SGN-CD30C, a new CD30-directed camptothecin antibody-drug conjugate (ADC), shows strong anti-tumor activity and superior tolerability in preclinical studies

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Background

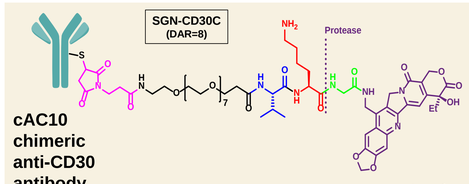
CD30 is a clinically validated ADC target

- Brentuximab vedotin (BV), a CD30-directed ADC that releases monomethyl auristatin E (MMAE) as the cytotoxic payload, has US approval for 6 CD30-expressing lymphoma indications, validating CD30 as an important ADC target

SGN-CD30C is a novel CD30-directed ADC with a distinct mechanism of action compared to BV

- SGN-CD30C induces cytotoxicity of tumor cells by delivering a potent camptothecin derivative, resulting in DNA damage and cell death
- SGN-CD30Cs' released payloads work by a different mechanism of action than MMAE, the payload released by BV. Namely, it inhibits topoisomerase I rather than disrupting microtubules
- In contrast to MMAE, camptothecin-based therapies are not associated with peripheral neuropathy clinically, suggesting that SGN-CD30C may have the potential to avoid the peripheral neuropathy associated with microtubule inhibitors
- SGN-CD30C shows strong anti-tumor activity and has improved tolerability relative to BV in preclinical studies

Structure of SGN-CD30C



[1]AMDCPT=7-aminomethyl-10,11-methenedioxycamptothecin
See Lyski et al. Abstract 2885 and Cochran et al. Abstract 2895

SGN-CD30C In Vitro Activity

- SGN-CD30C shows strong in vitro activity and comparable potency to BV

Summary of IC50 for SGN-CD30C and BV

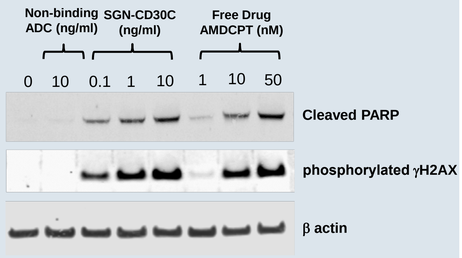
Cell Line	Indication	Copy Number[e]	SGN-CD30C IC50[a] (ng/ml)	BV IC50[a] (ng/ml)
Del	ALCL[c]	261,000	3.3	3.2
Del:BVR[b]	ALCL	179,000	5.9	>1000
Karpas 299	ALCL	238,000	1.7	0.7
L82	ALCL	389,000	2.2	1.3
L540cy	HL[d]	382,000	1.1	1.1
Hs445	HL	67,000	3.2	2

a Cell viability using Cell Titer Glo®
b Del:BVR=brentuximab vedotin resistant
c ALCL=anaplastic large cell lymphoma
d HL=Hodgkin lymphoma
e Copy number based on qFACs

SGN-CD30C Mechanism of Action

SGN-CD30C induces DNA damage, cell cycle arrest and apoptosis

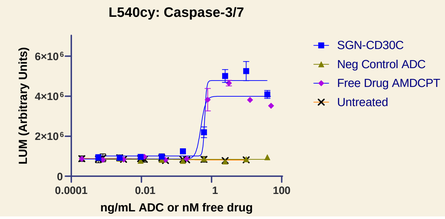
Western blot analysis of L540cy cells showing phosphorylation of H2A.X and cleaved PARP



Cell cycle analysis showing SGN-CD30C induced G2/M growth arrest of L540cy cells

- Cells analysis was performed on L540cy cells 24 hours after treatment with SGN-CD30C, non-binding camptothecin control ADC and free drug (AMDCPT). Cells were labeled with FITC-BrdU and propidium iodide. Analysis was performed in triplicate.

Induction of caspase-3/7 activation by SGN-CD30C and free drug AMDCPT

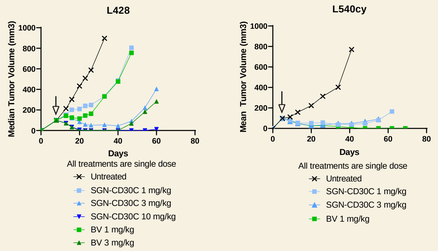


In Vivo Activity of SGN-CD30C

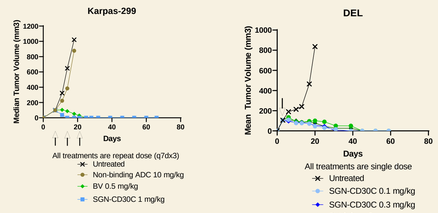
SGN-CD30C induces durable tumor regressions in preclinical models of lymphoma

- SGN-CD30C, like BV, shows strong anti-tumor activity in preclinical lymphoma models
- Immunological specificity of SGN-CD30C was confirmed using a non-binding camptothecin ADC control

Activity in Hodgkin lymphoma models

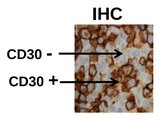


Activity in anaplastic large cell lymphoma models

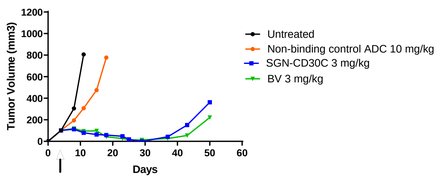


SGN-CD30C shows bystander activity in vivo

- Admixed tumor model mixes CD30-positive Karpas-299 cells with KarpasBVR cells that are resistant to BV due to loss of CD30 expression (Li, 2016)
- IHC confirms heterogeneous expression of CD30 (Li, 2016)
- Both SGN-CD30C and BV induce tumor regressions, indicative of bystander tumor killing



Karpas:KarpasBVR Bystander Model



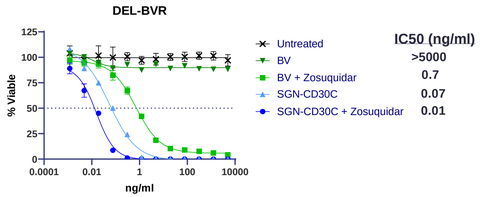
Single Dose

SGN-CD30C is Active in BV-resistant Model

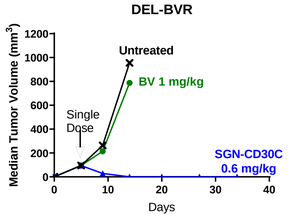
SGN-CD30C overcomes MDR1 resistance

- BV-resistance is associated with upregulation of MDR1 (Lewis, 2014; Chen, 2015)
- MDR1/P-glycoprotein activity is inhibited by zosuquidar
- SGN-CD30C is active on Del:BVR in the presence or absence of MDR1 inhibition by zosuquidar
- BV is inactive on Del:BVR unless MDR1 is inhibited with zosuquidar

In Vitro Activity of SGN-CD30C and BV +/- Zosuquidar



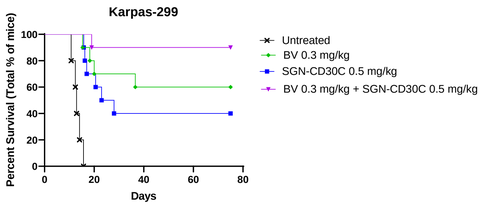
SGN-CD30C induces durable tumor regressions in BV-resistant model



Activity of SGN-CD30C + BV in Combination

- SGN-CD30C and BV have non-overlapping hematologic dose limiting toxicities (see panel 5) and offer the potential to improve anti-tumor activity by combining two drugs with distinct mechanisms of action

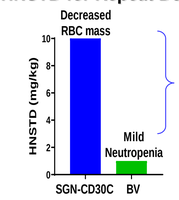
SGN-CD30C + BV show improved activity in vivo when combined at low doses



Tolerability in Non-human Primates (NHP)

NHP highest non-severely toxic dose (HNSTD) and dose limiting toxicity for SGN-CD30C and BV

HNSTD for Repeat Dose Toxicology (weekly x 4)

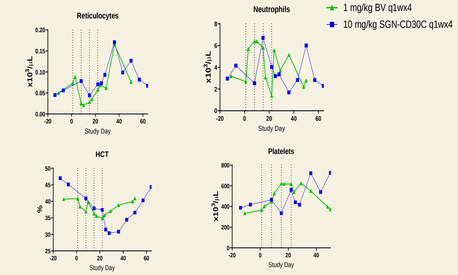


SGN-CD30C

- Improved tolerability
- Recoverable anemia is primary toxicity
- Different/non-overlapping toxicity compared to BV

SGN-CD30C is well-tolerated and offers potential for increased dose density

NHP hematology parameters show SGN-CD30C is well tolerated at 10-fold higher dose than BV



Single dose PK of SGN-CD30C at 0.1, 1, and 10 mg/kg in NHPs demonstrated relatively low clearance (0.408-0.541 mL/h/kg) of the antibody-conjugated drug with half-life of 3.9-5.6 days. Similar exposure was observed for the total antibody. Released camptothecins accounted for less than 0.1% of the plasma exposure.

Conclusions

- SGN-CD30C is a novel CD30-directed ADC under investigation as a potentially improved treatment option for patients with CD30-expressing lymphomas
- SGN-CD30C has equal to or greater activity compared to BV and demonstrates significantly improved tolerability with increased dose intensity in preclinical studies
- SGN-CD30C is active in a BV-resistant preclinical model with upregulated MDR1
- The distinct mechanism of action, strong anti-tumor activity and enhanced tolerability provide a strong rationale to clinically investigate SGN-CD30C across the CD30-expressing lymphoma landscape

References

Lyski, R. Abstract 2885, AACR Virtual Meeting II, June 22-24, 2020
Cochran J. Abstract 2895, AACR Virtual Meeting II, June 22-24, 2020
Lewis, T. Abstract No. 688, AACR Annual Meeting, April 6th, 2014, San Diego, CA
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AACR Virtual Annual Meeting II, June 22-24, 2020

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