POSEIDON: Prospective randomized phase II trial of the Safety and Efficacy of tamoxifen in combination with the Isoform selective PI3K inhibitor GDC-0032 (taselisib) compared with tamoxifen (TAM) alONe in hormone receptor positive, HER2 negative, metastatic breast cancer patients with prior exposure to endocrine treatment

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DECLARATION OF INTERESTS

Mafalda Oliveira

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Background

Rationale

- PI3K pathway activation leads to endocrine therapy resistance pre clinically
- Inhibitors of this pathway can reverse resistance[1–2]
- Taselisib is an oral inhibitor of class I α, δ, and γ isoforms of PI3K

Efficacy of PI3K inhibitors + HT in ER+ HER2- MBC

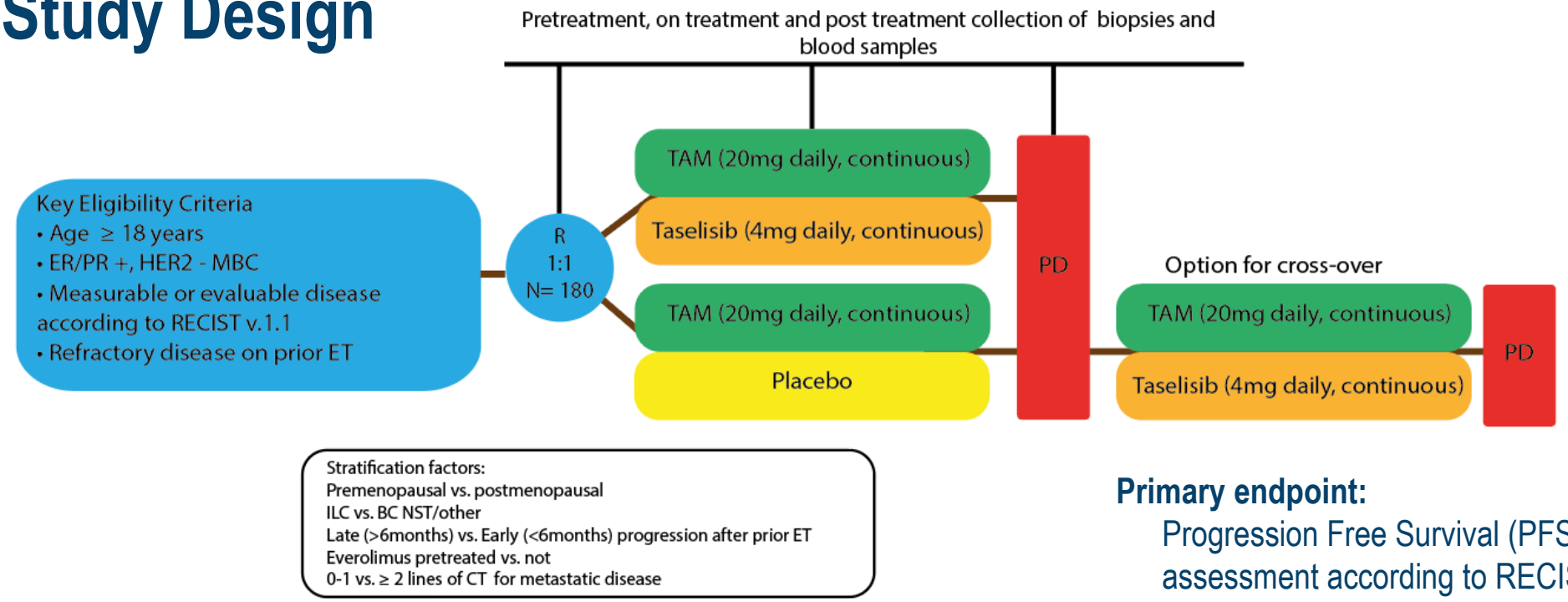
- SANDPIPER trial (taselisib/placebo + fulvestrant): median PFS 7.4 vs.5.4 months, stratified HR 0.70; 95% CI 0.56-0.89
  However, toxicity and reduced clinical benefit have limited the clinical utility of the combination.
- SOLAR-1: (alpelisib/placebo + fulvestrant in PIK3CA mutant cohort): median PFS 11.0 vs. 5.7 months, HR 0.65; 95% CI 0.50-0.85 → FDA and EMA approval for patients with *PIK3CA*-mutant tumors.

POSEIDON Phase Ib dose escalation part:

- Taselisib demonstrated clinical activity in combination with tamoxifen (ORR 24% in RECIST measurable group)[1]

[1]R. Baird et al. CCR 2019. [2]R. Riggins et al. Cancer Res 2008

Study Design



Primary endpoint:

Progression Free Survival (PFS) by local assessment according to RECIST v.1.1

Statistical considerations

- 180 patients required to detect a constant HR of 0.64 (ß=90%, 2-sided α=0.2)
- Accrual closed prematurely due to Covid-19, decreasing the power to 83%
- Median follow-up 26.4 months (IQR = 16.2 – 38.7)

Key Secondary endpoints:

ORR and CBR in both treatment arms
Safety according to CTCAE 4.03
Overall Survival

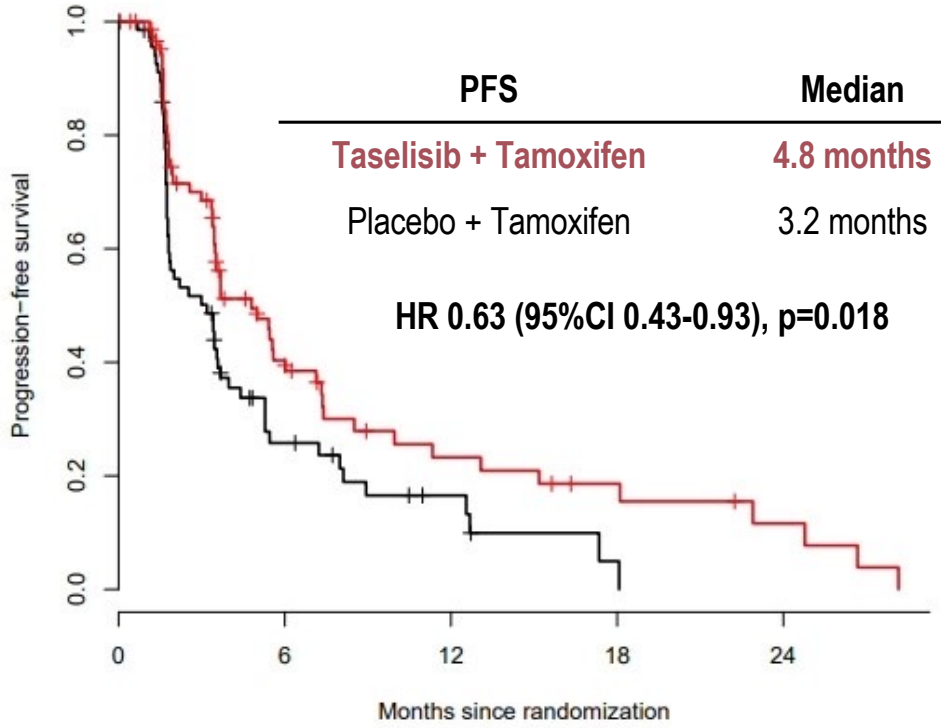
Baseline Characteristics

21 sites in 4 different European countries
195 registered patients / 152 patients randomized

Patient characteristics		Taselisib + Tamoxifen N=76 (%)	Placebo + Tamoxifen N=76 (%)	Total N=152 (%)
Age	Median (range)	62 (30 – 78)	63 (2 – 83)	63 (30 – 83)
Post-menopausal		72 (95)	70 (92)	142 (93)
WHO PS at baseline	0 1 2 Unk	50 (66) 22 (29) 3 (4) 1 (1)	27 (36) 47 (62) 2 (3) 0	77 (51) 69 (45) 5 (3) 1 (1)
Tumor type	Carcinoma NOS Invasive lobular Other	58 (76) 13 (17) 5 (7)	62 (82) 11 (15) 2 (3)	120 (79) 24 (16) 7 (4)
PIK3CA* mutation	Exon 20 Exon 9 Not detected Not tested	11 (14) 8 (11) 27 (36) 32 (42)	10 (13) 15 (20) 20 (26) 32 (42)	21 (14) 23 (15) 47 (31) 64 (42)
Time on prior ET for MBC	<6 months ≥6 months	25 (33) 51 (67)	24 (32) 52 (68)	49 (32) 103 (68)
Prior everolimus	Yes No	25 (33) 51 (67)	19 (25) 57 (75)	44 (29) 108 (71)
Number of prior CT for MBC	0-1 ≥2	49 (64) 27 (36)	51 (67) 25 (33)	100 (66) 52 (34)

*Three patients (2 in the taselisib arm and 1 in the placebo arm) had a double *PIK3CA* mutation in exon 20 and exon 9

PFS in the overall population and subgroup analysis

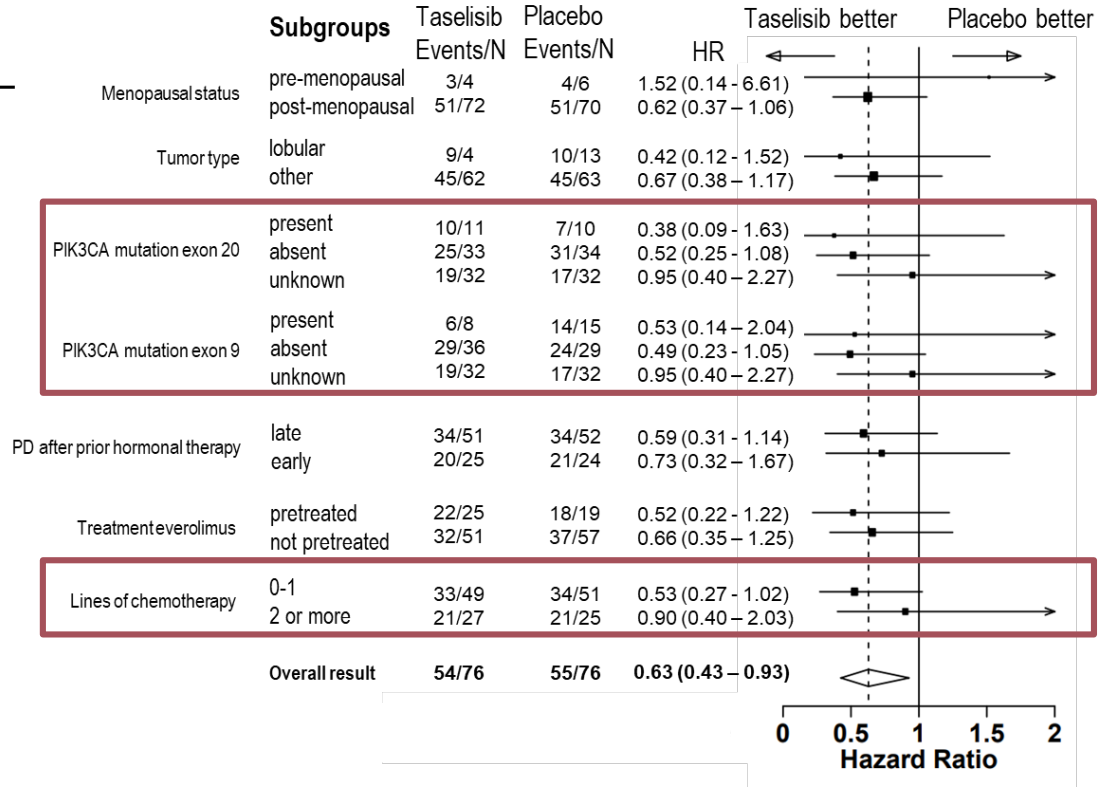


PFS	Median
Taselisib + Tamoxifen	4.8 months
Placebo + Tamoxifen	3.2 months

HR 0.63 (95%CI 0.43-0.93), p=0.018

Number at risk

Placebo +TAM	76	13	5	1	
Taselisib + TAM	76	22	10	6	3



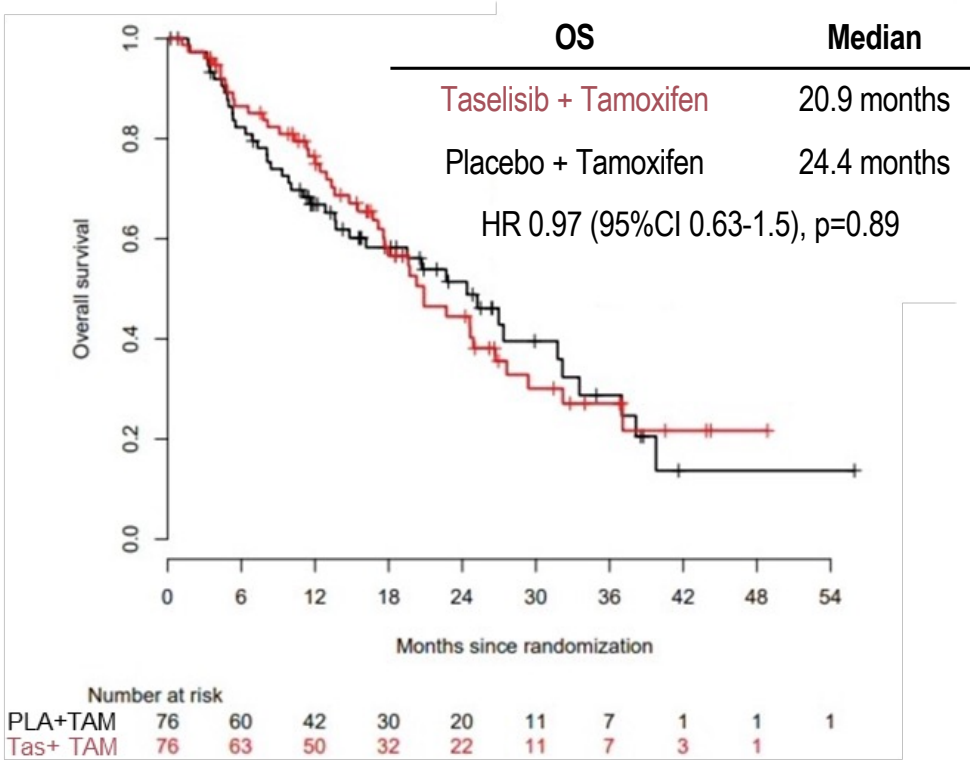
Key secondary efficacy endpoints: ORR and OS

Overall Response	Taselisib + Tam N=76 (%)	Placebo + Tam N=76 (%)
Best response		
Complete response	0 (0)	0 (0)
Confirmed Partial response	7 (9)	2 (3)
Unconfirmed Partial response*	5 (7)	2 (3)
Stable disease	40 (53)	39 (51)
PD	22 (29)	23 (30)
Unknown	2 (2)	10 (13)
Overall Response Rate**		
Number of patients	7	2
% of patients (95% CI)	9.2 (3.8-18.1)	2.6 (0.3-9.2)
Clinical Benefit Rate***		
Number of patients	17	11
% of patients (95% CI)	22.4 (13.6-33.4)	14.5 (7.5-24.4)

* No confirmation CT scan available
** CR + confirmed PR
*** CR + confirmed PR + SD ≥6 months

Overall Survival

34 patients were treated in cross-over
75% of cross-over patients switched after 6.5m



Safety

Most common Adverse Events	Taselisib + Tamoxifen N=76 (%)		Placebo + Tamoxifen N=76 (%)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Any AE	68 (90)	33 (43)*	52 (68)	4 (5)
Diarrhea	27 (36)	8 (11)	6 (8)	0
Nausea	26 (34)	2 (3)	16 (21)	0
Hyperglycemia	21 (28)	4 (5)	2 (3)	0
Fatigue	18 (24)	1 (1)	12 (16)	2 (1)
Mucositis	16 (21)	3 (4)	1 (1)	0
Anorexia	15 (20)	2 (3)	11 (14)	1 (1)
Rash	13 (17)	0	2 (3)	0
ALT/AST increase	12 (16)	4 (5)	3 (4)	0
Hot flashes	4 (5)	0	5 (7)	0
Colitis	2 (3)	0	0	0
AE leading to discontinuation of treatment	17 (22)		3 (4)	

*One G5 AE of cardiac arrythmia possibly related to taselisib (not to tamoxifen) was reported in taselisib arm; no G5 AEs were reported in the placebo arm

Summary and Conclusions

- **POSEIDON met its primary endpoint** in patients with HR+/HER2- MBC refractory to endocrine therapy
  - PFS: HR 0.63 (95%CI 0.43-0.93), p=0.018; median PFS 4.8 vs 3.2 months
- Overall **response rate** was modest but higher with taselisib and tamoxifen: 9.2% vs 2.6%
- **Overall survival** outcomes are hampered by the cross-over design of the trial
- **Toxicity profile of taselisib** was similar to that observed in prior studies
  - Concern of diarrhea, hyperglycemia and transaminitis as common G≥3 AEs

- Despite the statistical significant increase in PFS, the magnitude of the **benefit** of the addition of taselisib to tamoxifen does not counterweigh the poor **tolerability** of the combination
- Exploratory **biomarker analyses** are ongoing and will be presented in the future
- Combining **endocrine treatment** and **PI3K pathway inhibition** using **biomarkers** and **drugs** with a better safety profile warrants further study

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Investigators and site personnel from 21 sites in 4 countries

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