Dose escalation of POL6326 in combination with eribulin in HER2-negative relapsed metastatic breast cancer (MBC) patients

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Background and Purpose

Breast cancer is the most common cancer in women and, despite new targeted therapies and cytotoxic agents, overall survival in patients with metastatic breast cancer (MBC) remains poor and new treatment modalities are needed. [1]

POL6326 (balixafortide) 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 and its natural ligand stromal-derived-factor-1 (SDF-1) are involved in tumor growth, invasion, metastasis, and angiogenesis. CXCR4 inhibition may interfere with the tumor-protective microenvironment and sensitize tumor cells to chemotherapy.[2]

Eribulin (Halaven®) is a non-taxane inhibitor of microtubule dynamics of the halichondrin class of antineoplastic drugs and it is one of the recently approved cytotoxic agents for MBC patients.

This phase I study investigates the combination of eribulin with POL6326. The primary objectives are the safety, tolerability, and pharmacokinetics (PK) of this combination therapy, as well as the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) of POL6326 when added to eribulin. Efficacy, as measured by tumor response, was additionally assessed.

Methods

Patient Population:

- Histologically confirmed MBC and evidence of tumor cell CXCR4 expression by immunohistochemistry (Ab anti-CXCR4 E1844) on tumor tissue (primary tumor or metastatic) (Table 1)
- HER2 negative breast cancer patients with any estrogen (ER) or progesterone (PR) receptor status, meeting the criteria for receiving eribulin, but limited to 2nd-4th line of chemotherapy for this study

Study Design:

This is a phase I, open label, non-randomized, dose escalation study with a 3+3 design divided into two parts:

Part 1: Intra-patient assessment of POL6326 effects on eribulin-associated neutropenia and PK

- Patients received a 28 day run-in cycle with eribulin (1.1-1.4 mg/m^2) given on days 1 and 16 and POL6326 (0.5-1 mg/kg) given on days 15, 16 and 17 (Fig. 1) followed by 21 day cycles (Fig. 2).

Part 2: Main dose-escalation phase with 21 day cycles (Fig. 2)

- Patients received eribulin (1.4 mg/m^2) and escalating doses of POL6326 until the MTD and/or RP2D. MTD was defined as the highest dose at which dose limiting toxicity (DLT) occurred in no more than 1 of 6 pts during the 1st treatment cycle.

Figure 1: Run-in cycle (C0) of eribulin therapy alone and in combination with POL6326 (Part 1)

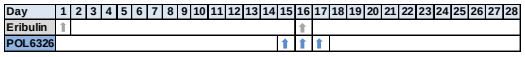
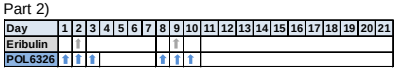


Figure 2: 21 day cycle of eribulin and POL6326 administration (Part 1 and Part 2)



Results

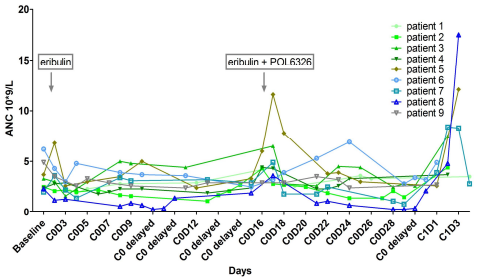
Table 1: Patient characteristics

Parameter	# of patients (n=33)
Age median (Range)	53 (38-74)
ECOG performance status	
0	13
1	20
Tumor receptor status	
ER+/PR+/HER2-	17
ER+/PR-/HER2-	5
Triple Negative	11
CXCR4 expression	
Low	19
Medium	8
High	6
Line of chemotherapy (metastatic setting)	
2	11
3	16
4	6
All previous anti-cancer therapies (from first diagnosis)	
1-3	7
4-6	15
7-10	11

Safety and Tolerability:

Part 1: Combination treatment was safe and well tolerated. There was no indication that POL6326 exacerbates neutropenia associated to eribulin at the tested doses (Fig. 3).

Figure 3: Absolute neutrophil count (ANC) change in run-in cycle (C0)



Part 2: Combination treatment was well tolerated with no significant or medically meaningful differences between the dose cohorts (Table 2). The most common TEAEs were transient Gr.1-2 histamine-like reactions (e.g. pruritus) manageable with anti-histamines and mainly occurring at first administration during the first cycle.

Of the 23 reported SAEs, 4 were considered related or possibly related to the combination of POL6326 and eribulin; one patient (POL6326 1 mg/kg) reported non-cardiac chest pain and died due to septic shock (not considered a DLT), and 2 patients (POL6326 2.5-3 mg/kg) were reported with febrile neutropenia.

No DLT emerged in any cohort and the MTD has not been reached.

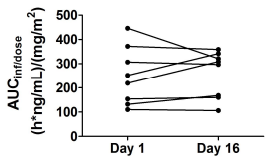
Table 2: Patients reporting adverse events Grade ≥3 regardless of drug relationship (Part 2, eribulin 1.4 mg/m^2, n=3 per cohort) (*cut off date 24 May 2016*)

Adverse Event Grade ≥3	POL6326 mg/kg								Total patients (n=24)
	1.0	2.0	2.5	3.0	3.5	4.0	4.5	5.5	
Hematological									
Neutropenia	1	1	2	2	1	2	1	1	11
Febrile neutropenia	1		1	1		1			4
Leukopenia	2			1					3
Anemia							1		1
Platelet count decreased	1								1
Non-Hematological									
Asthenia/fatigue						1	1		2
Alopecia			1						1
Neuropathy peripheral					1				1
Septic shock	1								1
Corona virus infection	1								1
Lung infection	1								1
Atrial fibrillation	1								1
Back pain			1						1
Colitis	1								1
Constipation	1								1
Diverticulitis	1								1
↑GT increased		1							1
Hypokalemia	1								1
Hyperglycemia								1	1
Hyponatremia							1		1
Infected neoplasm							1		1
Metabolic acidosis	1								1
Non-cardiac chest pain	1								1
Pericardial effusion	1								1
Pleural effusion	1								1

Pharmacokinetics (eribulin):

Part 1: There were no significant differences in $AUC_{inf/dose}$ of eribulin alone (Day 1) vs combination (Day 16), indicating that POL6326 does not affect eribulin PK (Fig. 4).

Figure 4: Eribulin $AUC_{inf/dose}$ (Part 1)

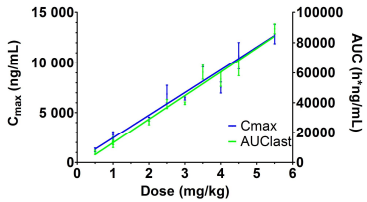


Part 2: Eribulin PK was within expected range when combined with POL6326, apart from one patient (POL6326 dose 1 mg/kg) with liver metastasis and slightly abnormal liver function tests at baseline who had unusually high plasma levels of eribulin.

Pharmacokinetics (POL6326):

Increases of C_{max} and AUC were linear among all the tested doses of POL6326 (Fig. 5).

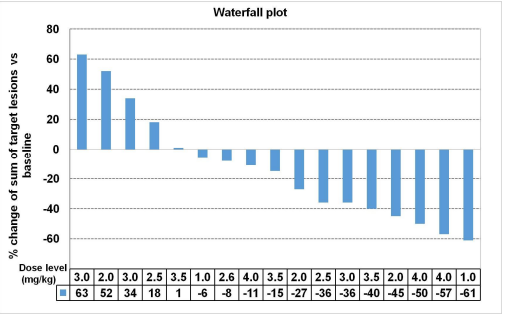
Figure 5: Dose linearity across POL6326 doses



Efficacy:

Of the 18 evaluable patients treated in the cohorts with 1.4 mg/m^2 eribulin and 1, 2, 2.5, 3, 3.5, and 4 mg/kg POL6326, 6 patients achieved a partial response. In all of these cohorts, there was a consistent response rate of 33% (Fig. 6).

Figure 6: Best lesion response at escalating POL6326 dose (4.5 and 5.5 mg/kg cohorts not yet available)



Conclusions

- POL6326 up to 5.5 mg/kg can be combined safely with eribulin in patients with pretreated MBC.
- POL6326 does not change the pharmacokinetic profile of eribulin.
- The combination of POL6326 may enhance the cytoreductive potential of eribulin, and this treatment approach therefore suggests further efficacy studies in MBC/triple-negative breast cancer.
- An expanded cohort of 24 patients within this trial is ongoing.

References

[1] GLOBOCAN 2012 v1.1, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Available from: http://globocan.iarc.fr/

[2] Massagué et al., Nature review, 9, 274, 2009; Andreef et al., Blood 116, 2179, 2011, ASH annual meeting