Phase Ib Study of the Combination of Balixafortide (a CXCR4 inhibitor) and Eribulin in HER2-Negative Metastatic Breast Cancer Patients

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BACKGROUND AND PURPOSE

- Breast cancer is the most common cancer affecting women. Despite advances in targeted therapies and cytotoxic agents, overall survival in metastatic breast cancer (MBC) remains poor.[1]
- Balixafortide (POL6326) is a cyclic synthetic peptide and a potent, selective inhibitor of the chemokine receptor CXCR4. CXCR4 is overexpressed in more than 20 human tumor types and its expression is correlated with aggressive metastatic phenotypes and poor prognosis. CXCR4 inhibitors interfere with several aspects of tumor biology including tumor survival and proliferation, angiogenesis, metastatic spread, and the immunosuppressive tumor microenvironment.[2] CXCR4 inhibition may interfere with the tumor-protective microenvironment and enhance the effects of chemotherapeutics and targeted cancer agents.[3]
- This phase I study investigated the combination of balixafortide with eribulin (Halaven®), an approved non-taxane inhibitor of microtubule dynamics.
- The dose expansion cohort assessed the anti-tumor activity, safety, tolerability, and pharmacokinetics (data not yet available) of the addition of the recommended phase 2 dose (RP2D) of balixafortide (5.5 mg/kg) to eribulin in patients with MBC (with any positive CXCR4 expression level at the tumor site). Secondary objectives included overall response rate (ORR), progression-free survival (PFS), and overall survival (OS).

METHODS

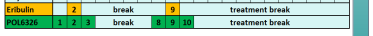
Patient Population:

- Histologically confirmed MBC (AJCC stage IV): Hormonal status: any estrogen (ER) or progesterone (PR); HER2 negative (immunohistochemistry (IHC) 0-1 or FISH HER2:CEP17 < 2.0) (Table 1)
- Evidence of any CXCR4 expression on tumor cells by IHC: archival tissue (primary or metastatic site) or a new biopsy of a metastatic site
- Patients (pts) in the 2nd-4th line of chemotherapy in the metastatic setting and meeting the criteria for eribulin treatment
- Absolute neutrophil count (ANC) > 1500 / ɛL

Study Design:

- Pts received eribulin (1.4 mg/m², i.v.) on days 2 and 9; flanked by balixafortide (5.5 mg/kg, i.v.) on days 1-3, and 8-10 of 21-day cycles (Figure 1).

Figure 1: Treatment scheme



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[1] GLOBOCAN 2012 v1.1, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Available from: http://globocan.iarc.fr/
[2] Walekamp et al., Eur. J. Cancer, 49, 219, 2013.
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RESULTS

Table 1: Patient characteristics

Parameter	# of patients (n=25)
Age median (Range)	59 (33-72)
ECOG performance status	
0	10 (40%)
1	15 (60%)
Tumor receptor status	
ER+/PR+/HER2-	12 (48%)
ER+/PR-/HER2-	7 (28%)
ER-/PR+/HER2-	2 (8%)
Triple Negative (TNBC)	4 (16%)
CXCR4 expression	
Low	18 (72%)
Medium	3 (12%)
High	4 (14%)
Line of prior chemotherapy (metastatic setting)	
1	5 (20%)
2	13 (52%)
3	7 (28%)
Most common metastatic sites*	
Liver	19 (76%)
Bone	15 (60%)
Lung	9 (36%)
Lymph nodes	5 (20%)

* Reported by at least 20% of the total population

Safety and Tolerability:

Twenty-five pts were enrolled in this expanded cohort. One pt discontinued therapy after the first treatment due to rapid disease progression. Data from all 25 pts were included in the safety analysis (Table 2).

The most common AEs related to balixafortide were histamine-like infusion reactions (22/25 pts, 88%), which were mainly mild (1 pt reported Gr3 pruritus) and manageable with anti-histamines and slower infusion rates.

Two pts (8%) had febrile neutropenia.

5/20 SAEs were considered related to the combination of balixafortide and eribulin: 1 pt reported Gr3 mucosal inflammation and Gr4 neutropenia, 1 pt was hospitalized because of mild fever of unknown origin (event resolved in one day), and 1 pt was found to have Gr4 neutropenia and was diagnosed with pneumonia that responded poorly to antibiotics. This pt received the full treatment schedule for cycle 2. Five days after the last treatment, the pt was hospitalized because of severe respiratory distress and later died of pneumonia.

All SAEs reported in this trial were related to either eribulin alone or the combination of balixafortide and eribulin. No SAEs were related to balixafortide alone.

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Table 2: Adverse events reported by 3 or more pts regardless of drug relationship (n=25, Cohort 11 + dose expansion cohort: balixafortide 5.5 mg/kg + eribulin 1.4 mg/m²) (*cut off date 11 April 2017*)

Adverse Event	All grades	Grade 3	Grade 4
Hematological			
Neutropenia	14 (56%)	4 (16%)	7 (28%)
Anemia	6 (24%)	2 (8%)	
Thrombocytopenia	5 (20%)	1 (4%)	1 (4%)
Lymphopenia	4 (16%)	2 (8%)	
Non-hematological			
IRR[1]/histaminergic reaction	22 (88%)	1 (4%)	
Asthenia/Fatigue	21 (84%)	1 (4%)	
Cough	14 (56%)		
Alopecia	11 (44%)		
Nausea	9 (36%)		
Constipation	9 (36%)		
Diarrhoea	8 (32%)		
Mucosal inflammation	8 (32%)	2 (8%)	
Pyrexia	8 (32%)		
Decreased appetite	7 (28%)	1 (4%)	
Dysgeusia	7 (28%)		
Hyperglycemia	7(28%)		
Vomiting	7(28%)		
Back pain	6 (24%)		
Muscle spasms	6 (24%)		
Oedema	6 (24%)		
Dizziness	5 (20%)		
Dyspnoea	5 (20%)	1 (4%)	
Headache	5 (20%)		
Musculoskeletal pain	5 (20%)		
Nasal congestion	5 (20%)		
Pain in extremity	5 (20%)		
Parasthesia	5 (20%)		
Upper respiratory tract infection	5 (20%)		
Anxiety	4 (16%)		
Aspartate aminotransferase increased	4 (16%)	1 (4%)	
Dry eye	4 (16%)		
Dry mouth	4 (16%)		
Erythema	4 (16%)		
Eye irritation	4 (16%)		
Fall	4 (16%)		
Myalgia	4 (16%)		
Neuropathy peripheral	4 (16%)		
Neurotoxicity	4 (16%)		
Abdominal pain	3 (12%)		
Alanine aminotransferase increased	3 (12%)	2 (8%)	
Arthralgia	3 (12%)		
Bone pain	3 (12%)		
Chest pain	3 (12%)		
Epistaxis	3 (12%)		
Hypokalemia	3 (12%)		
Muscular weakness	3 (12%)		
Neck pain	3 (12%)		
UTI	3 (12%)	3 (12%)	

[1]IRR = Infusion related reaction

RESULTS

Efficacy:

Efficacy data were calculated for the 24 pts who received at least 1 full cycle of treatment. Objective response rate (ORR) was 38% (Table 3 and Figure 2). 9/24 (38%) pts achieved a partial response and 7/24 (29%) pts had meaningful (Ó6 months) stable disease for a Clinical Benefit Ratio of 67% (Table 3). The median duration of treatment was 24 weeks (range 5-44) with 6 pts still on treatment at the cut off date 11 April 2017 (Figure 3).

Table 3: Tumor response

Response	Eribulin 1.4 mg/m² + Balixafortide 5.5 mg/kg (n=24*)
Complete Response (CR)	0
Partial Response (PR)	9 (38%)
Stable Disease (SD)	10 (42%)
Progressive disease (PD)	4 (17%)
Not evaluable	1** (4%)
ORR[1]	9 (38%)
CBR[2]	16 (67%)

[1]ORR = objective response rate = CR+PR (RECIST 1.1), [2]CBR = clinical benefit rate =CR+PR+SD Ó6 months
* 6 pts still on treatment at cut off date 11 April 2017
** pt died before end of cycle 2

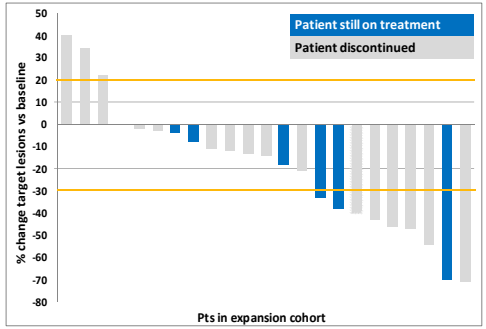

Figure 2: Best lesion response in expanded dose cohort (5.5 mg/kg balixafortide, 1.4 mg/m² eribulin)

RESULTS

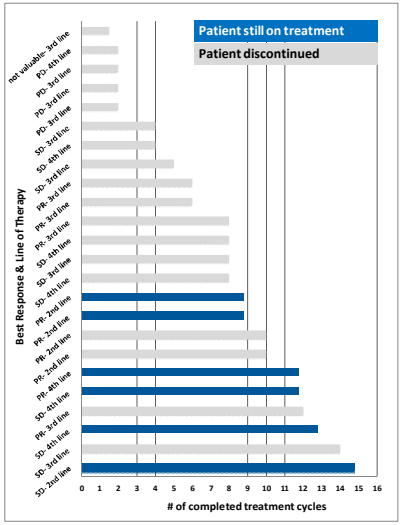

Figure 3: Treatment duration in expanded dose cohort (5.5 mg/kg balixafortide, 1.4 mg/m² eribulin), 1 cycle =3 weeks

CONCLUSIONS

- Balixafortide (5.5 mg/kg) added to eribulin (1.4 mg/m²) generated a very promising **ORR of 38% and CBR of 67%,** in a population of heavily pretreated MBC patients.
- 14/24 patients were on treatment for 8 cycles or longer, with 6 patients still on treatment at the cut off date of 11 April 2017.
- This follows a previously reported response rate of 33% in the phase I dose escalation study (ASCO 2016).
- Balixafortide can be combined safely with eribulin and the safety profile resembles eribulin monotherapy.
- This is the first study of the combination of eribulin with a CXCR4 inhibitor (balixafortide) tested in patients with advanced metastatic breast cancer.
- Further confirmatory studies are being considered.