Antibody Drug Conjugates Clinical Insights E-book

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Clinical Insights From World ADC

By reading this E-book you will gain insight on:

- ADC candidates which have entered the clinic so far this year.
- novel payloads used by ADCs which have recently entered the clinic.
- the latest clinical updates for 2016.

New Clinical Antibody-Drug Conjugates for 2016

- **AbGn-107** (AbGenomics)
- **ADCT-402** (ADC Therapeutics)
- **AMG-224** (Amgen)
- **CDX-414** (Celldex)
- **IMGN779** (ImmunoGen)
- **SGN-CD19b** (Seattle Genetics)
- **SGC-CD123A** (Seattle Genetics)

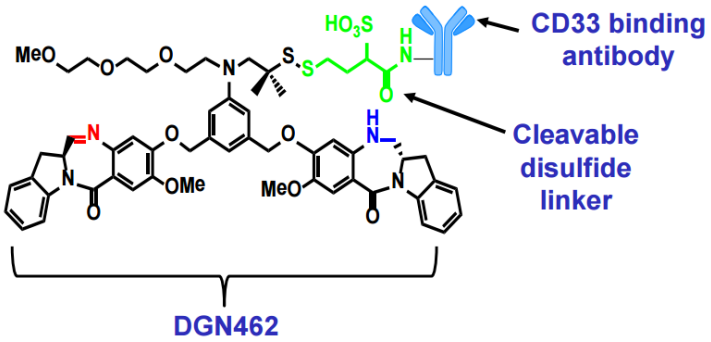
Novel Payloads

Used by ADCs That Have Entered the Clinic Recently*

DGN462

- This is the Immunogen indolino-benzodiazepine dimer that is found in IMGN779.
- The indolino-benzodiazepine dimer has a mono-imine moiety.
- DGN462 molecules are attached to the CD33 antibody via a cleavable linker(1).
- IMGN779 has a DAR of approximately 3.
- DGN462 acts by DNA alkylation rather than crosslinking(2).
- Cells treated with DGN462 are arrested in G2M phase of the cell cycle(2).

Structure of IMGN779



Source:
(1) Whiteman K, et al. Cancer Research 2014 October 01;74(19 Supplement):2644-2644.
(2) Krystal WM, et al. Blood 2015 American Society of Hematology;126(23):1366-1366.
* Accurate to May 2016

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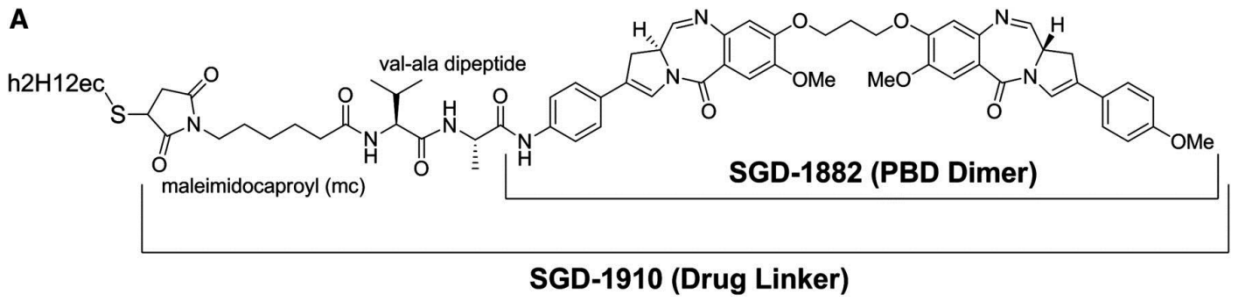
Novel Payloads

SGD-1882

- This is the Seattle Genetics pyrrolobenzodiazepine (PBD) that is found in vadastuximab talirine (SGN-CD33A)(3) and SGN-CD19b(4).
- SGD-1882 induced early DNA damage, consistent with DNA crosslinking as the mechanism of cytotoxicity.
- Antibodies are engineered to contain a cysteine to allow for site-specific conjugation – in the case of vadastuximab talirine this was a substitution of serine at position 239 on the heavy chain of IgG1(3).
- SGN-CD33a has an average DAR of 1.9

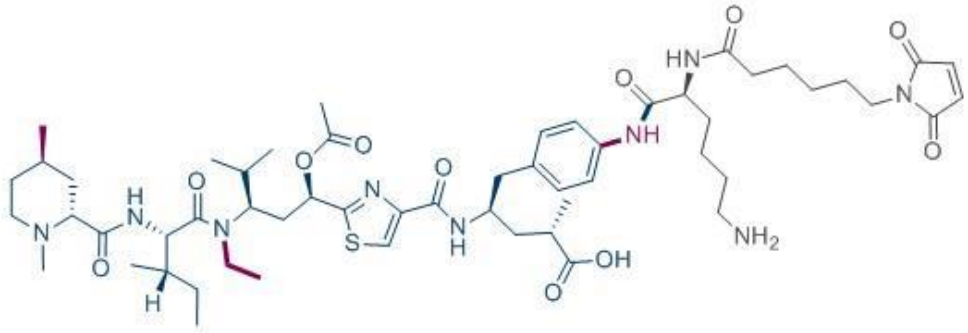


Source:
(3) Kung Sutherland MS, et al. Blood 2013 American Society of Hematology;122(8):1455-1463.
(4) Ryan MC, et al. Blood 2015 American Society of Hematology;126(23):594-594.

Novel Payloads

MMETA

- This is a tubulysin variant developed by AstraZeneca/Medimmune(1), and is the warhead for MEDI4276, a biparatopic HER2 targeting ADC.
- MMETA inhibits microtubule polymerisation during mitosis
- The ADC is generated by site-specific conjugation of mc-Lys-MMETA to 2 engineered cysteine residues on the heavy chain at positions S293C and S3442C(2) via a maleimidocaproyl linker
- MEDI4276 is a biparatopic HER2 targeting ADC.



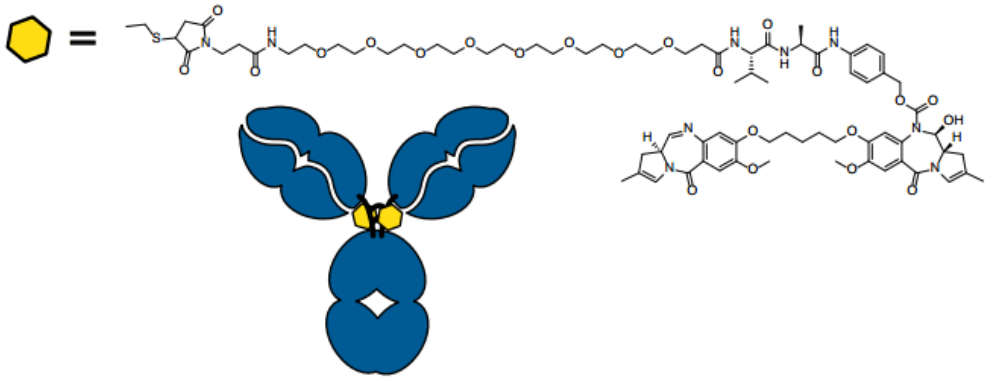
Source:

(1) Toader D, et al. Molecular Cancer Therapeutics 2015;14:B170
(2) (2) Li JY, et al. Cancer Cell 2016/04;29(1):117-129.

Novel Payloads

ADC Therapeutics PBD

•ADCT-301 and ADCT-402 both have a PBD payload, which has not been named.
•The structural formula was presented in a poster at ASH 2015(6), and you can find the full poster on Researchgate.
•With this poster it looks like the PBD may be the same as SJG-136 (SG2000)(7) which was in clinical testing as a single agent(8).
•ADCT- 301(6) and ADCT-402(9) both have a DAR of 2.3 +/- 0.3



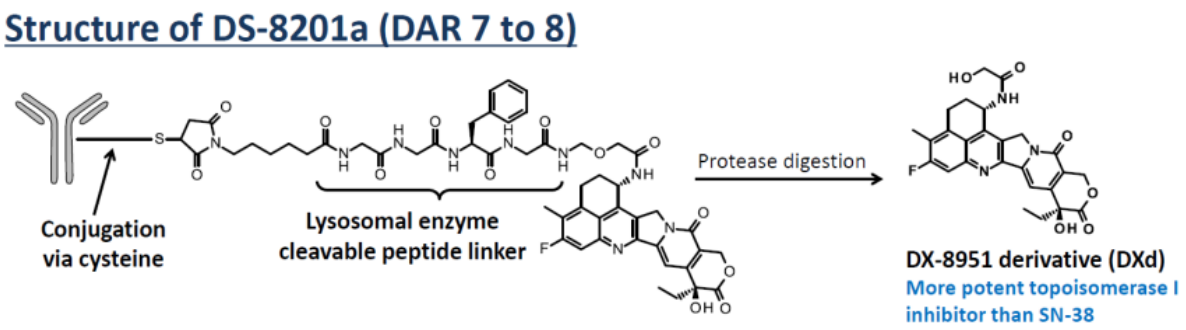
Source:
(6) Flynn MJ, et al. Blood 2015 American Society of Hematology;126(23):1559-1559
(7) Hartley JA, et al. Cancer Research 2004 September 15;64(18):6693-6699.
(8) Puzanov I, et al. Clinical cancer research 2011 02/23;17(11):3794-3802.
(9) Zammarchi F, et al. Blood 2015 American Society of Hematology;126(23):1564-1564.

Novel Payloads

DXd

This is the payload for Daiichi Sankyo's first ADC into the clinic, DS-8201a(10). It is a Topoisomerase I inhibitor which is thought to be more potent than SN-38 (11).

In DS-8201a the payload is cysteine conjugated via a cleavable linker to HER2, with a high DAR of 7-8(10,12).

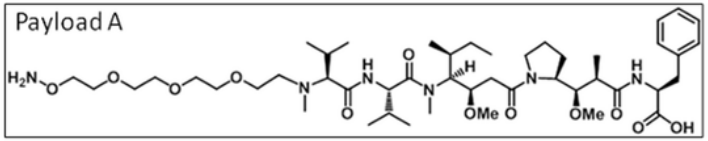


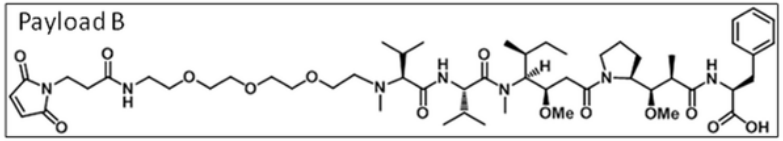
Source:
(10) Ogitani Y, et al. Molecular Cancer Therapeutics 2015 December 01;14
(12 Supplement 2):A145-A145. (11) Takiguchi S, et al. Jpn J Cancer Res 1997 Aug;88(8):760-769.
(12) Ogitani Y, et al. Clin Cancer Res 2016 Mar 29.

Novel Payloads

Amberstatin-269

- Ambrx have been developing ADCs using non-natural amino acids to provide site specific, homogeneous ADCs.
- A novel auristatin that is based on MMAF was first described by Axup in 2012 (13).
- It has an with an additional alkoxy-amine which is this is then coupled to antibodies via oxime ligation.
- An abstract from 2015 AACR suggests that this is the payload for ARX-788 (14) and a further development of this payload was described by Jackson et al in 2014 (15).
- Amberstatin-269 may be the same as payload A described by Jackson et al (15).
- ARX-788 has a DAR of 2





Source:
(13) Axup JY, et al. Proceedings of the National Academy of Sciences 2012 October 02;109(40):16101-16106.
(14) Humphreys RC, et al. Cancer Research 2015 August 01;75(15 Supplement):639-639.
(15) Jackson D, et al. PLoS One 2014 Jan 14;9(1):e83865.

2016 Clinical Program Updates

- Agensys started a phase II trial of AGS-16C3F in renal cell carcinoma.
- Bayer has progressed their mesothelin targeting ADC anetumab ravtansine, into phase II trials of mesothelioma patients, as well as a phase Ib combination trial.
- Seattle Genetics have announced they plan to start a phase III trial of SGN-CD33A (vadastuximab talirine), based on data presented at ASH last year (CASCADE).
- Immunogen have announced amendments to their planned FORWARD I trial, which will now be a phase III trial and is planned to start before the end of 2016.
- The European Medicines Agency has recommended that brentuximab vedotin (Adcetris) be approved for Hodgkin lymphoma patients in the AETHERA setting.

To hear more on the latest ADC clinical insights attend [World ADC San Diego (10-13 October)]