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Results from the Phase II Study of ROS1 Targeting with Crizotinib in Advanced E-cadherin Negative Lobular Breast Cancer (ROLo)

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Background and rationale for the study

- Lobular breast cancers are characterised by loss of function of the cell adhesion protein E-cadherin, which is commonly inactivated via *CDH1* mutation.
- Pre-clinical studies demonstrated synthetic lethality between ROS1 inhibition and E-cadherin loss in models of lobular breast cancer and diffuse gastric cancer (DGC)[1].
- We conducted a phase 2 study with the ALK/ROS1 inhibitor crizotinib to assess the potential of ROS1 inhibition in lobular advanced breast cancer (ABC).

Study Design and Definitions

ROLo was a phase 2 multi-centre study recruiting in parallel to two cohorts:

Er+ Lobular ABC Cohort:

Previously treated ER+/HER2-ve E-cadherin –ve locally advanced/metastatic ILC Planned n=29 → Crizotinib 250mg bd + Fulvestrant until progression/ toxicity

Basket Cohort:

Previously treated triple negative E-cadherin –ve locally advanced/metastatic ILC or E-cadherin –ve diffuse gastric cancer or *CDH1*-mutated advanced solid tumours Planned n=29 → Crizotinib 250mg bd until progression /toxicity

Key Eligibility criteria:

- E-cadherin negative locally advanced inoperable or metastatic ER positive/HER2 negative lobular breast cancer (ER+ Lobular ABC cohort) or metastatic diffuse gastric cancer (DGC) or inoperable or metastatic lobular triple negative breast cancer (TNBC) or inoperable or metastatic *CDH1*-mutated solid tumour (basket cohort)
- Assessment of E-cadherin, ER and HER2 status as per local assessment.
- Measurable disease (RECIST 1.1)
- Breast cohort: previously treated with at least one prior line of therapy including at least one prior line of hormone therapy and a CDK4/6 inhibitor for advanced disease or at least one line of hormone therapy and up to 3 lines of chemotherapy for advanced disease.
- Basket cohort: DGC patients previously treated with at 1-3 lines of prior therapy for advanced disease OR relapsing within one year of completing (neo) adjuvant chemotherapy OR unsuitable for chemotherapy in the opinion of the investigator, or lobular TNBC or *CDH1*-mutated solid tumour previously treated with 1-3 prior lines of chemotherapy for advanced disease.

Methods

- Eligible patients with measurable disease, had previously treated ER+ lobular ABC confirmed E-cadherin negative by immunohistochemistry (ER+ lobular cohort), or advanced diffuse gastric cancer (DGC), lobular triple negative breast cancer (TNBC) or other *CDH1*-mutated solid tumours (basket cohort).
- The ER+ lobular ABC cohort received crizotinib and fulvestrant, and the basket cohort crizotinib alone.
- The primary endpoint was confirmed response rate (RR).
- Secondary endpoints included clinical benefit rate (CBR: Partial response or stable response at 24 weeks), safety, progression-free (PFS) and overall survivals (OS).
- Optimal Simon 2 stage design with 80% power to exclude p0 5% and target p1 20% RR, with recruitment of 29 ER+ lobular and 29 DGC or lobular TNBC patients. At least 4 confirmed responses in 29 patients were required to consider crizotinib +/- fulvestrant worthy of future study.

Results - Patient Characteristics

Characteristic	ER+ Lobular ABC Cohort	Basket cohort
	Number of patients (n =27)	Number of patients (n =6)
Median age	57	63
Range	(35-73)	(37-83)
Female	27 (100%)	6 (100%)
Male	0	0
ER+/HER2- ABC	27 (100%)	0
Triple negative ABC	0	5 (83.3%)
Diffuse gastric cancer	0	1 (16.7%)
CDH1-mutated solid tumours	0	0
Number of lines of palliative endocrine therapy		
0	0	4 (66.7%)
1	18 (66.7%)	1 (16.7%)
2	7 (25.9%)	1 (16.7%)
3 or more	2 (7.4%)	0
Number of lines of palliative chemotherapy		
0	14 (51.9%)	0
1	7 (25.9%)	3 (50%)
2	4 (14.8%)	2 (33.3%)
3	2 (7.4%)	1 (16.7%)
Sites of metastatic disease at baseline:		
Bone	18 (66.7%)	3 (50%)
Liver	12 (44.4%)	1 (16.7%)
Locoregional nodal disease	8 (29.6%)	2 (33.3%)
Peritoneal	5 (18.5%)	3 (50%)
Menopausal status:		
Pre- or peri-menopausal	7 (25.9%)	5 (83.3%)
Post-menopausal	20 (74.1%)	1 (16.7%)

Results: Safety

Toxicity n(%)	ER+ Lobular ABC Cohort		Basket cohort	
	Number of patients (n =27)		Number of patients (n =6)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Nausea	20 (74%)	1 (4%)	1 (17%)	0
Vomiting	18 (67%)	2 (7%)	2 (33%)	0
Diarrhoea	13 (48%)	0	1 (17%)	0
Constipation	10 (37%)	0	2 (33%)	0
Abdominal pain	8 (30%)	1 (4%)	3(50%)	2 (33%)
AST increase	20 (74%)	8 (30%)	4 (67%)	1 (17%)
ALT increase	17 (63%)	3 (11%)	4 (67%)	1(17%)
Anaemia	12 (44%)	1 (4%)	1 (17%)	0
Neutropenia	5 (19%)	1 (4%)	0	0
Fatigue	12 (44%)	1 (4%)	1 (17%)	0
Dizziness	8 (30%)	1 (4%)	0	0

Results: Efficacy

- One patient in the first 10 patients with ER+ lobular ABC had a confirmed partial response, allowing continuation of recruitment to the study. However, no further responses were recorded in 17 further assessable patients (overall response rate 1/27 (4%).
- No patients with TNBC or DGC (0/6, 0%) responded to crizotinib and recruitment was terminated.
- CBR (partial response or stable disease at 24 weeks) was 11% (ER+ lobular ABC) and 0%(basket cohort).
- Median PFS was 1.8 months for both cohorts (Figures 1 and 3).
- Median OS was 17.5 months in the ER+ lobular ABC cohort (Figure 2) and 4.4 months in the basket cohort (figure 4).

Figure 1. Kaplan Meier curve for PFS in the breast cohort

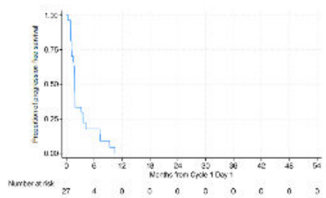


Figure 2. Kaplan Meier curve for OS in the breast cohort

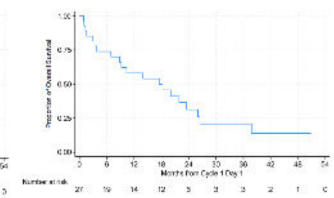


Figure 3. Kaplan Meier curve for PFS in the basket cohort

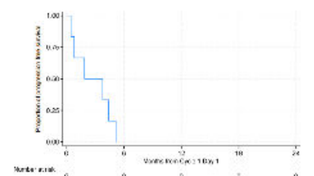
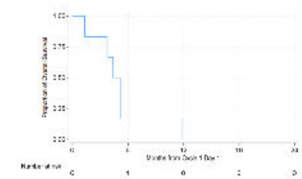


Figure 4. Kaplan Meier curve for OS in the basket cohort



Conclusions

- Neither single agent crizotinib, nor combination with fulvestrant showed activity in E-cadherin negative ABC/DGC.
- The combination of crizotinib with fulvestrant was associated with frequent raised ALT/AST
- Translational studies are ongoing to discover why the pre-clinical findings could not be replicated.

Study information: Status: Closed
Lead investigator: Dr Alicia Okines. ClinicalTrials.gov Identifier: NCT03620643
Study funding: Breast Cancer Now, catalyst grant with provision of drug by Pfizer

References: Bajrami I et al., Cancer Discov 2018