Abstract #1082: Association of 27-gene IO score with outcome in a phase Ib trial of pembrolizumab (pembro) plus chemotherapy (CT) in metastatic triple-negative breast cancer (mTNBC)

EARLE A. CHILES RESEARCH INSTITUTE [1] | PROVIDENCE Cancer Institute [2] | ONCOCYTE [3] | UT Southwestern Medical Center [4]

David B. Page MD[1,2], Krystle L. Collins MD[1], Venkatesh Rajamanickam MS[1], Nicole Moxon[1,2], Staci L.Mellinger[1,2], Alison K. Conlin MD[1,2], Robert Seitz[3], Kim McGregor MD[3], Tyler J. Nielsen MS[3], Heather L. McArthur MD[4]

Background

- Pembro plus CT is FDA approved for the treatment of PD-L1-positive mTNBC, based upon improved objective response rate (ORR), progression free survival (PFS) and overall survival (OS) in the Keynote-355 trial[1]
- Novel biomarkers beyond PD-L1 score are needed to improve prediction of clinical benefit to immune checkpoint inhibition (ICI) strategies
- The IO score is a 27-gene signature derived from the 101-gene TNBCtype genomic classification[2]
- IO score predicts ICI benefit in metastatic bladder cancer and lung cancer[3,4]
- The IO score predicts anti-PD-L1 (atezolizumab) benefit when combined with neoadjuvant CT in early stage TNBC (NeoTRIPaPDL1)[5]

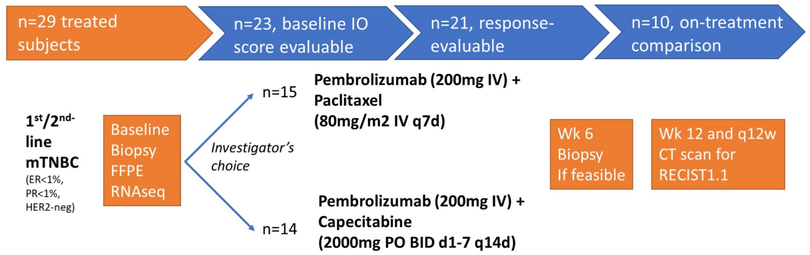
Objectives:

- To evaluate clinical response to pembro+CT in IO+ versus IO- mTNBC cohorts (week 12 OR by RECIST1.1)
- To evaluate survival (PFS, OS) in IO+ versus IO- cohorts
- To evaluate the relationship between PD-L1 score and IO Score
- To compare IO score of baseline biopsy versus matched on-treatment biopsy

Methods:

- Phase 1b trial of 1st/2nd line pembro (200mg IV q3w) + investigator's choice CT (paclitaxel 80mg/m2 IV q7d, or fixed-dose capecitabine 2000mg PO BID, d1-7 q14d) was evaluated
- 29 participants were enrolled from 2016-2018 at Providence Cancer Institute (Portland, OR) and Cedars-Sinai Medical Center (Los Angeles, CA)
- Association of IO score with week 12 RECIST OR (primary endpoint), PFS, OS
- IO Score measured by RNA exome sequencing (OncoCyte, Irvine, CA), analyzed as a binary IO+/IO- and continuous variable
- Association of IO score with week 12 RECIST objective response (OR, primary endpoint), PFS, and OS was interrogated
- Tumors were evaluated for PD-L1 IHC (SP263 combined Positive Score [CPS] cutoff >10%)
- Univariate outcomes are reported, as sample size was insufficient for multivariate analysis

Figure: Trial Schematic and sample sizes for IO score analysis



Results: Clinical Response & Survival

- 33% of evaluable cases were IO+ (n=7/21)
- Wk 12 response and median survival were higher in IO+ cohort (table 2)

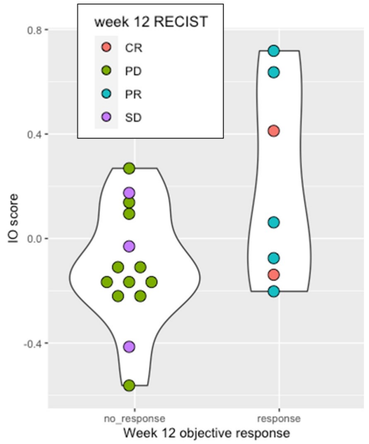
RECIST1.1 Week 12 Response

	IO+ (n=7)	IO- (n=14)
ORR	43% (3)	28% (4)
CR	14% (1)	7% (1)
PR	28% (2)	21% (3)
SD	14% (1)	14% (2)

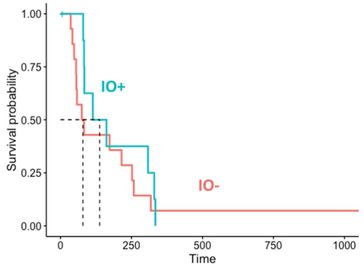
Median K-M Survival

	IO+	IO-
PFS range	138d (84d, NR)	79d (56d,318d)
OS range	687d (421d, NR)	305d (140d, NR)

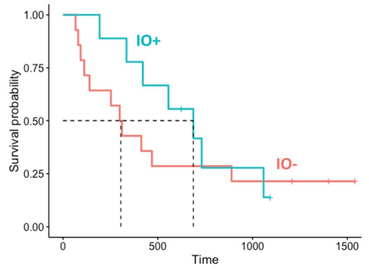
Distribution of IO Scores



PFS Kaplan Meier Curve



OS Kaplan Meier Curve



IO Score versus CPS score

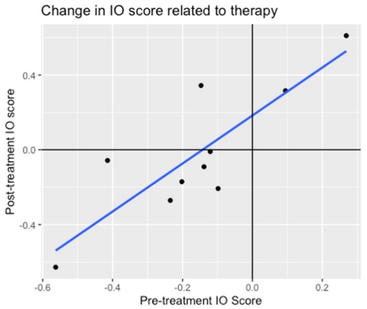
- IO score does not correlate with CPS score (r=0.27)
- 31% (n=5/16) of PD-L1 negative tumors were IO+, and meaningful clinical responses were observed in this category (40% ORR, table to right)

IO/PD-L1 discordant cases and outcomes

Category	PFS	OS	wk12 OR
IO+/PD-L1-	162d	193d	PR
	80d	421d	PD
	83d	687d	PD
	334d	731d	CR
	331d	556d	SD
IO-/PD-L1+	252d	311d	PR
	319d	1402+d	PR

Baseline versus on-treatment score

- On-treatment IO score correlated with baseline score (n=10 pairs, r=0.84, figure below), with a general increase in IO score related to treatment
- IO+/IO- classifications were concordant (kappa= 0.74, p=.02, figure below).
- Only one tumor was reclassified (IO- → IO+)
- TNBCtype classifications were not always concordant (figure below)



Pre v. on-treatment IO score and TNBCType

IO+/IO-		IO Score		TNBCType	
Pre-Tx	On-Tx	Pre-Tx	On-Tx	Pre-Tx	On-Tx
IO-	IO-	-0.56	-0.63	M	M
IO-	IO-	-0.41	-0.06	LAR	LAR
IO-	IO-	-0.24	-0.27	BL1	M
IO-	IO-	-0.20	-0.17	LAR	LAR
IO-	IO+	-0.15	0.34	MSL	BL2
IO-	IO-	-0.14	-0.09	LAR	MSL
IO-	IO-	-0.12	-0.01	BL1	BL1
IO-	IO-	-0.10	-0.21	BL2	UNS
IO+	IO+	0.09	0.32	UNS	LAR
IO+	IO+	0.27	0.61	BL2	UNS

Conclusions/take-aways:

- *IO Score associates with clinical outcome in this preliminary mTNBC dataset*
- *IO Score may identify PD-L1-negative tumors that respond to pembro + CT*
- *Ongoing evaluation of the IO score is warranted in randomized mTNBC datasets*

Clinical Trial Information:

- Clinicaltrials.gov ID: NCT02734290
- Correspondence: David B. Page, MD david.page2@providence.org
- Drug support and funding for trial and correlatives provided by Merck Sharpe & Dohme Merck Investigator Studies Program
- IO Score analyzed in collaboration with Oncocyte

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