE-1

- Adding abiraterone to ADT+docetaxel significantly improves rPFS by 2.5 years in median in men with *de novo* metastatic prostate cancer.
- Overall Survival is also improved with a **25% reduction in the risk of death**, even when 84% of mCRPC men in the control group receive at least one life-prolonging treatment (next generation androgen signaling inhibitors in 81%).
- This benefit translates in a median **lifetime gain of more than 1.5 year** for men with high-volume metastases (5.1 vs 3.5y). OS data for low volume men may be immature.
- Toxicity was as expected, with no apparent synergistic side effects from this combination.

PLAN

- CARCINOME UROTHELIAL
  - Chimiothérapie péri-opératoire : Etude VESPER
- CARCINOME A CELLULES RENALES METASTATIQUE
  - Pauses thérapeutiques avec les ITK en 1ère ligne : Etude STAR
  - Adaptation posologique de l'IPILIMUMAB en 1ère ligne : Etude PRISM
- **CANCER DE PROSTATE**
  - ABIRATERONE en plus du DOCETAXEL en hormono-sensible métastatique : Etude PEACE-1
  - **ABIRATERONE en hormono-sensible M0 à haut risque : Etude STAMPEDE**

Abiraterone acetate plus prednisolone with or without enzalutamide added to androgen deprivation therapy compared to ADT alone for men with high-risk nonmetastatic prostate cancer: primary combined analysis from two comparisons in the STAMPEDE platform protocol

Gerhardt Attard, Louise Brown, Noel Clarke, Laura Murphy, William Cross, Rob Jones, Silke Gillessen, J.Martin Russell, Adrian Cook, Jo Bowen, Anna Lydon, Ian Pedley, Omi Parikh, Simon Chowdhury, Zafar Malik, David Matheson, Chris Parker, Matthew Sydes, Mahesh Parmar, Nicholas James **on behalf of the STAMPEDE investigators***

Conducted by Medical Research Council Trials Unit at University College London, U.K.

ClinicalTrials.gov number, NCT00268476 & Current Controlled Trials number, ISRCTN78818544

*113 U.K. and Swiss sites: list of investigators and collaborators at www.stampedetrial.org

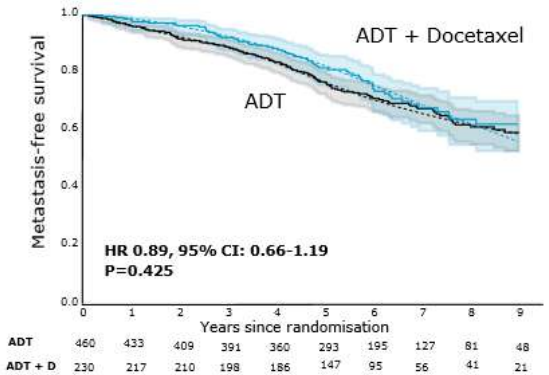
2021 ESMO congress

www.stampedetrial.org

Background: docetaxel

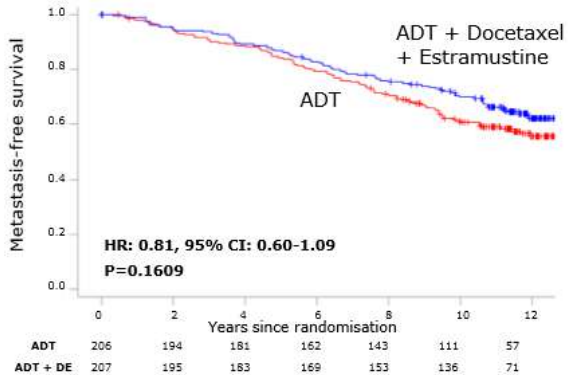
- Docetaxel improves survival in M1 PCa but **no improvement** in MFS/OS in M0

STAMPEDE trial



James et al, ESMO 2019, abstract 855PD

GETUG-12 trial

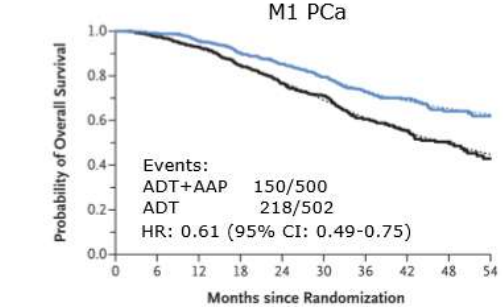


Fizazi et al, ESMO 2018, abstract 791O

Background: 2nd generation hormone therapies

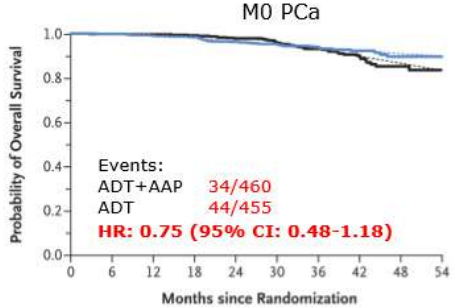
- ADT + AAP/ENZ/apalutamide improve outcomes of M1 PCa
- Uncertain benefit in M0 PCa – STAMPEDE trial

M1 PCa



No. of Patients (no. of deaths)									
Combination therapy	500	(22)	469	(50)	415	(57)	256	(18)	81
ADT alone	502	(35)	460	(80)	371	(73)	215	(23)	60

M0 PCa



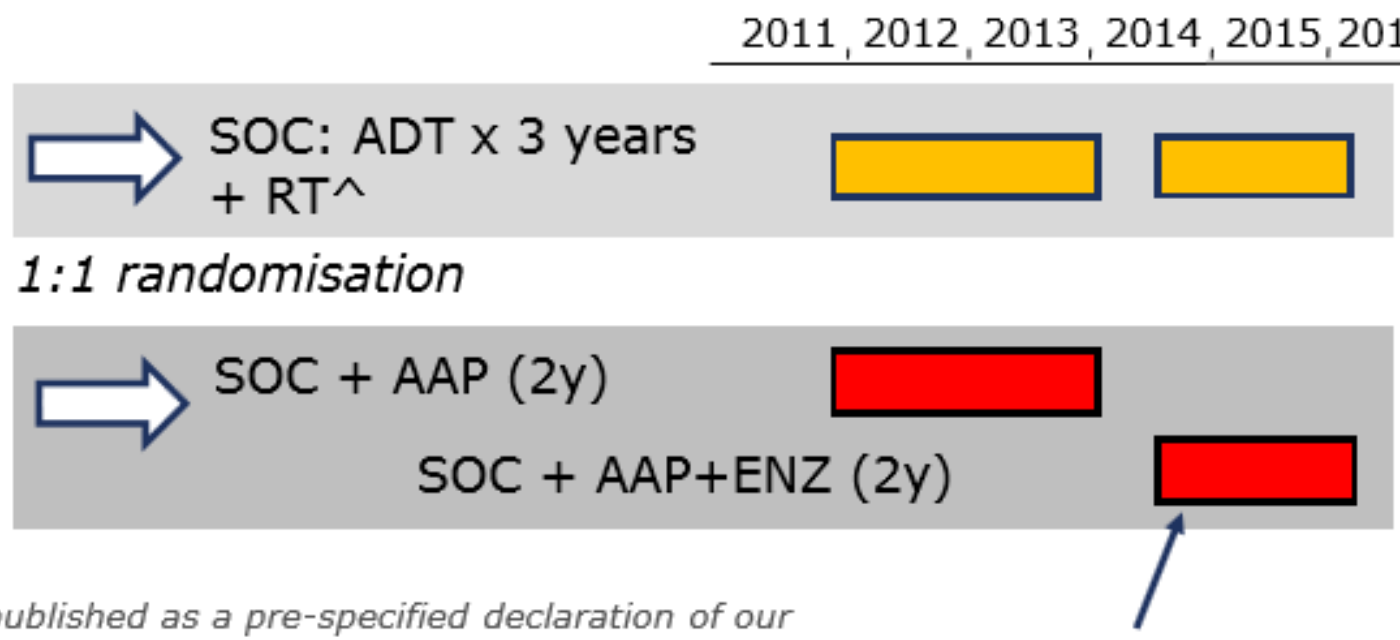
No. of Patients (no. of deaths)									
Combination therapy	460	(4)	448	(13)	425	(10)	285	(7)	80
ADT alone	455	(2)	449	(8)	435	(19)	276	(13)	63

Is there a benefit for AAP in high-risk M0 PCa?

Gerhardt Attard MD FRCP PhD

Study design

- M0 pts in AAP comparison: continued FU with **no further** efficacy inspections
- 2019 - amended the reporting plan* to split M1 & M0, power the 1[ary] end-point on MFS, meta-analyse with new data from AAP+ENZ comparison



- No overlapping controls
- Same protocol & eligibility criteria
- 2 years AAP+/-ENZ
- No evidence of OS benefit with AAP+/-ENZ in mCRPC [1]

*published as a pre-specified declaration of our intentions: Attard G, et al. Eur Urol. Epub 2021 Jul 14

Solid bars: period of accrual

SOC, standard of care
^when indicated

[1]Morris MJ, et al. J Clin Oncol 2019;37:5008

Patient population

M0

No evidence of metastases on bone and CT scan of pelvis, abdo, chest
(pre-defined stratification criterion)

Newly-diagnosed

Any of:

- Node-Positive
- ≥2 of: Stage T3 or T4
  PSA≥40ng/ml
  Gleason 8, 9 or 10

Relapsing after previous RP or RT

Any of:

- Node-positive
- PSA≥4ng/ml, rising & doubling time <6m
- PSA≥20ng/ml

All patients

Written informed consent
Fit for all protocol treatment
Fit for follow-up

Full criteria: www.stampedetrial.org

Patient characteristics

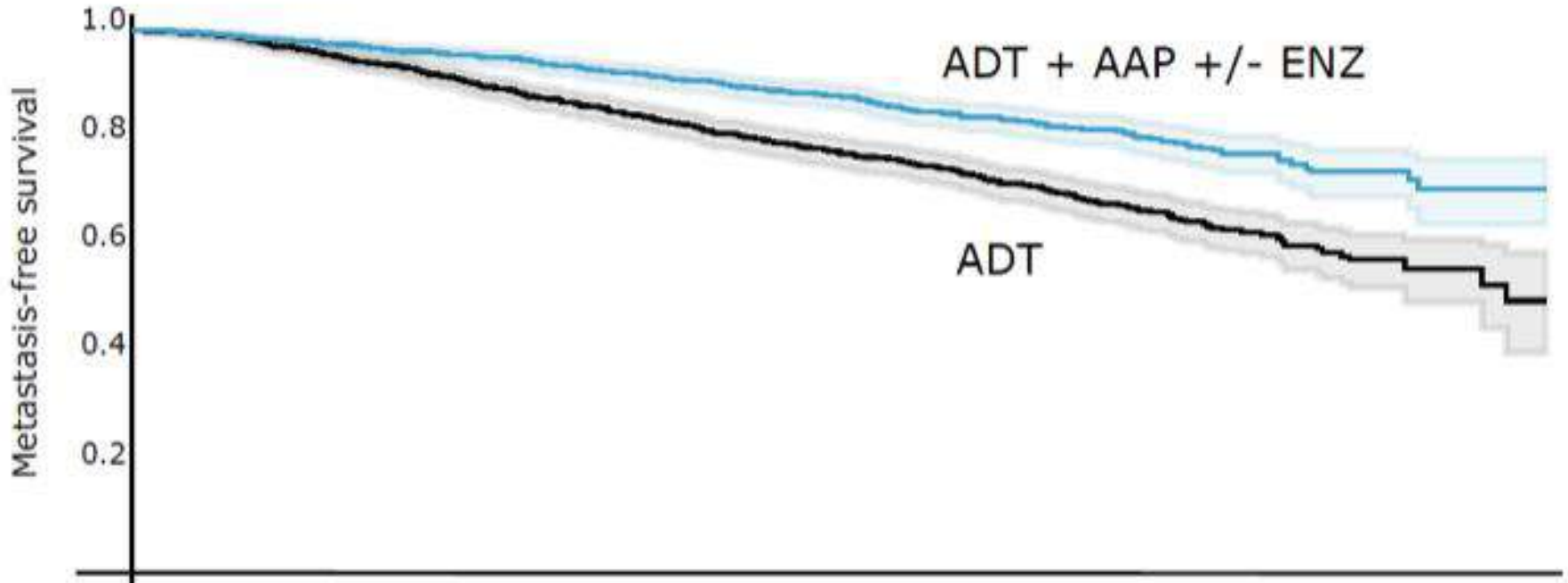
- Randomised groups were well balanced (**N=1974**)

- Median age = 68 years
- Median PSA = 34 ng/ml
- N1 = 39%
- 3% relapsing after prior treatment

- Planned for local radiotherapy:
  - 99% newly-diagnosed, N0
  - 71% newly-diagnosed, N1
  - 7% previously-treated patients

- Median follow-up = 72 months
  (85 months AAP comparison & 60 months AAP+ENZ comparison)

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

Events
180 ADT+ AAP +/- ENZ
306 ADT

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

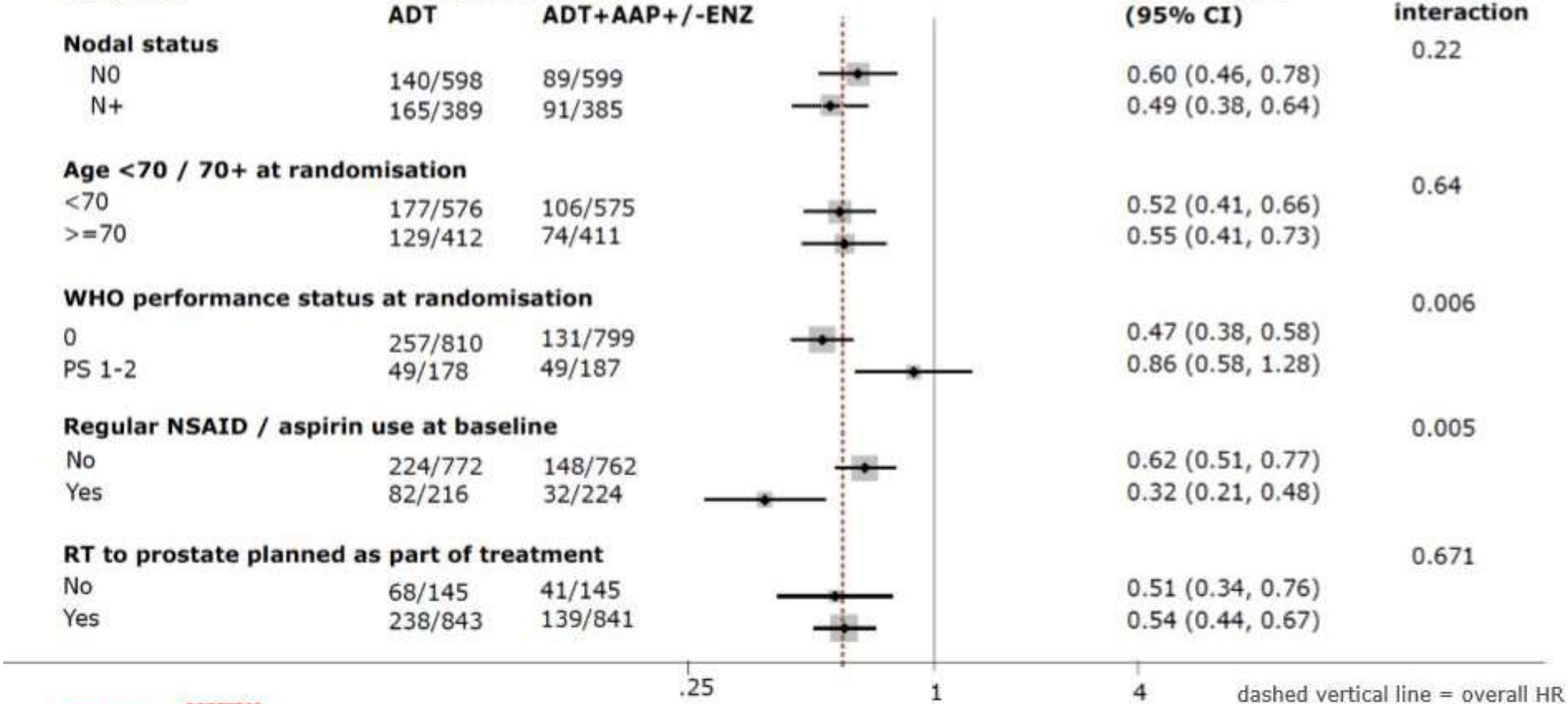
6-year MFS improved from 69% to 82%

Kaplan-Meier estimates with 95% CI in lighter shade

Non-proportional hazards P=0.46

Metastasis-free survival: Subgroup analysis

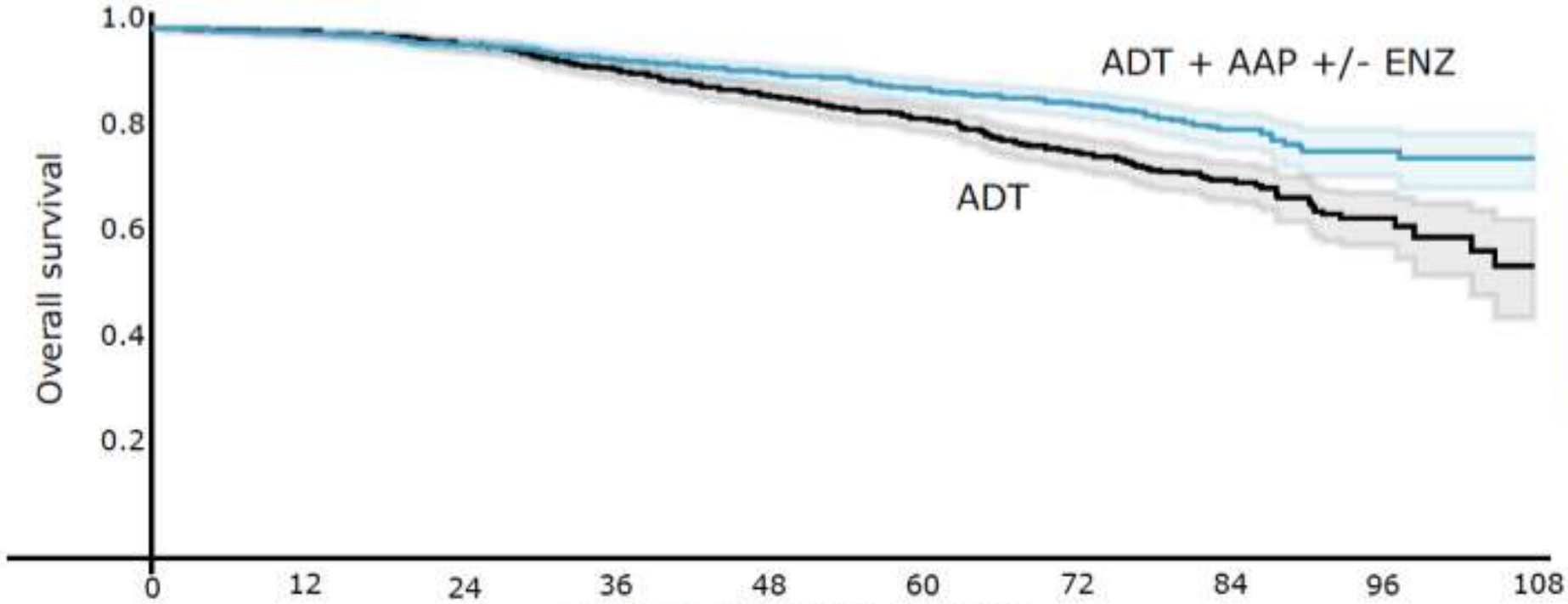
Subgroup	*N events/N patients* ADT	ADT+AAP+/-ENZ	Hazard Ratio (95% CI)	P value for interaction
Nodal status				0.22
N0	140/598	89/599	0.60 (0.46, 0.78)	
N+	165/389	91/385	0.49 (0.38, 0.64)	
Age <70 / 70+ at randomisation				0.64
<70	177/576	106/575	0.52 (0.41, 0.66)	
>=70	129/412	74/411	0.55 (0.41, 0.73)	
WHO performance status at randomisation				0.006
0	257/810	131/799	0.47 (0.38, 0.58)	
PS 1-2	49/178	49/187	0.86 (0.58, 1.28)	
Regular NSAID / aspirin use at baseline				0.005
No	224/772	148/762	0.62 (0.51, 0.77)	
Yes	82/216	32/224	0.32 (0.21, 0.48)	
RT to prostate planned as part of treatment				0.671
No	68/145	41/145	0.51 (0.34, 0.76)	
Yes	238/843	139/841	0.54 (0.44, 0.67)	



dashed vertical line = overall HR
weighting is by sample size

Overall survival

Events
147 ADT+AAP +/- ENZ
236 ADT



SOC										
At-risk	988	974	947	901	837	610	368	200	63	10
Censored	0	8	11	14	28	216	421	568	693	742
Event	0	6	30	73	123	162	199	220	232	236
SOC+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

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

6-year survival improved from 77% to 86%

Kaplan-Meier estimates with 95% CI in lighter shade

Non-proportional hazards P=0.1

Adverse events

Worst toxicity grade in 1st 2 years	ADT only (AAP comparison)		ADT only (AAP + ENZ comparison)		AAP		AAP + ENZ	
	N (454)	%	N (530)	%	N (456)	%	N (522)	%
3	118	26	160	30	151	33	**277**	**53**
4	12	3	12	2	17	4	**23¶**	**4**
5	0	0	0	0	**3***	**1**	**4^**	**1**

¶Toxicities with the largest difference between AAP vs AAP+ENZ = (Gr 3) erectile dysfunction, hypertension, fatigue, (Gr 3/4) transaminitis

*1 event each of rectal adenocarcinoma, pulmonary haemorrhage and a respiratory disorder

^2 events each of septic shock and sudden death

Conclusions

- **2 years** of AAP-based therapy significantly improves MFS & overall survival of high-risk M0 PCa starting ADT and should be considered **a new standard of care**

- Adding ENZ to AAP increases toxicity but has no discernible effect on efficacy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