600 POST-HOC ANALYSIS FROM TWO PHASE I/II NY-ESO-1-TCR T-CELL THERAPY CLINICAL TRIALS IN PATIENTS WITH ADVANCED SARCOMA (SS OR MRCLS) DEMONSTRATES RESPONSE ACROSS A RANGE OF NY-ESO-1 EXPRESSION

[1]Erika Klohe, [1]Sunil Suchindran, [1]Gurpreet Kapoor, [1]Jimson D'Souza, [1]Ellie Corigleano, [2]Dejka Araujo, [3]Sandra D'Angelo*. *[1]GlaxoSmithKline, Collegeville, PA, United States; [2]Univerity of Texas MD Anderson Cancer Center, Houston, TX, United States; [3]Memorial Sloan Kettering Cancer Center, New York, NY, United States*

Background An investigational use only immunohistochemical (IHC) clinical trial assay was used to prospectively identify NY-ESO-1-positive patients for eligibility in two phase I/II pilot clinical trials. NY-ESO-1 T-cell receptor (TCR) T-cell therapy was investigated in NY-ESO-1 expressing HLA-A*02:01, 05, or 06 positive patients with either metastatic or locally advanced synovial sarcoma (SS) (NCT01343043)[1], or advanced myxoid round cell liposarcoma (MRCLS) (NCT02992743).[2] Post-hoc analyses on both studies investigated the relationship of NY-ESO-1 expression levels in patients with response and no response as per RECIST1.1 (investigator assessed) to NY-ESO-1 TCR T-cell therapy.

Methods NY-ESO-1 expression was determined by total tumor percent staining at stain intensities 0, 1+, 2+, 3+ (TP-score) as assessed by a board-certified pathologist. Eligible SS patients were enrolled into study cohorts with differing cut-off criteria for NY-ESO-1 expression levels (table 1). MRCLS patients were enrolled into study cohorts using a single cut-off for NY-ESO-1 expression levels (≥2+, TP ≥30%). SS and MRCLS eligible patients received different dose lymphodepleting regimens (LDR) of fludarabine and cyclophosphamide depending on trial and cohort (table 1).[3,4] For the present NY-ESO-1 expression analysis, the distribution of the NY-ESO-1 TP-score is displayed as boxplots allowing simultaneous visual comparisons of the range of expression across response, indication, and LDR. In addition, an exploratory cut-off of ≥50% was used to evaluate responses. All analyses are exploratory and descriptive.

Results All MRCLS patients and most SS patients expressed NY-ESO-1 as predominately moderate/strong (2+/3+) in ≥50% tumor cells.[5] A pooled ORR assessment at ≥ 50% threshold was 33%. Responders and non-responders were observed across a range of NY-ESO-1 TP-scores in SS from ≥1% to 100% and in MRCLS ≥50% to 100% (figure 1). Of the six patients with threshold ≤30%; there were two SS responders expressing TP-score at 30% and one at 10% (figure 1, table 1).

Conclusions NY-ESO-1 expression as a biomarker of patient selection is a relevant approach for use with NY-ESO-1 TCR T-cell therapy. Observed range of response may be supportive of a cut-off in SS of less than 50% TP-score given that three patient responders had low to moderate (<50% TP-score) NY-ESO-1 expression, and that MRCLS cut-off was set at ≥30%. Further exploration of TP-score is underway in a current phase II trial of NY-ESO-1 TCR T-cell therapy (NCT03967223).

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Trial Registration NCT01343043; NCT02992743

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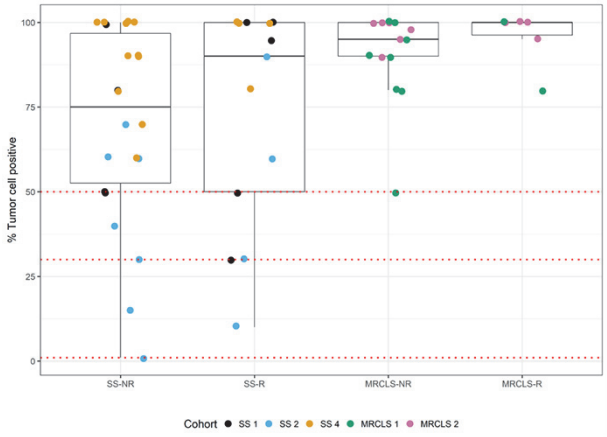
Ethics Approval NCT01343043: The study was conducted in accordance with ICH Good Clinical Practice (GCP), all applicable subject privacy requirements, and the guiding principles of the current version of the Declaration of Helsinki. NCT02992743: The investigator ensured this study was conducted in full compliance with the principals of the "Declaration of Helsinki" or with the laws and regulations of the country in which the research is conducted, whichever, affords the greater protection to the subject. The study fully adhered to the principles outlined in "Guideline for Good Clinical practice" ICH Tripartite Guideline (January 1997) or with local law if it affords greater protection to the subject.



Abstract 600 Figure 1 NY-ESO-1 TP-score across SS and MRCLS treated patient cohorts and TP-score cut-offs (≥1%, ≥30%, ≥50%) MRCLS, myxoid round cell liposarcoma; NR, non-responders; R, responders; SS, synovial sarcoma

Abstract 600 Table 1 Summary of NY-ESO-1 scoring algorithms and Lymphodepletion regimens by cohort

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Study	Cohort (number of patients)	R and NR (number of patients)	Scoring algorithm for NY-ESO-1 expression	Drug	Dose
NCT02992743	MRCLS 1 (n=10)	R (n=2) NR (n=8)	IHC intensity score ≥2+, TP ≥30%	Fludarabine	90 mg/m² (30 mg/m² x 3 days)
				Cyclophosphamide	1800 mg/m² (600 mg/m² x 3 days)
	MRCLS 2 (n=10)	R (n=4) NR (n=6)		Fludarabine	120 mg/m² (30 mg/m² x 4 days)
				Cyclophosphamide	2700 mg/m² (900 mg/m² x 3 days)
NCT01343043	SS 1 (n=9)	R (n=5) NR (n=4)	IHC intensity score ≥2+, TP ≥50%	Fludarabine	120 mg/m² (30 mg/m² x 4 days)
				Cyclophosphamide	3600 mg/m2 (1800 mg/m2 x 2 days)
	SS 2 (n=11)	R (n=4) NR (n=7)	IHC intensity score ≥1+, TP ≥1% not exceeding ≥2+, TP ≥50%	Fludarabine	120 mg/m² (30 mg/m² x 4 days)
				Cyclophosphamide	3600 mg/m² (1800 mg/m² x 2 days)
	SS 4 (n=15)	R (n=4) NR (n=11)	IHC intensity score ≥2+, TP ≥50%	Fludarabine	90 mg/m² (30 mg/m² x 3 days)
				Cyclophosphamide	1800 mg/m² (600 mg/m² x 3 days)

IHC, immunohistochemistry; LD, lymphodepletion; MRCLS, myxoid round cell liposarcoma; NR, non-responders; R, responders; SS, synovial sarcoma

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