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Tumor Microenvironment Associated with Complete Response to Tislelizumab Monotherapy in Relapsed/Refractory Classical Hodgkin Lymphoma Reveals a Potentially Different Mechanism of Action

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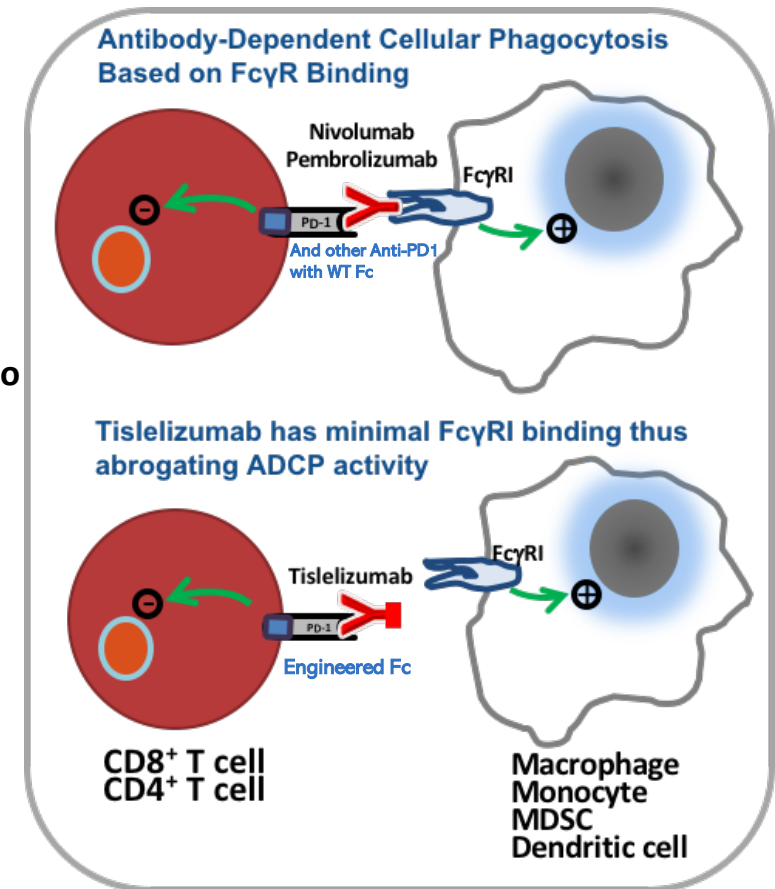


Introduction

- Classical Hodgkin lymphoma (cHL) is characterized by a small proportion of tumor cellularity (1-5%) and an extensively dominant tumor microenvironment composed of macrophages, T cells and other immune cells¹
- Anti-PD-1 Abs, including nivolumab, pembrolizumab, and other anti-PD-1s with wild-type Fc region are active in R/R cHL. However, only a minority of patients achieve durable complete remissions
- Binding to FcγR on macrophages compromises antitumor activity of PD-1 antibodies with wild-type Fc region through activation of antibody-dependent macrophage-mediated killing of T effector cells^{2,3}
- **Tislelizumab is a humanized IgG4 anti-PD-1 Ab, specifically engineered to minimize binding to FcγR on macrophages.** Preclinical data showed that in the macrophage and T cell enriched condition, tislelizumab did not induce ADCP and thus its anti-tumor activity was not compromised⁴
- A pivotal Phase 2 trial of tislelizumab in Chinese patients with cHL that have failed, or who are not candidates for, HDT/ASCT reveals a **high ORR of 87.1% and CR rate of 62.9%**⁵
- This study explored whether FcγR expression on macrophages in the cHL tumor microenvironment impact the efficacy of tislelizumab and also explored additional biomarkers associated with complete response to tislelizumab

Ab, antibody; ADCP, antibody-dependent cellular phagocytosis; ASCT, autologous stem-cell transplantation; cHL, classical Hodgkin lymphoma; CR, complete response; FcγR, Fc region of IgG receptors; HDT, high-dose chemotherapy; IgG, immunoglobulin; MDSC, myeloid-derived suppressor cell; ORR, overall response rate; PD-1, programmed cell death-1; WT, wild type.

1. Aoki T, et al., *Cancer Discov.* 2020;10(3):406-421. 2. Dahan R, et al. *Cancer Cell.* 2015;28:285-295. 3. Arlauckas S, et al. *Sci Transl Med.* 2017;9:eeal3504. 4. Zhang T, et al. *Cancer Immunol Immunother.* 2018;67:1079-1090. 5. Song Y, et al. *Leukemia.* 2020;34:533-542.



Methods

Multiplex immunohistochemistry

- Baseline tumor samples (formalin-fixed, paraffin-embedded slides) from study BGB-A317-203 were collected for mIHC testing. CD8 (CD8 T-cell marker), CD68 (macrophage marker), FcγR1, PD-L1, and CD30 were stained using Opal 7-color IHC kit
- Different cell phenotypes were annotated and the proximity of FcγR1+ macrophages (CD68+ FcγR1+ cells) within 30 μm of CD8 T cells was calculated using HALO software

Gene expression profiling

- Baseline tumor samples (formalin-fixed, paraffin-embedded blocks or cut slides) from study BGB-A317-203 were applied to GEP by HTG EdgeSeq Precision Immuno-Oncology Panel (1392 genes included)
- Signature scores were calculated using the Gene Set Variation Analysis package with publicly available gene signatures
- Differentially expressed gene and gene signatures analysis was performed between complete responders and non-complete responders

Statistical analysis

- Gene signature or mIHC marker statistical significance was tested by two-sided Wilcoxon rank-sum test, while modified t-test by limma was used for differentially expressed gene analysis
- Median value across the biomarker population was used as the cut-off to define biomarker high versus low group, based on which Fisher exact test was conducted to compare the distributions of complete responders and non-complete responders between different biomarker groups

GEP, gene expressing profiling; mIHC, multiplex immunohistochemistry.



Results

Baseline characteristics and clinical outcomes of overall, GEP-evaluable, and mIHC-evaluable populations

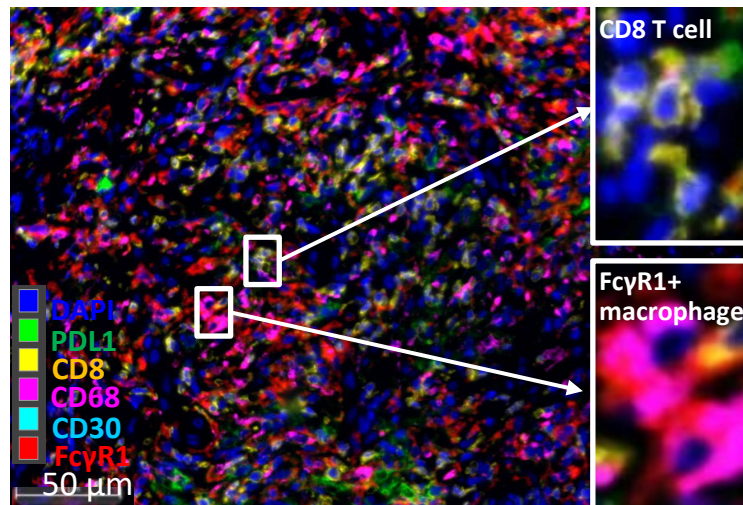
Variable	Overall population (N=70)	GEP-evaluable population (N=36)	mIHC-evaluable population (N=41)
Median age, years (range)	32.5 (18–69)	33.0 (19–69)	33.0 (19–67)
Age group, n (%)			
<65 years	66 (94.3)	32 (88.9)	38 (92.7)
≥65 years	4 (5.7)	4 (11.1)	3 (7.3)
Sex, n (%)			
Male	40 (57.1)	20 (55.6)	26 (63.4)
Female	30 (42.9)	16 (44.4)	15 (36.6)
Stage IV at study entry, n (%)	42 (60)	25 (69.4)	26 (63.4)
Bulky disease*, n (%)	8 (11.4)	2 (5.6)	3 (7.3)
Bone marrow involvement, n (%)	22 (31.4)	13 (36.1)	13 (31.7)
B-symptom(s), n (%)	26 (37.1)	15 (41.7)	13 (31.7)
Histology subtype, n (%)			
Nodular sclerosis	42 (60)	20 (55.6)	21 (51.2)
Mixed cellularity	19 (27.1)	11 (30.6)	14 (34.1)
Lymphocyte-rich	3 (4.3)	3 (8.3)	2 (4.9)
NA	6 (8.6)	2 (5.6)	4 (9.8)
Best response, n (%)			
Overall response	61 (87.1)	30 (83.3)	38 (92.7)
Complete response	44 (62.9)	20 (55.6)	27 (65.9)

*Mediastinal mass ratio of 0.33 or size of any single node/nodal mass ≥10 cm in diameter.
NA, not applicable.

Results

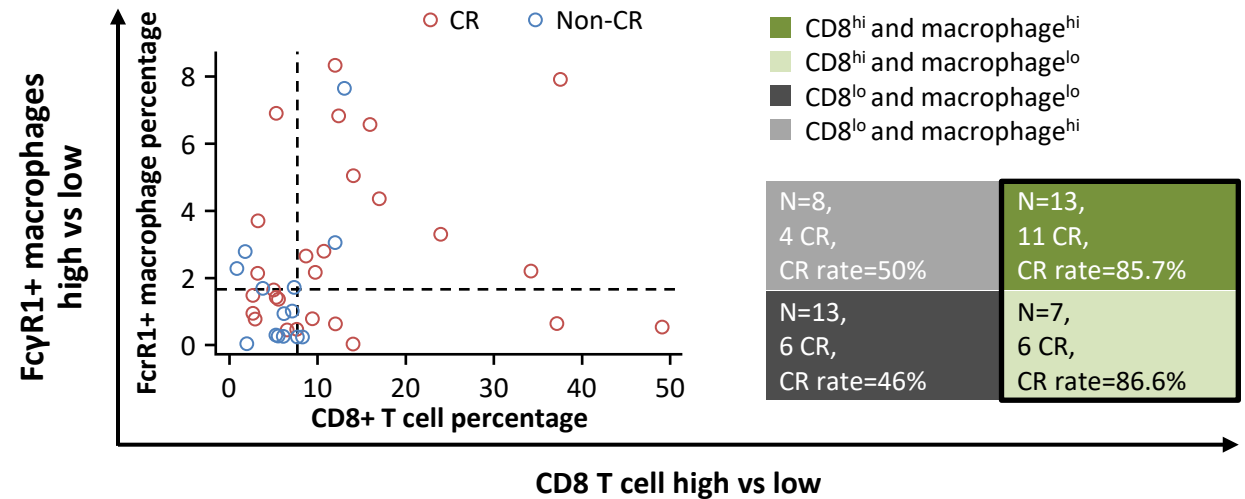
FcγR1+ macrophages in cHL tumor microenvironment have no observed impact on CR rate of tislelizumab

Representative case of mIHC



- Representative case exhibiting **precise phenotyping of CD8 T cell and FcγR1+ macrophages** on the same FFPE slides by mIHC
- CD8+ T cells were quantified by yellow fluorescence; macrophages were quantified by CD68+ marker (purple fluorescence); FcγR1+ macrophages were quantified by overlaid CD68+ and FcγR1+ marker (red fluorescence)

CD8 T cell, macrophage quantification and association with CR rate

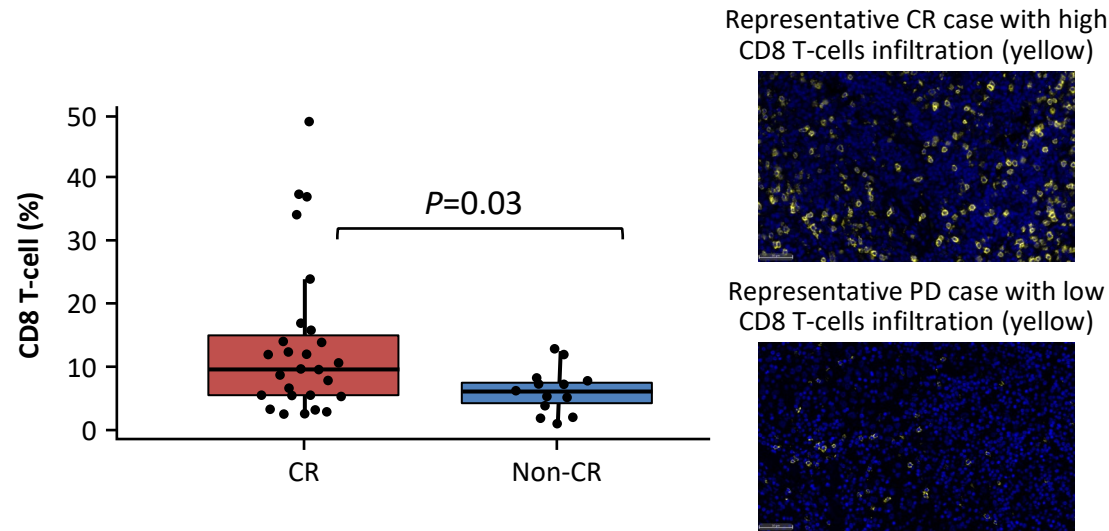


- In the CD8+ T-cell high microenvironment where ADCP-induced effector T-cell clearance is more likely, the **total number of FcγR1+ macrophages** was not observed to affect CR rates of tislelizumab (CR rate 86.6% for high vs 85.7% for low; not significant by Fisher exact test)
- In the CD8+ T-cell high microenvironment where ADCP-induced T-cell clearance is more likely, the average number of FcγR1+ macrophages **within 30 μm distance of CD8** was not observed to affect the CR rate (CR rate 85.7% for high vs 80% for low; not significant by Fisher exact test)

Results

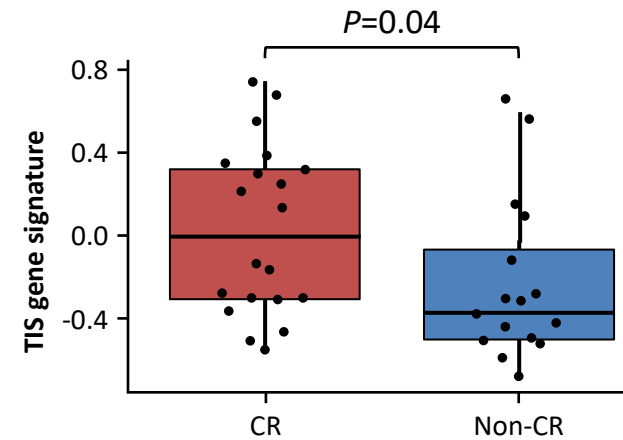
CD8 T cell abundance by mIHC and tumor inflammation signature (TIS) gene signatures by GEP are associated with complete response to tislelizumab

CD8 T cells infiltration associated with CR



CD8+ cell percentage	Patient number	CR patients	CR rate
CD8 percentage <8%	22	11	50.0%
CD8 percentage ≥8%	19	16	84.2%

TIS genes associated with CR



18-gene tumor inflammation signature

IFN biology	T-cell exhaustion	T/NK	Antigen-presenting cells
<i>CCL5</i>	<i>TIGIT</i>	<i>HLA-E</i>	<i>PSMB10</i>
<i>CXCL9</i>	<i>CD8A</i>	<i>NKG7</i>	<i>HLA-DQA1</i>
<i>CD27</i>	<i>LAG3</i>		<i>HLA-DRB1</i>
<i>CXCR6</i>	<i>CD274</i>		<i>CMKLR1</i>
<i>IDO1</i>	<i>PDCDL1G2</i>		
<i>STAT1</i>	<i>CD276</i>		

- TIS gene signature as predictive biomarker to response to pembrolizumab in solid tumors including melanoma and NSCLC¹
- CR patients have significantly higher inflamed tumor microenvironment indicated by TIS gene signature score (p<0.05)
- Single genes in TIS gene signature that are significantly different in CR vs non-CR were labeled as red

IFN, interferon; NK, natural killer; NSCLC, non-small cell lung cancer; TIS, tumor inflammation signature.

1. Ayers M, et al. *J Clin Invest*. 2017;127:2930-2940.

Conclusions

- Tislelizumab is an anti-PD-1 mAb specifically designed to minimize binding to FcγR on macrophages. Consistent with this characteristic, tislelizumab demonstrated high CR rates regardless of FcγR expression level on macrophages in the highly immune infiltrated microenvironment of cHL
- Multiple biomarkers were identified to associate with complete response to tislelizumab
 - Higher CD8+ T-cell infiltration and TIS gene signatures in the microenvironment were associated with a higher CR rate for cHL patients treated with tislelizumab
 - MC and NS histological subtypes showed specific gene signatures associated with CR

WT, wild type; MOA, mechanism of action; TIS, tumor inflammation signature; MC, mixed cellular subtype; NS, nodular sclerosis subtype; TME, tumor microenvironment.
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