A multivariate biomarker predicts sacituzumab govitecan (SG) response in solid tumors

Abstract #2171

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Introduction

Antibody-drug conjugates (ADC) represent an important new class of targeted cancer therapy for solid tumors, with several recent drug approvals and promising late-phase candidates[1]. Despite variable response rates, most ADC development strategies have not utilized predictive biomarkers. In some cases, target protein expression has been used to select patients (e.g. Her2-targeted ADCs[2,3] or enrich clinical trial results (e.g. Folate receptor-targeted ADC[4]), however most development strategies have pursued unselected patients in high unmet need tumor types known to express the target[1].

Sacituzumab govitecan (SG), is a Trop-2 ADC that combines a humanized anti-TROP2 monoclonal antibody with the topoisomerase I inhibitor, SN-38, via a cleavable CL2A linker[5]. SG is indicated for unresectable or metastatic triple-negative breast cancer (TNBC) after two or more prior systemic therapies[5], and locally advanced or metastatic bladder cancer patients who have previously received a platinum-containing chemotherapy and a PD-1 or PD-L1 inhibitor[6]. TROP2 protein expression was evaluated post-hoc in the TNBC study, and while all the objective responses occurred in patients with moderate or strong staining, this represented almost all the study population (88%), providing limited opportunity for stratification[7]. In the IMMU-12-01 basket trial, objective responses were observed in 8 of 9 solid tumor types with 10 or more patients enrolled, with response rates varying from 0% in pancreatic cancer (0 / 16) to 33.3% in TNBC (36 / 108)[8]. Given the significant variability in objective response rates observed across tumor types, we sought to develop a predictive biomarker of SG response. Because tissue samples from the clinical trials were not available to us, we leveraged available next generation sequencing (NGS)-based molecular profiling data from an advanced solid tumor cohort (n = 23,968) to develop a multivariate biomarker algorithm that predicts the observed objective response rates across tumor types.

Table 1. Biomarker Positive Rates by Tumor Type

Cancer Type	*n*	Average Biomarker Score	Biomarker Positive Rate	Objective Response Rate
Bladder Cancer	718	18.5	57.4%	29%
Endometrial Cancer	993	16.8	40.9%	22%
Breast Cancer	2,336	16.9	38.4%	32%
Small Cell Lung Cancer	215	17.5	33.5%	18%
Prostate Cancer	1,437	16.4	30.8%	9%
Esophagogastric Cancer	1,213	14.0	23.2%	5%
Non-Small Cell Lung Cancer	3,425	14.2	18.8%	17%
Pancreatic Cancer	927	12.3	14.5%	0%
Colorectal Cancer	3,146	13.6	9.9%	3%
Subtotal	**14,410**	**15.0**	**25.0%**	**14%**
Head and Neck Cancer	584	18.1	50.5%	
Cervical Cancer	151	17.6	49.7%	
Salivary Gland Cancer	120	17.5	40.8%	
Skin Cancer, Non-Melanoma	137	16.5	37.2%	
Ovarian Cancer	1,362	15.7	34.6%	
Cancer of Unknown Primary	1,812	14.2	23.6%	
Other Cancer	579	13.4	21.2%	
Small Bowel Cancer	96	13.6	17.7%	
Thyroid Cancer	270	14.1	17.4%	
Hepatobiliary Cancer	589	11.5	8.0%	
Appendiceal Cancer	95	8.0	7.4%	
Neuroendocrine Tumor	251	12.7	6.4%	
Lymphoma	100	9.1	4.0%	
Sarcoma	777	12.3	3.6%	
Renal Cell Carcinoma	434	9.3	2.5%	
Melanoma	868	11.5	2.1%	
Gastrointestinal Stromal Tumor	168	11.2	0.6%	
CNS and PNS Cancer	105	10.2	0.0%	
Glioma	1,060	8.7	0.0%	
Subtotal	**9,558**	**13.1**	**17.7%**	
Grand total	**23,968**	**14.2**	**22.1%**	

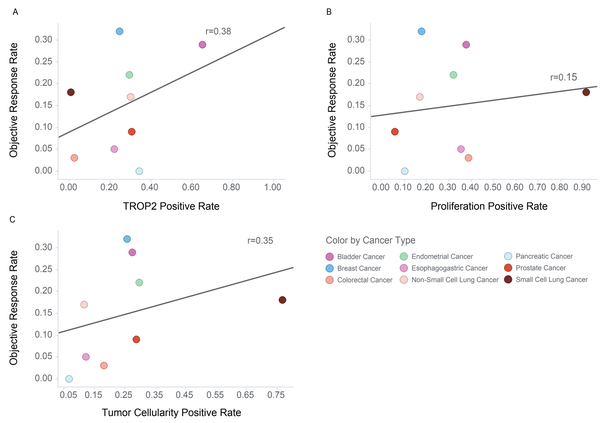
Average SG biomarker scores and biomarker positive rates by tumor type in the full molecular cohort, grouped by tumor types with 10 or more patients evaluated in the IMMU-12-01 basket trial 8 and sorted by biomarker positive rate.

Methods

Tumor type-specific objective response rates were collated from the IMMU-12-01 basket trial[8]. Molecular data were collected as part of the Strata Trial® (NCT03061305), a large multi-institutional observational study, with StrataNGS next-generation sequencing (NGS) test, as previously described [9,10]. RNA sequencing-based gene expression values were log2 transformed and median-centered to 10. Proliferation was calculated as the average of TOP2A and UBE2C expression. Molecularly-defined tumor cellularity was calculated based on somatic and germline variant allele frequencies and copy number profiles, as previously described[9].

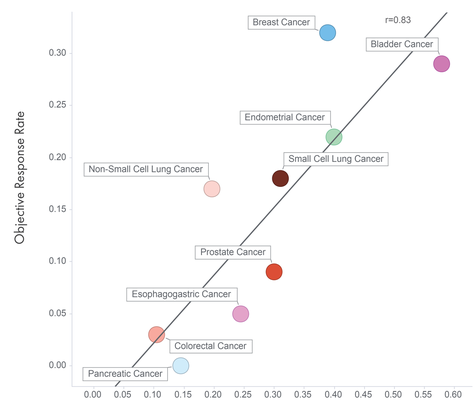
The molecular dataset was randomly divided into discovery and validation cohorts. For each quantitative biomarker evaluated, thresholds were set such that the top 25% of samples in the 9 tumor types with response data were biomarker positive and the bottom 75% were biomarker negative. SG biomarker score coefficients were optimized in the discovery cohort to maximize the Pearson correlation coefficient between tumor type-specific biomarker positive rates and objective response rates.

Figure 1. Individual Biomarker Rate Correlation with ORR



(A) TROP2, (B) proliferation gene expression and (C) tumor cellularity.

Figure 2. SG Biomarker Rate Correlation with ORR in Validation Cohort



A multivariate biomarker for sacituzumab govitecan (SG). Correlation analysis of the SG biomarker positive rate in the validation cohort with objective response rate observed in the IMMU-12-01 basket trial[8]

Results

We considered three candidate biomarkers: TROP2 gene expression, cell proliferation gene expression, and molecularly defined tumor cellularity. We randomly divided the 14,410 tumor profiles from the nine tumor types with response data into discovery (n=7,177) and validation cohorts (n=7,233). Based on the weighted mean objective response rate of 14.7%, we fixed the overall positive biomarker rate at 25% for each candidate biomarker. We then evaluated the Pearson correlation of tumor type-specific biomarker rates with objective response rates. The individual biomarkers produced only weak correlations with SG response (Figure 1), with none reaching statistical significance: TROP2 expression (r=0.38, p=0.23), proliferation gene expression (r=0.15, p=0.76) and tumor cellularity (r=0.35, p=0.43).

Eq1: **SG biomarker score = [TROP2] + 0.6 * [Proliferation] + 6 * log2 ([tumor cellularity])**

In contrast, an optimized linear equation combining all 3 biomarkers (Eq1) was strongly correlated with response, both when using tumor type-specific biomarker rates derived from the discovery cohort (r=0.83, p=0.006) and the independent validation cohort (r=0.82, p=0.007) (Figure 2).

Figure 3. Biomakers Factor Relationship with Response

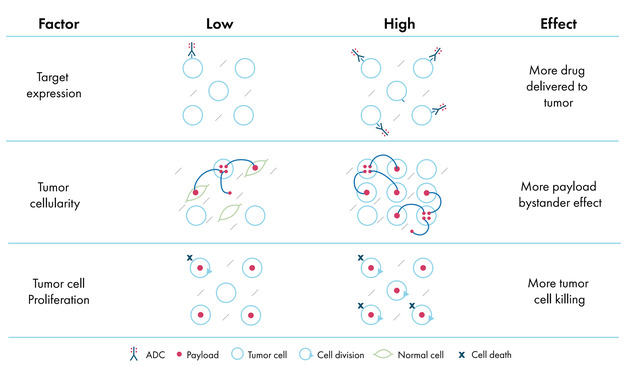
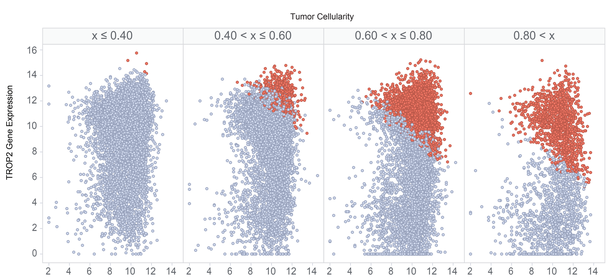


Illustration of the biomarker factors that contribute to the SG biomarker score and their relationship with response.

Figure 4. Relationship of Biomarker Factors in Full Molecular Cohort



SG biomarker status as related to the biomarker factors in the full molecular cohort: TROP2 expression (y-axis), proliferation gene expression (x-axis) and tumor cellularity (binned by panel). Biomarker positive samples are colored red and biomarker negative samples are colored blue.

Conclusions

Herein, we show that while the rate of TROP2 overexpression only weakly predicted objective response rates observed in solid tumor patients treated with the TROP2- targeted ADC, sacituzumab govitecan (SG) (r=0.40, p=0.29), a multivariate biomarker combining TROP2 expression with proliferation gene expression and tumor cellularity strongly predicted response (r=0.82, p=0.007). The biomarker has the potential to improve the selection of patients who are more likely to benefit from SG and may be generalizable to other ADCs.

Future studies should further evaluate the biomarker algorithm in patients previously treated with SG and in prospective clinical trials. The biomarker approach of combining target expression with proliferation and tumor cellularity to predict response may be generalizable to ADCs as a class, with the potential to further optimize use and maximize benefit.

Considering SG's mechanism of action, a plausible model for response is that (1) higher target expression increases ADC binding, internalization and payload cleavage, (2) higher tumor cellularity increases the proportion of released payload molecules that diffuse into neighboring tumor cells (i.e., ADC bystander effect)[11] and (3) higher tumor cell proliferation increases the likelihood of payload molecules blocking DNA replication and causing tumor cell death)[12] (Figure 3). The distribution of biovmarker factors and positive biomarker calls across the full cohort is depicted in Figure 4, with the level of TROP2 expression required for a positive biomarker call varying dynamically as a function of tumor cellularity and proliferation gene expression.

Next, we applied the biomarker algorithm to all tumor types represented in the full cohort (Table 1). Among tumor types with responses observed in the basket trial, biomarker positive rates ranged from 9.9% in colorectal cancer to 57.4% in bladder cancer. Additional tumor types with high biomarker positive rates represent a potential opportunity to expand the use of SG further - cancers of the head and neck, cervix, salivary gland, skin (nonmelanoma) and ovary had positive biomarker rates >30% and rare squamous cell carcinomas of the penis (89%), anus (67%) and vulva (44%) had among the highest biomarker rates.

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Additional Information

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