MEN1611, a PI3K Inhibitor, combined with trastuzumab (T) ± fulvestrant (F) for HER2+/PIK3CA mutant (mut) advanced or metastatic (a/m) breast cancer (BC): safety and efficacy results from the ongoing Phase 1b study (B-PRECISE-01)

B·PRECISE·01
BREAST-A·PI3K INHIBITOR WITH TARGETED COMBINATIONS IN SOLID TUMORS TREATMENT

M. Piccart[1], M. Ruiz Borrego[2], H.-T. Arkenau[3], S.I. Escrivá-de-Romaní[4], S. Howell[5], A. Hennequin[6], B. Jimenez-Rodriguez[7], G. Del Conte[8], M. Simonelli[9], M. Palleschi[10], F. Duhoux[11], B. Doger De Speville Uribe[12], G. Curigliano[13], S. Waters[14], P. Aftimos[1], H. Wildiers[15], D. Tosi[16], F. Amair-Pinedo[17], A. Pellacani[18], D. Laurent[19]

[1]Medical Oncology Clinic, Institute Jules Bordet, Brussels, Belgium, [2]Oncology Service, Hospital Universitario Virgen del Rocio, Seville, Spain, [3]SCRI, Sarah Cannon Research Institute SCRI UK, London, United Kingdom, [4]Vall d'Hebron Institute of Oncology (VHIO), Vall d'Hebron University Hospital, Barcelona, Spain, [5]Deptartment of Oncology, The Christie NHS Foundation Trust, Manchester, United Kingdom, [6]Unité de Phase I, Centre Georges François Leclerc, Dijon Cedex, France, [7]Oncology Service, Hospital Clinico Universitario Virgen de la Victoria, Málaga, Spain, [8]U.O. di Oncologia Medica, Ospedale San Raffaele, Milano, Italy, [9]U.O. di Oncologia Medica ed Ematologia, Istituto Clinico Humanitas, Rozzano, Italy, [10]Oncologia, IRCCS- Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Meldola, Italy, [11]Medical Oncology department, Cliniques Universitaires Saint-Luc (UCLouvain Saint-Luc), Woluwe-Saint-Lambert, Belgium, [12]START Madrid FJD - Oncology Phase I, Hospital Universitario Fundacion Jimenez Diaz, Madrid, Spain, [13]Divisione Oncologia Medica, IEO Istituto Europeo di Oncologia, Milan, Italy, [14]Clinical Trials Unit, Velindre Cancer Centre, Cardiff, United Kingdom, [15]PARENT, UZ Leuven, Leuven, Belgium, [16]Service d'Oncologie Régional Médicale, ICM Regional Cancer Institute of Montpellier, Montpellier, France, [17]Oncology Therapeutic Area, Menarini Ricerche S.p.A., Firenze, Italy, [18]R&D, Menarini Ricerche S.p.A., Firenze, Italy, [19]Oncology Therapeutic Area, Berlin Chemie AG/Menarini Ricerche S.p.A, Berlin, Germany

Background

- *PIK3CA* mutations have been related to resistance to Hormone Receptor (HR)-positive and HER2-targeted agents[1-5] in breast cancer. PI3K inhibitors has been shown to restore sensitivity to anti-HER2 therapies[6,7].
- MEN1611 (formerly named CH5132799) is an oral PI3K inhibitor active on the p110α mutant and WT, β and γ isoforms, while sparing the δ, that has shown anti-tumor activity combined with trastuzumab or with trastuzumab plus fulvestrant in patient-derived xenografts and breast cancer cell lines with different *PIK3CA* mutations[8].
- B-PRECISE-01 (NCT03767335, EudraCT No. 2017-004631-36) is an ongoing open-label, multicenter, phase 1b study in subjects with *PIK3CA* mutant, HER2-positive locally recurrent unresectable (advanced) or metastatic breast cancer who have progressed after at least 2 lines of anti-HER2 based therapy, including one regimen containing Trastuzumab.

Objectives

- **Primary:** to determine safety, maximum tolerated dose (MTD), and recommended phase 2 dose (RP2D) of MEN1611 in combination with trastuzumab ± fulvestrant.
- **Secondary:** assessment of preliminary anti-tumor activity, pharmacokinetics (PK) profile, and pharmacodynamics (PD) of MEN1611 combination with trastuzumab ± fulvestrant.

Study Design

- **Treatments:**
  - HR-negative male and female, and HR-positive premenopausal women: MEN1611 + trastuzumab. Hormonal treatment such as GnRH analogs as per clinical local practice is allowed in HR-positive premenopausal women and male subjects assigned to receive MEN1611 + Trastuzumab.
  - HR-positive postmenopausal women: MEN1611 + trastuzumab + fulvestrant.
- In dose escalation (Step 1) Trastuzumab was administered IV weekly, and fulvestrant when applicable. MEN1611 was administered twice a day, continously for 28-day cycles, following a standard 3 + 3 design in three cohorts: Cohort 1 (MEN1611 at 16 mg BID), Cohort 2 (MEN1611 at 32 mg BID) and Cohort 3 (MEN1611 at 48 mg BID). Dose-limiting toxicities (DLTs) were assessed during Cycle 1. No DLTs were observed during the Escalation step and 48 mg BID was selected as RP2D for Cohort Expansion (CE, Step 2)[9].
- In the CE the RP2D is being tested in 30 evaluable patients for each arm of treatment (considering also patients already included in Step 1). Three-weekly adminitration of Trastuzumab IV (loading dose 8 mg/Kg at Cyce 1 Day 1 followed by 6 mg/Kg if considered appropiate by investigators, followed by an infusion of 6 mg/Kg every 3 weeks) is allowed for newly enrolled pts in CE.

Pooled safety and efficacy data from the two subpopulations of CE are presented herein.

Patients Characteristics (Table 1)

As of March 2021, 42 female pts were treated: 36 of them with MEN 48 mg BID (18 MEN+T and 18 MEN+T+F).

Safety (Table 2)

- Most treatment-related AE (TRAEs) were reversible and manageable by supportive care.
- TRAEs caused treatment interruption in 14 pts (33.3%, 1 pt definitely) and dose reduction in 6 pts (16.7%, only allowed in CE) mostly hyperglycemia, diarrhea, nausea, asthenia and decreased appetite.
- Serious TRAEs were experienced by 8 pts (19%): hyperglycemia 3 pts, diarrhea 2 pts, general physical health deterioration, generalized edema, and pneumonitis (1 pt each).

Table 1. Patients demographics and baseline disease characteristics

MEN1611	16 mg (N=3)	32 mg (N=3)	48 mg (N=36)	Total (N=42)
Median age, years (range)	68 (56-71)	52 (50-76)	54 (34-78)	55 (34-78)
HR status, n (%)	3 (100)	3 (100)	36 (100)	42 (100)
Positive, n (%)	3 (100)	1 (33.3)	23 (63.9)	27 (64.3)
Negative, n (%)	0	2 (66.7)	13 (36.1)	15 (35.7)
Menopausal status, n (%)	3 (100)	3 (100)	36 (100)	42 (100)
Postmenopausal, n (%)	3 (100)	3 (100)	27 (75)	33 (78.6)
Premenopausal, n (%)	0	0	9 (25)	9 (21.4)
ECOG status at baseline 0-1, n (%)	2 (66.7)	3 (100)	35 (97.2)	40 (95.2)
ECOG status at baseline 2, n (%)	1 (33.3)	0	1 (2.8)	2 (4.8)
Number of prior treatment in advanced setting, median (range)	NA	NA	4 (1 - 8)*	4 (1 - 8)
Prior pertuzumab, n (%)	NA	NA	24 (66.7)	24 (57.1)
Prior T-DM1, n (%)	NA	NA	31 (86.1)	31 (73.8)
Safety population, n (%)	3 (100)	3 (100)	36 (100)	42 (100)
Efficacy population, n (%)	2 (66.7)	2 (66)	25 (69.4)	29 (69)

NA: not available.
*One patient who had rapidly progressed after adjuvant trastuzumab and received T-DM1 as first line treatment in the metastatic setting was enrolled in the CE. the patient was excluded from the efficacy population but she was included in the safety population analysis as per protocol.

- **Safety population:** all subjects receiving at least 1 dose of MEN1611.
- **Efficacy population:** all eligible subjects who receive at least 8 weeks of treatment and have at least 1 disease assessment. Disease assessments are performed every 8 weeks (±7 days) after Cycle 1 Day 1.

Table 2. Treatment Emergent Adverse Events (TEAEs) ocurring in ≥ 10% of patients

Preferred Term	Cohort 1 (16 mg) N=3, n (%)		Cohort 2 (32 mg) N=3, n (%)		Cohort 3 + Expansion (48 mg) N=36, n (%)		Total (N=42), n (%)
	Grade (G)1-2	G3-4	G1-2	G3-4	G1-2	G3-4	All grades
Diarrhoea	1 (33.33%)	1 (33.33%)	2 (66.67%)	0	23 (63.89%)	4 (11.11%)	27 (64.29%)
Nausea	2 (66.67%)	0	0	0	16 (44.44%)	1 (2.78%)	18 (42.86%)
Asthenia	1 (33.33%)	0	3 (100%)	0	8 (22.22%)	1 (2.78%)	13 (30.95%)
Decreased appetite	1 (33.33%)	0	1 (33.33%)	1 (33.33%)	8 (22.22%)	1 (2.78%)	12 (28.57%)
Anaemia	2 (66.67%)	0	0	1 (33.33%)	8 (22.22%)	1 (2.78%)	12 (28.57%)
Rash*	1 (33.33%)	0	0	0	8 (22.2%)	2 (5.6%)	11 (26.2%)
Hyperglycaemia	1 (33.33%)	1 (33.33%)	0	1 (33.33%)	5 (13.89%)	5 (13.89%)	10 (23.81%)
Vomiting	0	0	0	0	7 (19.44%)	1 (2.78%)	8 (19.05%)
Mucosal inflammation	0	0	1 (33.33%)	1 (33.33%)	7 (19.44%)	0	8 (19.05%)
Oedema peripheral	1 (33.33%)	0	2 (66.67%)	0	5 (13.89%)	0	8 (19.05%)
Headache	0	0	0	0	7 (19.44%)	0	7 (16.67%)
Pyrexia	0	0	0	0	7 (19.44%)	0	7 (16.67%)
AST increased	0	0	2 (66.67%)	0	2 (5.56%)	2 (5.56%)	6 (14.29%)
Dyspepsia	0	0	1 (33.33%)	0	4 (11.11%)	0	5 (11.9%)
Muscle spasms	1 (33.33%)	0	0	0	4 (11.11%)	0	5 (11.9%)
Stomatitis	1 (33.33%)	0	0	0	3 (8.33%)	1 (2.78%)	5 (11.9%)
Dyspnoea	0	0	1 (33.33%)	0	4 (11.11%)	0	5 (11.9%)
Urinary tract infection	0	0	1 (33.33%)	0	4 (11.11%)	0	5 (11.9%)

AST: aspartate aminotransferase
*Including rash erythematous, rash maculo-papular and rash pruritic

Clinical Efficacy

Figure 1. Best overall response: Trastuzumab + MEN1611

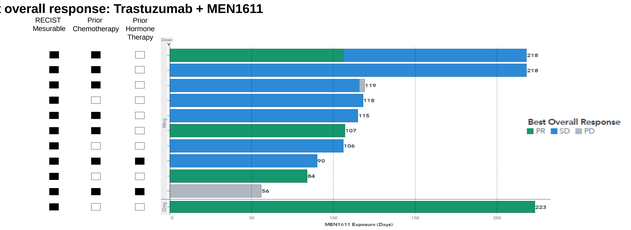

Figure 2. Best overall response: Trastuzumab + MEN1611 + Fulvestrant

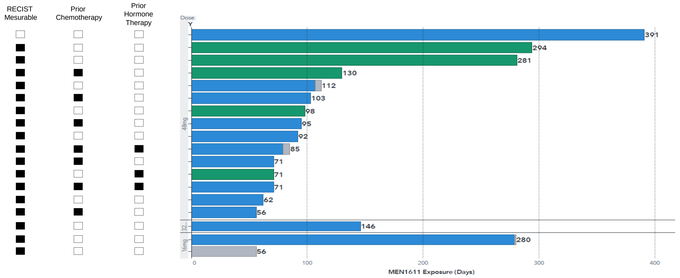

Table 3. Best overall response (all doses)

Efficacy population	MEN1611 + Trastuzumab (n = 11)	MEN1611 + Trastuzumab + Fulvestrant (n = 18)	Total (n = 29)
Partial response (PR)	4 pts (36.4%)	5 pts (27.8%)	9 pts (31%)
Stable disease (SD)	6 pts (54.5%)	12 pts (66.7%)	18 pts (62.1%)
Progression of Disease (PD)	1 pt (9,1%)	1 pt (5.7%)	2 pts (6.9%)

No complete responses (CR) were observed. Seven pts were on treatment > 6 months (MEN1611 + Trastuzumab: 3 pts, MEN1611 + Trastuzumab + Fulvestrant: 4 pts), and 1 pt received MEN1611 + Trastuzumab > 12 months.

Conclusions

MEN1611 combined with Trastuzumab ± Fulvestrant shows a manageable safety profile with encouraging anti-tumor activitiy (ORR 31%) and duration of response in heavily pre-treated pts with HER2+/PIK3CAmut a/m BC. Recruitment for CE is open.

References

[1]Berns K et al. Cancer Cell, 2007. 12 (4): p. 395-402; [2]O'Brien NA et al. Molecular Cancer Therapeutics, 2010. 9 (6): p. 1489-1502; [3]Chandarlapaty S et al. Clinical Cancer Research, 2012. 18(24): p. 6784-6791; [4]Loibl S et al. Ann Oncol, 2016. 27(8): p. 1519-25; [5]LoRusso PM. J Clin Oncol, 2016. 34(31): p. 3803-3815; [6]Eichhorn PJ et al. Cancer Res, 2008. 68(22): p. 9221-30; [7]Serra V et al. Cancer Res, 2008. 68(19): p. 8022-30; [8]Fiascarelli A et al. Annals of Oncology, 2019. 30: p. v781-v782; [9]Piccart M et al. Poster 347P ESMO Virtual Congress 2020.

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