SARCOMA oncology research center LLC

Designing New Clinical Trials for Desmoid Tumors

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Clinical Trials for Desmoid Tumors
www.clinicaltrials.gov

Currently, there are 32 clinical trials involving desmoid tumors:

Toremifene
VBL+MTX
Pazopanib vs VBL+MTX
Sulindac + Tamoxiphen
Gamma Secretase Inhibitor (PF-03084014)
Sirolimus
Imatinib
Sorafenib
Nab-paclitaxel

Clinical Trials for Desmoid Tumors
www.clinicaltrials.gov

Clinical Trials for Desmoid Tumors:
Radiation Therapy
Brachytherapy
F-18 16 Alpha-Fluoroestradiol
Cryoprobes
Photodynamic Rx with 5-ALA
(5-aminolevulinic acid)

Clinical Trials Using Inhibitors Against Notch
Delta-like-4 MoAb (Demicizumab)
Notch 2 and 3 MoAb (Tarextumab)

Clinical Trials for Sarcoma at the Sarcoma Oncology Research Center

Chemotherapy

Phase 3 Aldoxorubicin vs Physician's Choice

Aldoxorubicin + Ifosfamide/Mesna

Immunotherapy

Denosumab

Chemotherapy + Immunotherapy

Trabectedin and Nivolumab

Targeted Therapy + Immunotherapy

Nab-Rapamycin + Nivolumab

Designing New Clinical Trials for Desmoid Tumors

IN DEVELOPMENT:

Gene Therapy

Sig-Targeted Gene Therapy

DeltaRex-G + Reximmune-C

DN Mastermind-like Notch Inhibitor

Targeted Therapy (Future)

Oral Pan-Notch Inhibitor (CB-103; Cellestia Bio)

Alpha Secretase Inhibitors of Notch

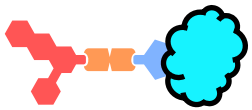
Beta-Catenin Inhibitor (Tegatrabetan)

Phase 3 Aldoxorubicin versus Physician's Choice
Proposed Mechanism of Action

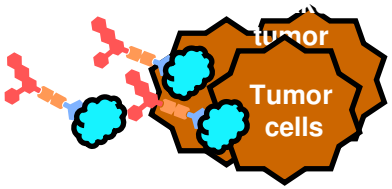
Targeting Ability
Localization of drug at tumor using albumin

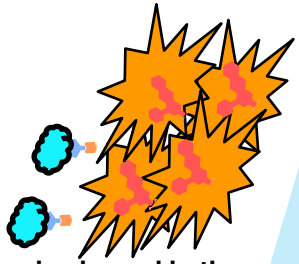
Cleavable Linker
Chemistries for controlled release of drug either extra- or intra-cellularly

Drug Payload
High potency cytotoxic agents: auristatins, maytansanoids, calicheamicin



Linker covalently binds within minutes to serum albumin





Linker is cleaved in the acidic environment, releasing the drug payload

Phase 3 Aldoxorubicin versus Physician's Choice

Study Design:

Aldoxorubicin 375 mg/m² (260mg/m² doxorubicin equivalents) every 3 weeks vs:

Investigators choice of : pazopanib, gemcitabine/docetaxel, dacarbazine, doxorubicin, ifosfamide; administer each per institution standard tx

Each site chooses 3 of 5 investigator choice drugs prior to enrollment of patients

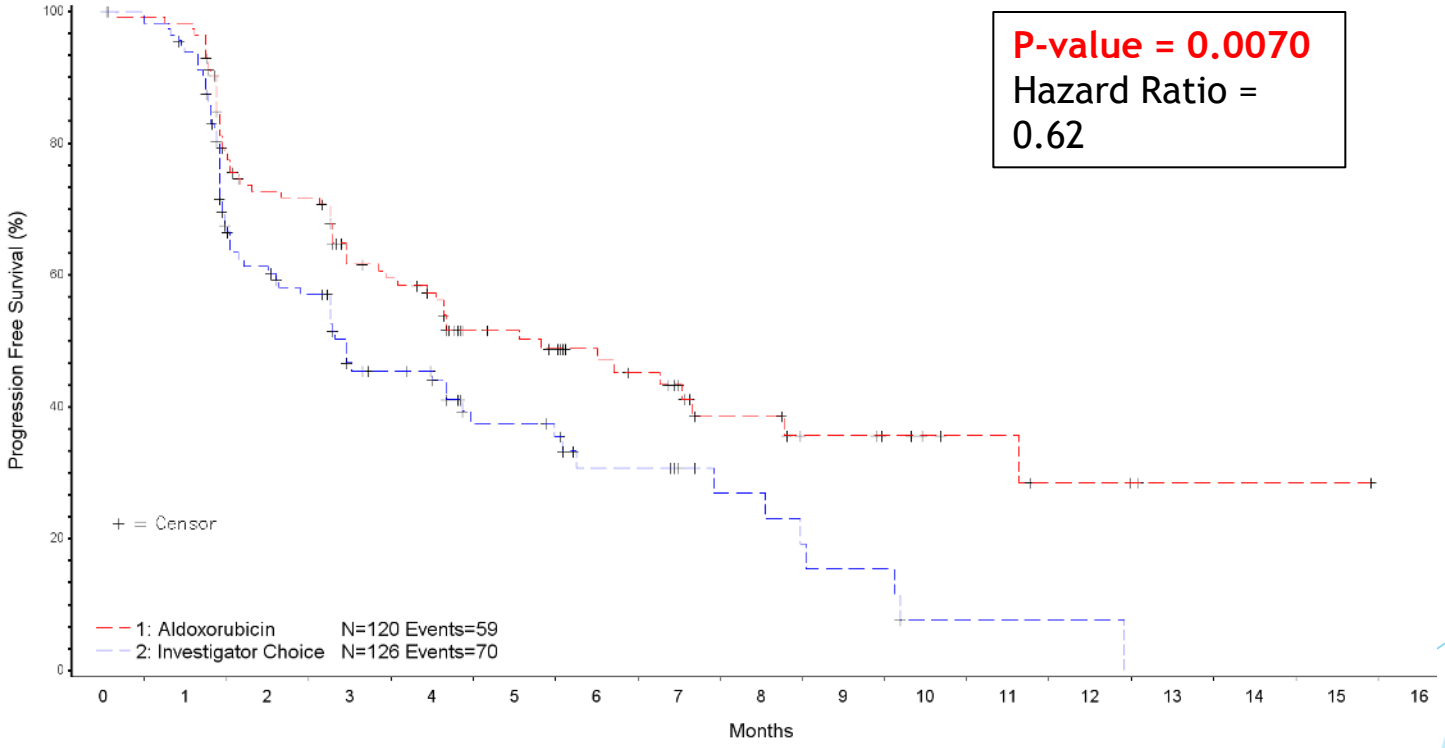
May use any of the 3 drugs on patients

Endpoints: Response/Progression per Blinded Central Review

- Primary: Progression-free survival (PFS)
- Secondary:
  - Overall Response Rate
  - Disease Control Rate (ORR + SD≥ 4 months)
  - PFS at 4 and 6 months
  - Overall Survival
  - Adverse Events
- Pre-specified analyses: Geography (North America + Australia vs Europe + Israel/Chile), Sarcoma Type (L-sarcomas, Others), Prior Doxorubicin

Phase 3 Aldoxorubicin versus Physician's Choice

PFS: L-Sarcomas



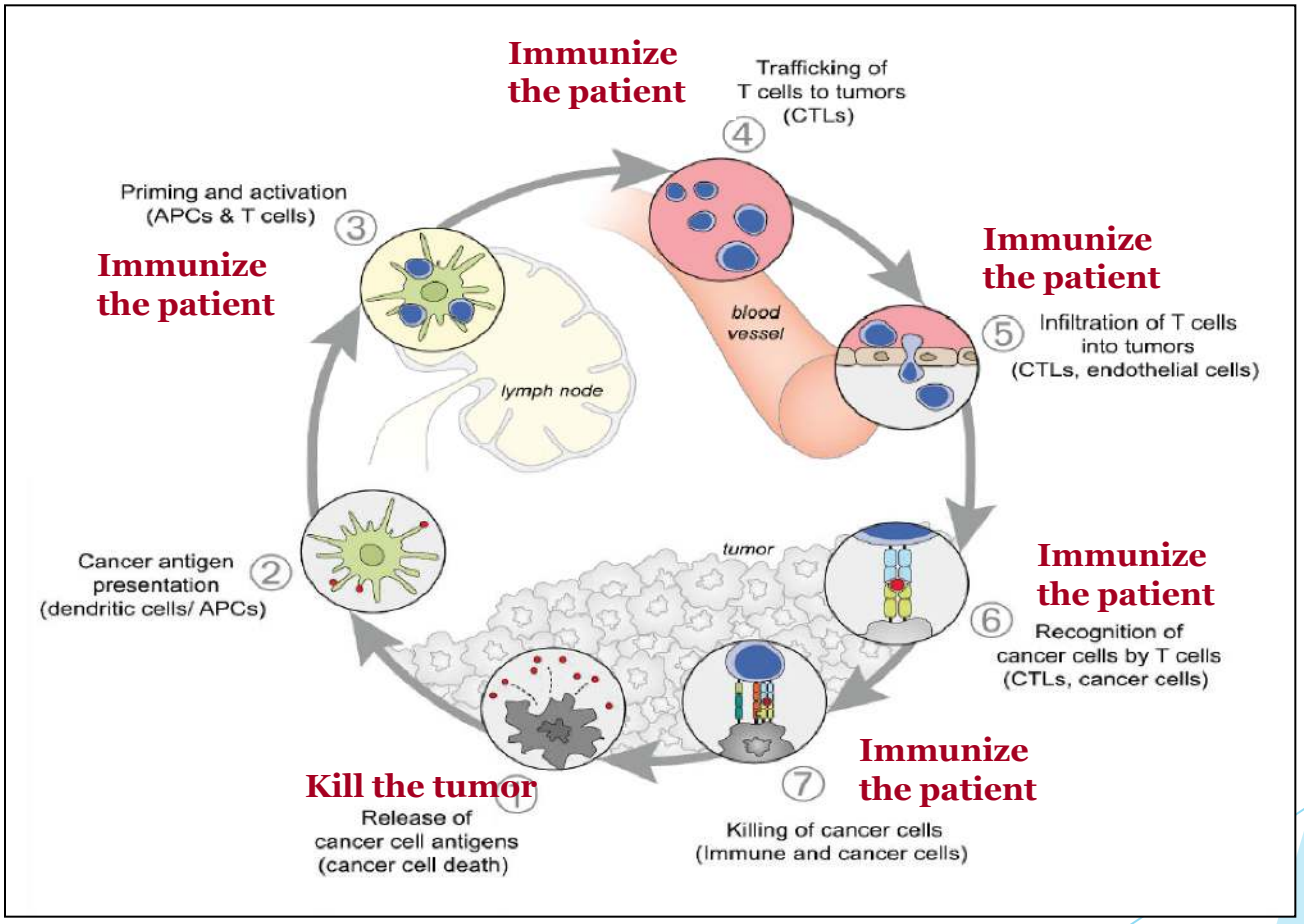
P-value = 0.0070
Hazard Ratio = 0.62

Phase 3 Aldoxorubicin versus Physician's Choice

Conclusions

- Aldoxorubicin, given at 375 mg/m2/cycle, has minimal or no cardiotoxicity up to 40 cycles, compared to doxorubicin.
- The non-cardiac grade 3/4 AEs of aldoxorubicin were similar to doxorubicin despite exposure to 3-4 times the doxorubicin dose.
- Taken together, aldoxorubicin may be a superior anthracycline for treating advanced soft tissue sarcoma.
- Finally, aldoxorubicin is a good alternative vs standard therapies for treatment of relapsed or refractory metastatic soft tissue sarcoma.

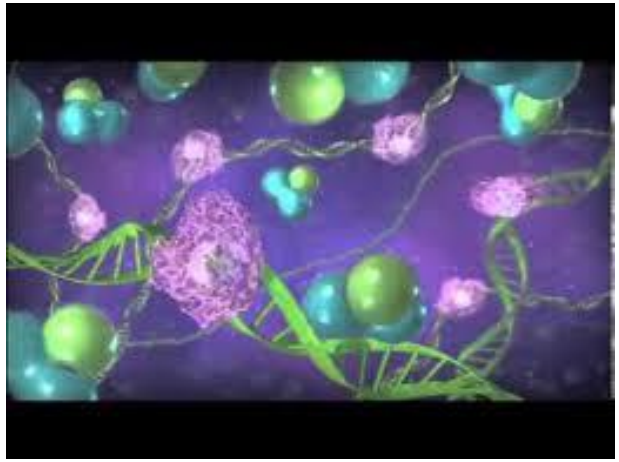
Designing New Clinical Trials for Desmoid Tumors



Chen & Mellman, Immunity 39, July 25, 2013

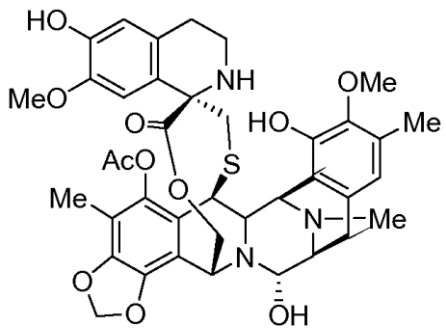
Designing New Clinical Trials for Desmoid Tumors

Cancer Eradication & Vaccination



Trabectedin (Yondelis ®) is a cytotoxic alkylating drug that binds guanine residues in the minor groove of DNA, forming adducts and resulting in a bending of the DNA helix towards the major groove, causing disruption of the cell cycle and cell death.

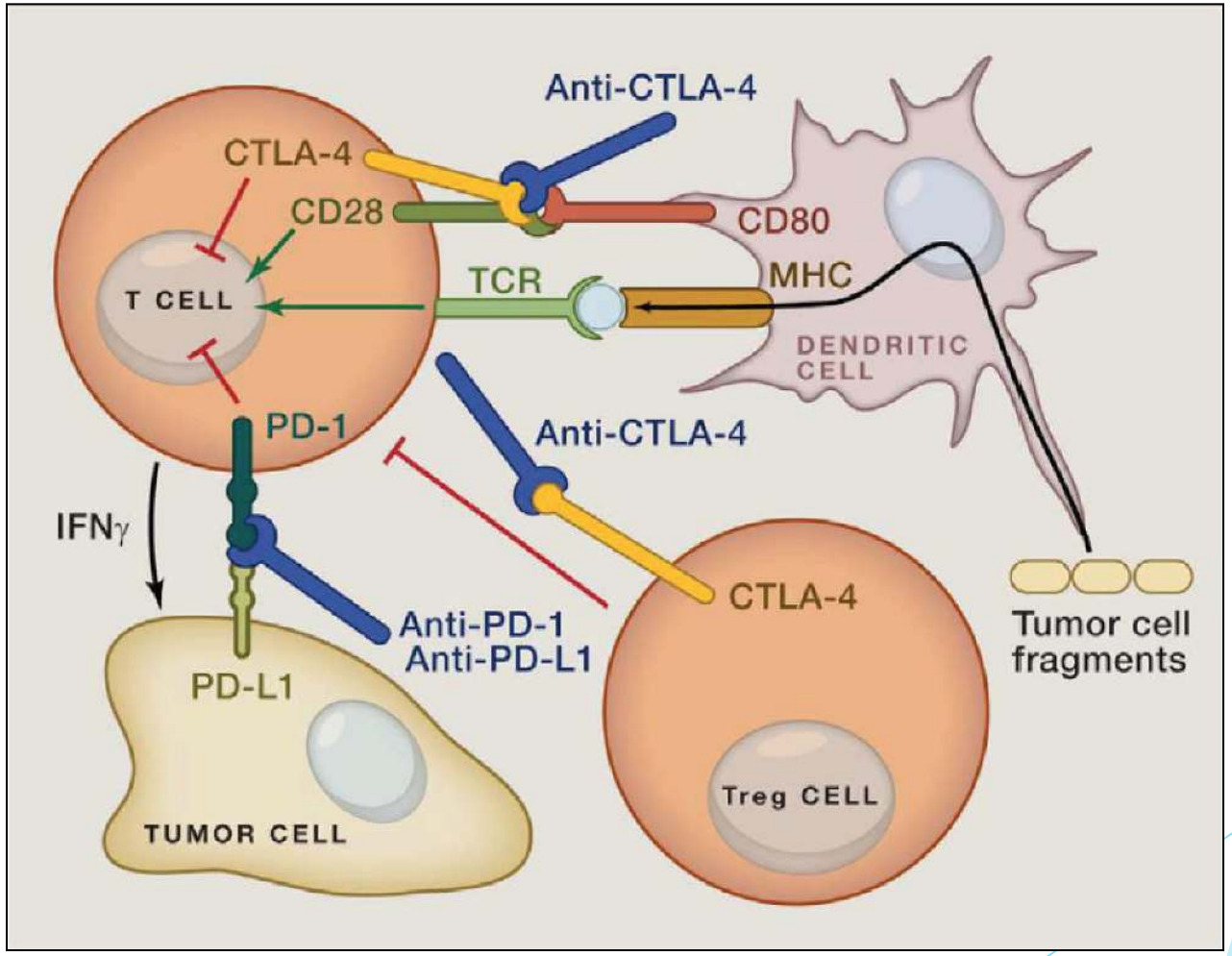
Trabectedin also depletes growth promoting M2 macrophages in the tumor microenvironment.



ET-743

Immune Checkpoint Inhibitors

For Cancer Immunization: Nivolumab



Miller and Sadelain Cancer Cell 27, April 13, 2015

Designing New Clinical Trials for Desmoid Tumors

Cancer Eradication & Vaccination

Sequential intravenous administration of:

- Trabectedin (Yondelis®), an alkylating agent, 1.5 mg/m2 over 24 hours every 3 weeks for cancer eradication

- Nivolumab (Opdivo®), programmed death-1 mAb, 3 mg/kg every 2 weeks, for cancer immunization

20 previously treated patients with sarcoma

Clinical Experience with Trabectedin & Nivolumab for Advanced STS

Cancer Eradication & Vaccination

Safety Analysis: NIH/NCI CTCAE v.4.03; N = 20

Efficacy Analysis: N = 13

Baseline and follow-up CT scans or MRIs were performed after every 2 cycles of the sequential chemo-/immuno-therapy.

Tumor responses were assessed by RECIST v1.1 and immune-related response criteria (irRECIST) and the results in patients who were followed up to 6 months are reported.

Clinical Experience with Trabectedin & Nivolumab for Advanced STS

Cancer Eradication & Vaccination

Histologic Subtypes	N = 20
Undifferentiated pleomorphic sarcoma	8
Leiomyosarcoma	4
Synovial sarcoma	3
Myxoid liposarcoma	4
Chondrosarcoma	1
# With Metastatic disease	20
Median # Chemotherapy Regimens	4

Clinical Experience with Trabectedin & Nivolumab for Advanced STS

Cancer Eradication & Vaccination

Safety analysis:

Grade 3 Treatment Emergent Adverse Events

	N = 20
Anemia	2
Fatigue	1
Decreased platelet count	1
Neutropenia	1
Increased creatine kinase	1
Immune-related adverse events	0

- *Dexamethasone was given with Trabectedin infusions which may have pre-empted the immune related adverse events*

Clinical Experience with Trabectedin & Nivolumab for Advanced STS

Cancer Eradication & Vaccination

Efficacy analysis: N = 13 (followed for at least 6 months)

Partial Response	3
Stable Disease	7
Progressive Disease	3
Best Overall Response Rate	23.1%
Disease Control Rate	76.9%

Median PFS (T + N)	>7.8 mos. (range: 3.5->10.4 mos.)
Median PFS (T alone)	4.2 mos. (Demetri et al., 2015)

Median OS	>8.4 mos. (range: 3.6->10.4 mos.)
PFS at 6 mos.	69.2%
OS at 6 month	92%

PFS = Progression free survival OS = Overall survival

Clinical Experience with Trabectedin & Nivolumab for Advanced STS

Cancer Eradication & Vaccination

Conclusions

Taken together, the data suggest that (1) sequential administration of trabectedin and nivolumab is safe, and (2) this chemo-/immuno-therapy approach has synergistic activity in soft tissue sarcoma.

Clinical Trials for Sarcoma at the Sarcoma Oncology Research Center

SOC-1702: Phase 1/2 Study of Safety/Efficacy Using Trabectedin, Ipilimumab and Nivolumab Triple Therapy as First Line Treatment of Advanced Soft Tissue Sarcoma (STS)

Investigator Initiated Research

Funded by Bristol Myers Squibb

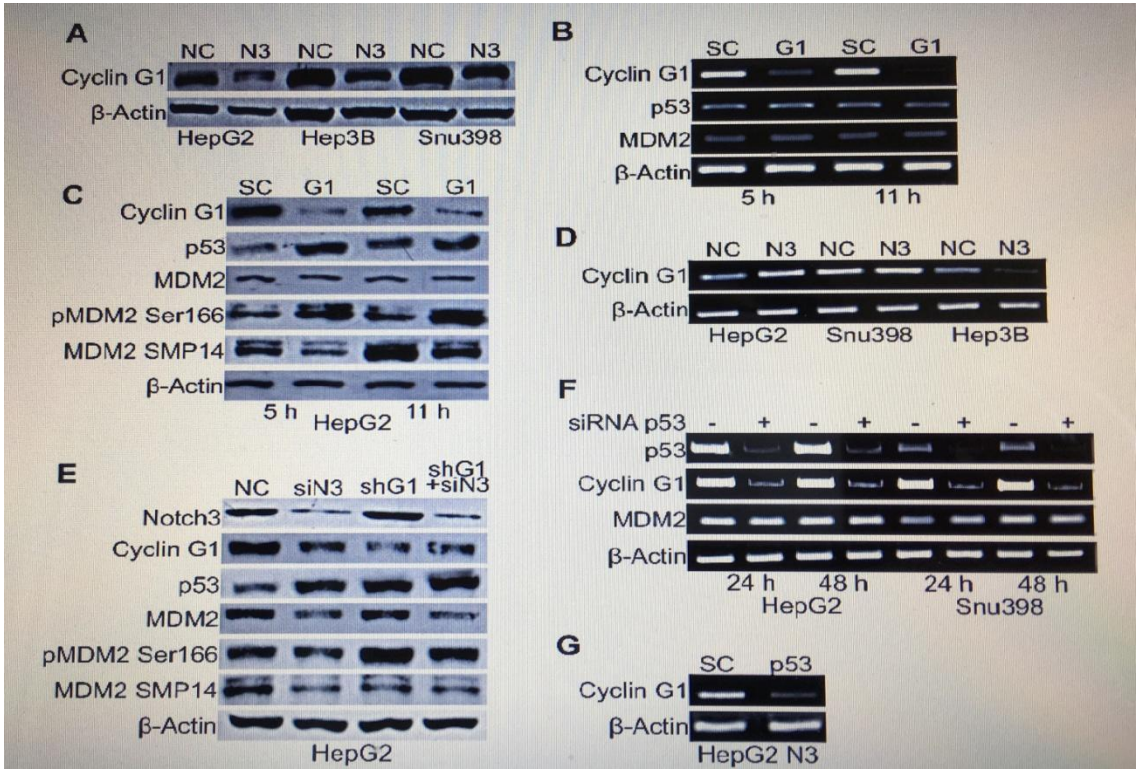
Clinical Trials for Sarcoma at the Sarcoma Oncology Research Center

SOC-1701: Phase 1b Study of Safety/Efficacy Using Nab-Rapamycin and Nivolumab for Advanced Undifferentiated Pleomorphic Sarcoma, Liposarcoma, Osteosarcoma, Chondrosarcoma and Ewing Sarcoma

Investigator Initiated Research

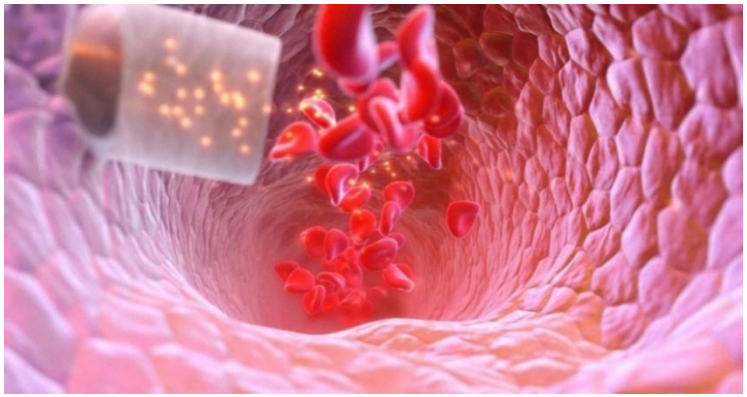
Funded by AADi Biosciences, LLC

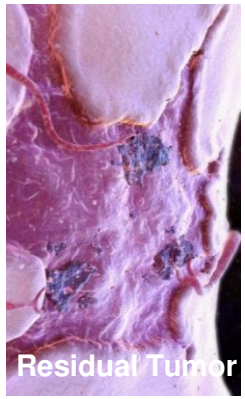
Cyclin G1 Regulates p53 Accumulation in Notch3Depleted Cells (Giovanni et al., 2014)

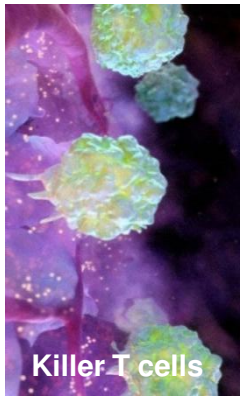


A) Efficacy of Notch3 KD on Cyclin G1 protein expression was measured by western blotting in HepG2, Hep3B and SNU398 cells. B-C) HepG2 cells were transiently transfected with a pool of siRNAs directed against Cyclin G1 or scramble RNA (SC) for 5h and 11h. The level of p53 and MDM2 expression was evaluated by RT-PCR and western-blot. MDM2 phosphorylation status at Ser166 and Thr216 was also evaluated by western blot in Cyclin G1 silenced cells. D) Cyclin G1 mRNA expression evaluated by RT-PCR in Notch3 KD cells. E) Efficacy of Cyclin G1 + Notch3 silencing on different proteins expression was measured by western blotting. F) Semi-quantitative RT-PCR expression analysis of Cyclin G1 and MDM2 in p53 silenced cells. G) HepG2 Notch3 silenced cells were transfected with p53 siRNA or scrambled RNA and Cyclin G1 mRNA levels were evaluated 48h post-transfection by RT-PCR. P53 silencing was verify by western blot as shown in Figure 2D. NC: negative control shRNA; N3; Notch3 shRNA; siN3: Notch3 siRNA; shG1: Cyclin G1 shRNA; SC: scramble RNA; G1: Cyclin G1 siRNA; p53: p53 siRNA.

Clinical Trials for Sarcoma at the Sarcoma Oncology Research Center, USA and Asian Hospital & Medical Center, Philippines







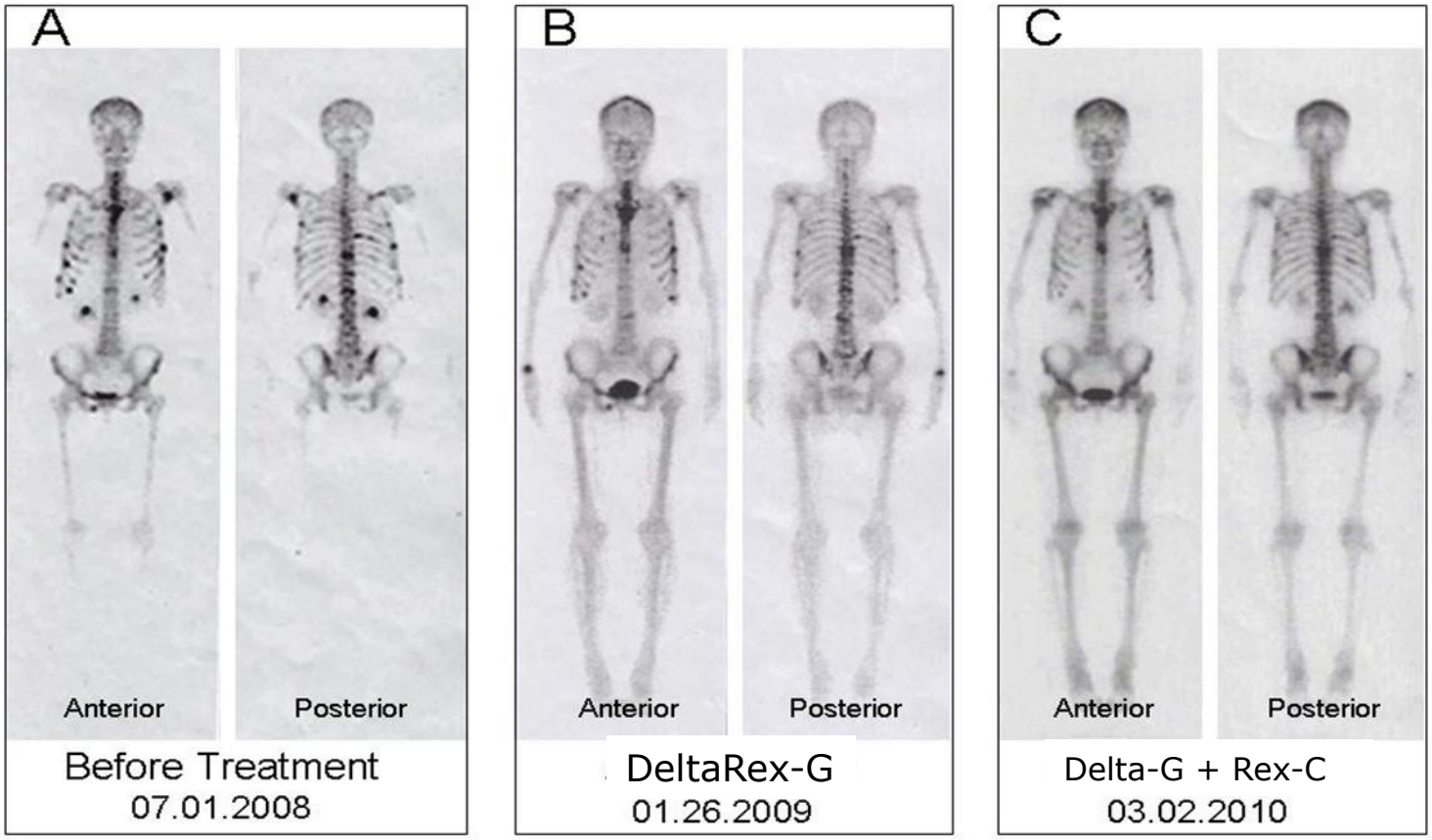
DeltaRex-G is a targeted gene therapy vector that carries a "killer gene", a cytocidal anti-Cyclin G1 construct. When injected intravenously, DeltaRex-G seeks out tumors selectively, and delivers its genetic payload to cancer cells with minimal systemic toxicity.

Reximmune-C is also a targeted gene therapy vector that carries a GM-CSF gene which recruits immune T lymphocytes into the residual tumors, and evokes a personalized vaccination against the patient's own cancer cells.

DeltaRex-G + Reximmune-C = 86% one year survival

Regression of Skeletal Metastases

Ductal Carcinoma of Breast



Note: Progressive tumor regression was seen in serial bone scans obtained over 20 months after DeltaRex-G and Reximmune-C.

Clinical Trials for Sarcoma at the Sarcoma Oncology Research Center, USA and Asian Hospital Medical Center, Philippines

Cancer Eradication & Vaccination

Conclusions

Taken together, the data suggest that (1) sequential administration of DeltaRex-G and Reximmune-C is safe, and (2) this dual-targeted gene therapy may have synergistic activity in solid tumors.

Clinical development of CB-103 with a first-in-human Phase I/IIA clinical study in advanced or metastatic solid tumors

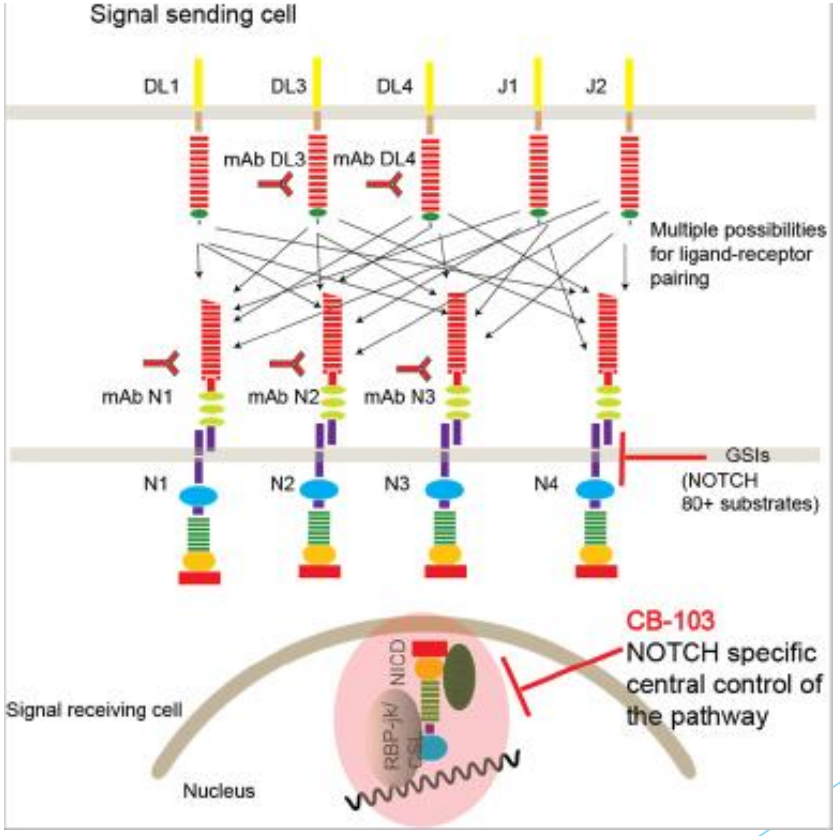
Background

NOTCH signaling is a developmental pathway known to play critical roles during embryonic development as well as for the regulation of self-renewing tissues. Aberrant activation of NOTCH signalling leads to deregulation of the self-renewal process resulting in sustained proliferation, evasion of cell death, loss of differentiation capacity, invasion and metastasis, all of which are hallmarks of cancer. When the NOTCH pathway is activated by genetic lesions (overexpression of NOTCH ligands/receptors, GOF mutations in NOTCH receptors as well as chromosomal translocations), it becomes a major driver for NOTCH-dependent cancers and resistance to standard of care.

Weber D et al: Cellestia Biotech AG, Basel, CH, University Children's Hospital, Zurich, CH, and Swiss Institute for Experimental Cancer Research, EPFL, CH. Poster presentation at ESMO, Madrid, Spain, 2017

Clinical Trials for Desmoid Tumors at the Sarcoma Oncology Research Center

- CB-103 is a first-in-class pan-NOTCH inhibitor
- CB-103 is specific for NOTCH pathway and inhibits NOTCH target genes
- CB-103 overcomes crosstalk and escape mechanisms of NOTCH and other pathways



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Clinical development of CB-103 with a first-in-human Phase I/IIA clinical study in advanced or metastatic solid tumors

Objectives

Pharmacodynamic (PD) studies were conducted to investigate **CB-103** in relation to its desired therapeutic effect in blood and solid cancers as a **pan-NOTCH pathway inhibitor**.

Results

Regarding the PD effect, in vitro studies showed for CB-103 a dose-dependent decrease in NOTCH signaling with a unique mechanism compared to gamma secretase inhibitors and mAbs. The NOTCH inhibitory potential of CB-103 was further confirmed by downregulation of NOTCH target genes in human T-cell acute lymphoblastic leukaemia (T-ALL), suggesting therapeutic efficacy in T-ALL.

In a panel of 123 cancer cell lines, CB-103 was active in 24 cell lines matching to tumor types with known activated NOTCH lesions.

Clinical development of CB-103 with a first-in-human Phase I/IIA clinical study in advanced or metastatic solid tumors

Conclusions

PD and toxicology studies have revealed an excellent efficacy and safety profile in the expected human therapeutic dose range. Clinical development of CB-103 with a first-in-human Phase I/IIA clinical study in advanced or metastatic solid tumours, lymphoma subtypes and multiple myeloma is under Health Authority review.

Weber D et al: Cellestia Biotech AG, Basel, CH, University Children's Hospital, Zurich, CH, and Swiss Institute for Experimental Cancer Research, EPFL, CH. Poster presentation at ESMO, Madrid, Spain, 2017

Disclosures: Consulting to

Amgen

Berg Pharma

Bristol Myer Squibb

Counterpoint Biomedica

CytRx

EISAI

GSK

Heron Therapeutics

Immune Design

Janssen

J&J

Morphotek

Novartis

Pharmamar

Prana

Roche

Threshold

Tracon

Uptick Health

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