Evorpacept (ALX148) combined with trastuzumab deruxtecan in patients with HER2 positive/HER2 low metastatic breast cancer (mBC): Results from the PRE-ISPY Phase Ib trial

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P. R. Pohlmann[1], N. Chen[2], J. A. Mouabbi[1], N. Jahan[3], M. Rampurwala[4], A. Discacciati[5], M. Eklund[5], A. Chapple[6], G. L. Hirst[7], S. Venters[7], L. Brown-Swigart[7], E. Petricoin III[8], A. D. Borowsky[7], L. J. van 't Veer[7], A. L. Delson[9], S. M. Asare[6], S. Jafari[6], P. Henderson[6], D. Tripathy[1], L. J. Esserman[7], H. S. Rugo[10], R. Nanda[2], E. Stringer-Reasor[3], D. Yee[11], F. Meric-Bernstam[1], D. A. Potter[11]

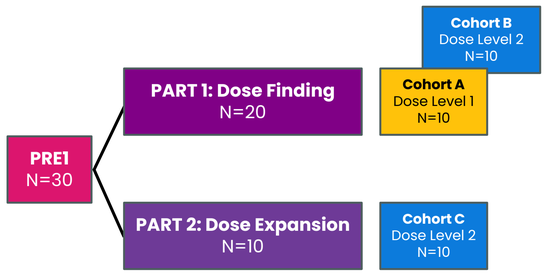
[1]University of Texas MD Anderson Cancer Center, Houston, TX, [2]University of Chicago, Chicago, IL, [3]University of Alabama at Birmingham O'Neal Comprehensive Cancer Center, Birmingham, AL, [4]UChicago Medicine Center for Advanced Care Orland Park, Orland Park, IL, [5]Karolinska Institutet, Stockholm, SWEDEN, [6]Quantum Leap Healthcare Collaborative, San Francisco, CA, [7]University of California San Francisco, San Francisco, CA, [8]George Mason University, Manassas, VA, [9]Breast Science Advocacy Core, University of California San Francisco, San Francisco, CA, [10]City of Hope Cancer Center, Duarte, CA, [11]Masonic Cancer Center, University of Minnesota, Minneapolis, MN.

BACKGROUND

The purpose of the PRE-I-SPY Phase I/Ib PRE1 trial is to test safety and tolerability of ALX148 (evorpacept) plus T-DXd in patients with (1) advanced or metastatic HER2-positive breast cancer who have received a prior anti-HER2-based regimen or (2) HER2-low breast cancer who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy. All participants had to be T-DXd naïve. HER2 status was evaluated locally. Our goal is to overcome the CD47 "don't eat me" signal on tumor cells using a combination of evorpacept (ALX148) and trastuzumab-deruxtecan (T-DXd). Evorpacept is a CD47 targeted fusion protein with a high affinity engineered D1 domain of human signal regulatory protein alpha (SIRPα) variant 1 (v1) linked to an inactive Fc domain of human immunoglobulin (Ig) G1. T-DXd is a HER2-targeted antibody-drug conjugate composed of a humanized IgG1 antibody linked to a topoisomerase I inhibitor.

PRE-ISPY TRIAL DESIGN

PRE1 is a dose escalation Phase 1b study to evaluate occurrence of dose limiting toxicities (DLTs) using a Bayesian optimal interval (BOIN) design. ALX148 was evaluated at 2 dose levels (with T-DXd): 30 mg/kg Q3W (**Cohort A; dose level 1; n=10**) and 45 mg/kg Q3W (**Cohort B; dose level 2; n=10**). An expansion cohort (**Cohort C; RP2D: dose level 2; n=10**) was also accrued. Enrollment was planned for groups of 3 participants. The max sample size for each cohort is 10 participants.



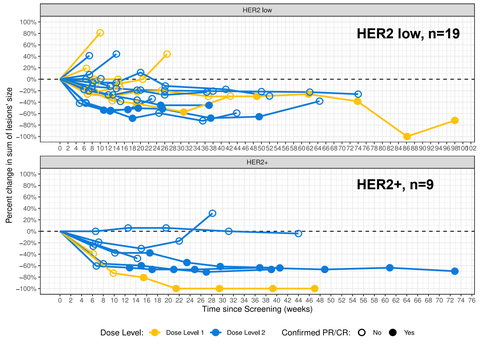
ENROLLMENT

Table 1. Baseline Characteristics.

	Overall (N = 30)	Dose Level 1 Cohort A (N = 10)	Dose Level 2 Cohort B (N = 10)	Dose Level 2 Cohort C (N = 10)
Age (years)				
Median	55	56	60	46
Min, Max	30, 76	33, 76	30, 66	36, 70
Sex, n(%)				
Female	30 (100)	10 (100)	10 (100)	10 (100)
Race, n(%)				
Asian	1 (3.3)	0	0	1 (10)
Black	8 (27)	0	3 (30)	5 (50)
White	17 (57)	8 (80)	6 (60)	3 (30)
Not Reported	4 (13)	2 (20)	1 (10)	1 (10)
ECOG-PS Score, n(%)				
0	15 (50)	6 (60)	3 (30)	6 (60)
1	15 (50)	4 (40)	7 (70)	4 (40)
Diagnosis*, n(%)				
HER2+ mBC	10 (33)	3 (30)	3 (30)	4 (40)
HER2 low mBC	20 (67)	7 (70)	7 (70)	6 (60)
Prior Therapy, n(%)				
Curative	18 (60)	5 (50)	8 (80)	5 (50)
Metastatic	30 (100)	10 (100)	10 (100)	10 (100)
Prior Line of Metastatic Therapy, n(%)				
0L	0	0	0	0
1L to 3L	24 (80)	6 (60)	10 (10)	8 (80)
≥4L	6 (20)	4 (40)	0	2 (20)

*HER2+ defined as IHC 3+ or IHC 2+/in situ hybridization (ISH)+; HER2 low defined as IHC 1+ or IHC2+/ISH-

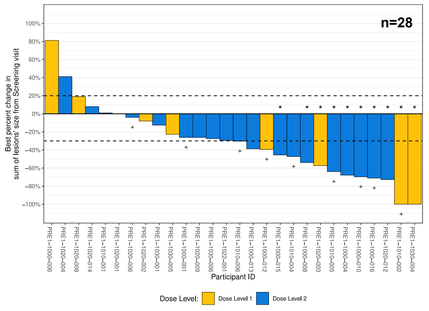
Fig.1 Spider Plot of Target Lesions by HER2 Status.



- This figure illustrates the longitudinal changes in the sum of RECIST measurements.
- 10/30 participants had progression of the target lesion.
- 2 participants did not have measurable disease at baseline (HER2 low n=1 and HER2+ n=1).

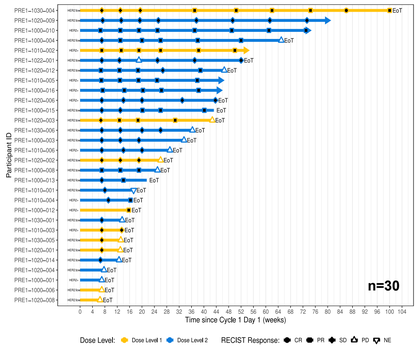
EFFICACY RESULTS

Fig.2 Waterfall Plot of Targeted Lesions by HER2 Status.



- The mean maximum decrease in target tumor lesions was -50% for HER2+ participants (Interquartile range or IQR = -69.7%,-30.2%) and -21.6% for HER2 low participants (IQR = -49.7%, 0%) .
- One HER2+ participant had a 100% reduction in target lesion size, but still had non-target lesions present so they were marked as a PR. Another HER2 low participant had a CR.

Fig.3 Swimmer plot by Dose Level.



Participants who have ended therapy are marked, as are RECIST responses at each scan.

Fig.4 Baseline *vs* C3D1 images of a participant with HR+HER2+ mBC.

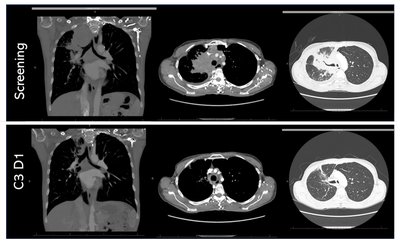


Table 2. Median PFS, Confirmed ORR, and CBR.

	Median PFS in months		
Group	**Total**	**Dose Level 1**	**Dose Level 2**
All	8.6	5.5	8.6
HER2 +	Not met	Not met	Not met
HER2 low	5.6	2.8	8.0
HR+	9.6	9.6	10.0
HR-	6.1	1.3	8.6
	Confirmed Objective Response Rate % (CR/PR)		
Group	**Total**	**Dose Level 1**	**Dose Level 2**
All	33.3	30	35
HER2 +	40	33.3	42.9
HER2 low	30	28.6	30.8
HR+	34.8	37.5	33.3
HR-	28.6	0	40
	Clinical Benefit Rate % (CR+PR+SD)		
Group	**Total**	**Dose Level 1**	**Dose Level 2**
All	73.3	60	80
HER2 +	90	100	85.7
HER2 low	65	42.9	76.9
HR+	78.3	75	80
HR-	57.1	0	80
	Median Follow-up in months		
Group	**Total**	**Dose Level 1**	**Dose Level 2**
All	9.1	8.2	9.1
HER2 +	8.2	3.4	10
HER2 low	9.1	9.7	9.1
HR+	9.7	10.3	9.1
HR-	6.6	5.3	9.1

Median Progression Free Survival (PFS) was not yet reached in HER2+ participants.

SAFETY RESULTS

Table 3. Treatment Emergent Adverse Events in >20% of Patients.

	N = 30					
Adverse Event (SOC)	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**	**Any Grade**
Gastrointestinal disorders	15 (50%)	9 (30%)	2 (6.7%)	—	—	26 (87%)
Nausea	18 (60%)	4 (13%)	—	—	—	22 (73%)
Diarrhoea	12 (40%)	3 (10%)	1 (3.3%)	—	—	16 (53%)
Constipation	10 (33%)	1 (3.3%)	—	—	—	11 (37%)
Stomatitis	5 (17%)	1 (3.3%)	—	—	—	6 (20%)
General disorders and administration site conditions	15 (50%)	9 (30%)	1 (3.3%)	—	—	25 (83%)
Fatigue	12 (40%)	8 (27%)	1 (3.3%)	—	—	21 (70%)
Investigations	4 (13%)	8 (27%)	7 (23%)	1 (3.3%)	—	20 (67%)
Alanine aminotransferase increased	8 (27%)	3 (10%)	—	—	—	11 (37%)
White blood cell count decreased	3 (10%)	8 (27%)	—	—	—	11 (37%)
Aspartate aminotransferase increased	9 (30%)	1 (3.3%)	—	—	—	10 (33%)
Blood alkaline phosphatase increased	8 (27%)	2 (6.7%)	—	—	—	10 (33%)
Lymphocyte count decreased	1 (3.3%)	4 (13%)	5 (17%)	—	—	10 (33%)
Neutrophil count decreased	1 (3.3%)	7 (23%)	2 (6.7%)	—	—	10 (33%)
Platelet count decreased	7 (23%)	—	1 (3.3%)	1 (3.3%)	—	9 (30%)
Metabolism and nutrition disorders	11 (37%)	5 (17%)	1 (3.3%)	—	—	17 (57%)
Decreased appetite	9 (30%)	2 (6.7%)	—	—	—	11 (37%)
Blood and lymphatic system disorders	8 (27%)	5 (17%)	3 (10%)	—	—	16 (53%)
Anaemia	9 (30%)	5 (17%)	2 (6.7%)	—	—	16 (53%)
Infections and infestations	1 (3.3%)	10 (33%)	3 (10%)	—	—	14 (47%)
Nervous system disorders	12 (40%)	—	1 (3.3%)	—	—	13 (43%)
Headache	6 (20%)	—	—	—	—	6 (20%)
Respiratory, thoracic and mediastinal disorders	9 (30%)	2 (6.7%)	2 (6.7%)	—	—	13 (43%)
Cough	6 (20%)	1 (3.3%)	—	—	—	7 (23%)
Musculoskeletal and connective tissue disorders	11 (37%)	1 (3.3%)	—	—	—	12 (40%)
Skin and subcutaneous tissue disorders	9 (30%)	3 (10%)	—	—	—	12 (40%)

[1] Total # of patients

- No patients experienced a Dose Limiting Toxicity (n =17).
- In Dose Level 1, there was one observed treatment emergent SAE (Grade 3 Infectious Pneumonia).
- In Dose Level 2, 5 (25%) participants experienced 8 treatment emergent SAEs (Grade 3 Haemolytic anemia*, Grade 2 Pyrexia, Grade 3 Portal Hypertension, Grade 3 Mastitis, Grade 3 Norovirus infection, Grade 4 Platelet count decreased, Grade 3 Pneumonitis*, and Grade 3 Embolism) and 2 (10%) participants experienced an AESI (Grade 2 Ejection fraction decreased, and Grade 3 Pneumonitis). *Considered immune related AEs.
- No treatment related Grade 5 adverse events, all deaths due to progression.

ADVOCATE SUMMARY

This metastatic breast cancer trial is testing a new drug combination – ALX148 plus T-DXd – to treat patients with HER2+ or HER2low therapy-resistant tumors. ALX148 enables the immune system to better fight cancer. T-DXd is an anti-HER2 drug which helps to deliver chemotherapy specifically into tumor cells. This new drug combination was tolerable for most patients and helped control tumors. The goal is to develop a new strategy to activate the immune system in HER2+ and HER2low subtypes where there are currently no approved immune activating therapies.

CONCLUSION

Results thus far demonstrate that the combination of ALX148 (evorpacept) and T-DXd is active and well tolerated, with no new safety signals and minimal impact on T-DXd-associated toxicity.

ACKNOWLEDGEMENTS

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