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Determinants of response to Daratumumab in Epstein-Barr virus-positive natural killer and T-cell lymphoma

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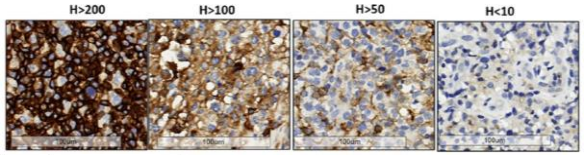
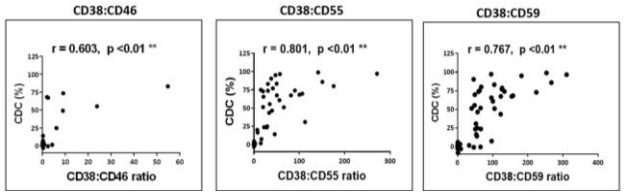
Background

- The off-label usage of daratumumab in natural killer T-cell lymphoma (NKTL) produced sustained remission in a patient with highly refractory disease
- This is corroborated by a phase II clinical trial which established that daratumumab monotherapy is well tolerated and displayed encouraging response in relapsed/refractory NKTL patients
- However, little is known regarding the molecular factors central to the induction and regulation of the daratumumab-mediated antitumor response in NKTL

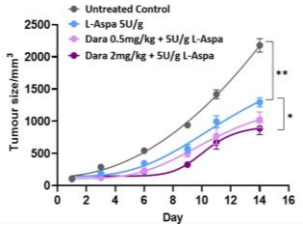


NKTL	H-Score		
(n)	>50	>100	>200
68	88%	78%	49%

The IHC scores demonstrated that almost all NKTL samples show CD38 positivity and the median H-score of CD38 expression in the patient samples was 190.



All the ratios of CD38:CIP that is CD38:CD46, CD38:CD55 and CD38:CD59 expression display not only a significant but also a high correlation coefficient with CDC lysis



The combination treatment of daratumumab and L-asparaginase in vivo found that the addition of daratumumab at 2 mg/kg to L-asparaginase was able to significantly further inhibit tumor growth over L-asparaginase alone, congruent with what was observed in vitro.
***P<0.01, *p<0.05.*

Findings

- Epstein-Barr virus-positive NKTL patients significantly express CD38 with half exhibiting high expression
- Daratumumab effectively triggers Fc-mediated ADCC and CDC in a CD38-dependent manner, and daratumumab monotherapy and combination therapy with L-asparaginase significantly suppresses tumor progression in vivo
- Ablation of complement inhibitory proteins (CIP) demonstrate that CD55 and CD59 are critical for the induction of CDC, where CD55 and CD59 expression were significantly elevated in the late stages of NKTL
- Increasing the CD38:CIP ratio potently augments complement-mediated lysis in cells previously resistant to daratumumab, and the CD38:CIP ratio has consistently demonstrates a statistically superior correlation to antitumor efficacy of daratumumab than CD38 or CIP expression alone

Clinical Significance

- ✓ **Characterizes CD38 as an effective target for a subset of NKTL patients and the utilization of the CD38:CIP ratio as a more robust identifier for patient stratification and personalised treatment**
- ✓ **Elucidation of factors which sensitize the complement-mediated response provides an alternative approach toward optimizing therapeutic efficacy of daratumumab where CDC remains a known limiting factor**
- ✓ **Therefore, these results propose a strategic rationale for further evaluation of single or combined daratumumab treatment in the clinic for NKTL**

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