DS-2243a, an HLA-A*02/NY-ESO–Directed Bispecific T-cell Engager, Shows Potent Anti-Tumor Activity in Preclinical Models of Solid Tumors

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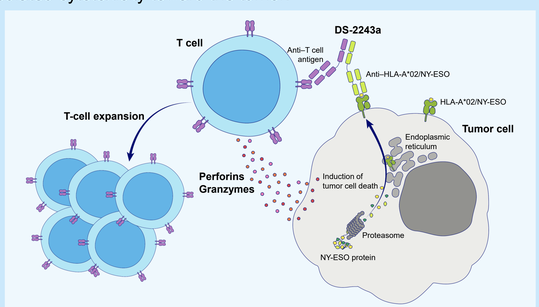
Background

NY-ESO-1 and LAGE-1 are homologous proteins commonly expressed in various tumor tissues but not in normal tissues other than the testis and placenta[1-4], making them potential tumor-specific therapeutic targets. Tumor types with prevalent NY-ESO-1 and/or LAGE-1 expression include SS, MRCLS, NSCLC, and UC. Following the intracellular processing of NY-ESO-1 and LAGE-1 proteins (hereafter referred as to NY-ESO) by the proteasome, the same highly immunogenic NY-ESO peptides are presented extracellularly by HLA-A*02[5]. DS-2243a is a first-in-class bispecific T-cell engager (BiTCE) with an effectorless Fc region. It is designed with a novel TCR-like antibody that engages both HLA-A*02/NY-ESO–expressing tumor cells and T-cells, redirecting T-cell–mediated cytotoxicity toward the tumor.



Methods

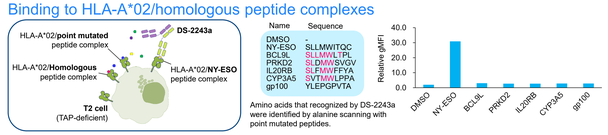
- The binding affinity of DS-2243a to HLA-A*02/NY-ESO complex was evaluated by surface plasmon resonance (SPR) analysis, and specificity of DS-2243a to human HLA-A*02/NY-ESO complex was evaluated by a flow cytometry-based binding assay using T2 cell line supplemented with HLA-A*02/NY-ESO peptide and various HLA-A*02/NY-ESO homologous peptides.
- The anti-tumor cytotoxicity, T-cell activation, and cytokine release were evaluated by coculturing tumor cells with human peripheral blood mononuclear cells (hPBMCs) in the presence of DS-2243a.
- The anti-tumor efficacy was evaluated against various HLA-A*02 positive tumors with different expression level of NY-ESO in human T-cell-transferred mouse models. For the mixture model, a mixture of NY-ESO positive NCI-H1703 cells and NY-ESO KO cells were inoculated subcutaneously in mice.
- H-score in NY-ESO IHC was calculated in the following formula: H-score = 3 × (% of strong positive tumor cells) + 2 × (% of moderate positive tumor cells) + 1 × (% of weak positive tumor cells). Tumor with NY-ESO IHC signal at any signal intensity was defined as NY-ESO positive.

Results

Binding Affinity and Specificity of DS-2243a

Binding affinity of DS-2243a to HLA-A*02/NY-ESO

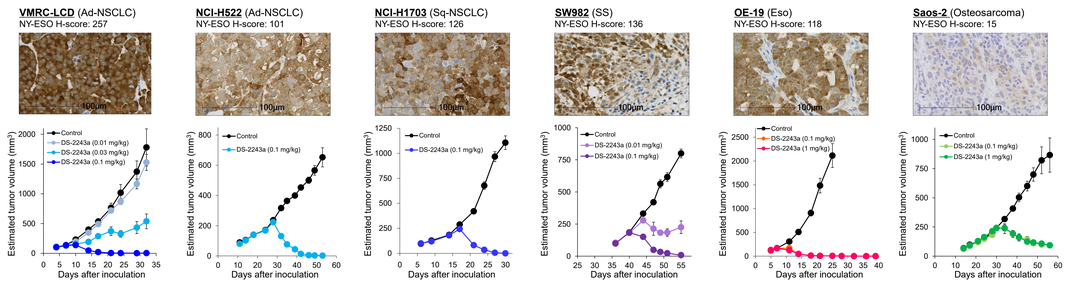
Binding to HLA-A*02/homologous peptide complexes



Amino acids that recognized by DS-2243a were identified by alanine scanning with point mutated peptides.

- DS-2243a specifically bound to human HLA-A*02/NY-ESO complex with high affinity of 1.31 × 10^{-9} mol/L, but not to other HLA-A*02/homologous peptide complexes.

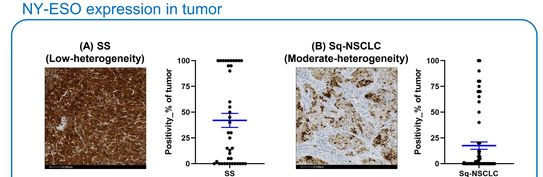
Anti-Tumor Efficacy of DS-2243a Across Multiple Tumor Types



- DS-2243a showed the anti-tumor efficacy across multiple tumor types, including Ad-NSCLC, Sq-NSCLC, esophageal cancer, synovial sarcoma, and osteosarcoma models.
- DS-2243a exhibited robust anti-tumor efficacy even in tumors with low NY-ESO expression (Saos-2; H-score 15).

NY-ESO positivity in SS and Sq-NSCLC

NY-ESO expression in tumor

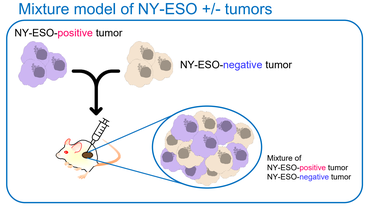


Representative NY-ESO IHC in SS (A) or Sq-NSCLC (B) tumor sample.
Mean values with SEM are shown (blue lines)

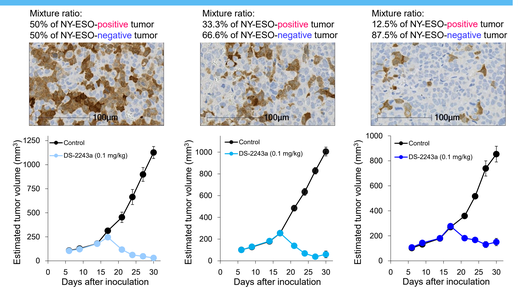
- SS tended to show uniform NY-ESO expression, while heterogeneous NY-ESO expression was observed in Sq-NSCLC.

Anti-tumor Efficacy of DS-2243a in Tumor Mixture Model

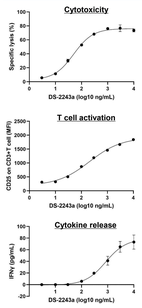
Mixture model of NY-ESO +/- tumors



- Although the anti-tumor activity of DS-2243a depended on the ratio of NY-ESO-positive tumors, tumor regression was still observed in low NY-ESO positivity model.



In vitro Activity of DS-2243a

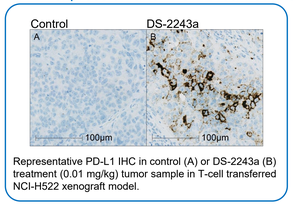


Geometric mean value	EC_{20} (ng/mL)		EC_{30} (ng/mL)		EC_{50} (ng/mL)	
	Estimated value	95% CI	Estimated value	95% CI	Estimated value	95% CI
Cytotoxicity	30.9	6.6 to 145.1	46.6	10.9 to 198.7	88.9	24.3 to 325.6
T cell activation	97.6	25.9 to 368.5	161.9	56.5 to 464.2	358.4	165.7 to 775.5
IFNγ	353.1	129.7 to 961.3	520.4	190.1 to 1424.5	957.7	335.8 to 2731.3
TNFα	155.6	74.4 to 325.3	233.2	132.7 to 409.9	398.2	138.9 to 1142.1
IL-2	118.3	36.3 to 385.2	154.3	41.3 to 575.7	237.7	53.1 to 1064.7
IL-6	82.5	8.4 to 812.3	151.6	26.0 to 884.4	394.9	137.0 to 1138.3
IL-10	202.2	51.1 to 801.0	319.2	153.6 to 663.6	654.3	425.1 to 1007.2

- DS-2243a induced T-cell activation, cytokine release, and target cell cytotoxicity in a dose-dependent manner (figures).
- Geometric mean values (n=3-4) of effective concentrations of DS-2243a for various in vitro assays are shown (table).

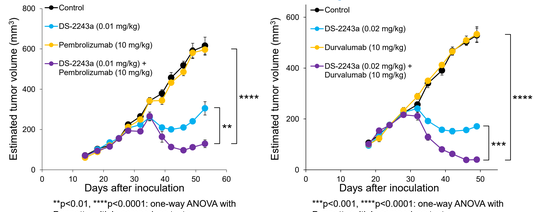
Combination Effect of DS-2243a with PD-1/PD-L1 Inhibitors

PD-L1 expression after DS-2243a treatment



Representative PD-L1 IHC in control (A) or DS-2243a (B) treatment (0.01 mg/kg) tumor sample in T-cell transferred NCI-H522 xenograft model.

T-cell transferred NCI-H522 xenograft model



**p<0.01, ****p<0.0001: one-way ANOVA with Dunnett multiple comparison tests

***p<0.001, ****p<0.0001: one-way ANOVA with Dunnett multiple comparison tests

- Increased PD-L1 IHC signal on tumor cells was observed after DS-2243a treatment.
- Combination of DS-2243a with pembrolizumab (PD-1 blockade) or durvalumab (PD-L1 blockade) augmented efficacy.

Conclusions

- Pre-clinical results suggest that DS-2243a has strong potential to demonstrate the anti-tumor efficacy in HLA-A*02 and NY-ESO-expressing cancers models, supporting continued clinical investigation.
- In pre-clinical models, combination with PD-1/PD-L1 inhibitors demonstrated enhanced activity, providing a rationale for further evaluation of combination approaches.
- The first-in-human study DS2243-054 (NCT06644755) is being conducted to evaluate DS-2243a monotherapy in patients with advanced or metastatic solid tumors[6].

Abbreviations

Ad/Sq, adenocarcinoma/squamous cell carcinoma; **CI**, confidence interval; **EC**, effective concentration; **Eso**, esophageal cancer; **Fc**, fragment crystallizable; **HLA-A*02**, human leukocyte antigen A*02; **IFNγ**, Interferon γ; **IHC**, immunohistochemistry; **IL-2**, Interleukin-2; **IL-6**, Interleukin-6; **IL-10**, Interleukin-10; **LAGE-1**, L antigen family member 1; **NSCLC**, non-small cell lung cancer; **NY-ESO(-1)**, New York esophageal squamous cell carcinoma (1); **MRCLS**, myxoid round cell liposarcoma; **SLLMWITQC**, serine-leucine-leucine-methionine-tryptophan-isoleucine-threonine-glutamine-cysteine; **SS**, synovial sarcoma; **TAP**, transporter associated with antigen processing; **TCR**, T-cell receptor; **TNFα**, Tumor Necrosis Factor α; **UC**, urothelial carcinoma.

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Disclosures

All authors are employees of Daiichi Sankyo Co., Ltd.

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