ESMO VIRTUAL JOURNAL CLUB

INTRODUCTION

Domenica Lorusso

Chair

Humanitas University of Milan

ESMO WEBINAR SERIES

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

LEARNING OBJECTIVES

- To discuss and critically evaluate notable recent publications.
- To enhance the understanding and application of the latest research in the field.
- To assess the study's robustness, its significance to oncology practice, limitations, and its place within existing research.
- To identify and highlight any unclear aspects or unmet needs.

PROGRAMME AND SPEAKERS

10 July 2024

5 min	**Welcome and introduction** Domenica Lorusso
15 min	**Maintenance olaparib rechallenge in patients with platinum-sensitive relapsed ovarian cancer previously treated with a PARP inhibitor (OReO/ENGOT-ov38): a phase IIIb trial** Alexandra Leary
15 min	**Atezolizumab plus bevacizumab versus active surveillance in patients with resected or ablated high-risk hepatocellular carcinoma (IMbrave050): a randomised, open-label, multicentre, phase 3 trial** Thomas Yau
15 min	**Capivasertib in Hormone Receptor–Positive Advanced Breast Cancer** Shani Paluch Shimon
10 min	**Live Q&A and Discussion** All speakers

Domenica Lorusso
Chair
Catholic University of Rome

Alexandra Leary
Speaker
Gustave Roussy

Thomas Yau
Speaker
University of Hong Kong

Shani Paluch-Shimon
Speaker
Hadassah University Hospital

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MAINTENANCE OLAPARIB RECHALLENGE IN PATIENTS WITH PLATINUM-SENSITIVE RELAPSED OVARIAN CANCER PREVIOUSLY TREATED WITH A PARP INHIBITOR (OREO/ENGOT-OV38): A PHASE IIIB TRIAL

Alexandra Leary, MD, PhD

Co-Director Dpt Medical Oncology, Gustave Roussy

President elect GINECO Group

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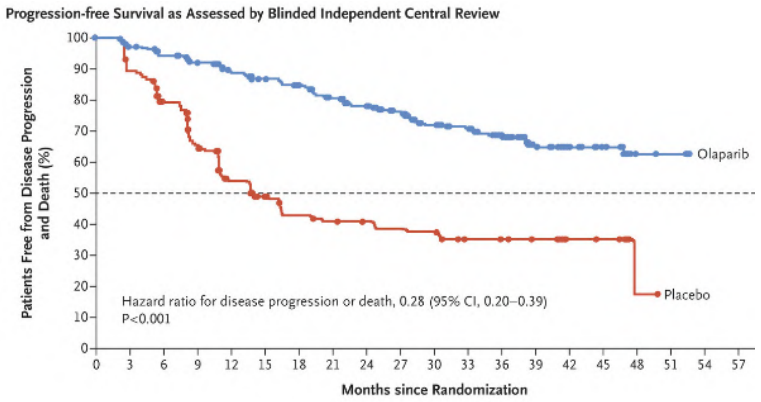
BACKGROUND AND RATIONALE

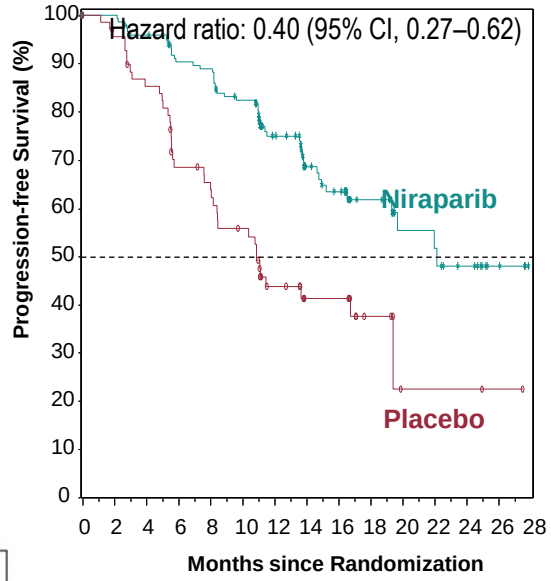
Ovarian Cancer has led innovation with PARP inhibitors in BRCA mutated OC, and beyond, especially other HRD+ OC

BENEFIT OF PARP INHIBITORS IN BRCA MUTATED OC 1ST LINE TRIALS

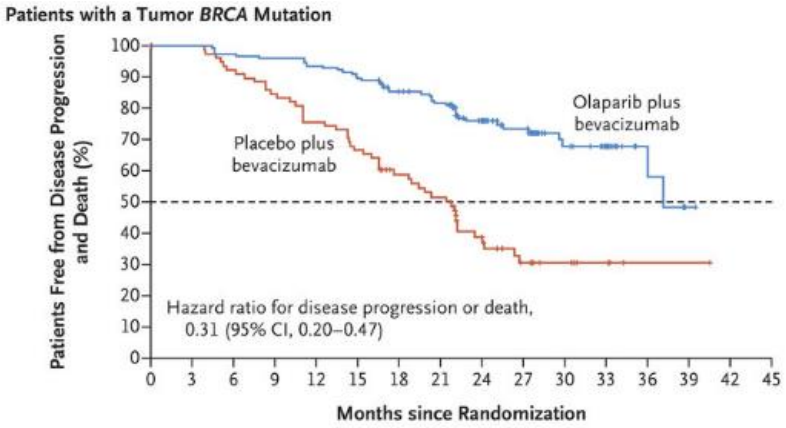
SOLO1



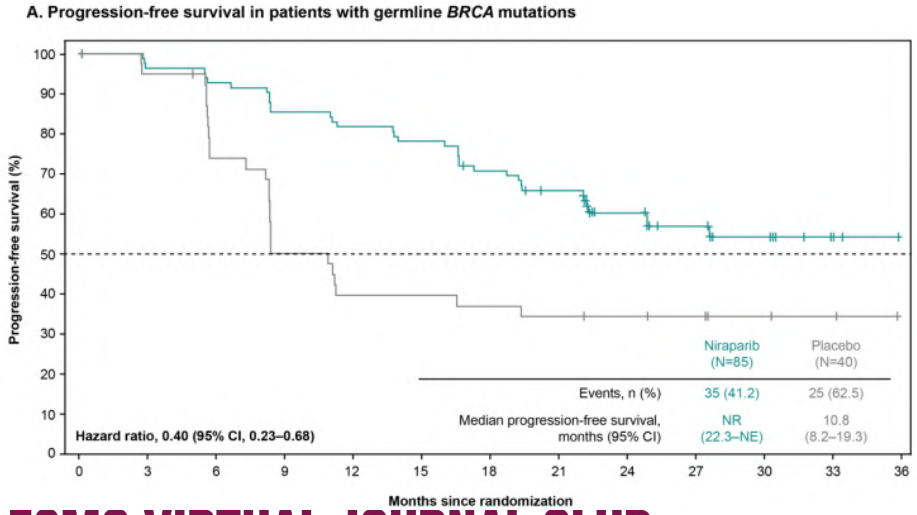
PRIMA



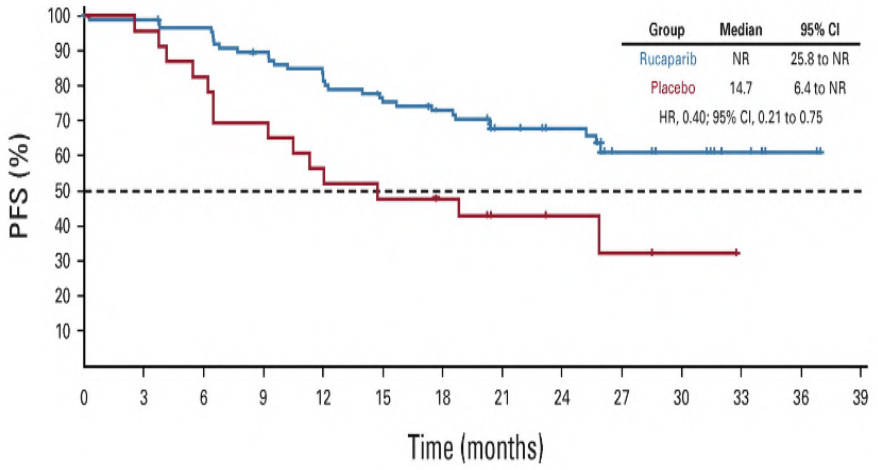
PAOLA



PRIME



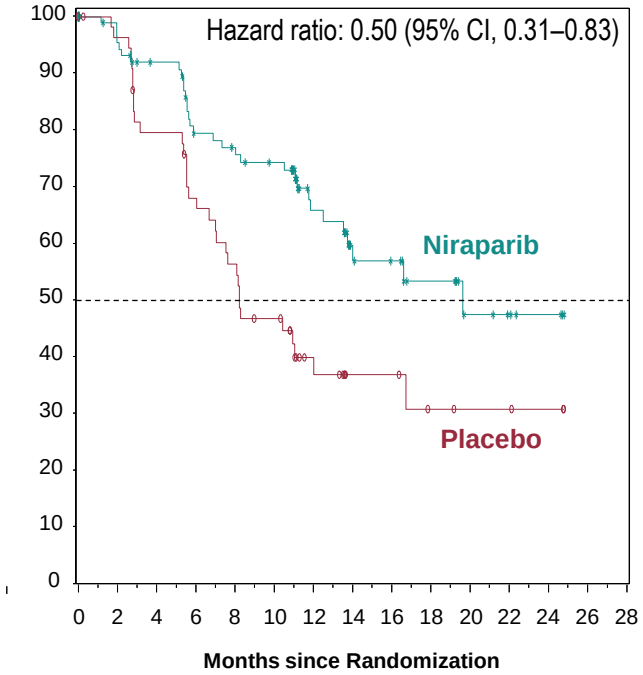
ATHENA



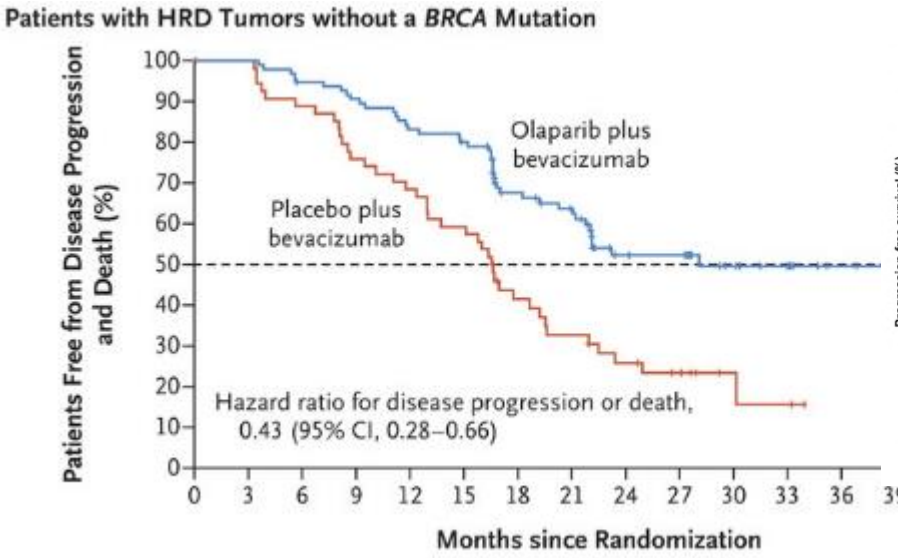
Moore et al 2018, Gonzalez-Martin et al 2019, Ray-Coquard et al 2019, Monk et al 2022, Ning Li 2023

Benefit of parp inhibitors in BRCA wild-type GIS+ OC - 1st line trials

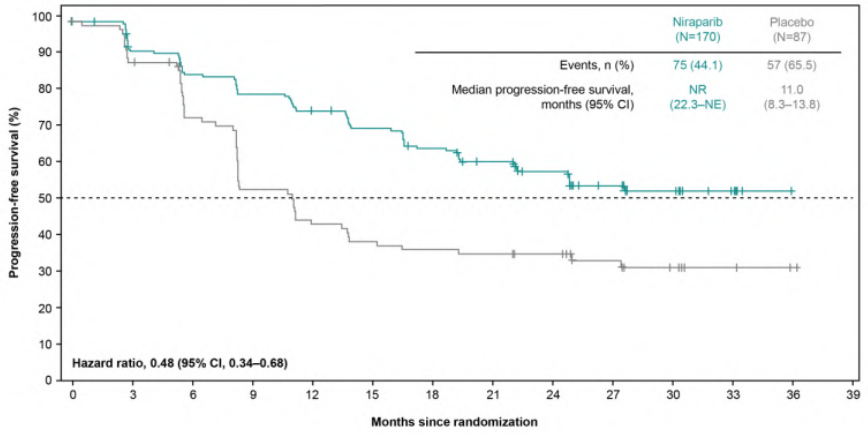
PRIMA, BRCAwt/GIS+



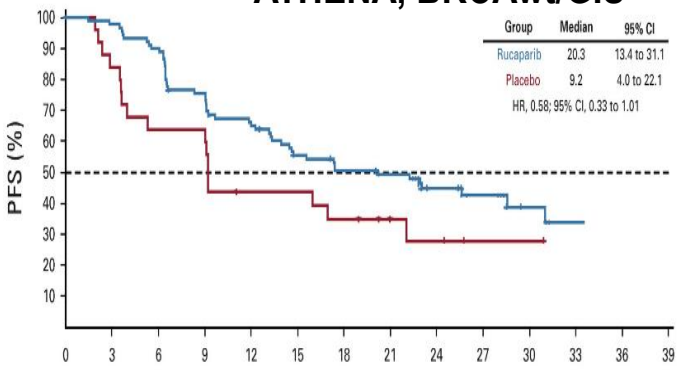
PAOLA, BRCAwt/GIS+



PRIME, BRCAm or BRCAwt/GIS+



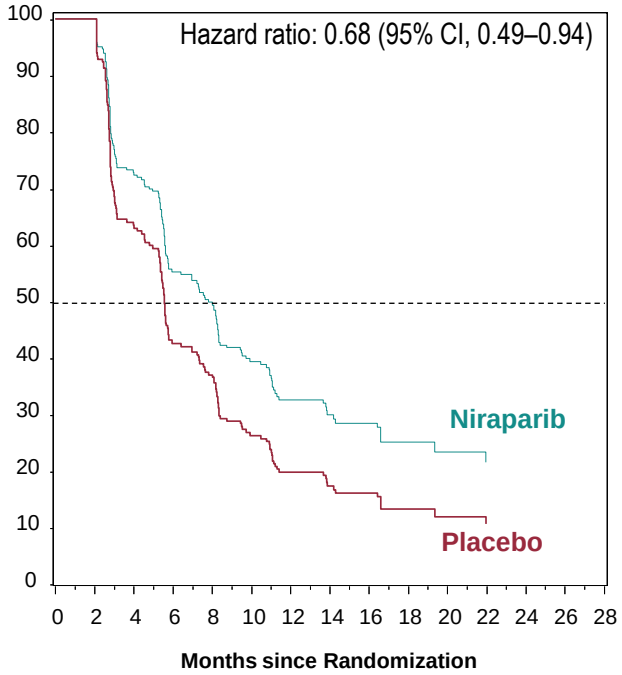
ATHENA, BRCAwt/GIS+



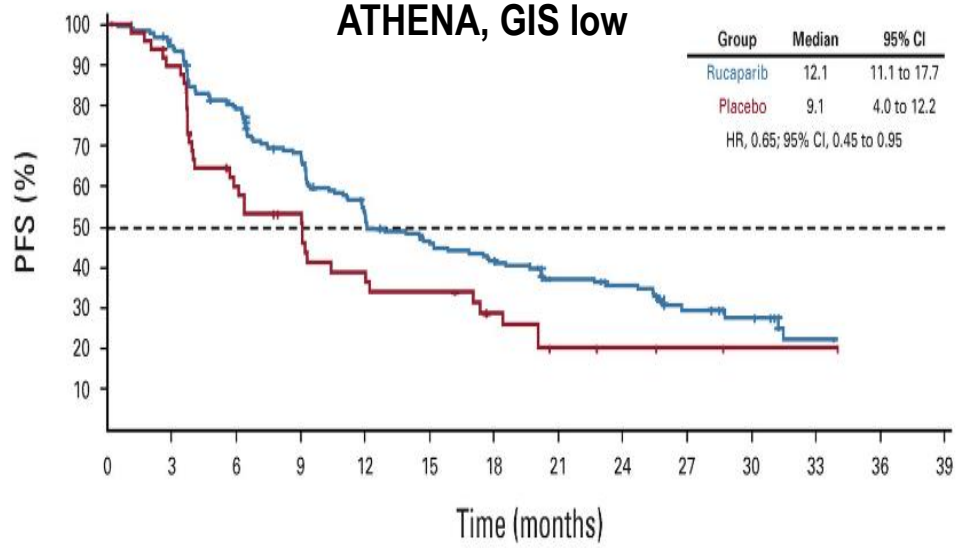
Gonzalez-Martin et al 2019, Ray-Coquard et al 2019, Monk et al 2022, Ning Li 2023

BENEFIT OF PARP INHIBITORS IN BRCA-WT AND GIS LOW

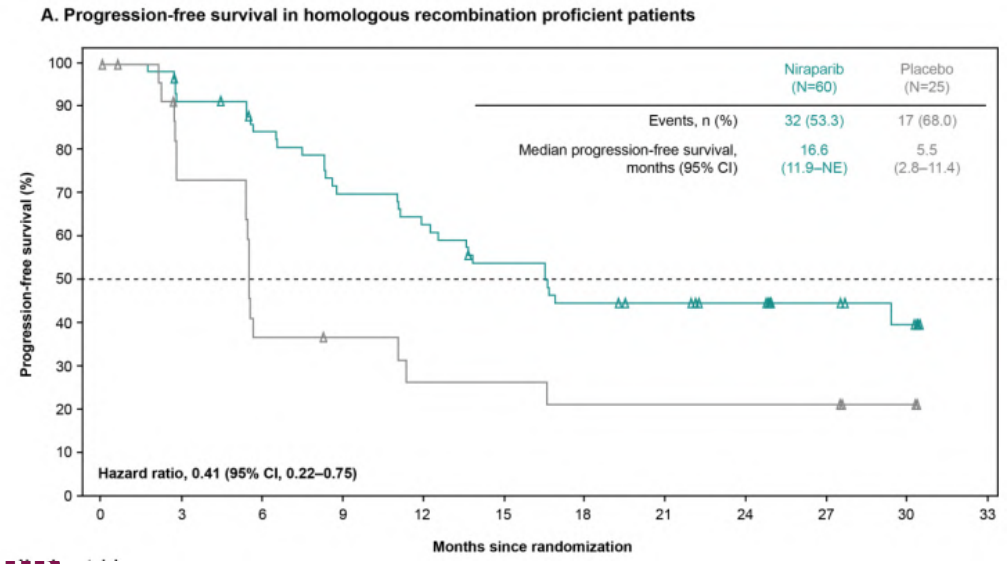
PRIMA, GIS-low



ATHENA, GIS low



PRIME, GIS low



But amplitude of benefit much more modest…

Gonzalez-Martin et al 2019, Monk et al 2022, Ning Li 2023

MOST PATIENTS WITH HIGH GRADE OC WILL RECEIVE PARP INHIBITORS

- Either as 1st line maintenance for fixed duration (2 or 3 years)
- In addition, historically, first approvals for PARP inhibitors were in the platinum sensitive setting as maintenance until disease progression
- What is the benefit of PARP inhibitor re-challenge as maintenance after platinum chemotherapy?

OREO: OLAPARIB RETREATMENT IN LATE RECURRENT OC

An academically sponsored randomized trial

Design

- Non-mucinous OC
- Prior exposure to PARPi as maintenance
- Known BRCA1/2 status
- PR/CR after platinum for platinum sensitive relapse and CA 125 stable

mBRCA (N=112)

- Prior PARPi exposure :
  ≥ 18 mo if received in L1 maintenance
  ≥ 12 mo if received as maintenance in PSROC

non mBRCA (N=108)

- Prior PARPi exposure:
  ≥ 12 mo if received in L1 maintenance
  ≥ 6 mo if received as maintenance in PSROC

PR or CR to platinum (w/o bevacizumab)

R 2:1

Olaparib BD

Placebo

Stratification :
- Prior Bevacizumab
- ≤3 *vs* ≥4 prior lines of platinum chemo

1° Objective
- PFS (RECIST)

2° Objectives
- OS
- TTST
- HRQoL
- Toxicity

Table 1. Patient characteristics at baseline[a]

	BRCAm cohort		Non-BRCAm cohort	
	Olaparib ($N = 74$)	Placebo ($N = 38$)	Olaparib ($N = 72$)	Placebo ($N = 36$)
Median (range) age, years	58.5 (37-80)	61.5 (44-87)	66.5 (29-81)	62.5 (43-77)
ECOG performance status, *n* (%)				
0	56 (76)	26 (68)	52 (72)	21 (58)
1	18 (24)	12 (32)	20 (28)	15 (42)
Primary tumor location, *n* (%)				
Ovary	65 (88)	34 (89)	61 (85)	29 (81)
Fallopian tube	4 (5)	2 (5)	6 (8)	2 (6)
Primary peritoneal	4 (5)	2 (5)	5 (7)	4 (11)
Other	1 (1)	0	0	1 (3)
Number of prior lines of any chemotherapy, *n* (%)				
2[b]	5 (7)	3 (8)	10 (14)	5 (14)
3	31 (42)	16 (42)	31 (43)	17 (47)
4	21 (28)	11 (29)	11 (15)	6 (17)
>4	17 (23)	8 (21)	20 (28)	8 (22)
Median (range) duration of previous PARP inhibitor therapy, months	21.2 (12-58)	18.3 (12-55)	12.6 (6-102)	12.4 (3-36)
Duration of previous PARP inhibitor exposure, *n* (%)				
<12 months	1 (1)[c]	1 (3)[c]	31 (43)	17 (47)
≥12 to <18 months	26 (35)	15 (39)	20 (28)	12 (33)
≥18 months	47 (64)	22 (58)	21 (29)	7 (19)
Type of previous maintenance PARP inhibitor, *n* (%)				
Olaparib	69 (93)	34 (89)	15 (21)	8 (22)
Niraparib	3 (4)	2 (5)	46 (64)	21 (58)
Rucaparib	1 (1)	2 (5)	7 (10)	6 (17)
Veliparib	0	0	3 (4)	0
Other	1 (1)[d]	0	1 (1)[e]	1 (3)[e]

Table 1. Patient characteristics at baseline[a]

	BRCAm cohort		Non-BRCAm cohort	
	Olaparib ($N = 74$)	Placebo ($N = 38$)	Olaparib ($N = 72$)	Placebo ($N = 36$)
Response after most recent chemotherapy before randomization, *n* (%)				
Complete response[f]	15 (20)	13 (34)	19 (26)	11 (31)
Partial response	58 (78)	25 (66)	53 (74)	25 (69)
Missing	1 (1)	0	0	0
BRCAm category at screening, *n* (%)				
Deleterious or suspected deleterious mutation	72 (97)	37 (97)	0	1 (3)[g]
No deleterious or suspected deleterious mutation detected	0	0	71 (99)	34 (94)
Missing[h]	2 (3)	1 (3)	1 (1)	1 (3)
BRCAm type at screening, *n* (%)				
*BRCA1*m	51 (69)	29 (76)	0	1 (3)[g]
*BRCA2*m	20 (27)	7 (18)	0	0
*BRCA1*m and *BRCA2*m	2 (3)	1 (3)	0	0
Missing[h]	1 (1)	1 (3)	0	0
HRD status,[i] *n* (%)				
HRD-positive	—	—	29 (40)[j]	16 (44)[j]
HRD-negative	—	—	30 (42)	11 (31)
HRD-unknown	—	—	13 (18)[k]	9 (25)[k]

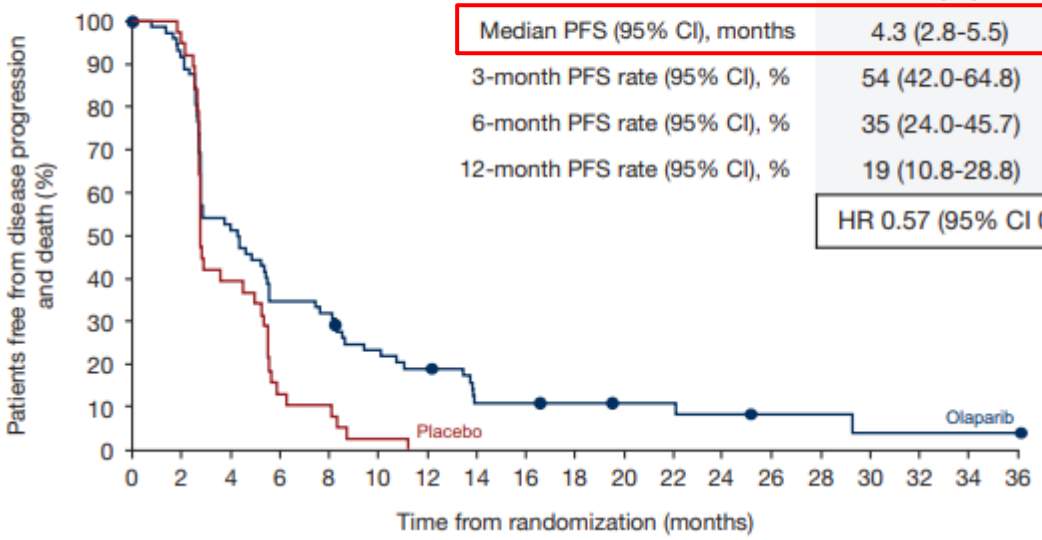
220 pts recruited between June 2017 and Feb 2021

RESULTS: PFS BENEFIT OF PARP INHIBITOR RE-CHALLENGE

A

BRCAm cohort

	Olaparib (*N* = 74)	Placebo (*N* = 38)
Median follow-up for PFS, months	4.1	2.8
Events, *n* (%)	65 (88)	38 (100)
Median PFS (95% CI), months	4.3 (2.8-5.5)	2.8 (2.7-5.0)
3-month PFS rate (95% CI), %	54 (42.0-64.8)	42 (26.4-57.0)
6-month PFS rate (95% CI), %	35 (24.0-45.7)	13 (4.8-25.8)
12-month PFS rate (95% CI), %	19 (10.8-28.8)	0 (NC-NC)
HR 0.57 (95% CI 0.37-0.87); *P* = 0.0220		

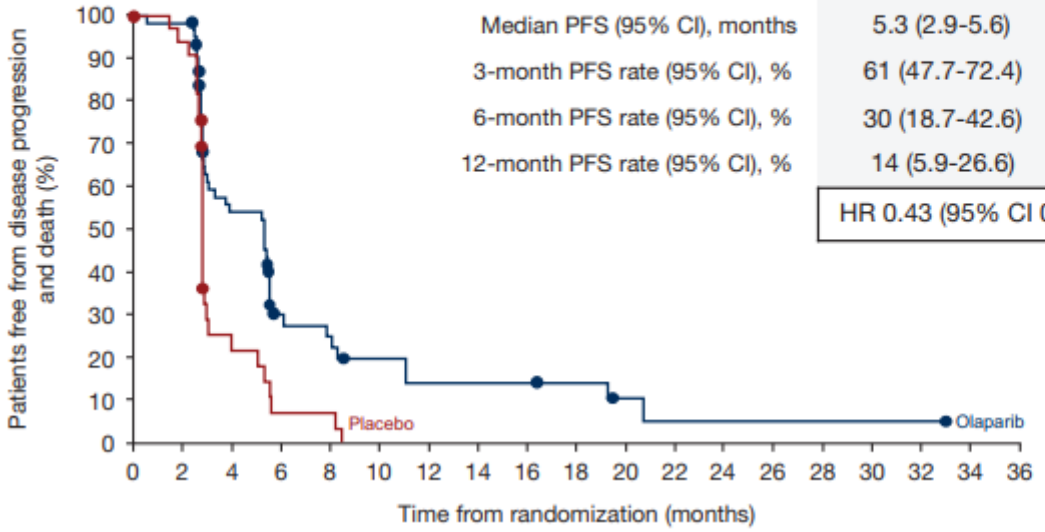


Statistically significant improvement in PFS with PARPi re-challenge: HR=0.57 and p=0.02 in BRCAm cohort

B

BRCAwt cohort

	Olaparib (*N* = 72)	Placebo (*N* = 36)
Median follow-up for PFS, months	2.9	2.8
Events, *n* (%)	48 (67)	30 (83)
Median PFS (95% CI), months	5.3 (2.9-5.6)	2.8 (2.8-2.9)
3-month PFS rate (95% CI), %	61 (47.7-72.4)	29 (14.3-45.7)
6-month PFS rate (95% CI), %	30 (18.7-42.6)	7 (1.3-20.6)
12-month PFS rate (95% CI), %	14 (5.9-26.6)	0 (NC-NC)
HR 0.43 (95% CI 0.26-0.71); *P* = 0.0023		

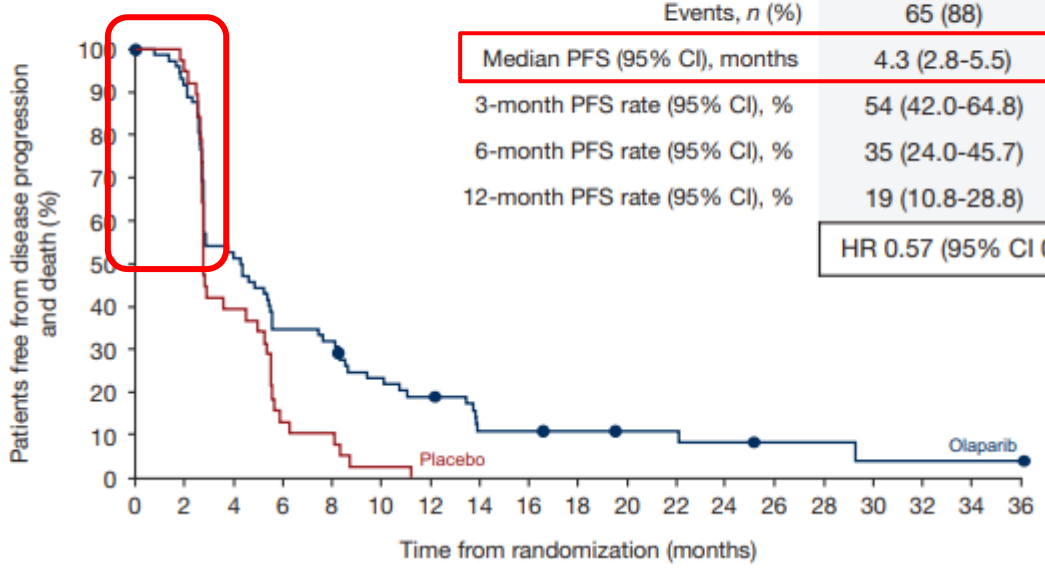


Statistically significant improvement in PFS with PARPi re-challenge: HR=0.43 and p=0.002 in BRCAwt cohort

A

BRCAm cohort

	Olaparib (*N* = 74)	Placebo (*N* = 38)
Median follow-up for PFS, months	4.1	2.8
Events, *n* (%)	65 (88)	38 (100)
Median PFS (95% CI), months	4.3 (2.8-5.5)	2.8 (2.7-5.0)
3-month PFS rate (95% CI), %	54 (42.0-64.8)	42 (26.4-57.0)
6-month PFS rate (95% CI), %	35 (24.0-45.7)	13 (4.8-25.8)
12-month PFS rate (95% CI), %	19 (10.8-28.8)	0 (NC-NC)
HR 0.57 (95% CI 0.37-0.87); *P* = 0.0220		



Statistically significant, but clinically significant?

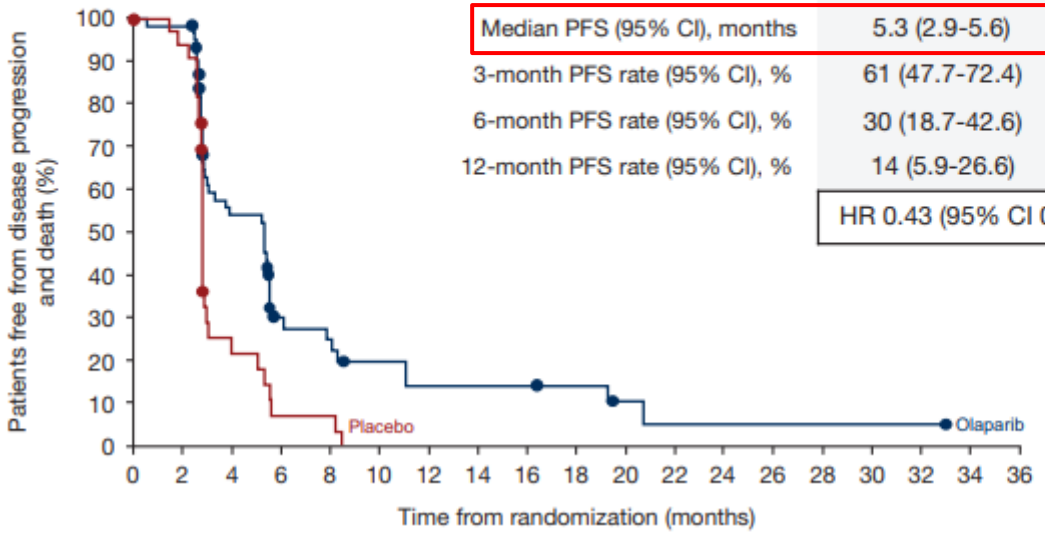
Almost half BRCAm patients PD at 1st scan with PARPi or placebo!!

PARPi re-challenge provides the same benefit regardless of BRCAm vs wt?

B

BRCAwt cohort

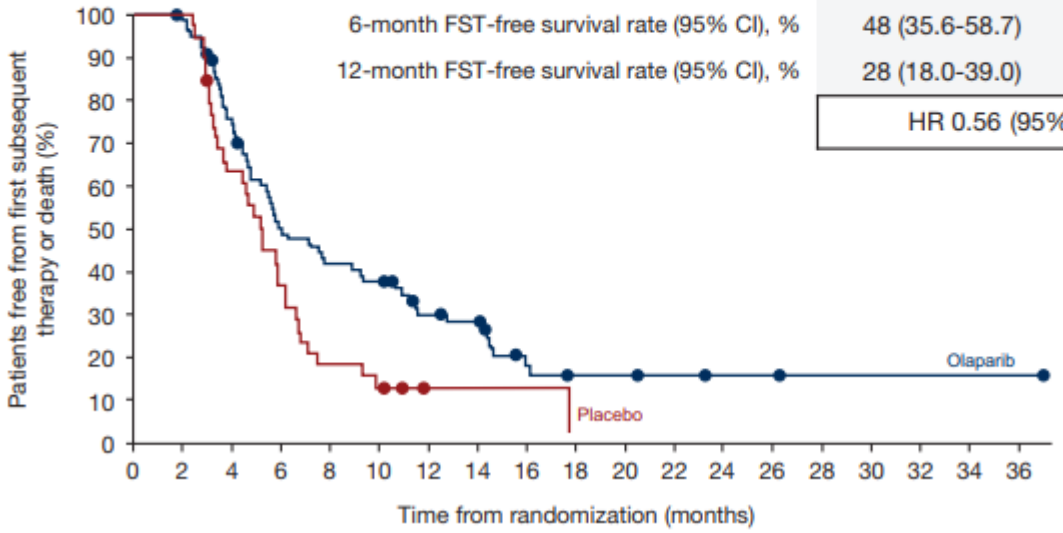
	Olaparib (*N* = 72)	Placebo (*N* = 36)
Median follow-up for PFS, months	2.9	2.8
Events, *n* (%)	48 (67)	30 (83)
Median PFS (95% CI), months	5.3 (2.9-5.6)	2.8 (2.8-2.9)
3-month PFS rate (95% CI), %	61 (47.7-72.4)	29 (14.3-45.7)
6-month PFS rate (95% CI), %	30 (18.7-42.6)	7 (1.3-20.6)
12-month PFS rate (95% CI), %	14 (5.9-26.6)	0 (NC-NC)
HR 0.43 (95% CI 0.26-0.71); *P* = 0.0023		



RESULTS: TTST WITH PARP INHIBITOR RE-CHALLENGE

A

	Olaparib (*N* = 74)	Placebo (*N* = 38)
Events, *n* (%)	57 (77)	34 (89)
Median TFST (95% CI), months	5.8 (4.7-9.2)	5.1 (3.6-6.1)
6-month FST-free survival rate (95% CI), %	48 (35.6-58.7)	35 (20.5-50.4)
12-month FST-free survival rate (95% CI), %	28 (18.0-39.0)	11 (3.5-23.2)
HR 0.56 (95% CI 0.36-0.88)		

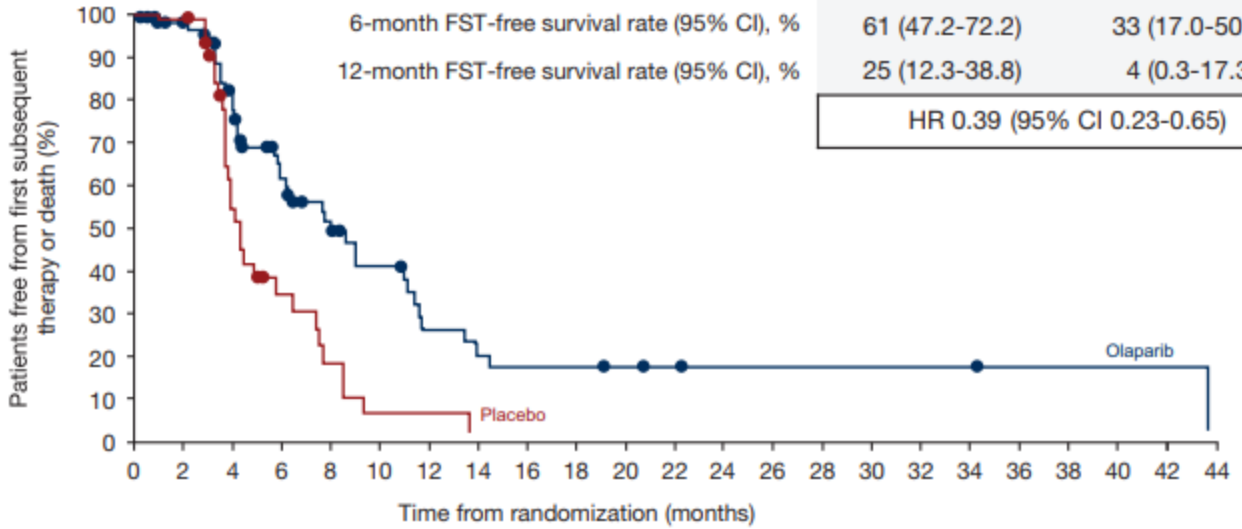


Statistically significant improvement in TTST with PARPi re-challenge in BRCAm cohort

Statistically significant improvement in TTST with PARPi re-challenge in BRCAwt cohort

B

	Olaparib (*N* = 72)	Placebo (*N* = 36)
Events, *n* (%)	41 (57)	28 (78)
Median TFST (95% CI), months	7.9 (5.9-11.1)	4.3 (3.7-6.4)
6-month FST-free survival rate (95% CI), %	61 (47.2-72.2)	33 (17.0-50.0)
12-month FST-free survival rate (95% CI), %	25 (12.3-38.8)	4 (0.3-17.3)
HR 0.39 (95% CI 0.23-0.65)		



Toxicity

Patients with adverse event, *n* (%)	Olaparib		Placebo	
	Any grade	Grade ≥3	Any grade	Grade ≥3
BRCA-mutated cohort	***N* = 74**		***N* = 38**	
Any	64 (86)	11 (15)	33 (87)	2 (5)
Fatigue or asthenia	31 (42)	0	8 (21)	0
Nausea	29 (39)	0	4 (11)	0
Anemia[b]	13 (18)	2 (3)	2 (5)	0
Diarrhea	10 (14)	0	5 (13)	0
Constipation	9 (12)	0	6 (16)	0
Abdominal pain	8 (11)	0	11 (29)	0
Vomiting	8 (11)	0	4 (11)	0
Dyspnea	7 (10)	0	2 (5)	0
Upper abdominal pain	7 (10)	0	0	0
Neutropenia[c]	6 (8)	2 (3)	4 (11)	1 (3)
Thrombocytopenia[d]	4 (5)	1 (1)	0	0
Urinary tract infection	2 (3)	0	4 (11)	0
Decreased appetite	2 (3)	0	1 (3)	0
Arthralgia	0	0	3 (8)	0
Leading to dose modification	18 (24)	—	6 (16)	—
Leading to treatment discontinuation	2 (3)	—	0	—
Non-BRCA-mutated cohort	***N* = 72**		***N* = 36**	
Any	66 (92)	15 (21)	31 (86)	3 (8)
Nausea	30 (42)	0 (0)	3 (8)	0
Fatigue or asthenia	28 (39)	2 (3)	4 (11)	0
Anemia[b]	17 (24)	1 (1)	1 (3)	0
Diarrhea	12 (17)	0	2 (6)	0
Neutropenia[c]	9 (13)	3 (4)	4 (11)	0
Constipation	9 (13)	0	2 (6)	1 (3)
Decreased appetite	7 (10)	0	1 (3)	0
Dyspnea	7 (10)	0	0	0
Thrombocytopenia[d]	7 (10)	0	0	0
Abdominal pain	6 (8)	0	6 (17)	0
Vomiting	6 (8)	0	1 (3)	0
Upper abdominal pain	4 (6)	0	2 (6)	0
Urinary tract infection	3 (4)	0	0	0
Arthralgia	2 (3)	0	4 (11)	0
Leading to dose modification	18 (24)	—	6 (16)	—
Leading to treatment discontinuation	2 (3)	—	0	—

CONCLUSIONS

- OReO is the first study to demonstrate that in a heavily pretreated ovarian cancer population, maintenance olaparib rechallenge provided a statistically significant, albeit modest, improvement in PFS compared with placebo.

- The benefit of olaparib re-challenge in patients previously exposed to PARPi was seen regardless of BRCAm status.

DISCUSSION

- Benefit is modest… and prognosis was poor regardless of cohort or treatment arm
- Almost half of patients progressed at 1st scan, regardless of Olaparib or placebo!

Table 1. Patient characteristics at baseline[a]

	BRCAm cohort		Non-BRCAm cohort	
	Olaparib ($N = 74$)	Placebo ($N = 38$)	Olaparib ($N = 72$)	Placebo ($N = 36$)
Number of prior lines of any chemotherapy, *n* (%)				
2[b]	5 (7)	3 (8)	10 (14)	5 (14)
3	31 (42)	16 (42)	31 (43)	17 (47)
4	21 (28)	11 (29)	11 (15)	6 (17)
>4	17 (23)	8 (21)	20 (28)	8 (22)

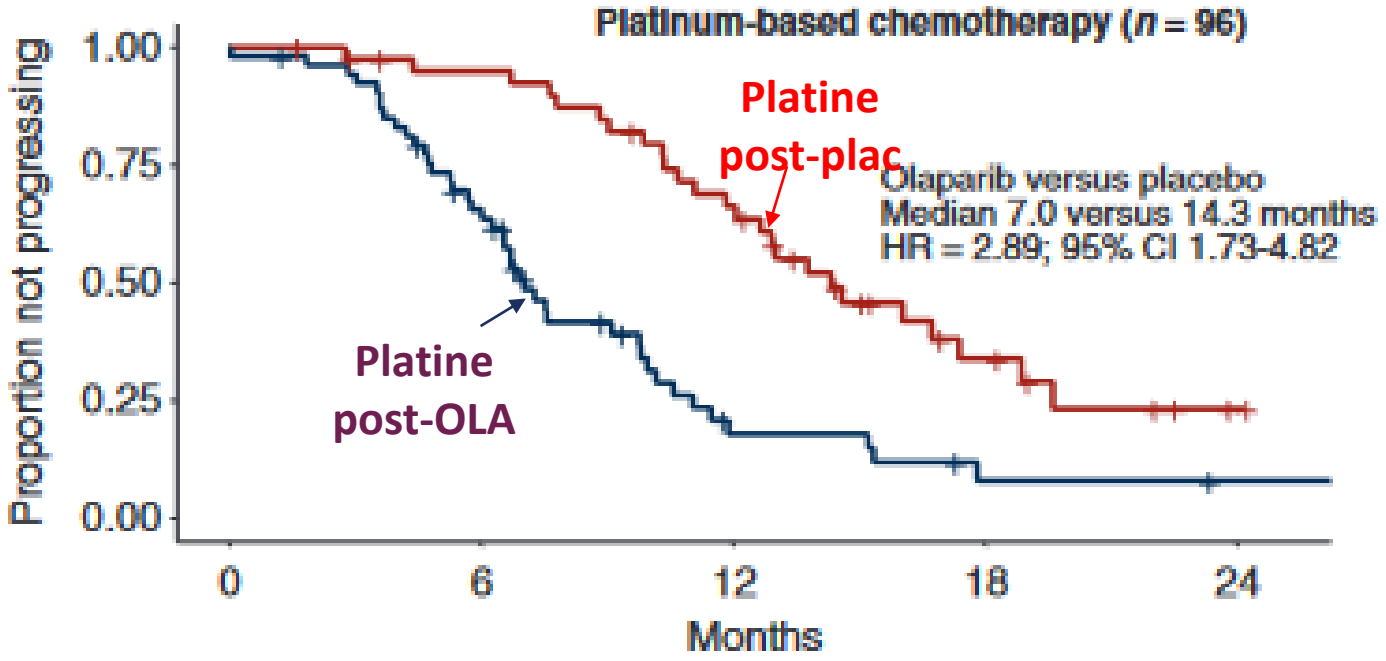
- Only 23/220 pts had received PARPi maintenance in 1st line
- 197/220 pts received in relapsed setting, meaning they likely progressed **UNDER PARPi not AFTER PARPi**
- Pts progressing UNDER PARPi may have platinum and/or PARPi resistance!

What do we know about the platinum responsiveness of pts progressing under PARPi? - SOLO2: Benefit of subsequent platinum post PARPi vs placebo

SOLO2: BRCAm OC in platinum sensitive relapse and in CR/PR randomized to olaparib vs placebo until progression

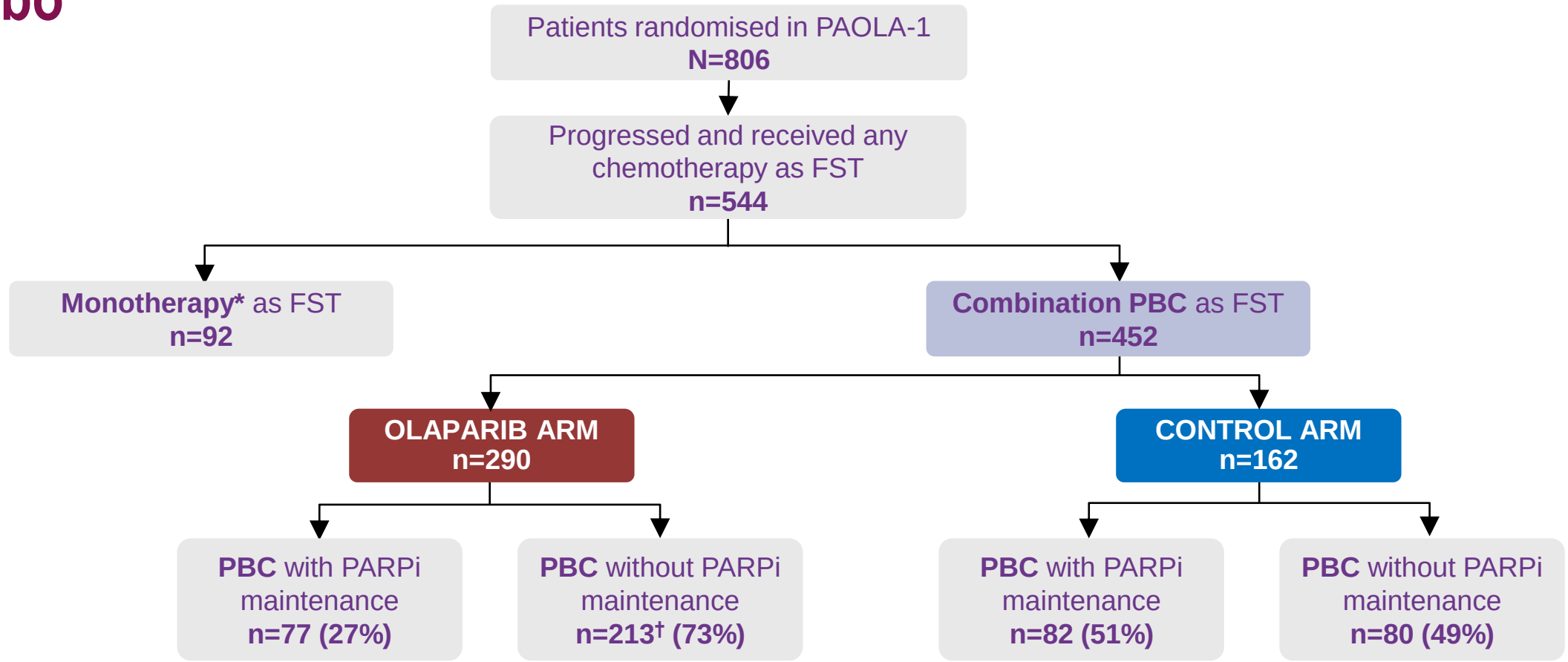
What do we know about the platinum responsiveness of pts progressing under PARPi? - SOLO2: Benefit of subsequent platinum post PARPi vs placebo

SOLO2: BRCAm OC in platinum sensitive relapse and in CR/PR randomized to olaparib vs placebo until progression



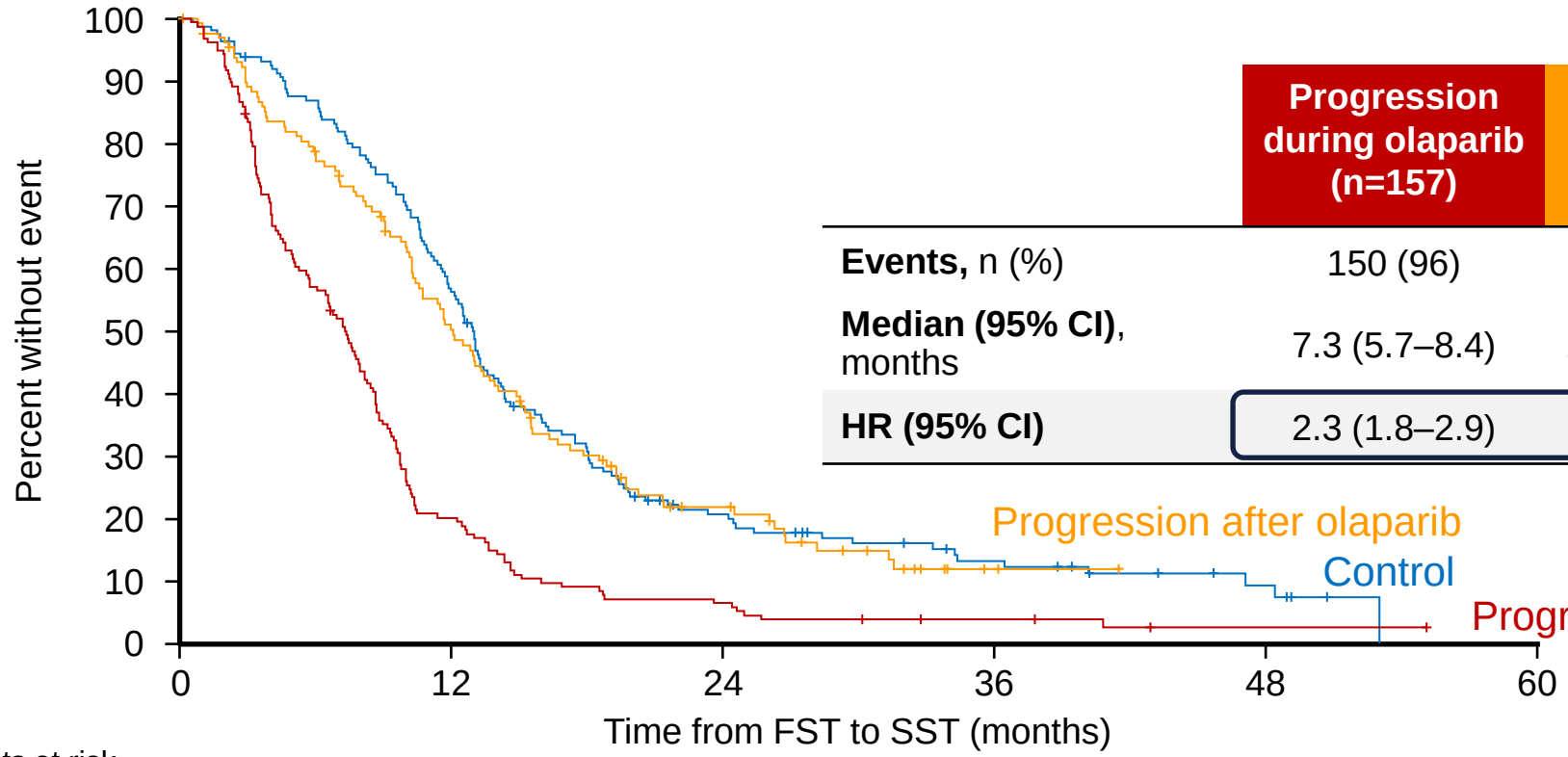
Progression UNDER PARPi diminishes sensitivity to subsequent platinum!
Logical! Mecanisms of PARPi and platinum resistance likely overlap!

What do we know about the platinum responsiveness of pts progressing AFTER PARPi? - PAOLA: Benefit of subsequent platinum post PARPi vs placebo



Disease progression by subgroups analysis with subsequent Platinum chemo

- A *post hoc* exploratory PAOLA-1 analysis suggested the efficacy of subsequent chemotherapy at first relapse was reduced in patients with disease progression during vs after olaparib plus bevacizumab maintenance[1]

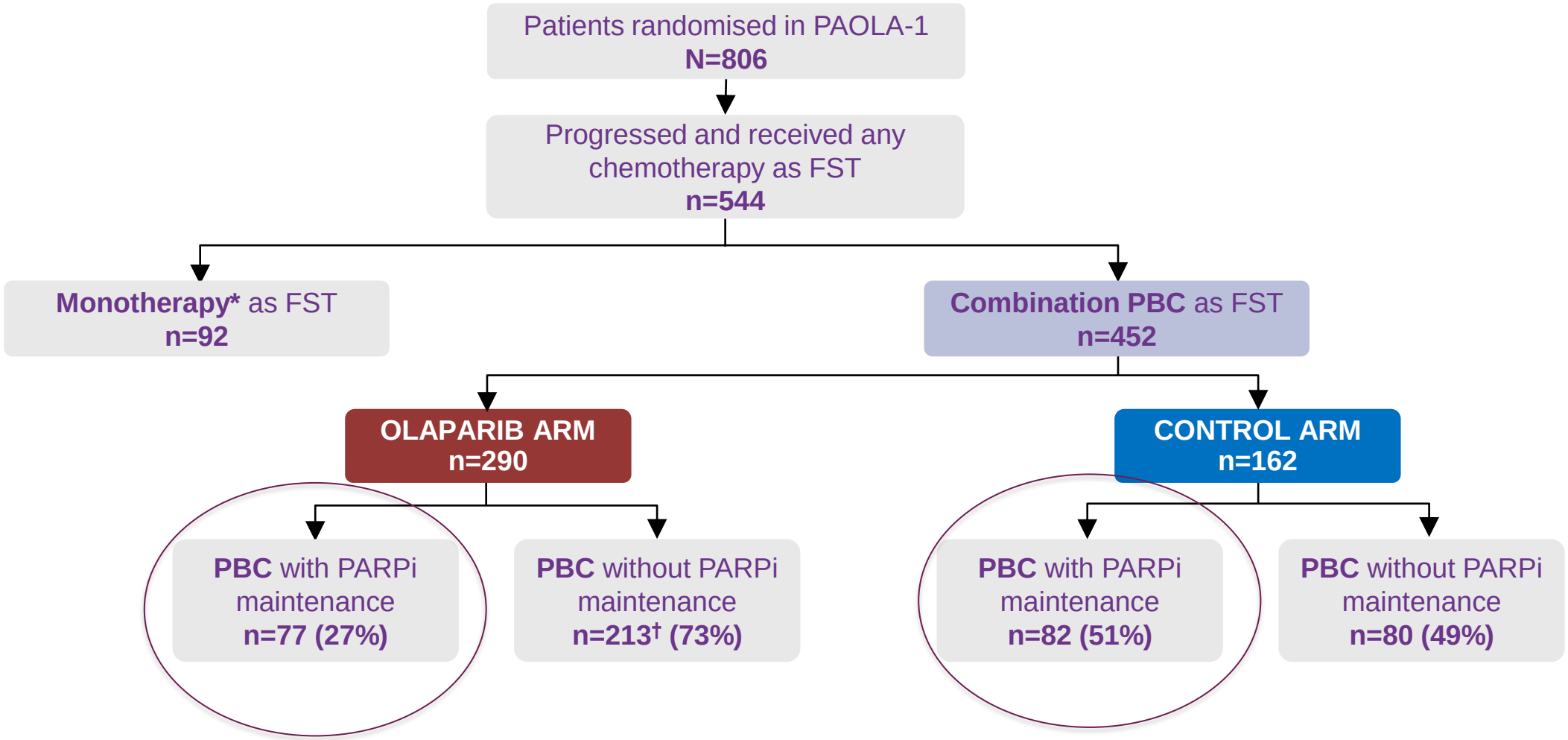


	Progression during olaparib (n=157)	Progression after olaparib (n=132)	Control (n=162)
Events, n (%)	150 (96)	103 (78)	139 (86)
Median (95% CI), months	7.3 (5.7–8.4)	12.0 (10.3–14.8)	12.9 (11.8–14.1)
HR (95% CI)	2.3 (1.8–2.9)	1.1 (0.8–1.4)	Ref

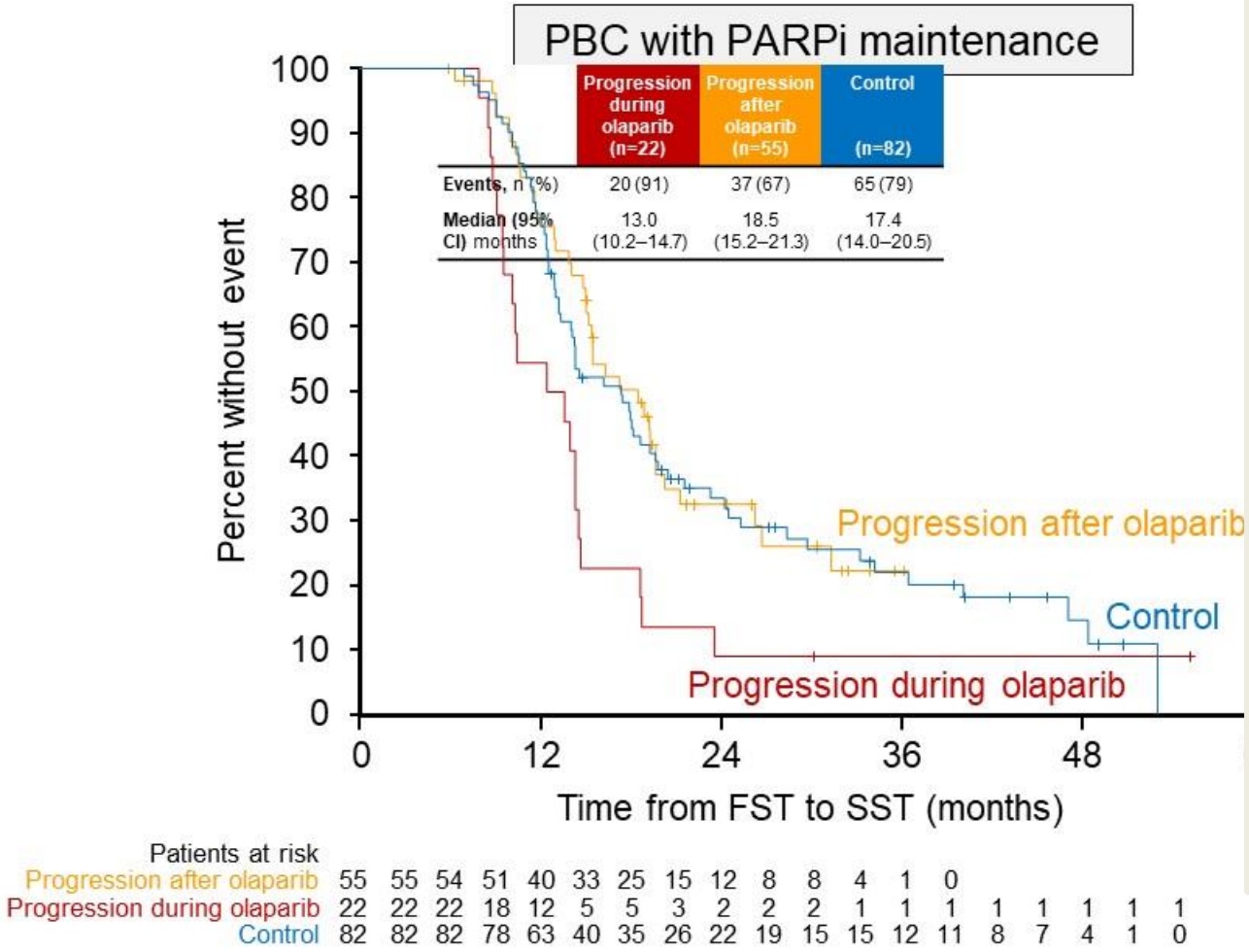
Patients at risk

Progression after olaparib	132	113	97	83	60	46	35	25	21	14	11	5	2	1	0				
Progression during olaparib	157	130	88	54	31	17	14	11	10	6	6	4	4	3	2	1	1	1	1
Control	162	150	139	120	90	58	45	33	28	24	19	18	14	12	9	8	5	1	0

PARP re-challenge in patients who received olaparib or placebo in PAOLA



Patients who received PBC+PARPi re-challenge AFTER PARPi discontinuation did as well as the placebo arm (C Marth, et al ESGO September 2023)



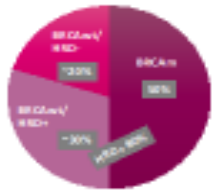
- Very promising results
- But need to be confirmed by a large prospective randomized clinical trial
- Integrating the benefice risk for patients and myeloid toxicity
- Time to consider a “fixed” period maintenance duration also in the relapse setting

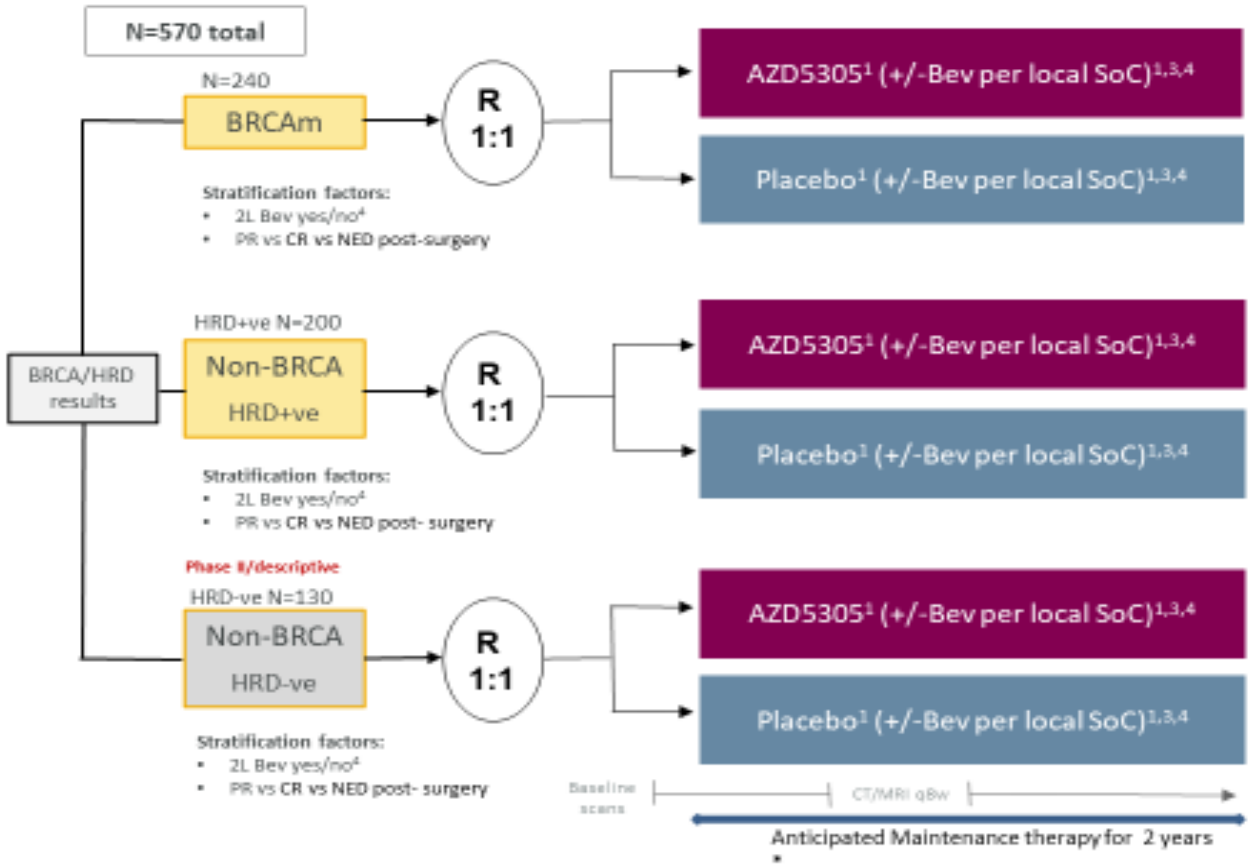
A Proposed Phase III Study of Saruparib (PARP1 selective inhibitor) as 2L maintenance in Platinum- Sensitive Relapsed Ovarian Cancer previously exposed to PARPi

BRCAm and nonBRCAm HRD+ve in powered cohorts, HRD –ve in a separate descriptive/phase II cohort

Key Eligibility

- **Documented BRCA and HRD status**
- **PR/CR** following 4-6 cycles 2L platinum-based chemo +/- Bev per local SoC
- Must have received 1L platinum-taxane followed by maintenance PARPi +/- Bev and:
  - **>2 months** after last dose PARPi
  - **>12months** after last platinum
- High grade serous or endometrioid ovarian, fallopian tube and/or primary peritoneal cancer
- Secondary surgical cytoreduction permitted
- Tumour sample for prospective or retrospective HRD or BRCA testing





Endpoints BRCAm	Measure
Primary	PFS (Inv)
Key Secondary	OS
Other secondary/ exploratory	PFS (BICR), PFS2, TFST, TTST, Safety, PROs

Endpoints HRD	Measure
Primary	PFS (Inv)
Key Secondary	OS
Other secondary/ exploratory	PFS (BICR), PFS2, TFST, TTST, Safety, PROs

Endpoints HRD-ve	Measure
Key Exploratory	PFS

2 Prevalence is based on 1L PARPi use and eligibility for EvoPar-Ov01; enriched for BRCAm

[1]AZD5305/placebo/bevacizumab continue until disease progression, [2]HRD unknown subjects without a BRCAm are excluded, [3] Bev should be administered with chemo as per local SoC, [4] Bevacizumab will be capped at 30%.

IMPLICATIONS FOR PRACTICE TODAY?

- Benefit of PARPi re-challenge in patients who have previously **progressed UNDER PARPi** is minimal
- OrEO has not led to approvals for PARPi re-challenge
- **Progression under PARPi** undermines subsequent platinum sensitivity
- If given in the platinum sensitive maintenance setting, should we consider stopping PARPi after 2-3 years?
- **Progression after PARPi** may be a different story…
- Trial planned to answer the question of PARPi re-challenge in patients who discontinued PARPi maintenance in 1st line

ESMO VIRTUAL JOURNAL CLUB

Thank you for your attention

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ATEZOLIZUMAB PLUS BEVACIZUMAB VERSUS ACTIVE SURVEILLANCE IN PATIENTS WITH RESECTED OR ABLATED HIGH-RISK HEPATOCELLULAR CARCINOMA (IMBRAVE050): A RANDOMISED, OPEN-LABEL, MULTICENTRE, PHASE 3 TRIAL

Lancet. 2023 Nov 18;402(10415):1835-1847.

Dr Thomas Yau, MD

The University of Hong Kong

MBBS(HK), MD(HK), MRCP (UK), FRCP(London)

FHKCP (Med Onc), FHKAM(Medicine)

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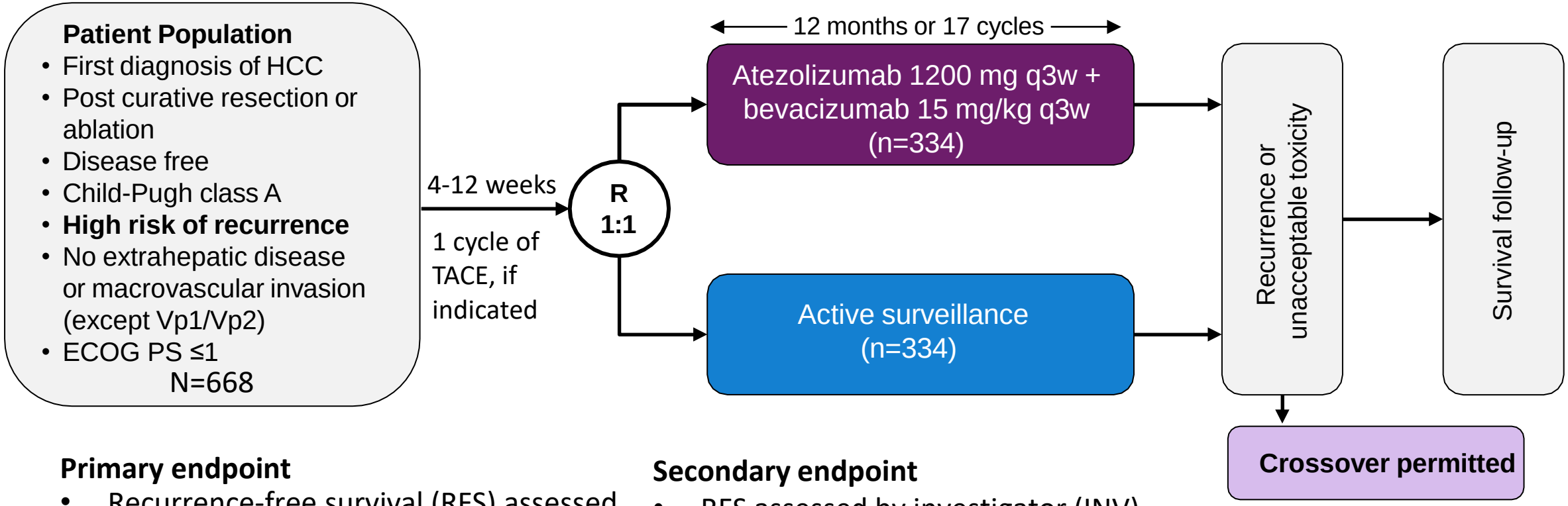
IMBRAVE050 STUDY DESIGN

Randomised, open-label, multicentre, phase 3 trial



Primary endpoint

- Recurrence-free survival (RFS) assessed by independent review facility (IRF)

Secondary endpoint

- RFS assessed by investigator (INV)
- Time to recurrence assessed per IRF
- Overall survival (OS)

Other endpoints

- Safety

Qin et al. The Lancet 2023

IMBRAVE050

Criteria for high-risk of HCC recurrence by curative treatment

Resection	Ablation
• ≤3 tumors, with **largest >5 cm** regardless of vascular invasion or poor tumor differentiation (grade 3/4) • **≥4 tumors**, with largest ≤5 cm regardless of vascular invasion or poor tumor differentiation (grade 3/4) • ≤3 tumors, with largest ≤5 cm with **vascular invasion**, and/or **poor tumor differentiation** (grade 3/4)	• 1 tumor >2 cm but ≤5 cm • Multiple tumors (≤4 tumors), all ≤5 cm

Qin et al. The Lancet 2023

IMBRAVE050: BASELINE CHARACTERISTICS

Characteristic	Atezo + Bev (n = 334)	Active Surveillance (n = 334)
Median age, years (range)	60 (52-68)	59 (50-70)
Sex, n (%)		
Male	277 (83)	278 (83)
Female	57 (17)	56 (17)
Race, n (%)		
Asian	276 (83)	269 (81)
White	35 (10)	41 (12)
Other	23 (7)	24 (7)
Geographical region		
Asia-Pacific (excluding Japan) / Rest of world	237 (71)/97 (29)	238 (71)/96 (29)
ECOG PS score, n (%) 0/1	258 (77)/76(23)	269(81)/65(19)
PD-L1 status, n (%) ≥1%/<1%	154 (54)/131 (46)	140 (50)/139 (50)
Etiology, n (%)		
Hepatitis B	209 (63)	207 (62)
Hepatitis C	34 (10)	38 (11)
Nonviral/unknown	45 (13)/46 (14)	38 (11)/51 (15)
BCLC stage at initial diagnosis, n (%)		
0	2(1)	3(1)
A	287 (86)	277(83)
B	25(7)	32(10)
C	20(6)	22(7)

Qin et al. The Lancet 2023

IMBRAVE050: BASELINE CHARACTERISTICS BY CURATIVE PROCEDURES

Characteristic	Atezo + Bev (n = 334)	Active Surveillance (n=334)
Resection, n (%)	293 (88)	292 (87)
Longest diameter of largest tumor at diagnosis, median cm (range)	5.3 (3.3-8.0)	5.9 (3.5-9.0)
Tumors, n (%)		
1	266 (91)	260 (89)
2	20 (7)	29 (10)
3	4 (1)	2 (1)
≥4 tumors	3 (1)	1 (<1)
Adjuvant TACE following resection, n (%)	32 (11)	34 (12)
Any tumors **>5 cm**, n (%)	152 (52)	175 (60)
Microvascular invasion present, n (%)	178 (61)	176 (60)
Segmental portal vein invasion (Vp1/Vp2) present, n (%)	22 (8)	17 (6)
Poor tumor differentiation (grade 3 or 4), n (%)	124 (42)	121 (41)
Ablation, n (%)	41 (12)	42 (13)
Longest diameter of the largest tumor at diagnosis, median (range), cm	2.5 (2.3-3.0)	2.6 (2.3-3.0)
Tumors, n (%)		
1	29 (71)	31 (74)
2	11 (27)	8 (19)
3	1(2)	3(7)

Qin et al. The Lancet 2023

STATISTICAL DESIGN

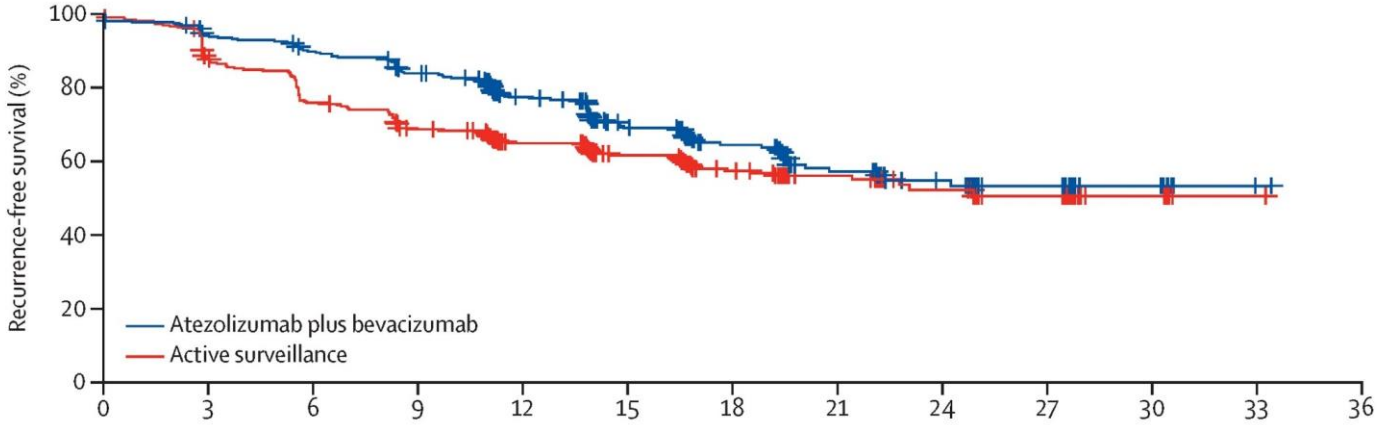
- Primary end-point: independent review facility (IRF)-assessed recurrence-free survival (RFS)
- To detect an improvement in RFS, approximately 323 RFS events will be required to achieve 80% overall power assuming a target HR of 0.73.
- Interim analysis at 236 RFS events, and final analysis at 323 RFS events
- The secondary endpoint of OS was to be tested if statistical significance was reached for independent review facility-assessed RFS
- This paper reported the first pre-determined event-driven interim analysis

Qin et al. The Lancet 2023

PRIMARY ENDPOINT

IRF-assessed RFS

	Atezolizumab plus bevacizumab (n=334)	Active surveillance (n=334)	
Patients with events, n (%)	110 (33%)	133 (40%)	
Median RFS, months (95% CI)	NE (22·1–NE)	NE (21·4–NE)	
12-month IRF-RFS event-free rate, % (95% CI)	78% (73–82)	65% (60–71)	
Stratified hazard ratio (adjusted 95% CI)			0·72 (0·53–0·98)
p value (log rank)			0·012



Number at risk (number censored)												
Atezolizumab plus bevacizumab	334 (0)	305 (10)	290 (12)	268 (15)	211 (53)	139 (105)	97 (139)	63 (164)	37 (188)	22 (202)	9 (215)	1 (223)	NE (NE)
Active surveillance	334 (0)	283 (12)	245 (12)	214 (20)	179 (44)	131 (84)	93 (114)	57 (148)	36 (166)	20 (181)	6 (195)	1 (200)	NE (NE)

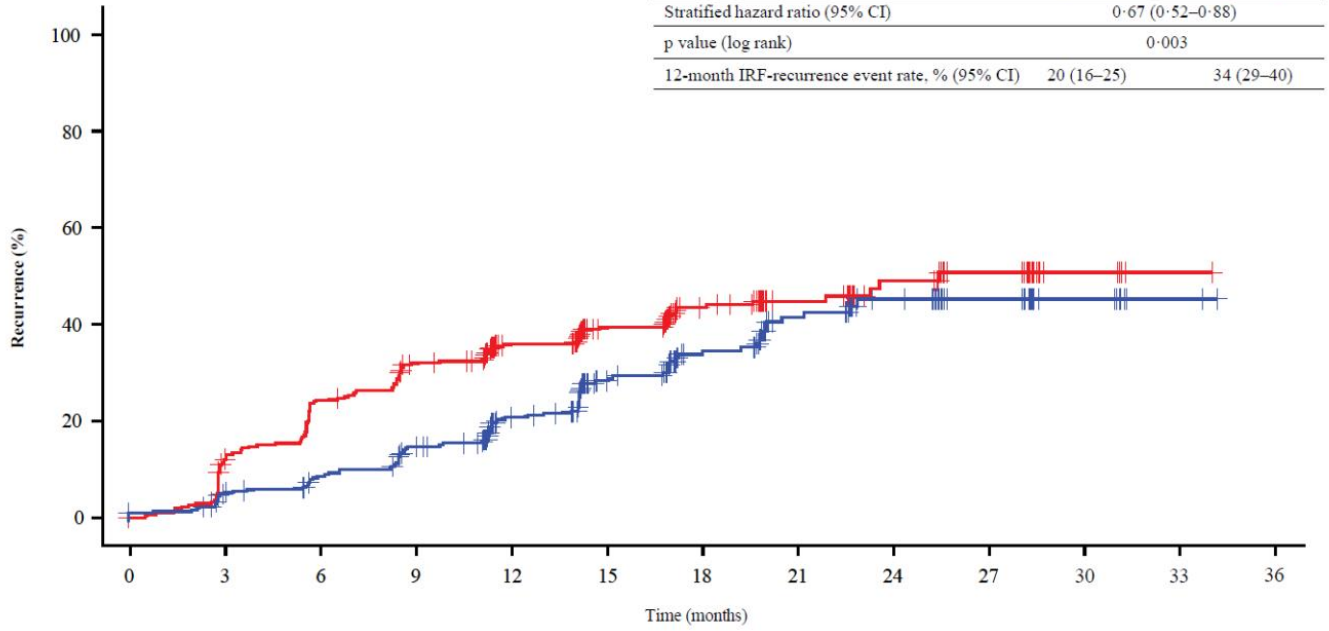
At the prespecified interim analysis, adjuvant atezolizumab + bevacizumab met its primary endpoint for superiority of recurrence-free survival (HR 0.72, 95% CI: 0.53-0.98; P=0.012) vs. active surveillance after a median follow-up of 17.4 months

Qin et al. The Lancet 2023

SECONDARY ENDPOINT

Time to Recurrence

	Atezolizumab plus bevacizumab (n=334)	Active surveillance (n=334)
Stratified hazard ratio (95% CI)	0·67 (0·52–0·88)	
p value (log rank)	0·003	
12-month IRF-recurrence event rate, % (95% CI)	20 (16–25)	34 (29–40)

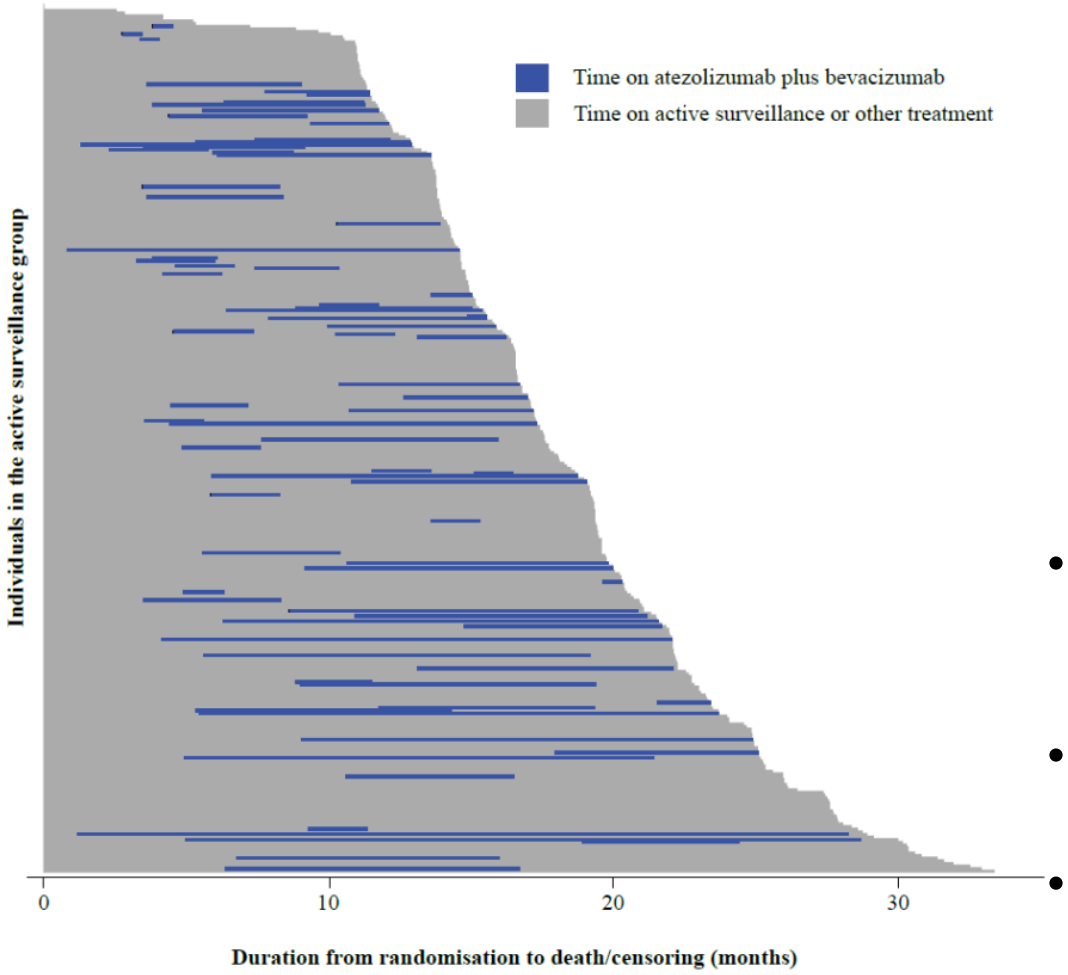


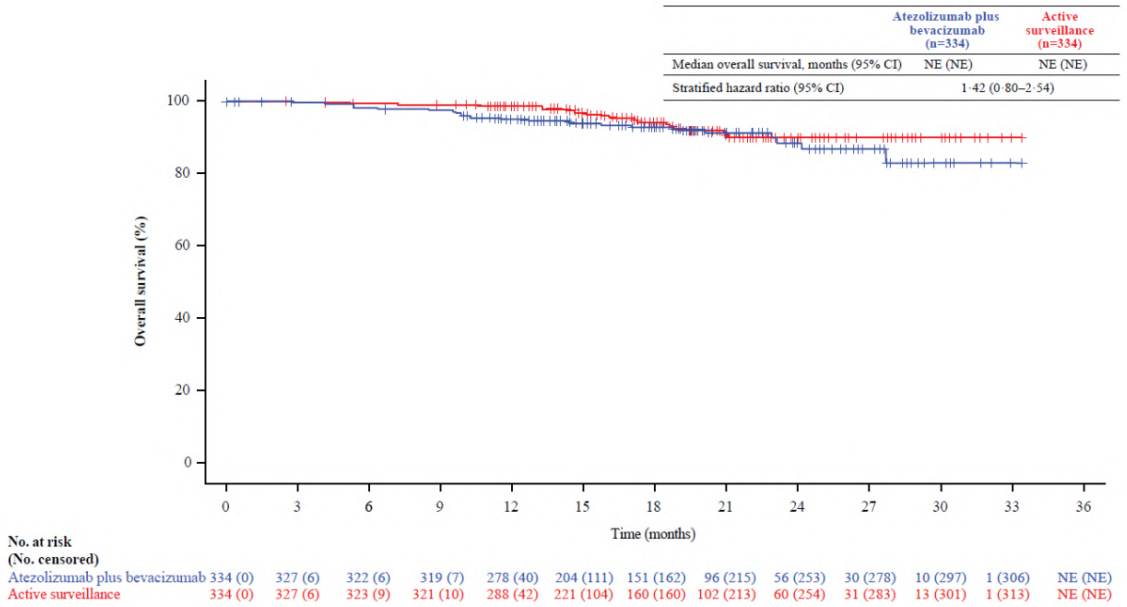
No. at risk (No. censored)													
Atezolizumab plus bevacizumab	334 (0)	302 (14)	287 (19)	263 (25)	209 (63)	138 (115)	96 (149)	62 (174)	36 (198)	22 (212)	9 (225)	1 (233)	NE (NE)
Active surveillance	334 (0)	282 (13)	245 (13)	214 (21)	179 (45)	131 (85)	92 (116)	57 (150)	36 (168)	20 (183)	6 (197)	1 (202)	NE (NE)

- Patients in the atezolizumab plus bevacizumab group had a 33% reduction in the risk of IRF-assessed disease recurrence compared with the active surveillance group (HR 0.67; 0.52-0.88; descriptive p=0.0030)

Qin et al. The Lancet 2023

OS WAS HIGHLY IMMATURE





- OS was very immature, with only a 7% event-to--patient ratio and 47 deaths (HR = 1.42, 95% CI: 0.80–2.54)
- mOS was not reached in either group
- 61% of the surveillance arm have already crossed over to atezolizumab and bevacizumab

Qin et al. The Lancet 2023
Guo & Chow. Hepatology Communications 2024

SAFETY OF IMBRAVE 050 VS IMBRAVE 150

	IMbrave 050 Atezo + bev (n=332)	IMbrave150 Atezo + Bev (n=329)
Treatment duration, median, mo	Atezo: 11.1 Bev: 11.0	Atezo: 7.4 Bev: 6.9
Patients with ≥1 AE, n (%)	326 (98)	323 (98)
Treatment-related AE	293 (88)	276 (84)
Grade 3/4 AE, n (%)	136 (41)	186 (57)
Treatment-related Grade 3/4 AE	116 (35)	117 (36)
Serious AE, n (%)	80 (24)	125 (38)
Treatment-related serious AE	44 (13)	56 (17)
Grade 5 AE, n (%)	6 (2)	15 (5)
Treatment-related Grade 5 AE	2 (<1)	6 (2)
AE leading to dose interruption of any study treatment, n (%)	155 (47)	163 (50)
AE leading to withdrawal from any study treatment, n (%)	63 (19)	51 (16)

Qin et al. The Lancet 2023
Finn et al. New England Journal of Medicine 2020

IMBRAVE050

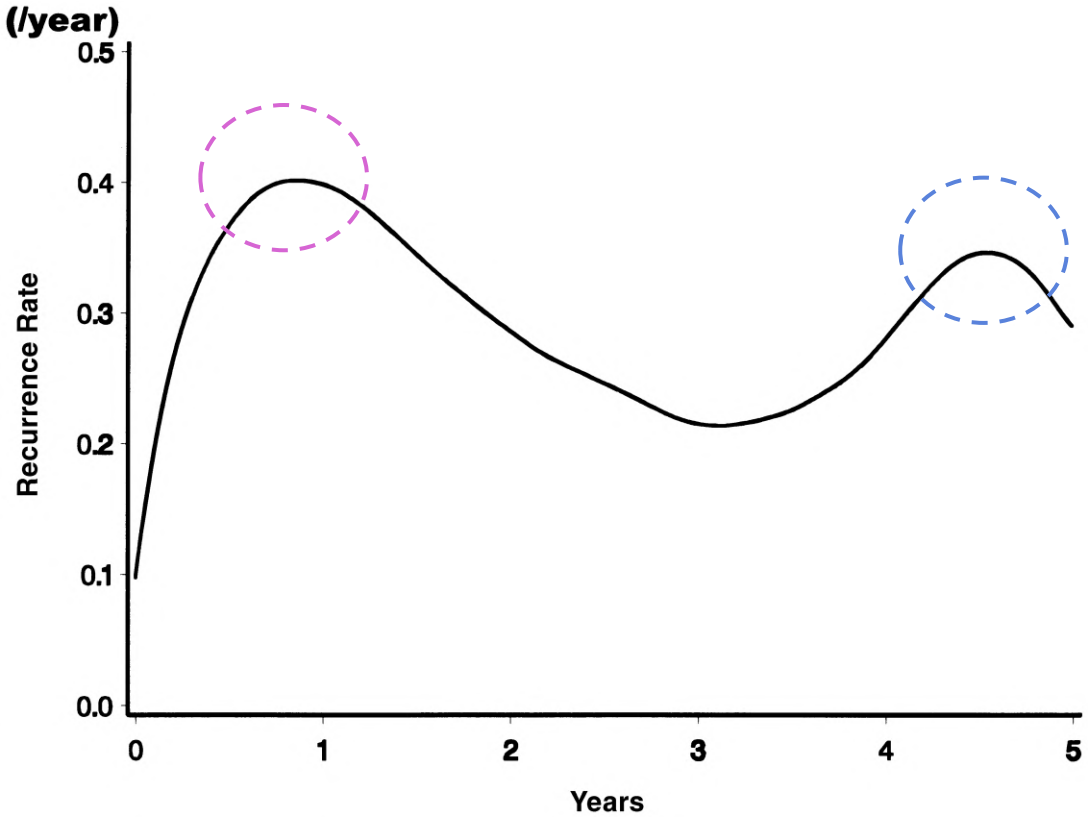
AE with an incidence rate of ≥10% in either treatment group by preferred term

Event, n (%)	Atezo + bev (n=332)		Active surveillance (n=330)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Proteinuria	154 (46)	29 (9)	12 (4)	0
Hypertension	127 (38)	61 (18)	10 (3)	3 (1)
Platelet count decreased	66 (20)	15 (5)	22 (7)	4 (1)
Aspartate aminotransferase increased	52 (16)	3 (1)	18 (5)	2 (1)
Alanine aminotransferase increased	47 (14)	2 (1)	18 (5)	3 (1)
Hypothyroidism	47 (14)	0	1 (<1)	0
Arthralgia	40 (12)	1 (<1%)	8 (2)	1 (1)
Pruritus	40 (12)	1 (<1%)	3 (1)	0
Rash	40 (12)	0	1 (<1)	0
Blood bilirubin increased	34 (10)	1 (<1%)	23 (7)	1 (1)
Pyrexia	34 (10)	0	7 (2)	0

Qin et al. The Lancet 2023

RATIONAL FOR ADJUVANT TREATMENT IN HCC

- 5-year survival rate post curative resection or ablation is 70% only
- Bimodal pattern of recurrence after HCC resection
  - Early recurrence: peaks at around 12 months due to micrometastases from the original tumor
  - Late recurrence: peaks at 4-5 years, related to de novo cancer arising from the underlying liver parenchymal disease
- The aim of adjuvant therapy is to prevent or delay recurrence by eradicating micrometastatic tumour deposits



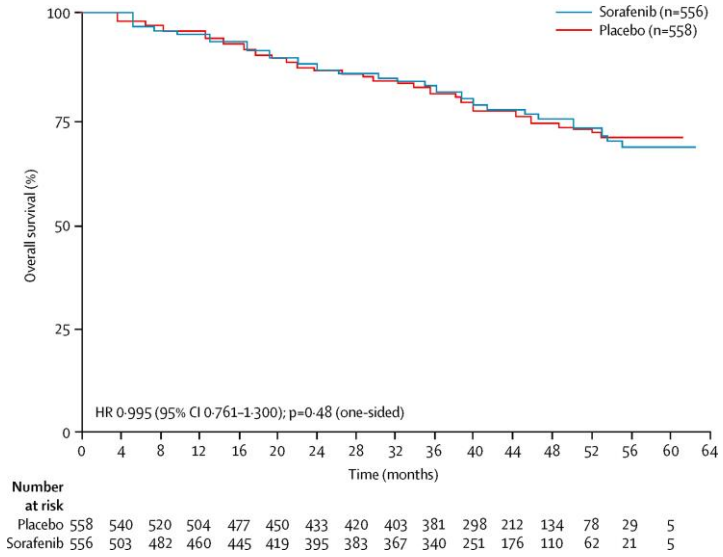
Pinna et al. Annals of Surgery 2018
Imamura et al. Journal of Hepatology 2003
Vogel et al. The Lancet 2022
Guo & Chow. Hepatology Communications 2024

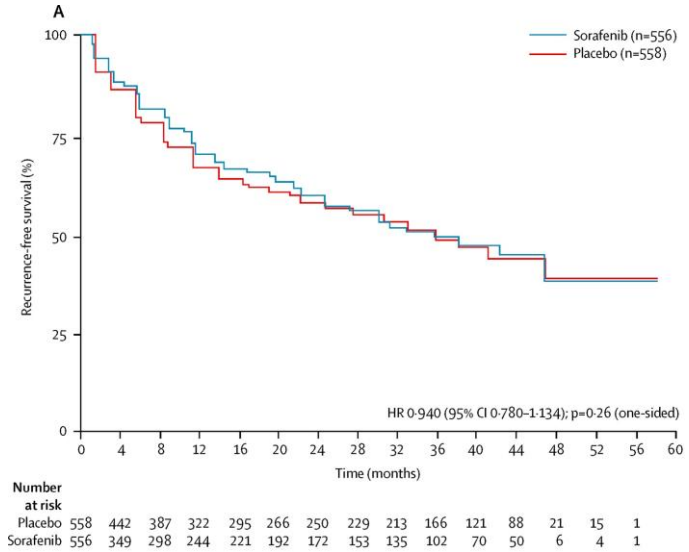
ADJUVANT PHASE 3 TRIALS IN EARLY HCC

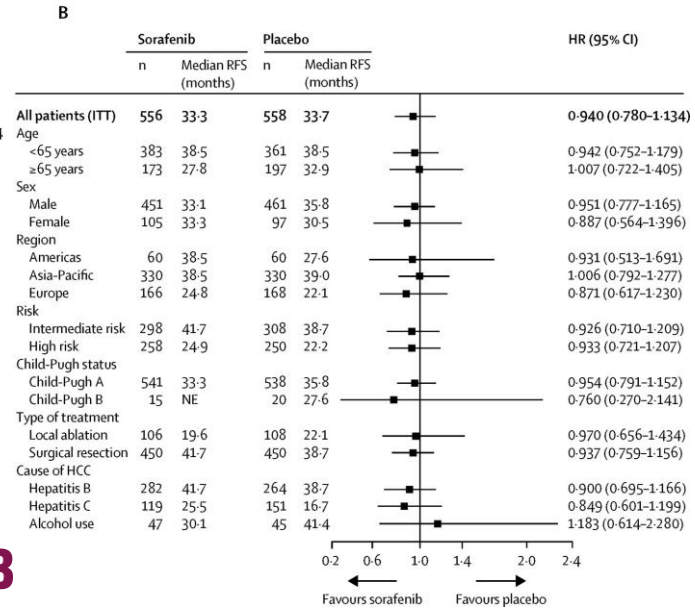
Trial	Design	Result
Yoshida H et al. Hepatology 2011	Vitamin K2 vs Placebo	No improvement in DFS
NIK-333 J Gastroenterol 2014	Peretinoin vs Placebo	No improvements in RFS
STORM Lancet Oncology 2015	Sorafenib vs Placebo	No improvement in RFS, TTR, and OS
IMbrave050 **Lancet 2023**	**Atezolizumab plus bevacizumab vs active surveillance**	**Improvement in RFS** 

Yoshida et al. Hepatology 2011
Okita et al. Journal of Gastroenterology 2015
Bruix et al. The Lancet Oncology 2015
Qin et al. The Lancet 2023

WHY ARE STORM AND IMBRAVE 050 DIFFERENT?







- Drug (targets angiogenesis vs dual inhibition of PD-L1 and VEGF signalling)
- Patient selection (different high risk criteria)
- Treatment schedule (4 years vs 1 year)
- Higher than expected treatment discontinuation rate in STORM (50% at 1 year)
- Different toxicities
- Both trials have no biomarker selection

STORM: No RFS or OS benefit between adjuvant Sorafenib vs placebo

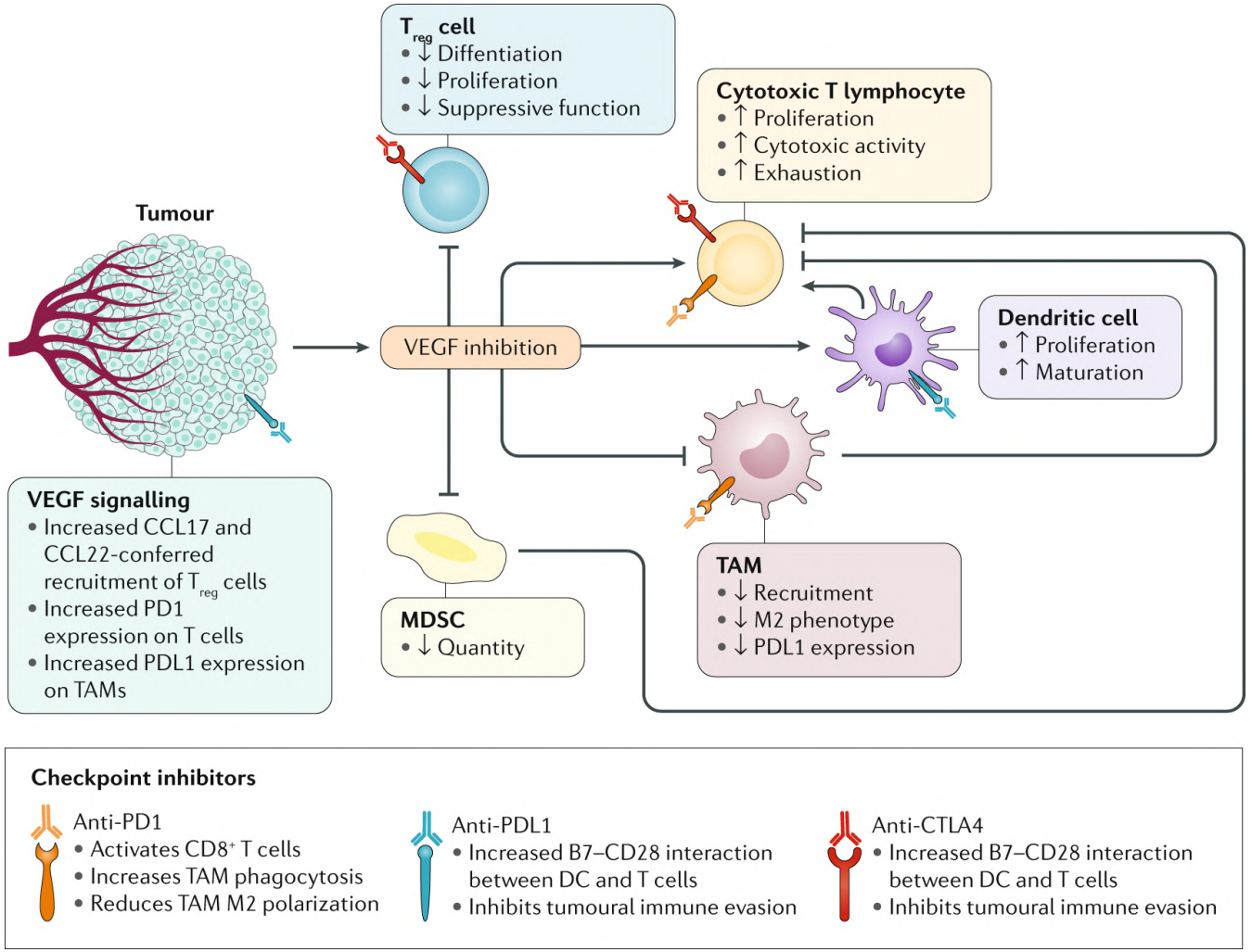
Bruix et al. The Lancet Oncology 2015
Qin et al. The Lancet 2023

IMMUNE MECHANISMS IN HCC RECURRENCES

- To evade from the host immune system is a hallmark of cancer
- Lesson from STORM: targeting angiogenesis alone is probably insufficient to prevent HCC recurrence
- Liver resection and radiofrequency ablation increase immunogenicity in HCC
- Tumor infiltration by immune cells e.g. CD8+ T cells and natural killer cells, production of interferon-γ is associated with a lower recurrence rate; while infiltration by suppressive cells e.g. Tregs and myeloid-derived suppressor cells is associated with a higher incidence of recurrence and poorer outcome

Hanahan. Cancer Discovery 2022
Kudo. Liver Cancer 2021

SCIENTIFIC RATIONALE FOR COMBINING VEGF INHIBITORS WITH IMMUNE THERAPIES



Llovet et al. Nature Reviews Gastroenterology Hepatology 2021

SCIENTIFIC RATIONALE FOR COMBINING ATEZOLIZUMAB AND BEVACIZUMAB IN ADJUVANT SETTING

- VEGF modulate numerous immune mechanism that contribute to immunosuppression in the liver's tumor microenvironment

- A phase 1b study (NCT02715531) showed superiority of the combination of atezolizumab and bevacizumab over atezolizumab monotherapy in patients with untreated unresectable HCC

- IMBRAVE 150 was the first study that showed a significant survival benefit of Atezolizumab and Bevacizumab compared with Sorafenib in unresectable HCC, representing the current first-line standard-of-care

Lee et al. The Lancet Oncology 2020
Finn et al. New England Journal of Medicine 2020,
Kudo. Liver Cancer 2023

PATIENT SELECTION IN IMBRAVE 050

- The majority of patients in IMbrave 050 were recruited in Asia, where HBV is the predominant cause of HCC. Eligibility criteria for resection are more aggressive in Asian guidelines. This well reflects the real world data on surgical resection of HCC globally.

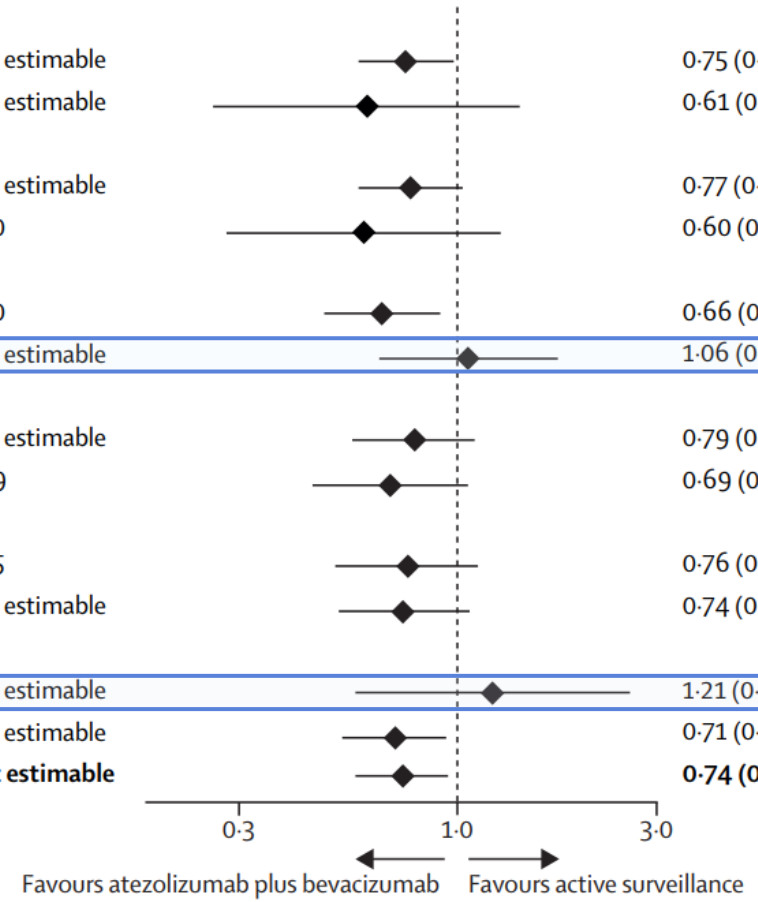
- Robust predictive biomarkers are not well established

- RFS benefit of adjuvant atezolizumab plus bevacizumab in key subgroups

Qin et al. The Lancet 2023

PATIENT SELECTION IN IMBRAVE 050

	Number of patients	Median recurrence-free survival, months		Unstratified hazard ratio (95% CI)
		Atezolizumab plus bevacizumab (n=334)	Active surveillance (n=334)	
Curative procedure				
Resection	585	Not estimable	Not estimable	0·75 (0·58–0·98)
Ablation	83	Not estimable	Not estimable	0·61 (0·26–1·41)
Number of tumours†				
1	526	Not estimable	Not estimable	0·77 (0·58–1·03)
>1	59	20·7	7·0	0·60 (0·28–1·27)
Tumour size, cm†				
>5	327	19·4	14·0	0·66 (0·48–0·91)
≤5	258	Not estimable	Not estimable	1·06 (0·65–1·74)
Microvascular invasion†				
Yes	354	22·1	Not estimable	0·79 (0·56–1·10)
No	231	Not estimable	24·9	0·69 (0·45–1·06)
Poor tumour differentiation†				
Yes	245	Not estimable	18·5	0·76 (0·51–1·12)
No	340	Not estimable	Not estimable	0·74 (0·52–1·07)
Transarterial chemoembolisation†				
Yes	66	14·9	Not estimable	1·21 (0·57–2·59)
No	519	Not estimable	Not estimable	0·71 (0·53–0·94)
All patients	**668**	**Not estimable**	**Not estimable**	**0·74 (0·57–0·95)**

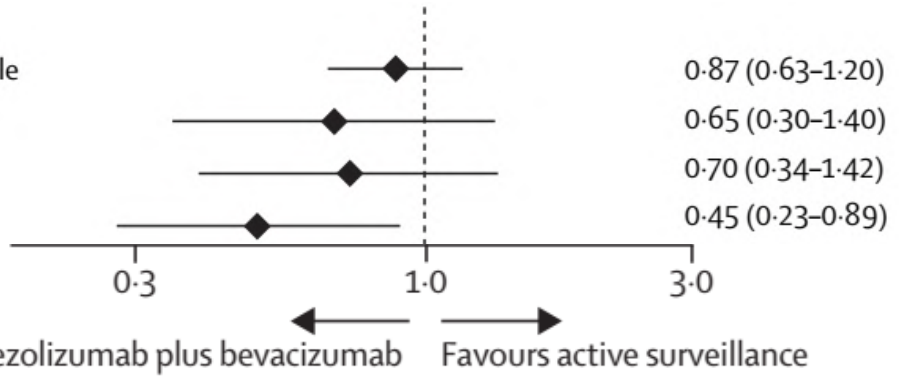


Qin et al. The Lancet 2023

ADJUVANT ATEZOLIZUMAB PLUS BEVACIZUMAB APPEAR TO SUPPRESS RECURRENCE IN HCC OF NON-VIRAL ETIOLOGY

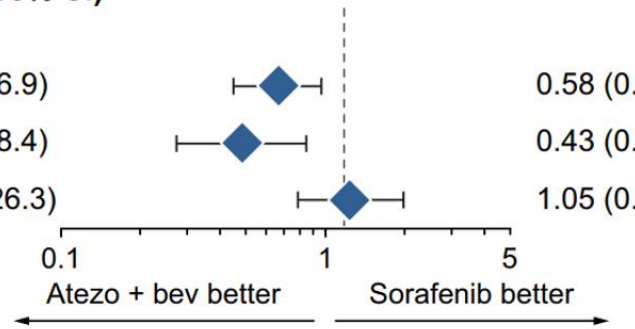
IMbrave 050

	Number of patients	Median recurrence-free survival, months		Unstratified hazard ratio (95% CI)
		Atezolizumab plus bevacizumab (n=334)	Active surveillance (n=334)	
Hepatocellular carcinoma cause				
Hepatitis B	416	Not estimable	Not estimable	0·87 (0·63–1·20)
Hepatitis C	72	Not estimable	24·9	0·65 (0·30–1·40)
Non-viral	83	Not estimable	22·7	0·70 (0·34–1·42)
Unknown	97	Not estimable	16·7	0·45 (0·23–0·89)



IMbrave 150

Subgroup	Atezolizumab plus bevacizumab		Sorafenib		Hazard ratio for death (95% CI)
	Events/ patients	Median OS, months (95% CI)	Events/ patients	Median OS, months (95% CI)	
Etiology					
Hepatitis B	86/164	19.0 (16.1-NE)	46/76	12.4 (6.7-16.9)	0.58 (0.40-0.83)
Hepatitis C	31/72	24.6 (19.8-NE)	24/36	12.6 (7.4-18.4)	0.43 (0.25-0.73)
Non-viral	63/100	17.0 (11.7-22.8)	30/53	18.1 (11.7-26.3)	1.05 (0.68-1.63)



Qin et al. The Lancet 2023
Cheng et al. Journal of Hepatology 2022

TOXICITY CONCERN IN ADJUVANT SETTING

- Be mindful of toxicities particularly in patients who could have already been cured by resection/ablation alone
- 88% of patients in the adjuvant atezolizumab plus bevacizumab arm suffered treatment-related AEs;
- 35% suffered ≥ grade 3 AEs and 19% had to discontinue bevacizumab due to AE
- Two of the grade 5 events in the experimental arm are related to treatment (esophageal varices hemorrhage and ischemic stroke)
- What are the trade-offs between risks and benefits when considering adjuvant atezolizumab plus bevacizumab?

Qin et al. The Lancet 2023

ATEZOLIZUMAB WITH A LOWER DOSE OF BEVACIZUMAB IN THE ADJUVANT SETTING?

- The recommended dosage of bevacizumab is 15 mg/kg every 3 weeks to synchronize with Atezolizumab 1200 mg every 3 weeks in IMbrave 150 and IMbrave 050

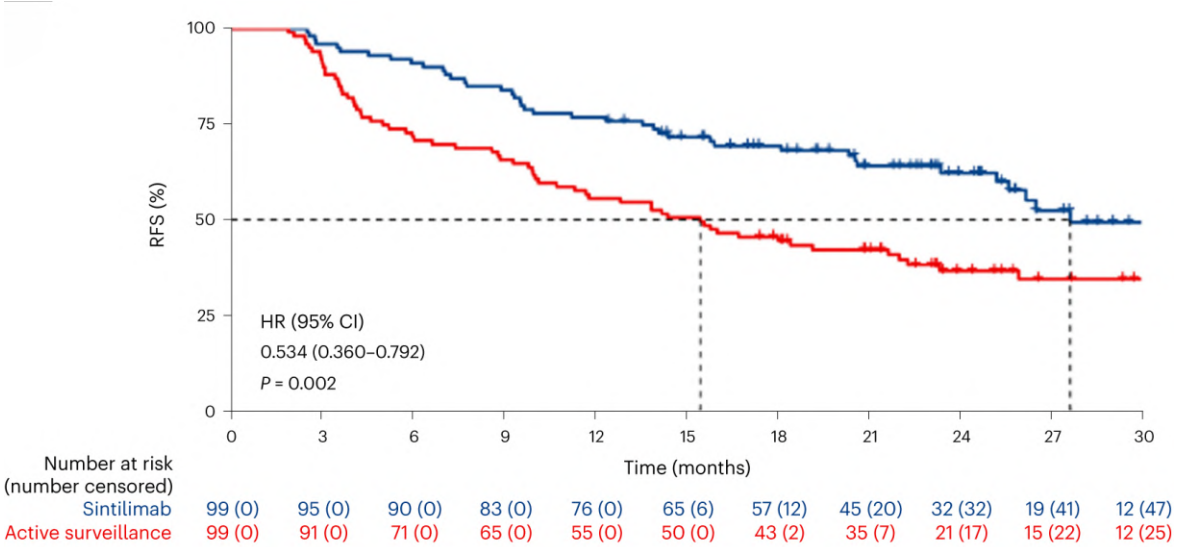
- In preclinical model, low dose or high dose bevacizumab in combination with immune checkpoint blockade improve survival compared with control

- In pharmacokinetic studies in human, Bevacizumab 5 or 10 mg/kg every 2 weeks or 7.5 mg/kg every 3 weeks were well tolerated in advanced HCC

- Pharmacokinetics of Bevacizumab 10 mg/kg every 2 weeks and 15 mg/kg every 3 weeks were comparable in advanced HCC

Shigeta et al. Hepatology 2020, Liu et al. Future Oncology 2021
Ratain & Strohbehn. European Journal of Cancer 2023
Slamon et al. New England Journal of Medicine 2024
Hortobagyi. New England Journal of Medicine 2022

DOES ADJUVANT IMMUNOTHERAPY ALONE SUFFICE?

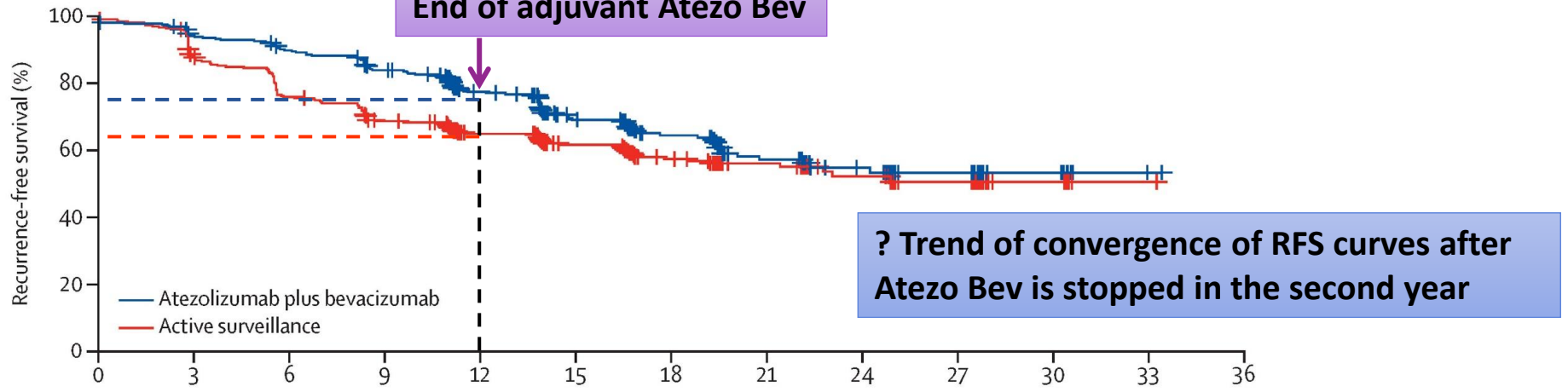


- Randomized, controlled, phase 2 trial in China evaluating adjuvant Sintilimab (PD-1 inhibitor) in resected high-risk HCC
- Focused on HCC with microvascular invasion
- **6 months** of adjuvant Sintilimab significantly prolonged RFS compared to active surveillance (median RFS, 27.7 vs 15.5 months; HR 0.53; P = 0.002) in resected high-risk HCC
- Subgroup analysis shows benefits in patients with tumour diameter >5 cm, multiple tumours or high-risk MVI grade
- In the sintilimab group, 12.4% of patients experienced Grade 3/4 treatment-related AEs

Wang et al. Nature Medicine 2024

DOES ADJUVANT ATEZOLIZUMAB PLUS BEVACIZUMAB DELAY OR PREVENT RECURRENCE?

	Atezolizumab plus bevacizumab (n=334)	Active surveillance (n=334)	
Patients with events, n (%)	110 (33%)	133 (40%)	
Median RFS, months (95% CI)	NE (22·1–NE)	NE (21·4–NE)	
12-month IRF-RFS event-free rate, % (95% CI)	78% (73–82)	65% (60–71)	
Stratified hazard ratio (adjusted 95% CI)			0·72 (0·53–0·98)
p value (log rank)			0·012



Number at risk (number censored)													
Atezolizumab plus bevacizumab	334 (0)	305 (10)	290 (12)	268 (15)	211 (53)	139 (105)	97 (139)	63 (164)	37 (188)	22 (202)	9 (215)	1 (223)	NE (NE)
Active surveillance	334 (0)	283 (12)	245 (12)	214 (20)	179 (44)	131 (84)	93 (114)	57 (148)	36 (166)	20 (181)	6 (195)	1 (200)	NE (NE)

- Whether the RFS benefit translate into an improvement in OS is crucial in a curative setting
- Long term follow up survival data is crucial to assess risk benefit profile (late recurrences occur between 4-5 years)
- OS benefits of adjuvant Atezolizumab plus Bevacizumab may be compromised by crossing over

Qin et al. The Lancet 2023

DOES ADJUVANT ATEZOLIZUMAB PLUS BEVACIZUMAB ALTER THE TUMOUR BIOLOGY?

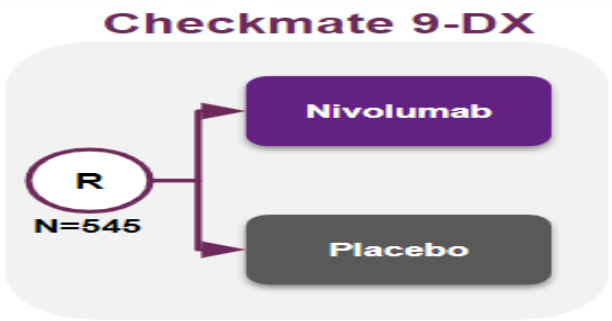
	Atezolizumab plus bevacizumab (n=334)	Active surveillance (n=334)
Total number of HCC recurrences	100	131
Intrahepatic recurrence only	67 (67%)	86 (66%)
Extrahepatic recurrence only	31 (31%)	40 (31%)
Both intra- and extrahepatic recurrence	2 (2%)	5 (4%)

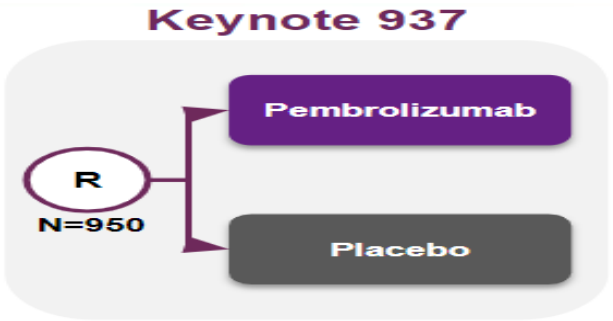
Site of HCC recurrence (IMbrave 050 supplementary appendix)

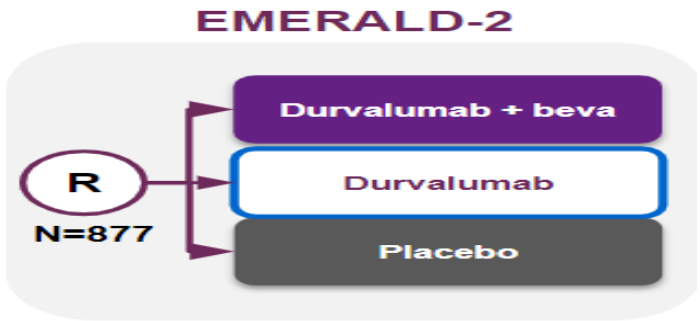
- Recurrences with vascular invasion, extrahepatic spread or TACE unsuitable disease greater than 6 months are more likely to be responsive to atezolizumab and bevacizumab
- ? Development of antidrug antibodies after receiving Atezolizumab plus Bevacizumab in the adjuvant setting
- Intrahepatic recurrence (the majority) may be amenable to locoregional therapies or liver transplant

Qin et al. The Lancet 2023
Singal et al. Hepatology 2023
Kim et al. JAMA Oncology 2022

Ongoing Clinical Trials in Adjuvant HCC Immunotherapy







Study name	n	No. arms	Experimental Rx	Control arm	High-risk pts only	TACE allowed	Blinding	Primary endpoint
IMbrave050[1]	662	2	Atezo + Bev	Active Surveillance	Yes (medium)	TACE	Open-label	RFS
CheckMate 9DX[2]	545	2	Nivolumab	Placebo	Yes (narrow)	no TACE	Blinded	RFS
Keynote 937[3]	950	2	Pembrolizumab	Placebo	Yes (broad)	no TACE	Blinded	RFS/OS
EMERALD-2[4]	877	3	Durva or Durva + Bev	Placebo	Yes (narrow)	TACE	Blinded	RFS (central review)

1. Hack, Stephen P., et al. Future Oncology 16.15 (2020): 975-989.
2. Exposito, MJ Jimenez, et al. Annals of Oncology 29 (2018): viii267-viii268.
3. Zhu, Andrew, et al. Cancer Research 80.16_Supplement (2020): CT284-CT284.
4. Knox, J., et al. Annals of Oncology 30 (2019): iv59-iv60..

CONCLUSION

- IMbrave 050 is the groundbreaking first positive adjuvant phase III study in HCC at high risk of recurrence after resection or ablation and potentially practice-changing

- Longer follow up is required to determine whether RFS benefit translates into OS benefit
- The next step is to optimize dosage, duration of adjuvant therapy, mitigate toxicity and identify predictive biomarkers (e.g. PD-L1 status, ctDNA) to intensity and de-escalate
- Neoadjuvant immunotherapy for high-risk HCC is on the horizon

ESMO VIRTUAL JOURNAL CLUB

CAPIVASERTIB IN HORMONE RECEPTOR–POSITIVE ADVANCED BREAST CANCER

Shani Paluch-Shimon, MBBS, MSc

Hadassah University Hospital

Jerusalem, Israel

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MSD: Speakers bureau, honoraria, consultancy

Exact Sciences/Rhenium: Speakers bureau, honoraria

Gilead: Consultancy, speakers bureau

Stemline: Consultancy

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Capivasertib in Hormone Receptor–Positive Advanced Breast Cancer

N.C. Turner, M. Oliveira, S.J. Howell, F. Dalenc, J. Cortes, H.L. Gomez Moreno, X. Hu, K. Jhaveri, P. Krivorotko, S. Loibl, S. Morales Murillo, M. Okera, Y.H. Park, J. Sohn, M. Toi, E. Tokunaga, S. Yousef, L. Zhukova, E.C. de Bruin, L. Grinsted, G. Schiavon, A. Foxley, and H.S. Rugo, for the CAPItello-291 Study Group*

Turner NC, Oliveira M, Howell SJ, Dalenc F, Cortes J, Gomez Moreno HL, Hu X, Jhaveri K, Krivorotko P, Loibl S, Morales Murillo S, Okera M, Park YH, Sohn J, Toi M, Tokunaga E, Yousef S, Zhukova L, de Bruin EC, Grinsted L, Schiavon G, Foxley A, Rugo HS; CAPItello-291 Study Group. Capivasertib in Hormone Receptor-Positive Advanced Breast Cancer. N Engl J Med. 2023 Jun 1;388(22):2058-2070. doi: 10.1056/NEJMoa2214131. PMID: 37256976.

https://www.nejm.org/doi/full/10.1056/NEJMoa2214131

CAPItello-291: Study overview

Phase III, randomized, double-blind, placebo-controlled study (NCT04305496)

Patients with HR+/HER2– ABC

- Men and pre-/post-menopausal women
- Recurrence or progression while on or <12 months from end of adjuvant AI, or progression while on prior AI for ABC
- ≤2 lines of prior endocrine therapy for ABC
- ≤1 line of chemotherapy for ABC
- Prior CDK4/6 inhibitors allowed (at least 51% required)
- No prior SERD, mTOR inhibitor, PI3K inhibitor, or AKT inhibitor
- HbA1c <8.0% (63.9 mmol/mol) and diabetes not requiring insulin allowed
- FFPE tumor sample from the primary/recurrent cancer available for retrospective central molecular testing

R1:1 (N=708)

Capivasertib	400 mg twice daily, 4 days on, 3 days off
Fulvestrant	500 mg: cycle 1, days 1 & 15; then every 4 weeks
Placebo	Twice daily, 4 days on, 3 days off
Fulvestrant	500 mg: cycle 1, days 1 & 15; then every 4 weeks

Stratification factors:
- Liver metastases (yes/no)
- Prior CDK4/6 inhibitor (yes/no)
- Region*

Dual primary endpoints

PFS by investigator assessment
- Overall
- AKT pathway-altered tumors (≥1 qualifying *PIK3CA*, *AKT1*, or *PTEN* alteration)

Key secondary endpoints

Overall survival
- Overall
- AKT pathway-altered tumors

Objective response rate
- Overall
- AKT pathway-altered tumors

HER2– was defined as IHC 0 or 1+, or IHC 2+/ISH–. *Region 1: United States, Canada, Western Europe, Australia, and Israel, Region 2: Latin America, Eastern Europe and Russia vs Region 3: Asia.
ABC, advanced (locally advanced [inoperable] or metastatic) breast cancer.
Pre- or peri-menopausal women also received a luteinizing hormone-releasing hormone agonist for the duration of the study treatment

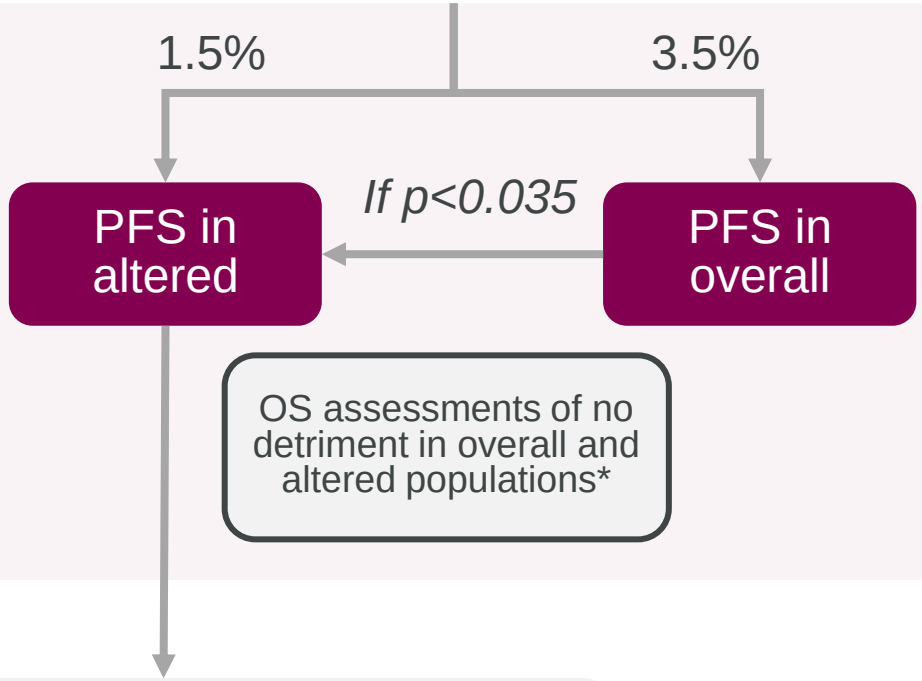
Turner et al, SABCS 2022

CAPItello-291: Statistical design

R1:1

Multiple testing procedure

5% (2-sided)



Dual primary endpoints

PFS primary analysis (15 August 2022)

Two further formal OS analyses

Primary analysis for PFS by investigator assessment

With 542 PFS events in the overall population and 217 PFS events in the AKT pathway-altered population, the study had:

- >99% power to detect a difference in the overall population
- 91% power to detect a difference in the AKT pathway altered population

This assumed PFS HR=0.64 and 3.5% alpha is recycled to the AKT pathway altered population

*0.01% alpha penalty assigned to OS analyses of no detriment. Formal analysis not prespecified.

Baseline and tumor characteristics

Characteristic		Overall population		AKT pathway-altered population	
		Capivasertib + fulvestrant (N=355)	Placebo + fulvestrant (N=353)	Capivasertib + fulvestrant (N=155)	Placebo + fulvestrant (N=134)
Median age; years (range)		59 (26–84)	58 (26–90)	58 (36–84)	60 (34–90)
Female; n (%)		352 (99.2)	349 (98.9)	153 (98.7)	134 (100)
Post menopausal; n (%)		287 (80.8)	260 (73.7)	130 (83.9)	105 (78.4)
Race; n (%)	White	201 (56.6)	206 (58.4)	75 (48.4)	76 (56.7)
	Asian	95 (26.8)	94 (26.6)	48 (31.0)	35 (26.1)
	Black or African American	4 (1.1)	4 (1.1)	2 (1.3)	1 (0.7)
	Other	55 (15.5)	49 (13.9)	30 (19.4)	22 (16.4)
Region*; n (%)	1	197 (55.5)	198 (56.1)	80 (51.6)	76 (56.7)
	2	68 (19.2)	68 (19.3)	29 (18.7)	24 (17.9)
	3	90 (25.4)	87 (24.6)	46 (29.7)	34 (25.4)
Metastatic sites; n (%)	Bone only	51 (14.4)	52 (14.7)	25 (16.1)	16 (11.9)
	Liver*	156 (43.9)	150 (42.5)	70 (45.2)	53 (39.6)
	Visceral	237 (66.8)	241 (68.3)	103 (66.5)	98 (73.1)
Hormone receptor status; n (%)†	ER+/PR+	255 (71.8)	246 (69.7)	116 (74.8)	101 (75.4)
	ER+/PR-	94 (26.5)	103 (29.2)	35 (22.6)	31 (23.1)
	ER+/PR unknown	5 (1.4)	4 (1.1)	4 (2.6)	2 (1.5)
Endocrine resistance; n (%)	Primary	127 (35.8)	135 (38.2)	60 (38.7)	55 (41.0)
	Secondary	228 (64.2)	218 (61.8)	95 (61.3)	79 (59.0)

*Baseline stratification factors. †One patient in the capivasertib + fulvestrant group was ER negative. Region 1: United States, Canada, Western Europe, Australia, and Israel, Region 2: Latin America, Eastern Europe and Russia, Region 3: Asia. Primary and secondary resistance were defined using the 4th ESO-ESMO International Consensus Guidelines for ABC.

Prior treatments

Characteristic		Overall population		AKT pathway-altered population	
		Capivasertib + fulvestrant (N=355)	Placebo + fulvestrant (N=353)	Capivasertib + fulvestrant (N=155)	Placebo + fulvestrant (N=134)
Prior endocrine therapy for ABC; n (%)	0	40 (11.3)	54 (15.3)	14 (9.0)	20 (14.9)
	1	286 (80.6)	252 (71.4)	130 (83.9)	96 (71.6)
	2	29 (8.2)	47 (13.3)	11 (7.1)	18 (13.4)
Previous CDK4/6 inhibitor for ABC; n (%)		245 (69.0)	244 (69.1)	113 (72.9)	91 (67.9)
Previous chemotherapy; n (%)	Adjuvant/neoadjuvant	180 (50.7)	170 (48.2)	79 (51.0)	67 (50.0)
	ABC	65 (18.3)	64 (18.1)	30 (19.4)	23 (17.2)

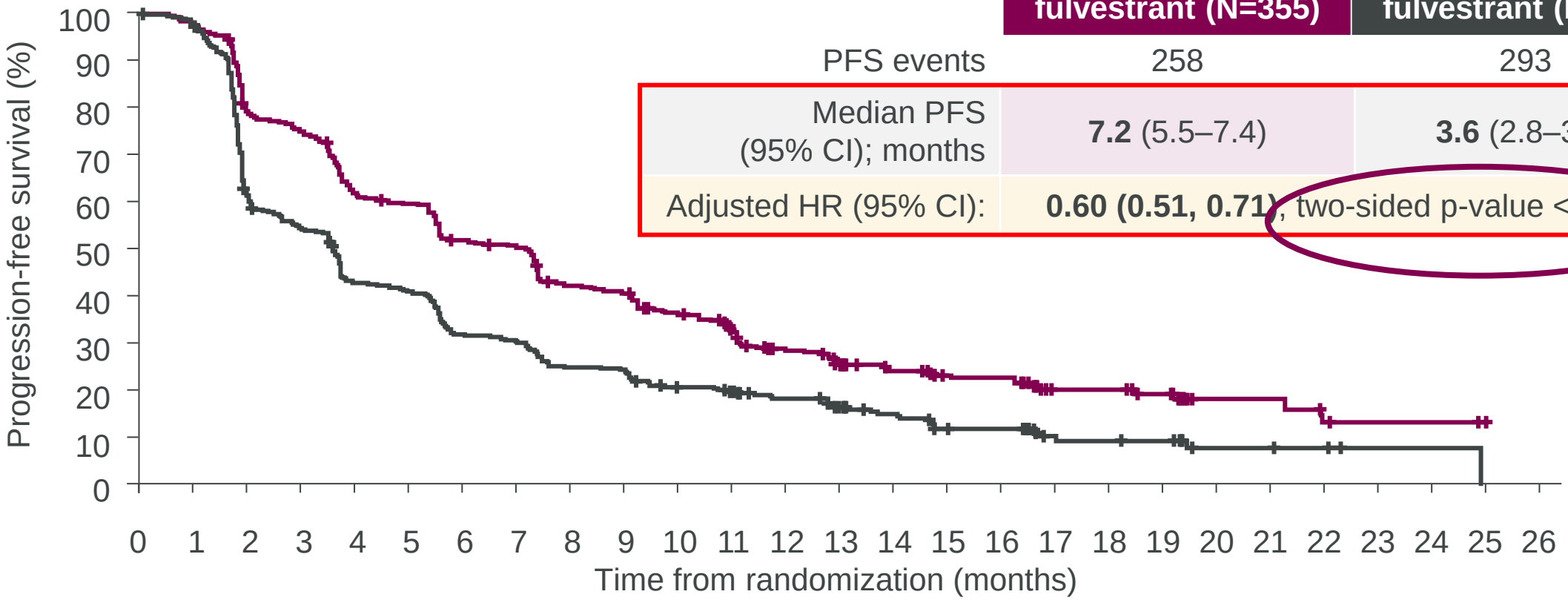
AKT pathway alterations

Alteration; n (%)		Capivasertib + fulvestrant (N=355)	Placebo + fulvestrant (N=353)
Any AKT pathway alteration		**155 (43.7)**	**134 (38.0)**
PIK3CA	Any	116 (32.7)	103 (29.2)
	PIK3CA only	110 (31.0)	92 (26.1)
	PIK3CA and *AKT1*	2 (0.6)	2 (0.6)
	PIK3CA and *PTEN*	4 (1.1)	9 (2.5)
AKT1 only		18 (5.1)	15 (4.2)
PTEN only		21 (5.9)	16 (4.5)
Non-altered		**200 (56.3)**	**219 (62.0)**
AKT pathway alteration not detected		142 (40.0)	171 (48.4)
Unknown		58 (16.3)	48 (13.6)
No sample available		10 (2.8)	4 (1.1)
Preanalytical failure		39 (11.0)	34 (9.6)
Post analytical failure		9 (2.5)	10 (2.8)

AKT pathway alteration status was determined centrally using next-generation sequencing in tumor tissue with the FoundationOne®CDx assay (and Burning Rock assay in China)

Dual-primary endpoint: Investigator-assessed PFS in the overall population

	Capivasertib + fulvestrant (N=355)	Placebo + fulvestrant (N=353)
PFS events	258	293
Median PFS (95% CI); months	**7.2** (5.5–7.4)	**3.6** (2.8–3.7)
Adjusted HR (95% CI):	**0.60 (0.51, 0.71)**, two-sided p-value <0.001	



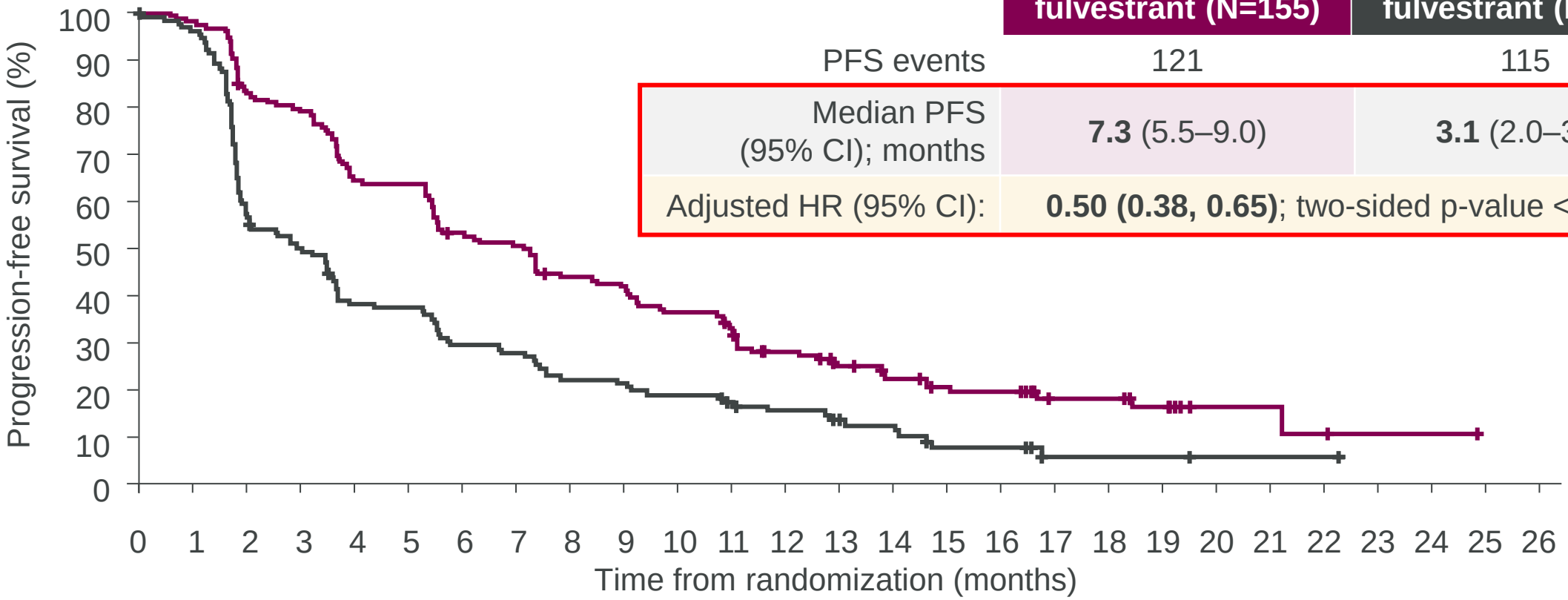
Number of patients at risk

Capivasertib + fulvestrant	355	330	266	252	207	199	172	166	138	133	115	98	78	64	55	44	43	25	25	21	8	8	5	2	2	1	0
Placebo + fulvestrant	353	329	207	182	142	136	106	100	83	81	66	59	51	41	33	24	23	12	11	10	4	4	3	1	1	0	0

+ indicates a censored observation. HR was estimated using the Cox proportional hazard model stratified by the presence of liver metastases, prior use of CDK4/6 inhibitor, and geographic region.

Dual-primary endpoint: Investigator-assessed PFS in the AKT pathway-altered population

	Capivasertib + fulvestrant (N=155)	Placebo + fulvestrant (N=134)
PFS events	121	115
Median PFS (95% CI); months	**7.3** (5.5–9.0)	**3.1** (2.0–3.7)
Adjusted HR (95% CI):	**0.50 (0.38, 0.65)**; two-sided p-value <0.001	



Number of patients at risk

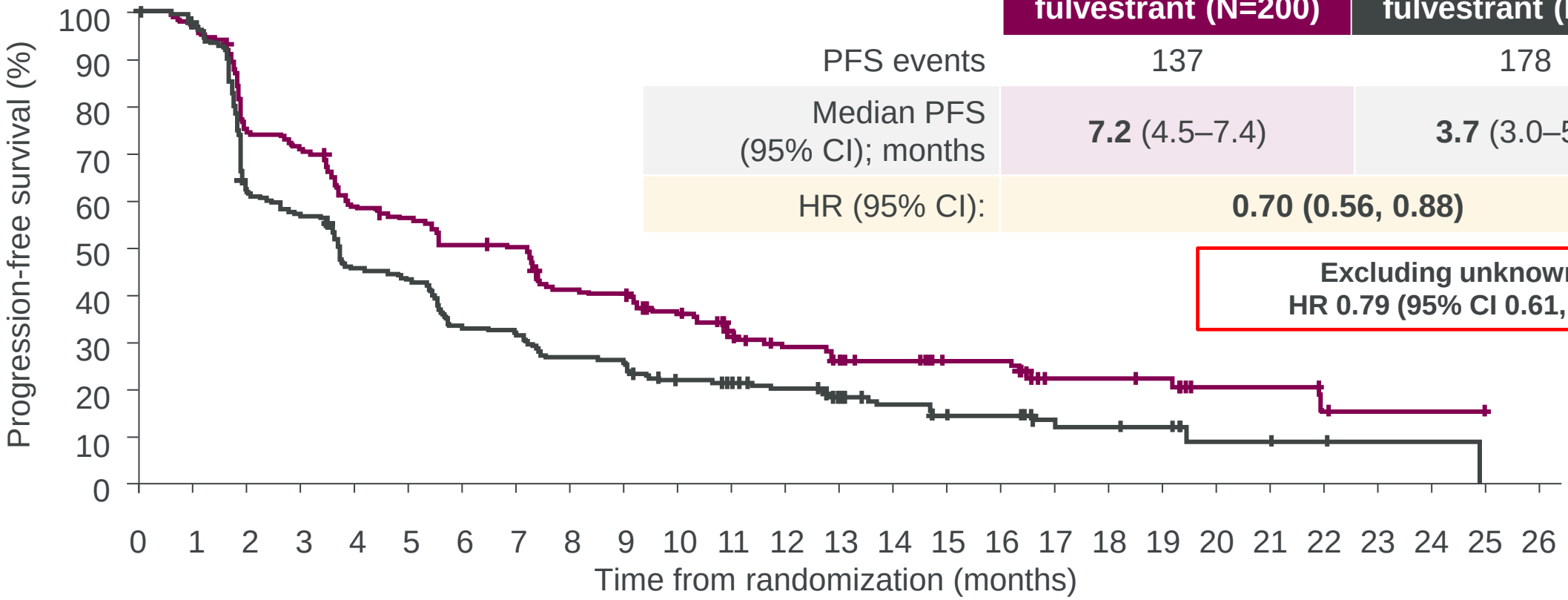
Capivasertib + fulvestrant	155	150	127	121	99	97	80	76	65	62	54	49	38	31	26	22	21	12	12	9	3	3	2	1	1	0	0
Placebo + fulvestrant	134	124	77	64	48	47	37	35	28	27	24	20	17	14	11	6	6	2	2	2	1	1	1	0	0	0	0

+ indicates a censored observation. HR was estimated using the Cox proportional hazard model stratified by the presence of liver metastases and prior use of CDK4/6 inhibitor.

Exploratory analysis: Investigator-assessed PFS in the non-altered population (including unknown†)

	Capivasertib + fulvestrant (N=200)	Placebo + fulvestrant (N=219)
PFS events	137	178
Median PFS (95% CI); months	**7.2** (4.5–7.4)	**3.7** (3.0–5.0)
HR (95% CI):	**0.70 (0.56, 0.88)**	

Excluding unknowns:
HR 0.79 (95% CI 0.61, 1.02)



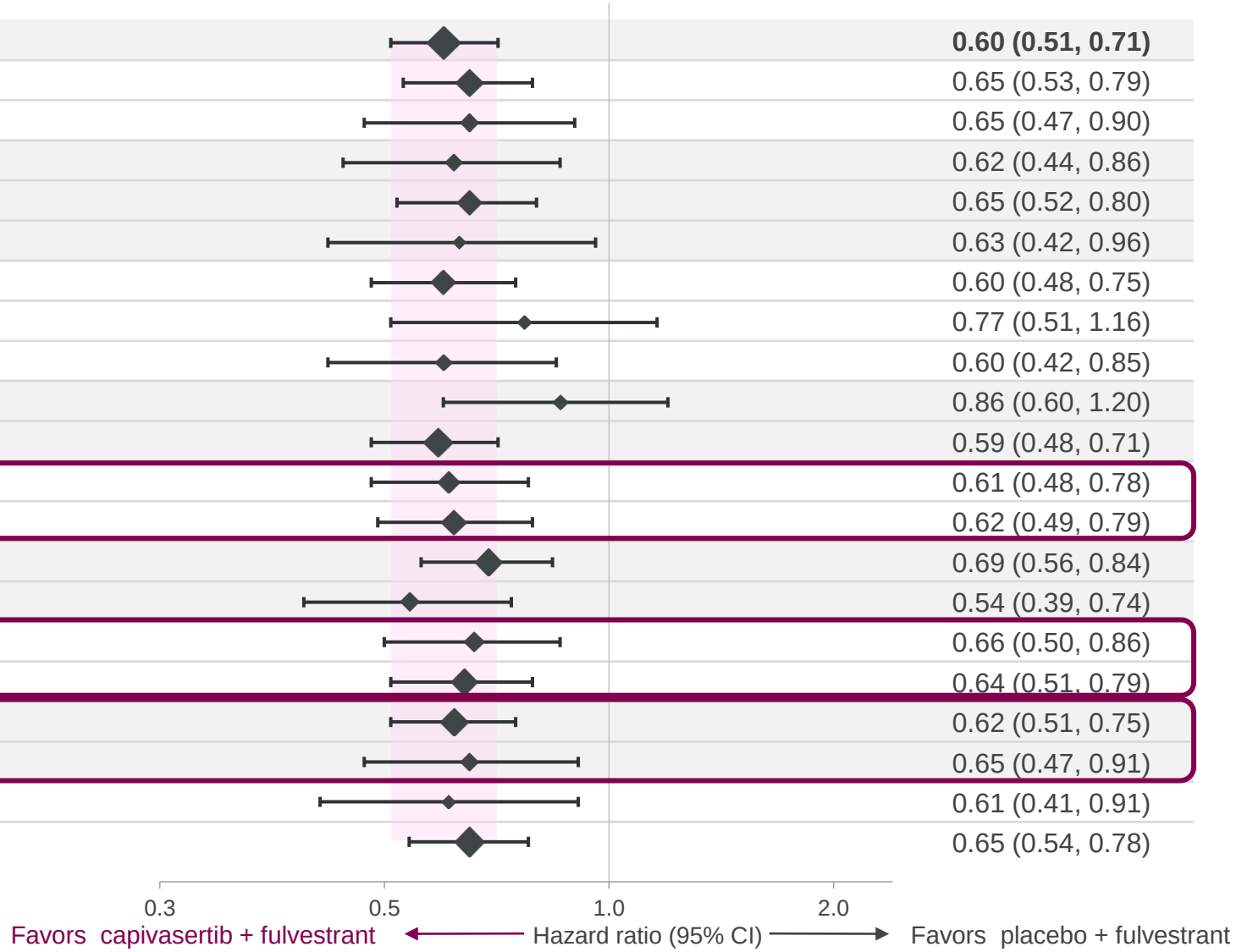
Number of patients at risk

Capivasertib + fulvestrant	200	180	139	131	108	102	92	90	73	71	61	49	40	33	29	22	22	13	13	12	5	5	3	1	1	1	0
Placebo + fulvestrant	219	205	130	118	94	89	69	65	55	54	42	39	34	27	22	18	17	10	9	8	3	3	2	1	1	0	0

+ indicates a censored observation. †Patients with no valid NGS results. HR was estimated using the Cox proportional hazard model stratified by the presence of liver metastases and prior use of CDK4/6 inhibitor.

Investigator-assessed PFS by subgroup: Overall population

		Number of patients	HR (95%CI)
All patients		**708**	**0.60 (0.51, 0.71)**
Age	<65 years	491	0.65 (0.53, 0.79)
	≥65 years	217	0.65 (0.47, 0.90)
Race	Asian	189	0.62 (0.44, 0.86)
	White	407	0.65 (0.52, 0.80)
	Other	112	0.63 (0.42, 0.96)
Region	1	395	0.60 (0.48, 0.75)
	2	136	0.77 (0.51, 1.16)
	3	177	0.60 (0.42, 0.85)
Menopausal status (females only)	Pre/peri	154	0.86 (0.60, 1.20)
	Post	547	0.59 (0.48, 0.71)
Liver metastases	Yes	306	0.61 (0.48, 0.78)
	No	402	0.62 (0.49, 0.79)
Visceral metastases	Yes	478	0.69 (0.56, 0.84)
	No	230	0.54 (0.39, 0.74)
Endocrine resistance	Primary	262	0.66 (0.50, 0.86)
	Secondary	446	0.64 (0.51, 0.79)
Prior use of CDK4/6 inhibitors	Yes	496	0.62 (0.51, 0.75)
	No	212	0.65 (0.47, 0.91)
Prior chemotherapy for ABC	Yes	129	0.61 (0.41, 0.91)
	No	579	0.65 (0.54, 0.78)



Region 1: United States, Canada, Western Europe, Australia, and Israel, Region 2: Latin America, Eastern Europe and Russia; Region 3: Asia. Primary and secondary resistance as per ESMO definition.

Response per investigator assessment

	Overall population		AKT pathway-altered population	
	Capivasertib + fulvestrant	**Placebo + fulvestrant**	**Capivasertib + fulvestrant**	**Placebo + fulvestrant**
Patients with measurable disease at baseline	310	320	132	124
Objective response rate; n (%)	71 (22.9)	39 (12.2)	38 (28.8)	12 (9.7)
Odds ratio (95% CI)*	2.19 (1.42, 3.36)		3.93 (1.93, 8.04)	
Best objective response in all patients; n (%)	355	353	155	134
Complete response	4 (1.1)	1 (0.3)	3 (1.9)	0
Partial response	68 (19.2)	38 (10.8)	35 (22.6)	12 (9.0)
Stable disease (≥ 8 weeks)	187 (52.7)	152 (43.1)	84 (54.2)	55 (41.0)
Progressive disease	83 (23.4)	149 (42.2)	31 (20.0)	62 (46.3)
Non evaluable	13 (3.7)	13 (3.7)	2 (1.3)	5 (3.7)

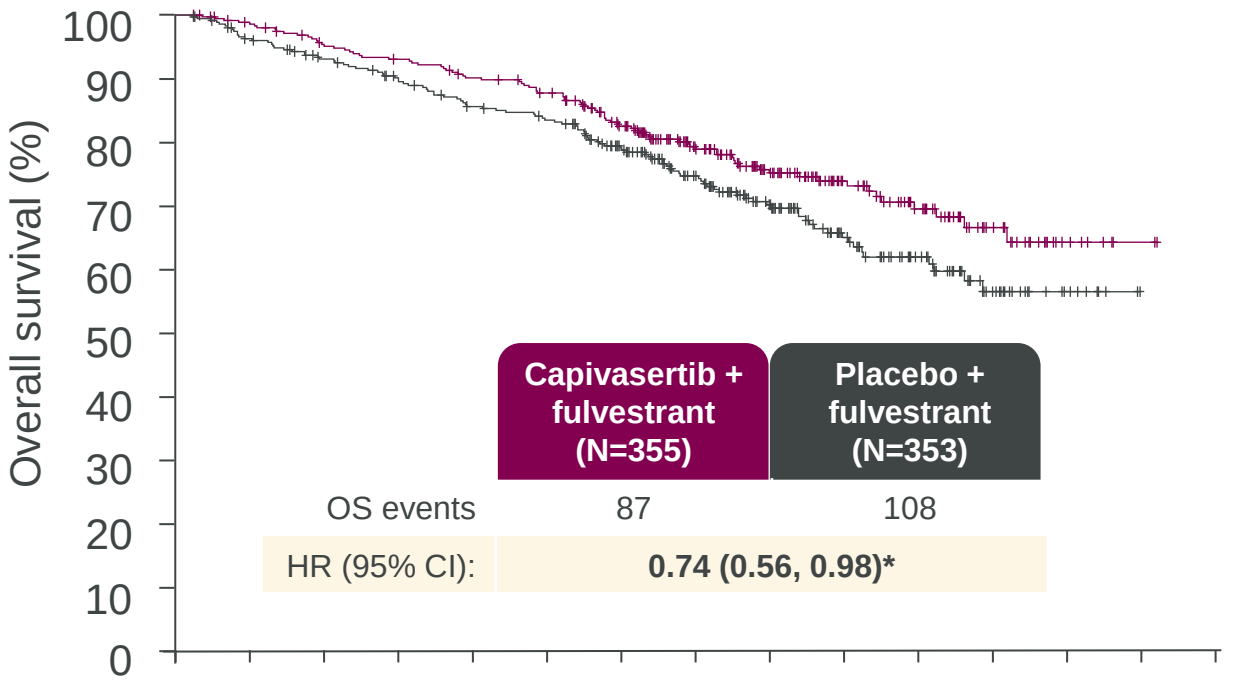
As per the multiple testing procedure, formal comparison of ORR will only be conducted if overall survival is significant in both populations.

Objective response rates were assessed in patients with measurable disease at baseline.

*Analysis was performed using logistic regression adjusted for stratification factors. Odds ratio >1 favors capivasertib + fulvestrant.

Overall survival at 28% maturity overall

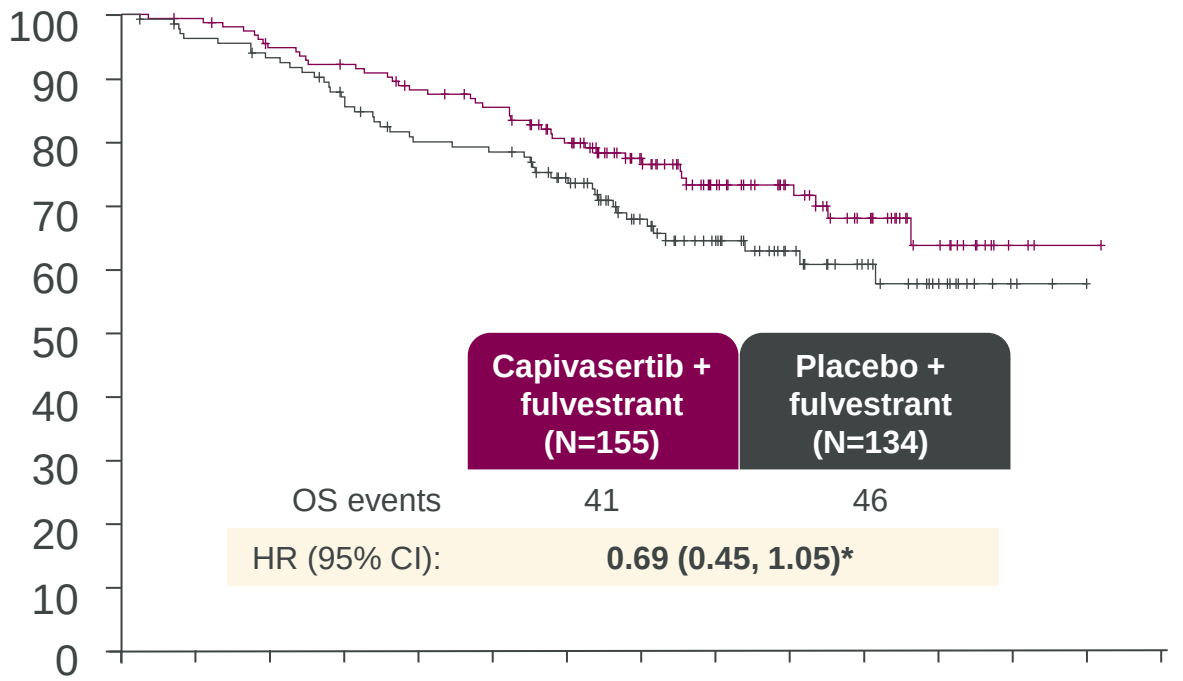
Overall population



Number of patients at risk

Capivasertib + fulvestrant	355	343	327	318	306	295	258	198	144	95	63	33	9	2	0
Placebo + fulvestrant	353	334	316	301	283	274	237	181	134	90	59	30	11	0	0

AKT pathway-altered population



Capivasertib + fulvestrant	155	153	144	139	131	125	111	83	60	45	30	14	3	1	0
Placebo + fulvestrant	134	127	122	112	101	99	87	62	46	31	22	13	3	0	0

*0.01% alpha penalty assigned to OS analyses of no detriment. Formal analysis not prespecified. HR was estimated using the Cox proportional hazard model stratified by the presence of liver metastases (overall population only) and prior use of CDK4/6 inhibitor.

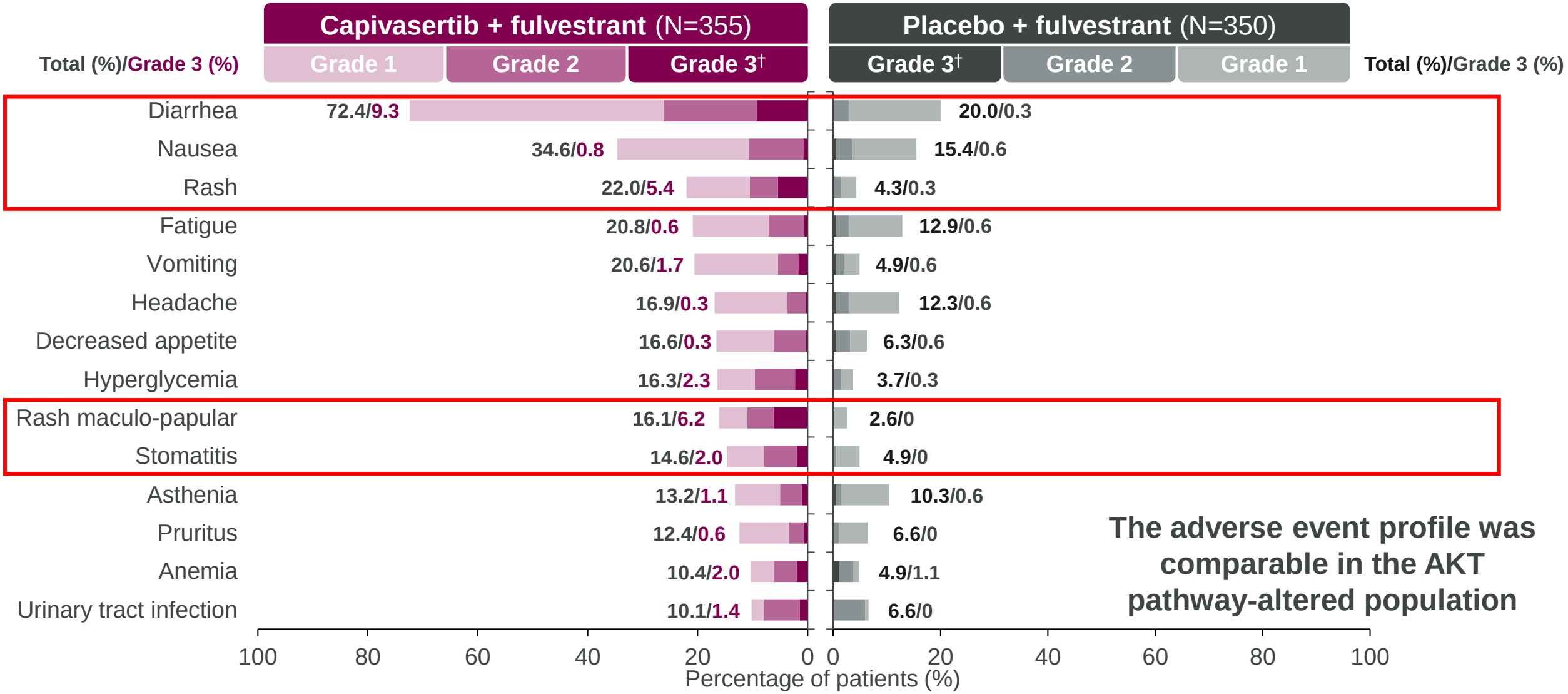
Safety summary: Overall population

n (%)	Capivasertib + fulvestrant (N=355)	Placebo + fulvestrant (N=350)
Any adverse event	343 (96.6)	288 (82.3)
Any serious adverse event	57 (16.1)	28 (8.0)
Any adverse event leading to death*	4 (1.1)	1 (0.3)
Any adverse event leading to discontinuation	46 (13.0)	8 (2.3)
Discontinuation of capivasertib/placebo only	33 (9.3)	2 (0.6)
Discontinuation of both capivasertib/placebo and fulvestrant	13 (3.7)	6 (1.7)
Any adverse event leading to dose interruption of capivasertib/placebo only	124 (34.9)	36 (10.3)
Any adverse event leading to dose reduction of capivasertib/placebo only	70 (19.7)	6 (1.7)

The safety profile was comparable in the AKT pathway-altered population

*Grade 5 events included acute myocardial infarction, cerebral hemorrhage, pneumonia aspiration and sepsis (all n=1) in the capivasertib + fulvestrant group and COVID-19 (n=1) in the placebo + fulvestrant group. No grade 5 events were classified as related to capivasertib/placebo by local investigator. The safety analysis population included all patients who received at least one dose of the study drug.

Adverse events (>10% of patients) – overall population

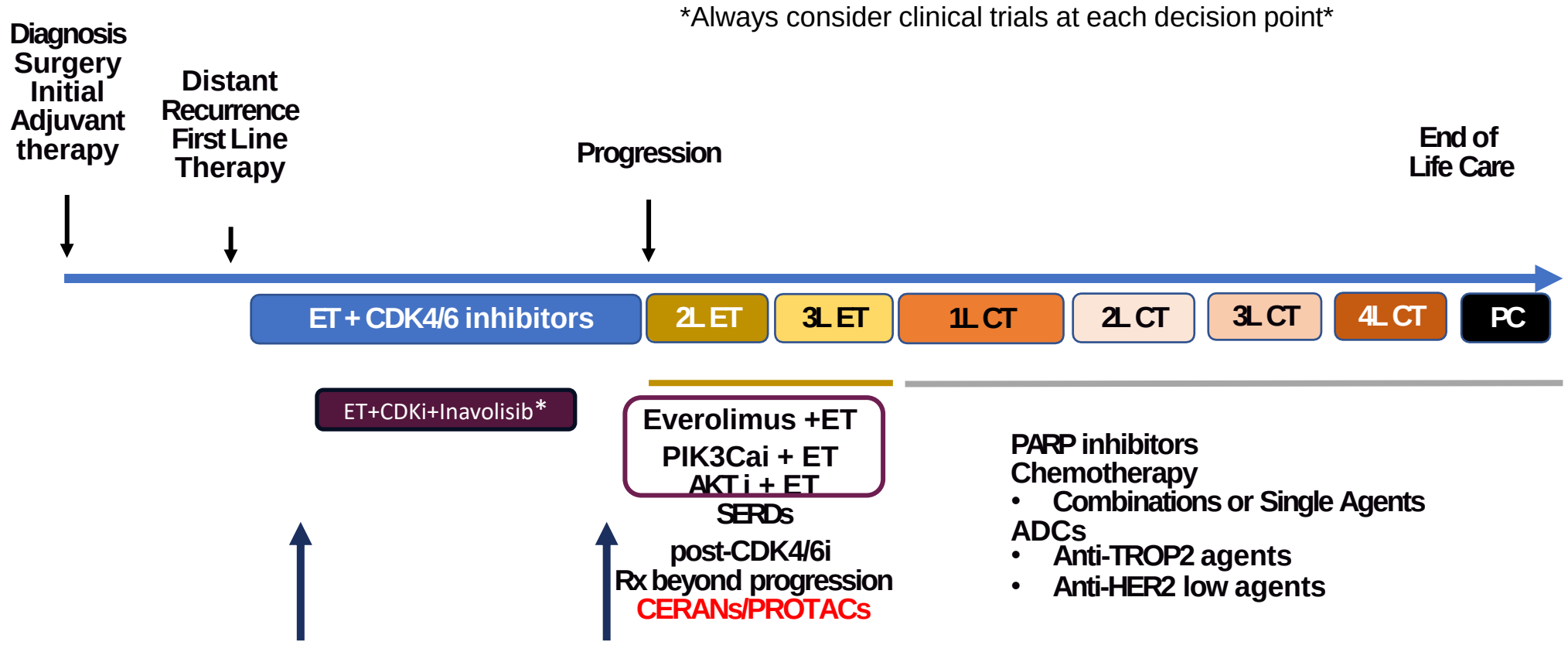


The adverse event profile was comparable in the AKT pathway-altered population

Adverse events of any grade related to rash (group term including rash, rash macular, maculo-papular rash, rash papular and rash pruritic) were reported in 38.0% of the patients in the capivasertib + fulvestrant arm (grade ≥3 in 12.1%) and in 7.1% of those in the placebo + fulvestrant group (grade ≥3 in 0.3%). †All events shown were Grade 3 except one case of Grade 4 hyperglycemia in the capivasertib + fulvestrant arm.

DISCUSSION

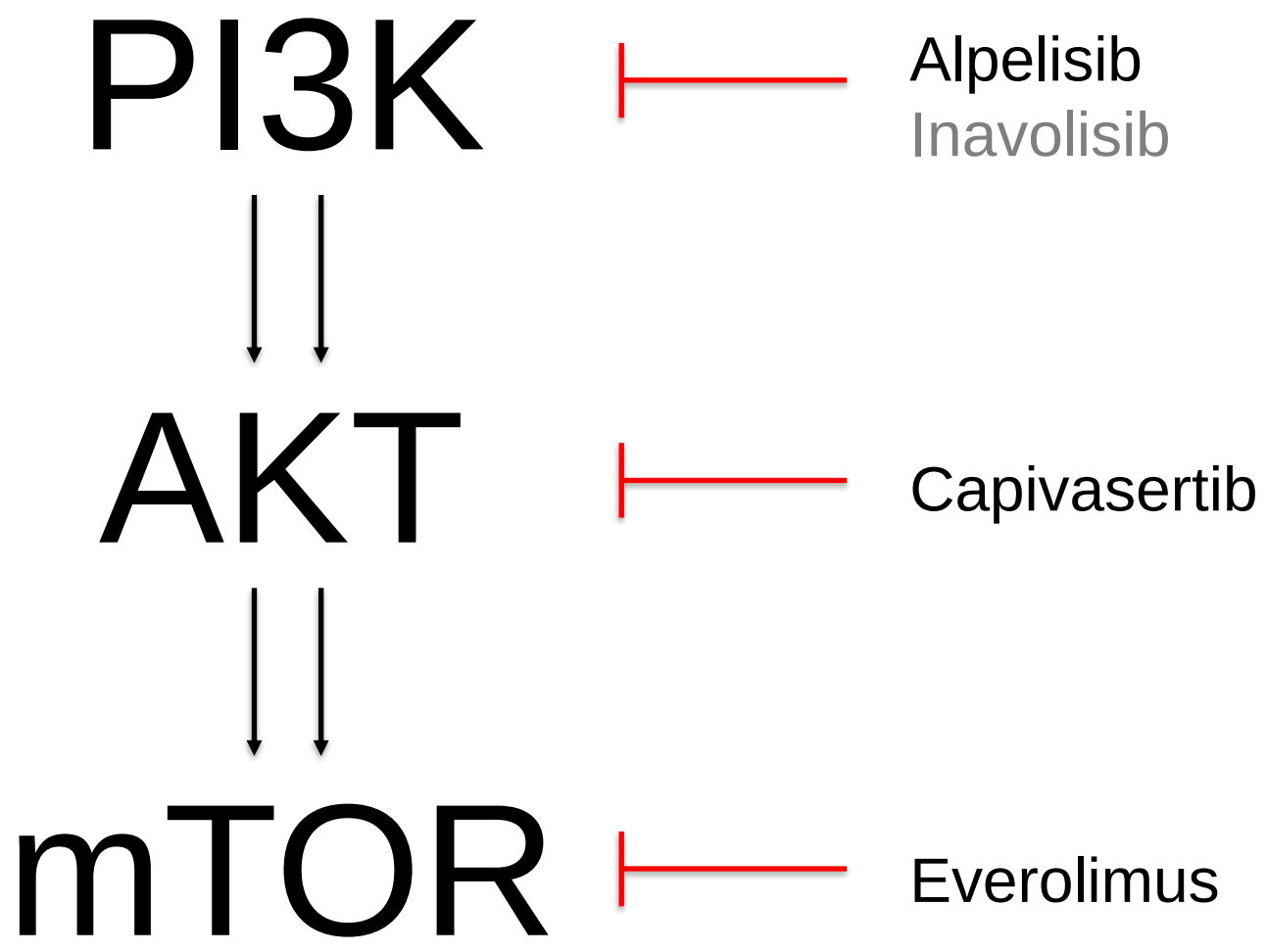
The Treatment Landscape for Metastatic HR+/HER2- BC



Genomic testing (tissue/liquid): PIK3ca/PTEN/AKT, ERBB2m,sBRCA, MSI, NTRK, TMB
ESR1 testing (liquid)

* ET resistant & PIK3Ca-mutant

Targeting PI3K pathway in 2024



CLINICAL CONTEXT

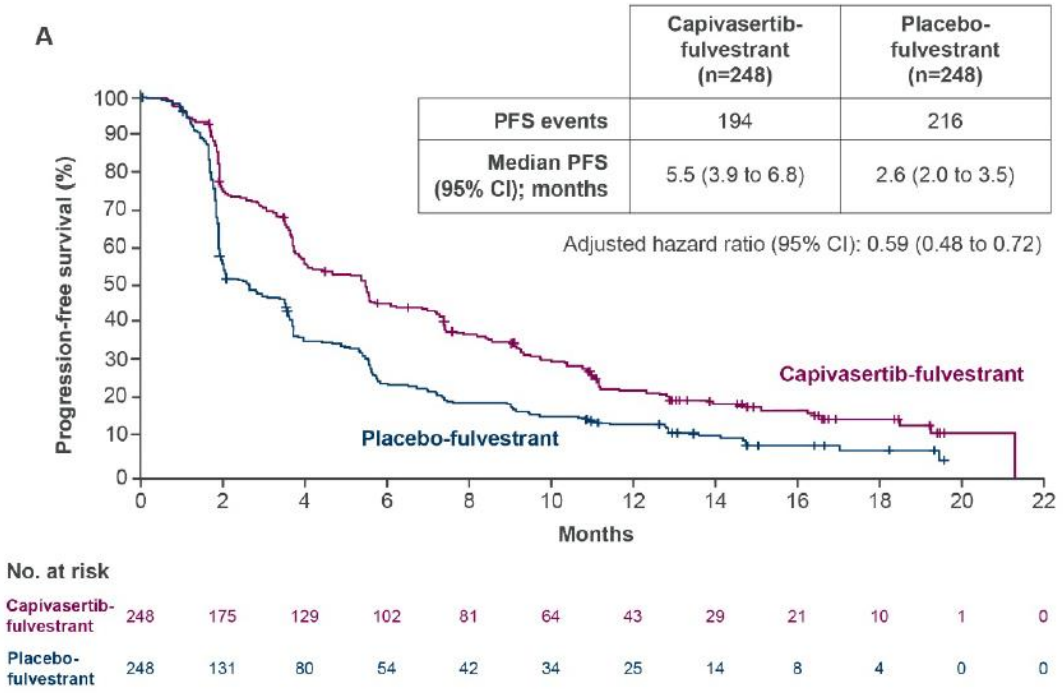
	BOLERO-2	SOLAR-1 (N-572)	CAPITELLO-291 (N-708)
Intervention	Everolimus	Alpelisib	Capivasertib
ET partner	Exemestane	Fulvestrant	Fulvestrant
Progression on prior AI	X*	X	X
1st line in ABC	21%	52%	10%
Exposure to prior CDK4/6i	0	6%	69%
Primary endocrine resistance	?	13% (mPIK3ca arm)	35-38%
PFS (months) - ITT	6.9 vs 2.8 (11 vs 4)¥	PIK3Ca mut vs wt analysed separately	7.2 vs 3.6
PFS in p/way mutant cohort	(6.7 vs 2.8)**	11 vs 5.7	7.3 vs 3.1
HBA1C	-	<6.4%	<8%
Discontinuation rate	19%	25%	13%

Baselga, NEJM, 2012; Moynahan. Br J Cancer. 2017; Andre, NEJM, 2019; Turner, NEJM, 2023

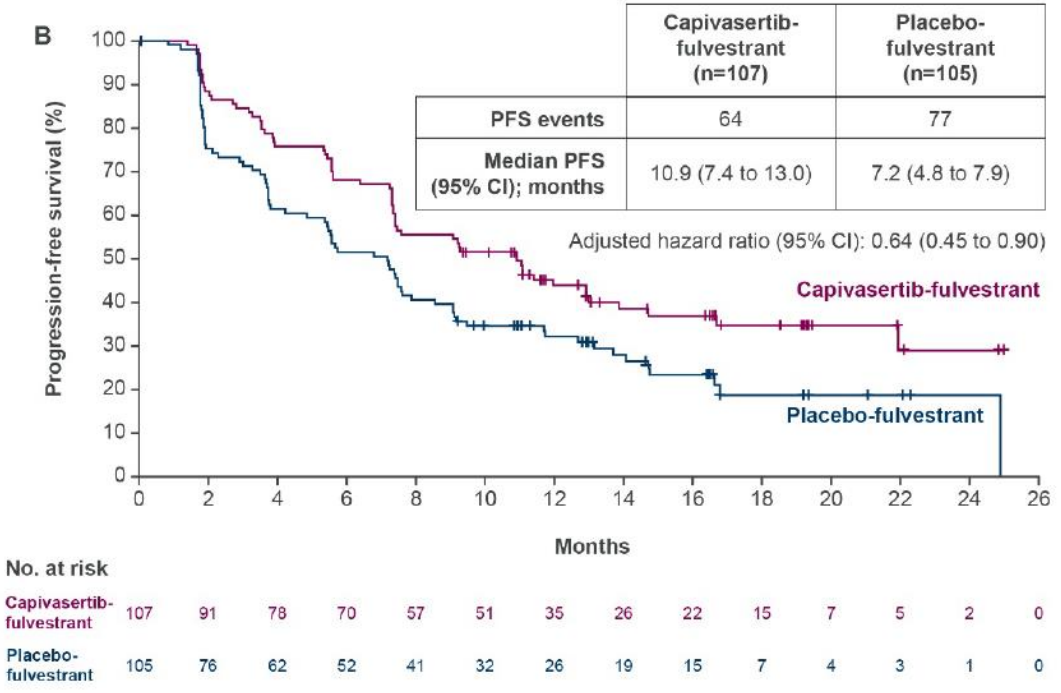
*=letrozole or anastrozole; ¥ Central review-not primary endpoint);**exploratory analysts

WHAT IF THE PATIENT HAD A PREVIOUS CDK4/6 INHIBITOR?

Study enriched for patients who previously received CDK4/6i



	Capivasertib-fulvestrant (n=248)	Placebo-fulvestrant (n=248)
PFS events	194	216
Median PFS (95% CI); months	5.5 (3.9 to 6.8)	2.6 (2.0 to 3.5)



	Capivasertib-fulvestrant (n=107)	Placebo-fulvestrant (n=105)
PFS events	64	77
Median PFS (95% CI); months	10.9 (7.4 to 13.0)	7.2 (4.8 to 7.9)

Had CDK4/6i exposure

No CDK4/6i exposure

SIDE EFFECTS AND QUALITY OF LIFE

- Patients could participate with a HBA1C <8%

- intermittent administration schedule of capivasertib:
  - selected early in clinical development, due to in part to preclinical modeling, to maximize AKT inhibition and optimize the therapeutic window.
  - possible that the reduced toxic-effect profile of capivasertib, with a low incidence of hyperglycemia, reflects this intermittent schedule

Side effects & quality of life:

- Need to pro-actively manage side effects
- Global health status and quality of life were maintained in both study arms (QLQ-C30)
- Global health status and quality of life were maintained for longer with capivasertib–fulvestrant

Adverse Events from Phase III Trials: Inavolisib, Alpelisib, Capivasertib

Patients with key AEs,† %	INAVO120[1] Inavo + Palbociclib+ Fulvestrant (N=162)		INAVO120[1] Palbocilib + fulvestrant Control arm (n = 162)		SOLAR-1[2] Alpelisib + fulvestrant (n = 284)		CAPitello-291[3] Capivasertib + fulvestrant (n = 355)	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Hyperglycemia#	59	6	9	0	64	33	16	2
Diarrhea	48	4	16	0	58	7	72	9
Rash	25	0	17	0	54	20	38	12
Stomatitis*	51	6	27	0	25	3	15	2
Nausea	28	1	17	0	45	3	35	1
AEs leading to study treatment discontinuation	7	N/A	1	N/A	25	N/A	13	N/A

Cross-trial comparisons should be interpreted with caution due to differences in patient populations and AE reporting.

Notes:

†For INAVO120, the key AEs were assessed as a medical concept (grouped terms),

#Eligibility varied widely between trials. For INAVO120, FBG <126 and HGBA1c <6%; For SOLAR-1, HGBA1c < 6.5%; For Capitello-291, HGBA1c <8%

***For INAVO120, stomatitis grouped term includes mucosal inflammation.**

***For SOLAR-1 and CAPitello-291, stomatitis was reported as a single term; for Solar 1 mucosal inflammation was 18% for any Grade and 2% for Grade ≥3**

1. Jhaveri K, et al. SABCS 2023; 2. André F, *et al. N Engl J Med* 2019 3. Turner NC, et al. *N Engl J Med.* 2023

Adapted from Hope Rugo, SABCS 2023

MOVING FORWARD

- Optimal sequencing of therapies?
- When should genomic testing be performed along the advanced breast cancer journey? Should we test tissue or liquid biopsy?
- Will inavolisib+palbociclib+ET become a SOC for patients with first line HR+ ABC with endocrine resistance and PIK3Ca mutation?
- Will there be value in targeting PIK3Ca/AKT/mTOR pathway more than once during management of ABC?

MOVING FORWARD

- How and when to test for *ESR1* mutations and how to incorporate into treatment plan?

  - if there's an *ESR1* mutation & *AKT* p/way alteration and a low burden of disease – what is best treatment choice? Elacestrant or Capivasertib & Fulvestrant?

- Optimal combination of therapies ?
  - Capivasertib+CDK4/6i+ET(CAPITELLO-292)
  - Capivasertib + oral SERD
- What will be the 1st/2nd line therapies as the treatment landscape in early breast cancer changes?

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