Avacta Therapeutics Science Day

23 February, 2023

Avacta®

13:20 **Strategic Overview** Alastair Smith, CEO

13:35 Transforming treatment outcomes for cancer patients Fiona McLaughlin, CSO

14:05 **Opportunities and challenges for cell and gene therapies for oncology and beyond** Dr Krishna Komanduri

14:45 Break

14:55 **ALS-6000-101 Phase 1a Clinical Study Update** Andrew Saunders, Medical Advisor

15:30 **Current & Future Treatment Strategies for Soft Tissue Sarcoma** Dr William Tap

16:10 Break

16:20 **Panel Discussion on 'Targeted Oncology 2030'**

17:00 **Closing Remarks**

Strategic Overview

Dr. Alastair Smith, Chief Executive Officer,
Avacta Therapeutics

Avacta Therapeutics Science Day

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Our guests

Krishna Komanduri, MD
Physician-in-chief of the Helen Diller Family Comprehensive Cancer Center (HDFCCC) and Clinical Director of the UCSF Living Therapeutics Initiative

William D. Tap, MD
Chief, Sarcoma Medical Oncology Service
Memorial Sloan Kettering Cancer Center

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Avacta Group plc

Our purpose is to improve patients' lives and grow shareholder value by developing novel cancer therapies and powerful diagnostics using our proprietary Affimer® and pre|CISION™ platforms

Therapeutics

Harnessing our proprietary technologies to deliver innovative oncology drugs that transform treatment outcomes and improve cancer patients' lives

Diagnostics

M&A-led strategy to build an integrated and differentiated in-vitro diagnostics (IVD) business with global reach serving professionals and consumers

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Avacta Therapeutics

Improving cancer patients' lives through innovation and partnership

Vision

Our vision is to deliver innovative oncology drugs that transform treatment outcomes to improve cancer patients' lives

Strategy

- Use our proprietary pre|CISION™ and Affimer® platforms to develop best-in-class and first-in-class cancer therapies
- Combine our in-house drug development expertise with a focused partnership strategy

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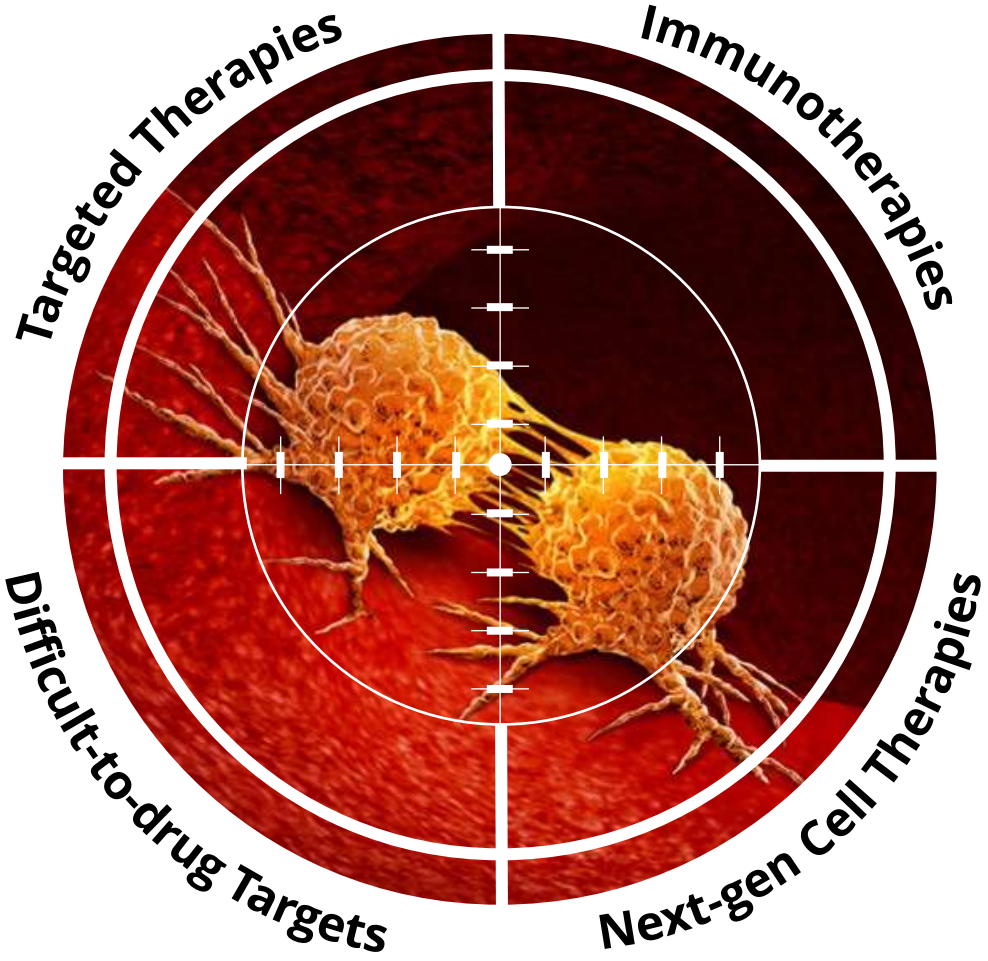
Avacta Therapeutics

Harnessing the pre|CISION™ and Affimer® drug platforms enables a differentiated approach to delivering innovative cancer therapeutics

pre|CISION™



Affimer®

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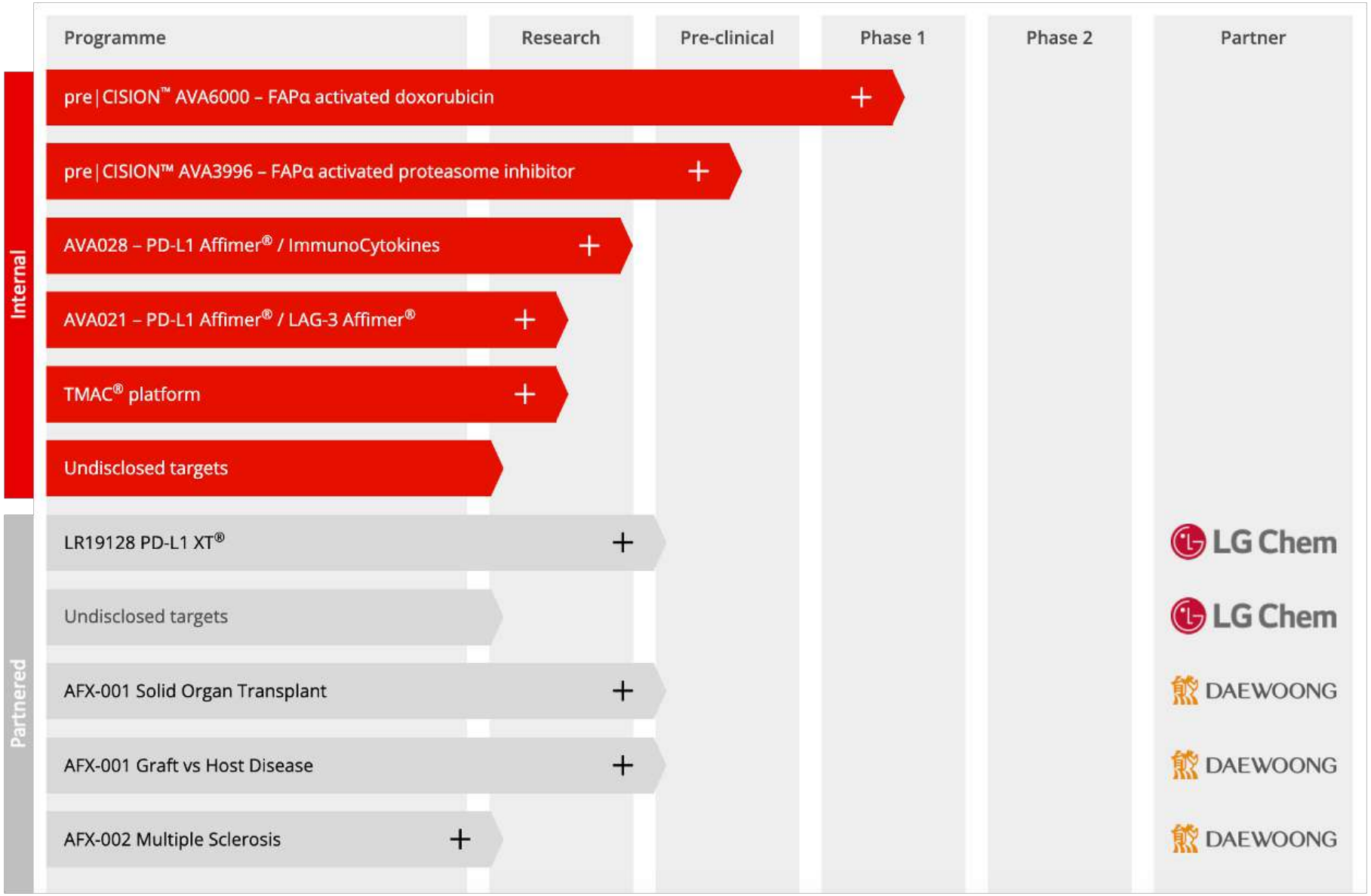
Avacta®
www.avacta.com

Avacta®

Transforming treatment outcomes for cancer patients

Dr. Fiona McLaughlin, Chief Scientific Officer,
Avacta Therapeutics

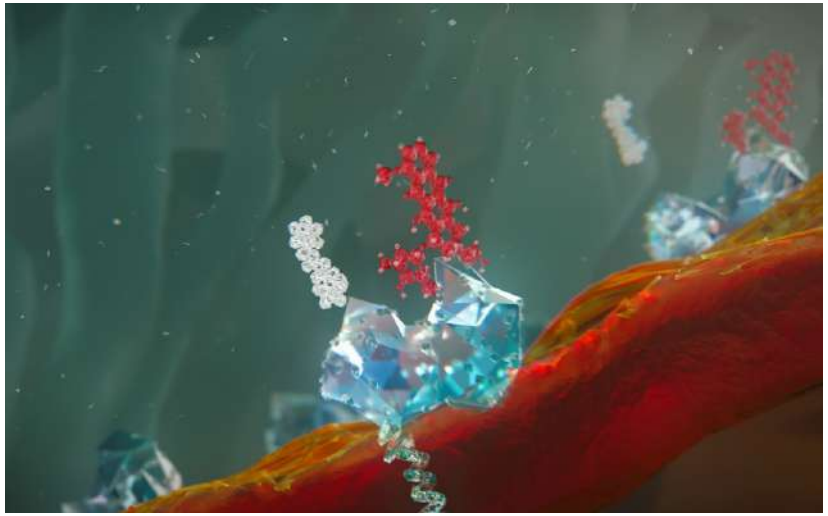
Avacta Therapeutics Pipeline – 2023



pre|CISION™ tumour targeted masking technology

Cancer-associated fibroblasts (CAFs) are a major component of the tumour microenvironment

FAP is a membrane bound protease that is expressed on the surface of CAFs



pre|CISION™ substrate is cleaved by FAP to release a warhead selectively in the tumour microenvironment

pre|CISION™ new MOA video animation available

View the video at www.avacta.com/therapeutics

Avacta

pre|CISION™

Delivering warheads direct to the tumour

THE PROBLEM WITH EXISTING CHEMOTHERAPY

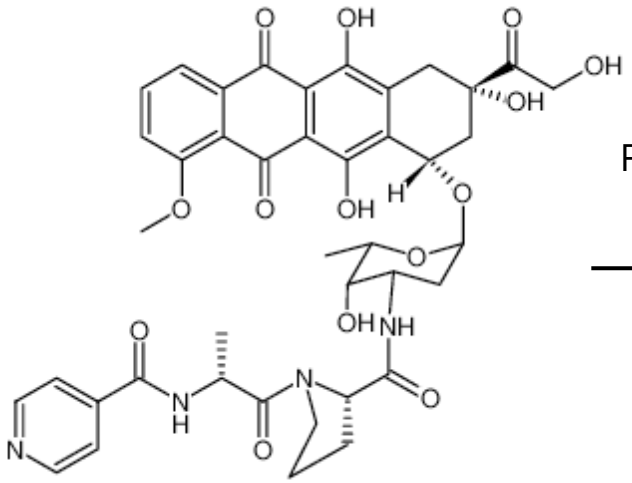
- Chemotherapy, cytotoxic payloads and IO drugs are not tumour-selective
- Off and on target effects systemically limit Therapeutic Index
- Unmet need to differentiate between tumour and normal cells

THE SOLUTION

- Mask the activity of highly active agents systemically
- Activate selectively in the TME to unleash the active agent
- Unlike other targeted agents, there is no need for receptor mediated internalisation

AVA6000: Targeting chemotherapy to the tumour microenvironment

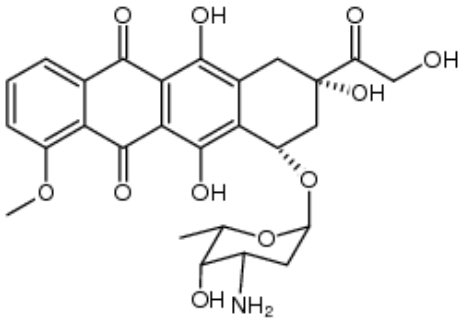
AVA6000



FAPα Enzyme-Mediated Hydrolysis of AVA6000

H_2O

Doxorubicin (warhead)



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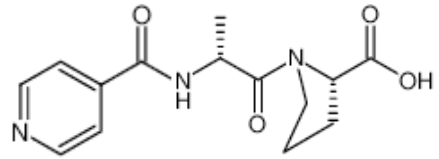
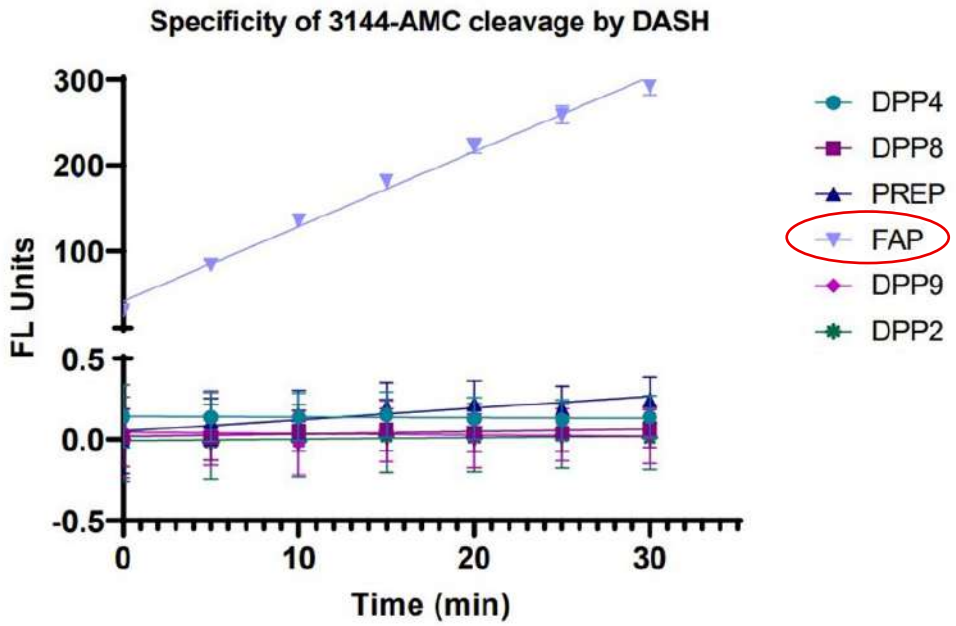
Inactive "leaving group"



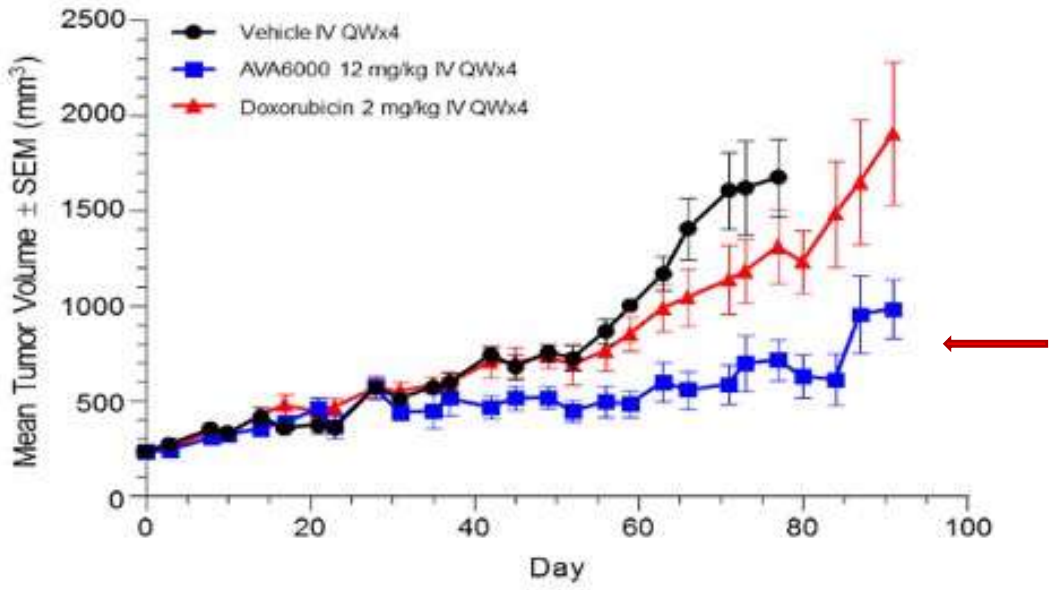
AVA6000 is inactive until it is cleaved by Fibroblast Activating Protein (FAP) to release the anthracycline Doxorubicin

AVA6000 is selectively cleaved by FAP to release its warhead and kills tumours

AVA6000 is **exquisitely** selective for cleavage by the protease FAPα

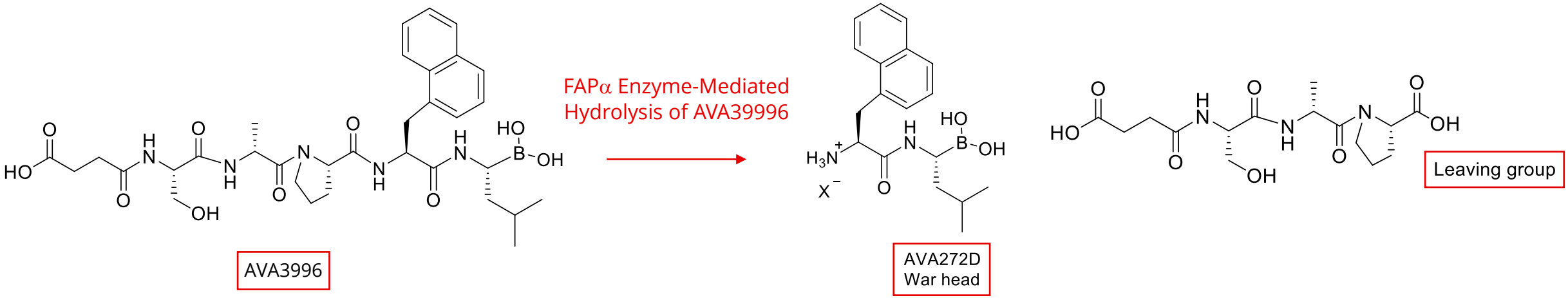


In this PDX model using tumour cells from a heavily pretreated sarcoma patient, AVA6000 markedly reduces tumour growth



Data presented at AACR April 2022 and available to download here https://avacta.com/about/resources/

AVA3996 – the 2nd pre|CISION™ Candidate



FAP activated proteasome inhibitor

New Chemical Entity

Proven specificity for FAPα versus other proteases

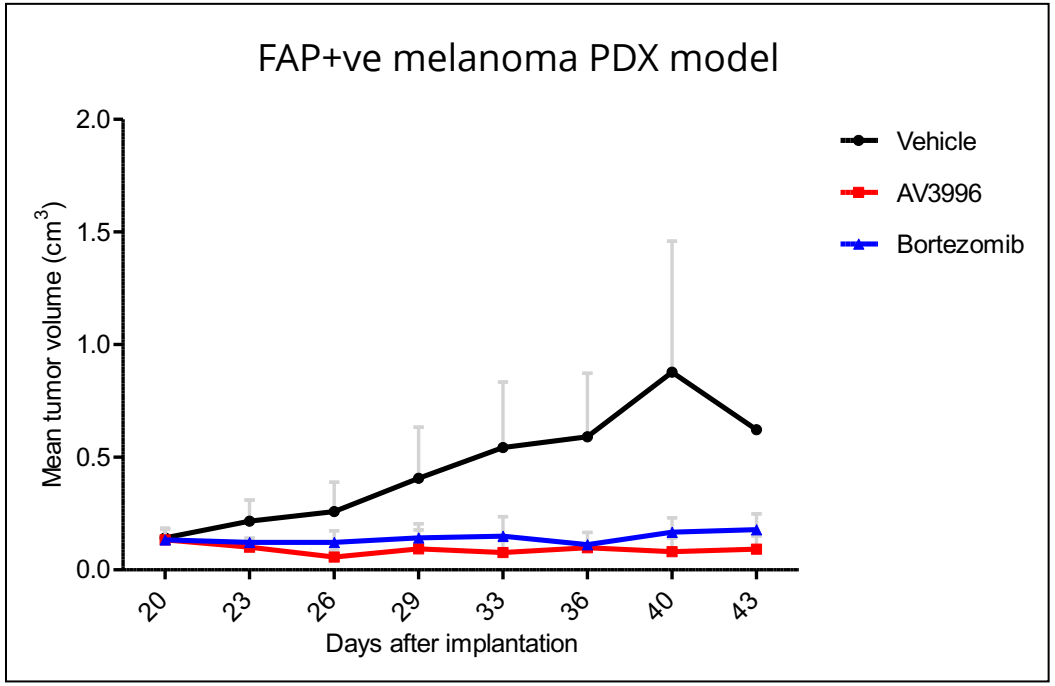
Delivers proteasome inhibitor directly to the tumour microenvironment

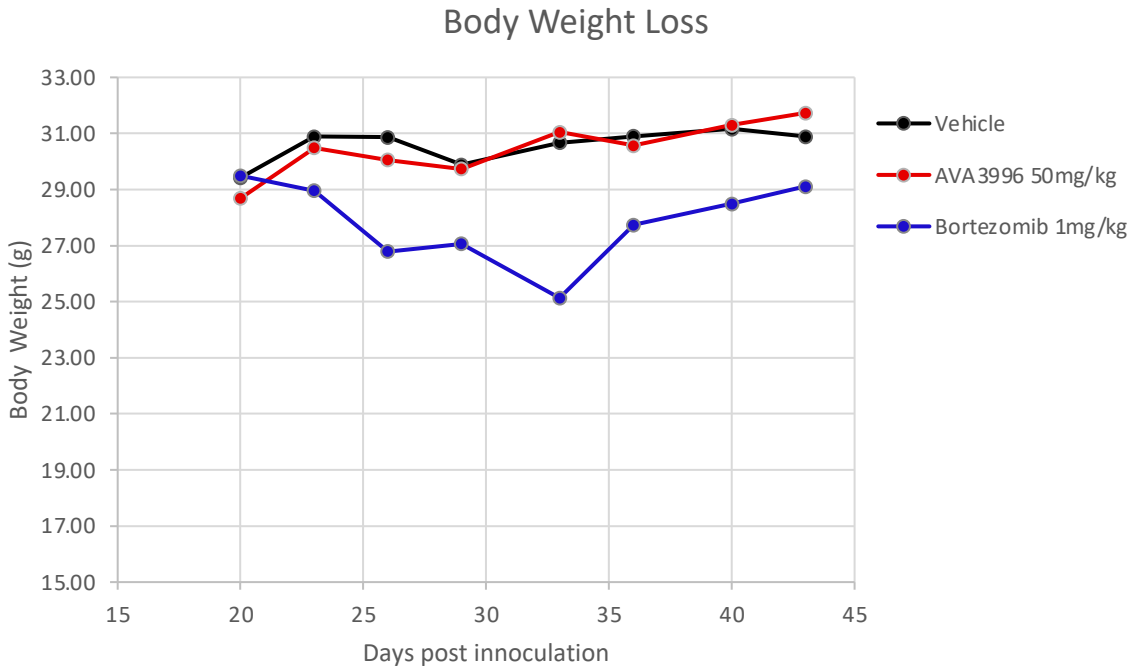
In IND enabling studies

FIH planned 2024

AVA3996 – Improved Therapeutic Index vs Velcade in patient derived tumours

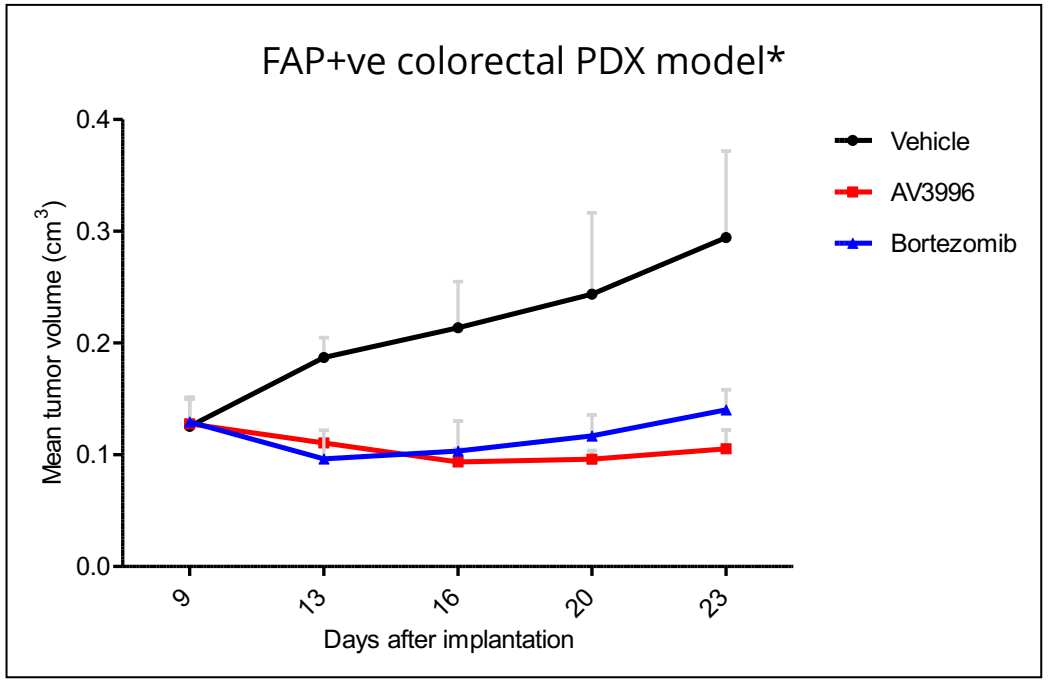
AVA3996 flat lines tumour growth without weight loss

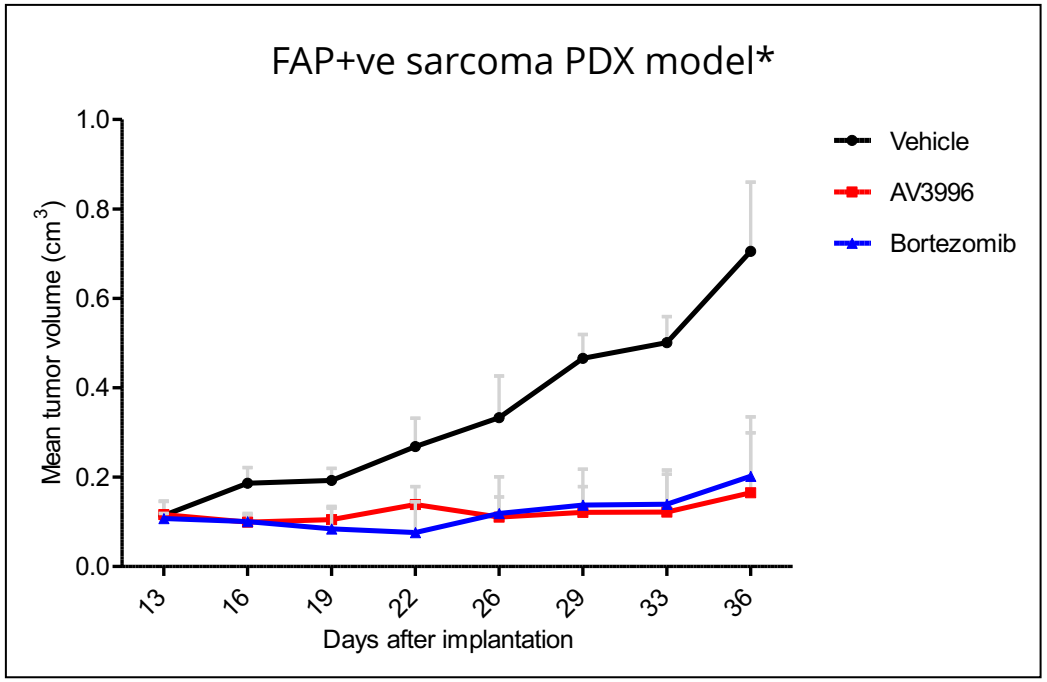




Patient derived xenograft melanoma
Animals dosed twice weekly for three weeks
Velcade group – mice in poor condition and BW loss, had to have a dosing holiday (D29, D33)

AVA3996 – Efficacy demonstrated in two further patient derived, solid tumour models





*Studies still ongoing

Data will be presented at AACR April 2023 (David Jones and Fiona McLaughlin)

Affimer®

Exquisitely selective for target of interest

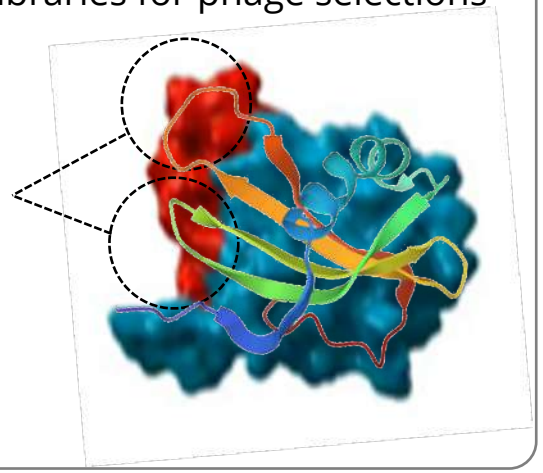
Flexible solutions for difficult-to-drug targets

Affimer® Next Generation Biotherapeutics

What is an Affimer®?

Based on a naturally occurring human protein (stefin A) and engineered to display two loops that create an antigen binding surface

Variable loop regions of 9 amino acids each create a target recognition surface and can be randomised to create very large (10^{10}) libraries for phage selections



Affimer®

Technical Benefits

Smaller (14 kD), simpler and more robust, soluble and stable than antibodies

High affinity Affimer® candidates generated for new targets rapidly

Flexible formatting for multi-specifics, agonism, drug conjugates

High expression levels in a range of cells and tissues

Fully human: lower immunogenicity risk

Commercial Advantages

Proprietary and unencumbered IP

Freedom to operate where there is antibody-based IP

Differentiated Biotherapies

Flexible solutions for **difficult-to-drug** targets **eg GPCRs**

Exquisitely selective for target antigen

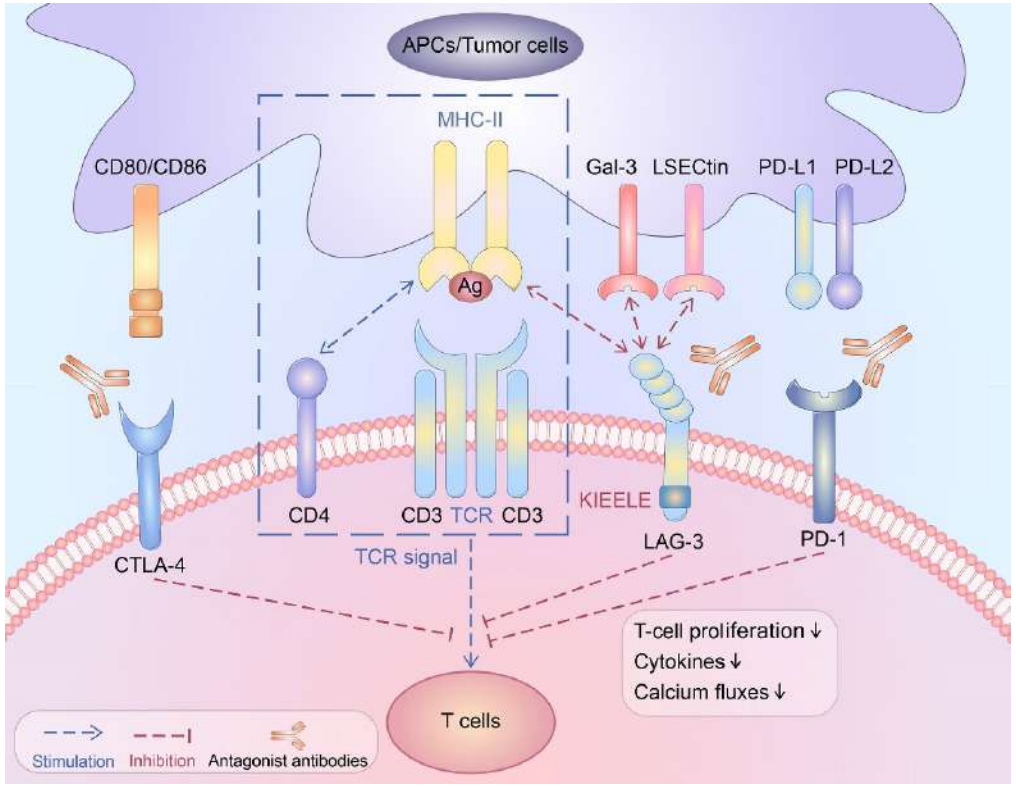
Building blocks for **developable multi-specific** formats

(Proof-of-concept multi-specific Affimers (LG Chem collaboration PD-L1 / XT) have demonstrated the developability of the platform)

Half-life extension capability and tunable pharmacokinetics

AVA021: PDL1/LAG3

Immunosuppressive functions of the immune checkpoint inhibitor LAG-3



https://www.frontiersin.org/

Next Generation Immunotherapies

Tumour cells have the ability to evade adaptive immune-mediated killing

The tumour microenvironment becomes immunosuppressive and over time tumour infiltrating T cells (TILs) become dysfunctional or exhausted

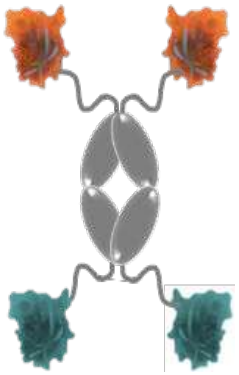
Exhausted T cells have a reduced ability to proliferate and have high-level expression of inhibitory receptors, programmed cell death-1(PD-1) and lymphocyte-activation gene 3 (LAG-3)

LAG3 is involved in immune tolerance and is associated with poor clinical outcomes

Preclinically, combination of anti-LAG-3 and anti-PD-(L)1 antibodies has shown synergistic effects vs blocking either one alone

In March 2022, the FDA approved the first LAG-3-blocking mAb combination – Opdualag™ [(nivolumab(PD-1) and relatlimab(LAG3)] for the treatment of unresectable or metastatic melanoma. Opdualag™ more than doubled the median PFS when compared to nivolumab monotherapy, 10.1 months versus 4.6 months

Avacta's AVA021 candidate provides PoC for the bispecific Affimer® human Fc fusion format

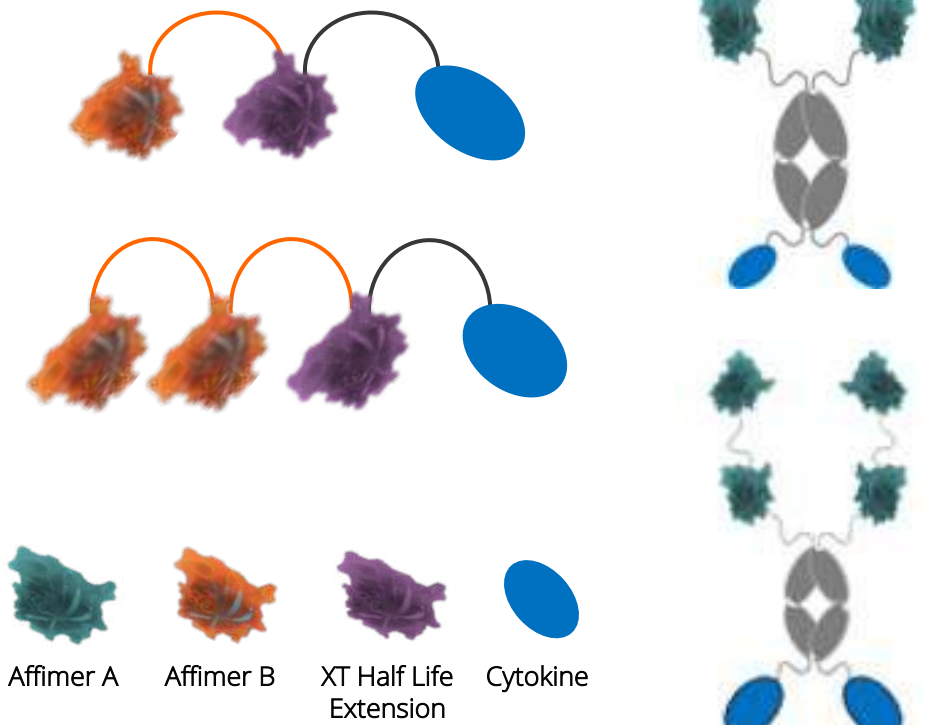


AVA028: Immunocytokine PD-L1/IL-2

Flexible solutions for multi-specifics

In-line-fusion Formats

Fc Formats



Prototype Affimer Immunocytokine – PD-L1/IL-2

Immune checkpoint inhibitors have revolutionised the treatment of certain tumour types. However, despite major advances in immunotherapy to treat cancer, most patients either do not respond to immune checkpoint blockade or will acquire resistance.

Next generation immunotherapies aim to overcome this lack of response with combination strategies aimed at increasing response to checkpoint blockade.

Avacta's Immunocytokine approach combines immune checkpoint blockade with cytokine driven T cell stimulation

The cytokine IL2 can potently activate both NK and T cells

However, its short in vivo half-life, severe toxicity, and ability to amplify Treg cells are major barriers that prevent IL-2 from being widely used

The IL-2 component of the molecule preferentially promotes tumour-infiltrating CD8+ T-cell response

The PD-1/PD-L1 blockade using the antagonistic PD-L1 also confers tumour targeting of IL-2

These combined activities have the potential to increase immune cell recruitment, expansion and anti-tumour activity in the tumour microenvironment

Tumour Microenvironment Activated Conjugates

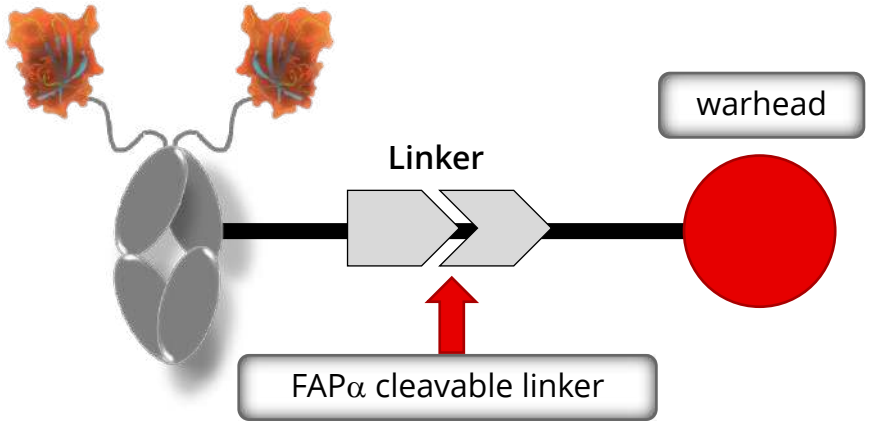
Tumour Microenvironment Activated Conjugates and Targeting Affimers

Cytotoxin linked to Affimer® immunotherapy/targeting by pre|CISIONTM linker

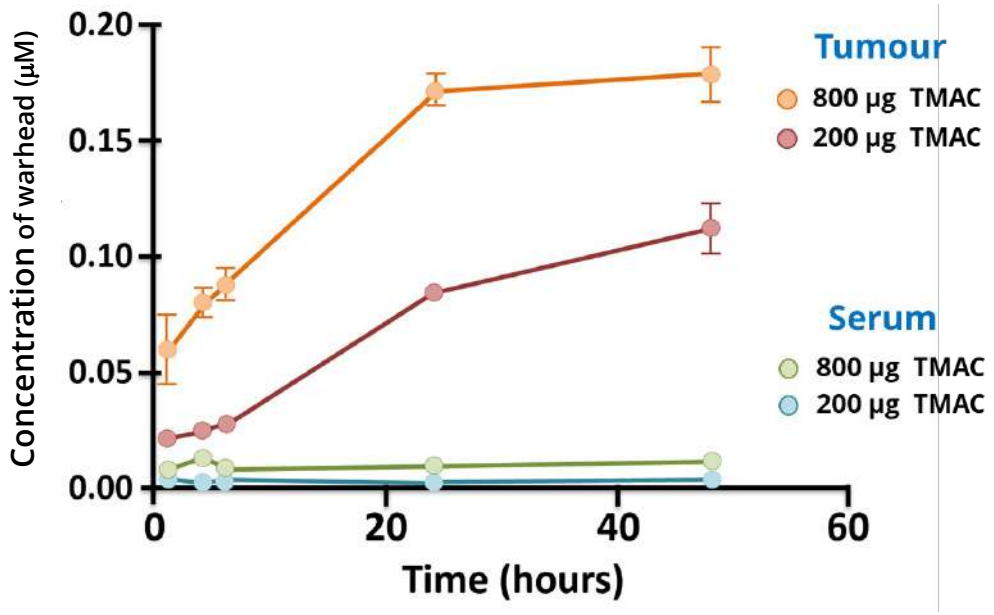
Cytotoxin released in the TME/stroma by FAP

Undisclosed Affimer® targets

Targeting first-in-class therapies



Proof of concept – FAPα release of warhead in tumour vs serum



CT26 tumours engineered to overexpress FAPα

PD-L1 Affimer targeted TMAC with toxic warhead

High levels of warhead detected in CT26 tumours– very low levels in mouse serum

Key Partnerships

Fully funded key partnerships potentially accelerate clinical validation of our platforms

AffyXell – Joint Venture in the Cell & Gene Space

AffyXell THERAPEUTICS

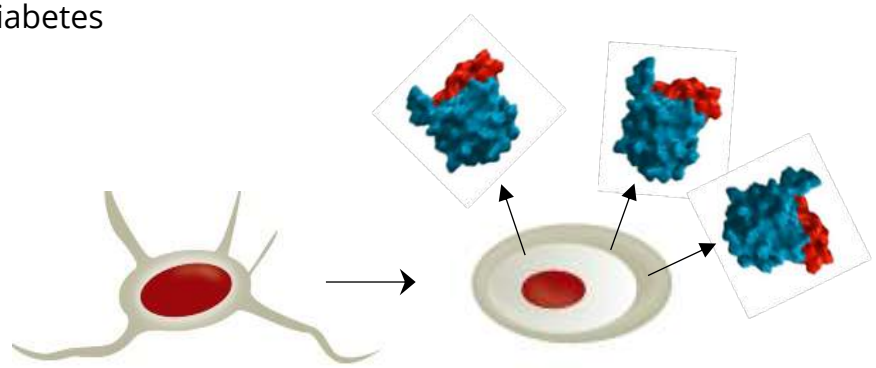
A joint venture in South Korea with Daewoong Pharmaceutical to develop engineered mesenchymal stem cells that express and secrete immuno-modulatory Affimer molecules to treat autoimmune diseases

Next-generation Stem Cell Therapies

Renewable “off the shelf” mesenchymal stem cells

AFX001: MSC secreting anti-CD40L Affimer for use in GvHD

AFX002: MSC secreting agonist Affimer for use in MS and T1 diabetes



COMPANY TECHNOLOGY PIPELINES AffyXell THERAPEUTICS INVESTORS & MEDIA CONTACT KR | EN

Development stage

Product Candidate	Target Indication	Discovery	Pre-clinical	Phase1	Phase2	Phase3
AFX-001	SOT					
	GvHD					
AFX-002	MS					

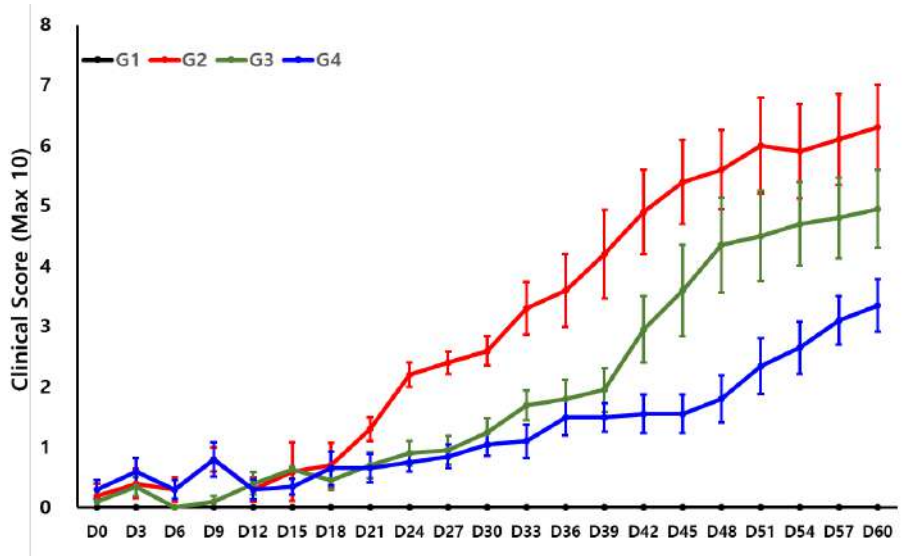
Data will be presented at International Society for Cell & Gene Therapy, May 2023 (AffyXell and Avacta) https://www.isctglobal.org/isct2023/home

[AFX-001] *In vivo* Efficacy in GvHD mouse models of the Anti-CD40L Affimer secreted from AFX-001

AFX-001 demonstrated superior efficacy in mouse acute GvHD model.
AFX-001 has been confirmed the MoA *in vitro* and *in vivo* proof-of-concept (PoC) studies.

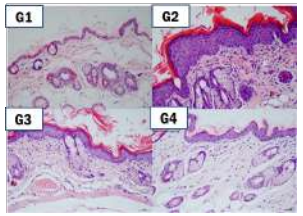
Group	Animal Model	Test Article	Injection Volume	Injection Interval
G1	Normal control	-	-	-
G2	GvHD	Vehicle	200 µL	D0 and D7
G3	GvHD	Naïve MSCs	200 µL	D0 and D7
G4	GvHD	AFX-001	200 µL	D0 and D7

Clinical Score in GvHD

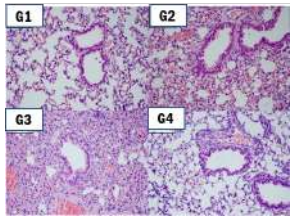


Histopathology

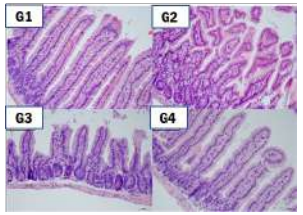
Skin (H&E)



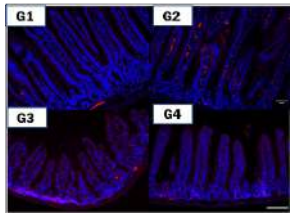
Lung (H&E)



Small Intestine (H&E)



CD3+ T cell in Small Intestine



LG Chem – multi-target partnership

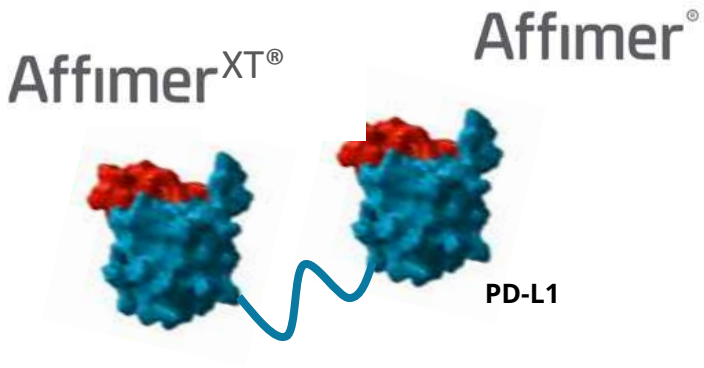
A multi-target development partnership and licensing deal worth up to $310 million with a focus on oncology and inflammatory diseases

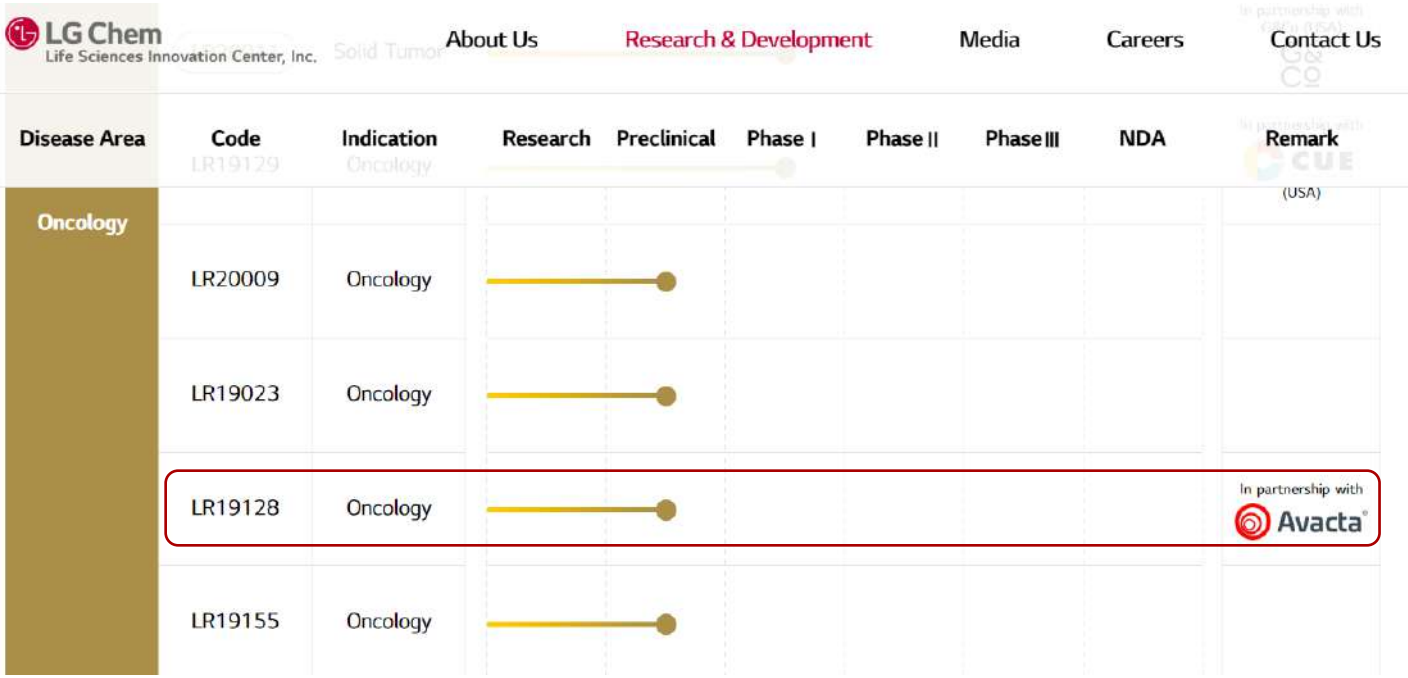
PDL1/XT Antagonist

PD1/PDL1 axis Affimer inhibitor

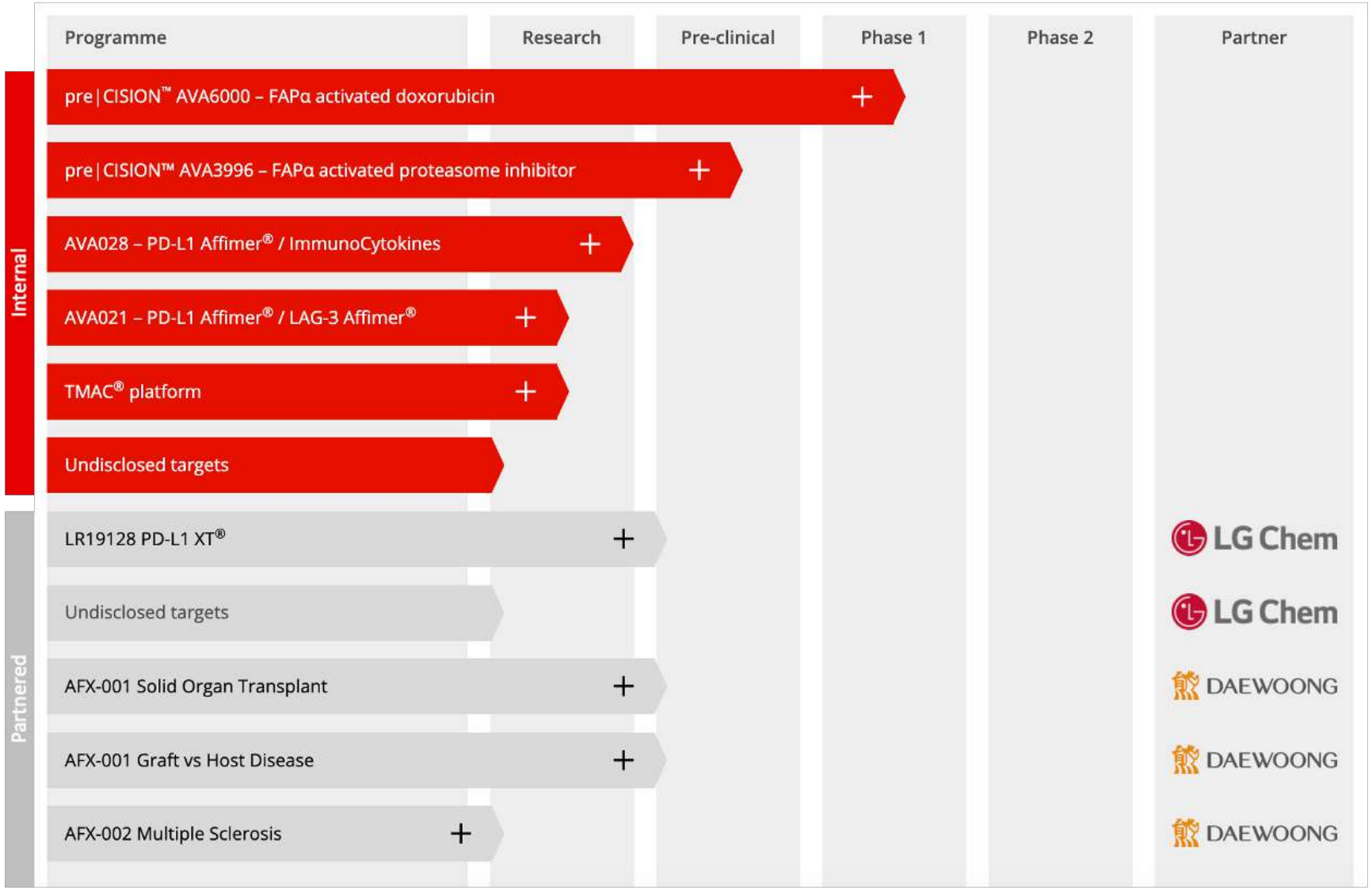
Half-life extension using Affimer XT® a human serum albumin binder

Small size potentially leads to better tumour penetration





Avacta Therapeutics Pipeline



Multiple internal assets from research to clinic

Next-Gen preCISION assets designed and developed in-house

Affimers targeting tumour/IO compartment validate platform

Novel Affimer programmes include multi-specific and difficult-to-drug targets

Multiple Partnered Affimer programmes progressing – further validates the platform

Avacta®

Q&A

Opportunities and challenges for cell and gene therapies for oncology and beyond

Krishna Komanduri, MD, FASTCT

Julius R. Krevans Distinguished Professor of Medicine

Chief, Division of Hematology/Oncology, UCSF Health

Physician-in-Chief, Helen Diller Family Comprehensive Cancer Center

Scientific Advisory Board Member, Avacta Therapeutics Division

Disclosures

- *Ad hoc* Consulting: Iovance, Incyte, BMS, Cargo Therapeutics, Instil Bio, CRISPR therapeutics, Genentech/Roche
- Scientific Advisory Board: Aegle Therapeutics, Avacta Therapeutics

Alfred Velpeau describes leukemia in 1825

La Leçon d'anatomie de Velpeau à la Charité, François-Nicolas-Augustin Feyen-Perrin, 1864

1825-1950: ~1000 publications about leukemia

1825

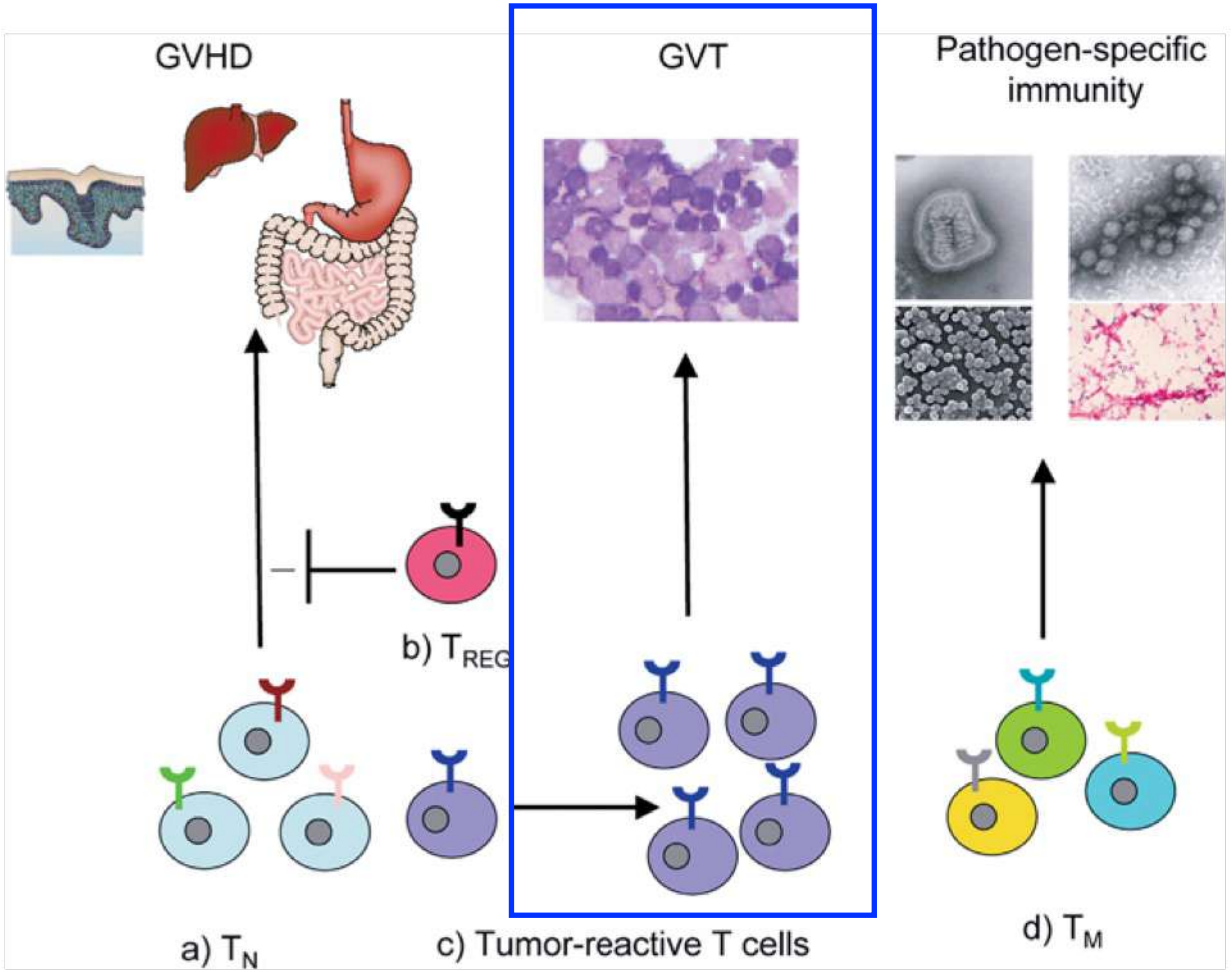
First description
of acute leukemia

1960s

Combination
chemotherapy +
stem cell transplants

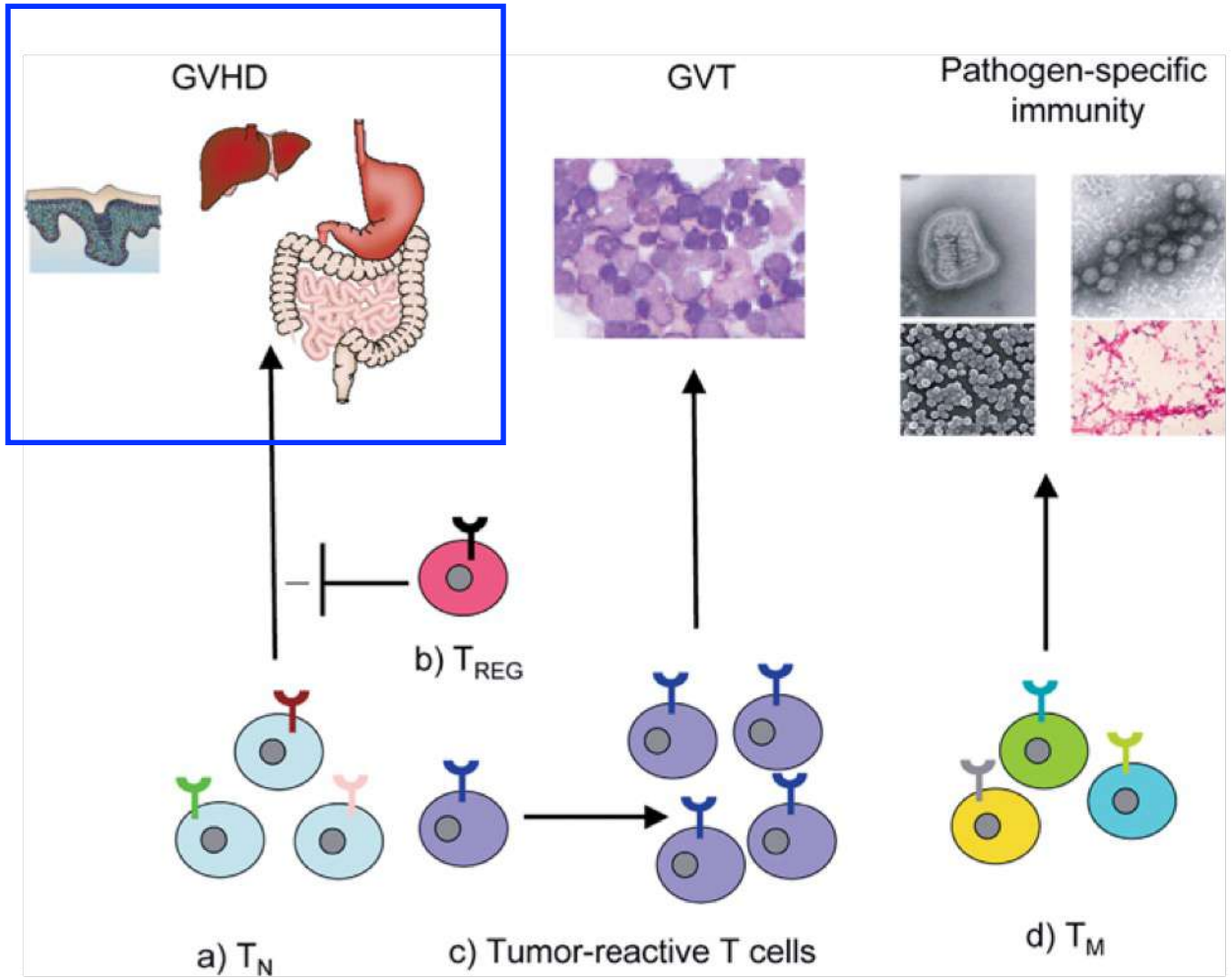
1950-2000: ~175,000 publications about leukemia

T cells from stem cell transplant donors eliminate residual cancer…



Riddell & Appelbaum,
Graft v. Host Disease,
PLOS Medicine, 2007

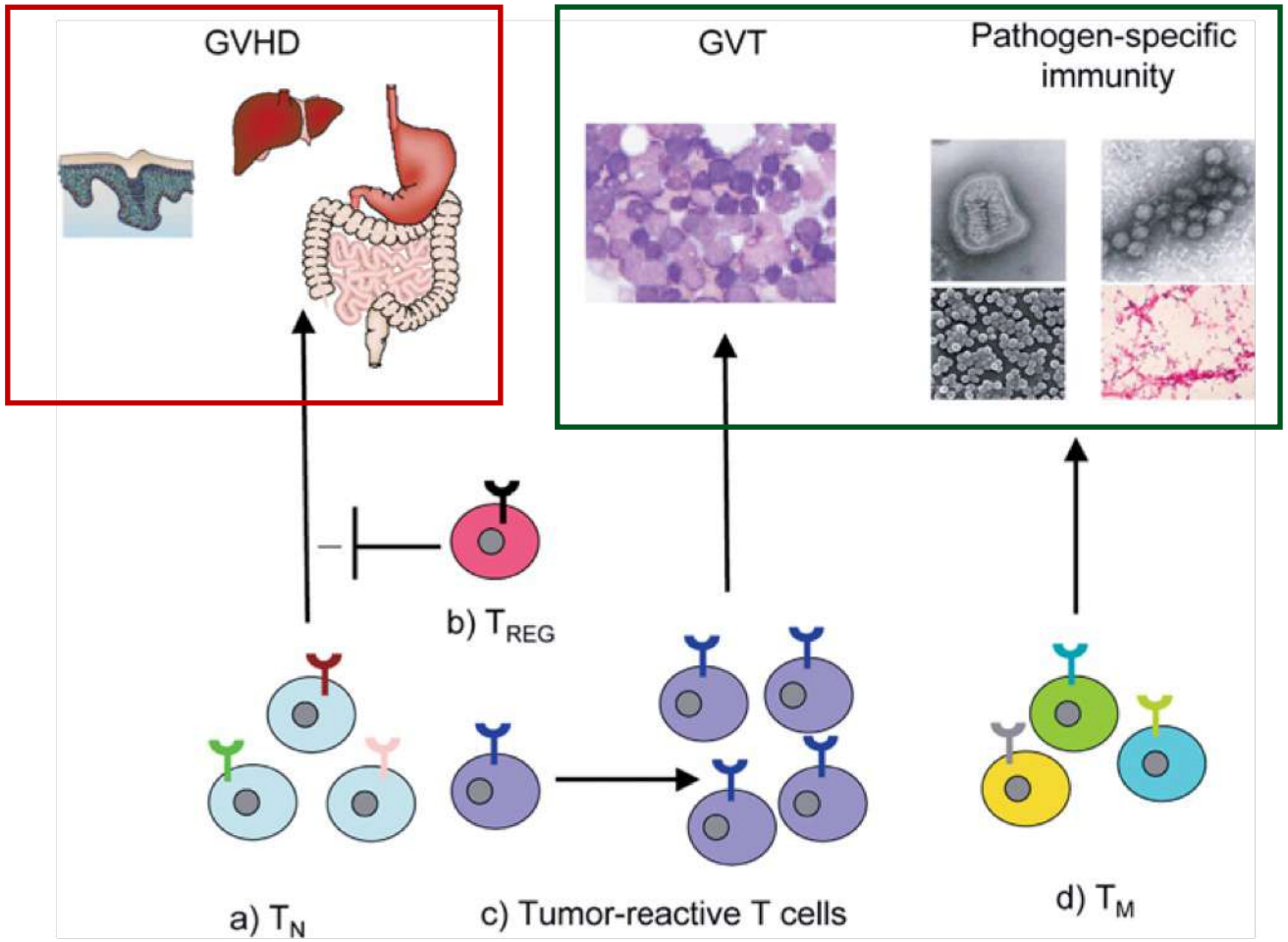
…but can attack healthy tissues in the patient



Riddell & Appelbaum,
Graft v. Host Disease,
PLOS Medicine, 2007

Improving immune outcomes of stem cell transplants

Can we selectively inhibit these...



But not these?

Riddell & Appelbaum, Graft v. Host Disease, PLOS Medicine, 2007

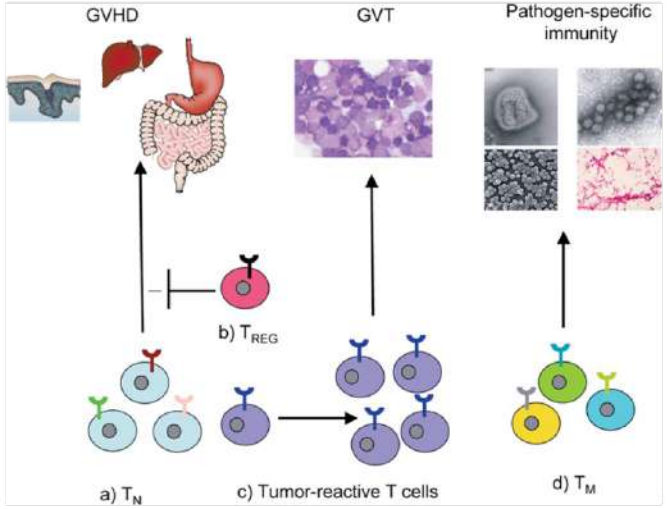
From stem cell transplants to personalized immunotherapy

1825

First description of acute leukemia

1960s

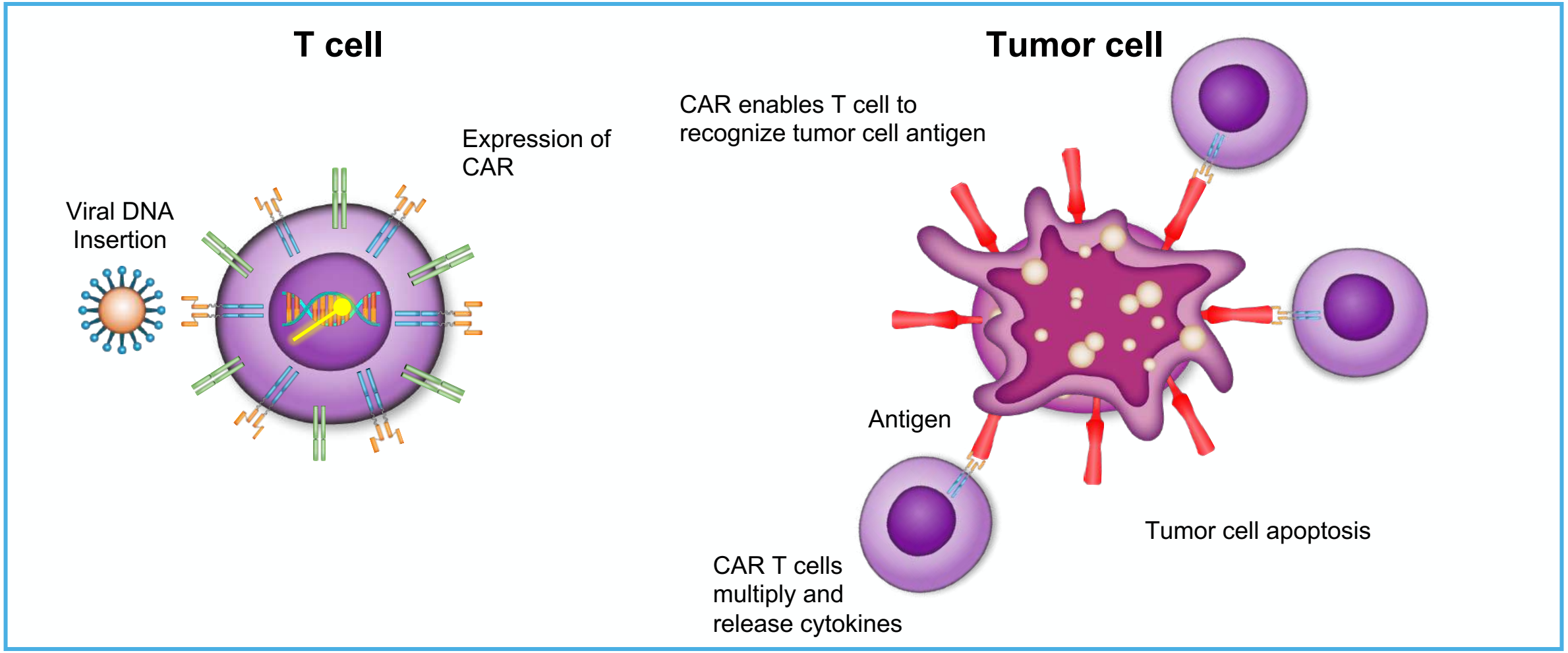
Combination chemotherapy + stem cell transplants



1990s

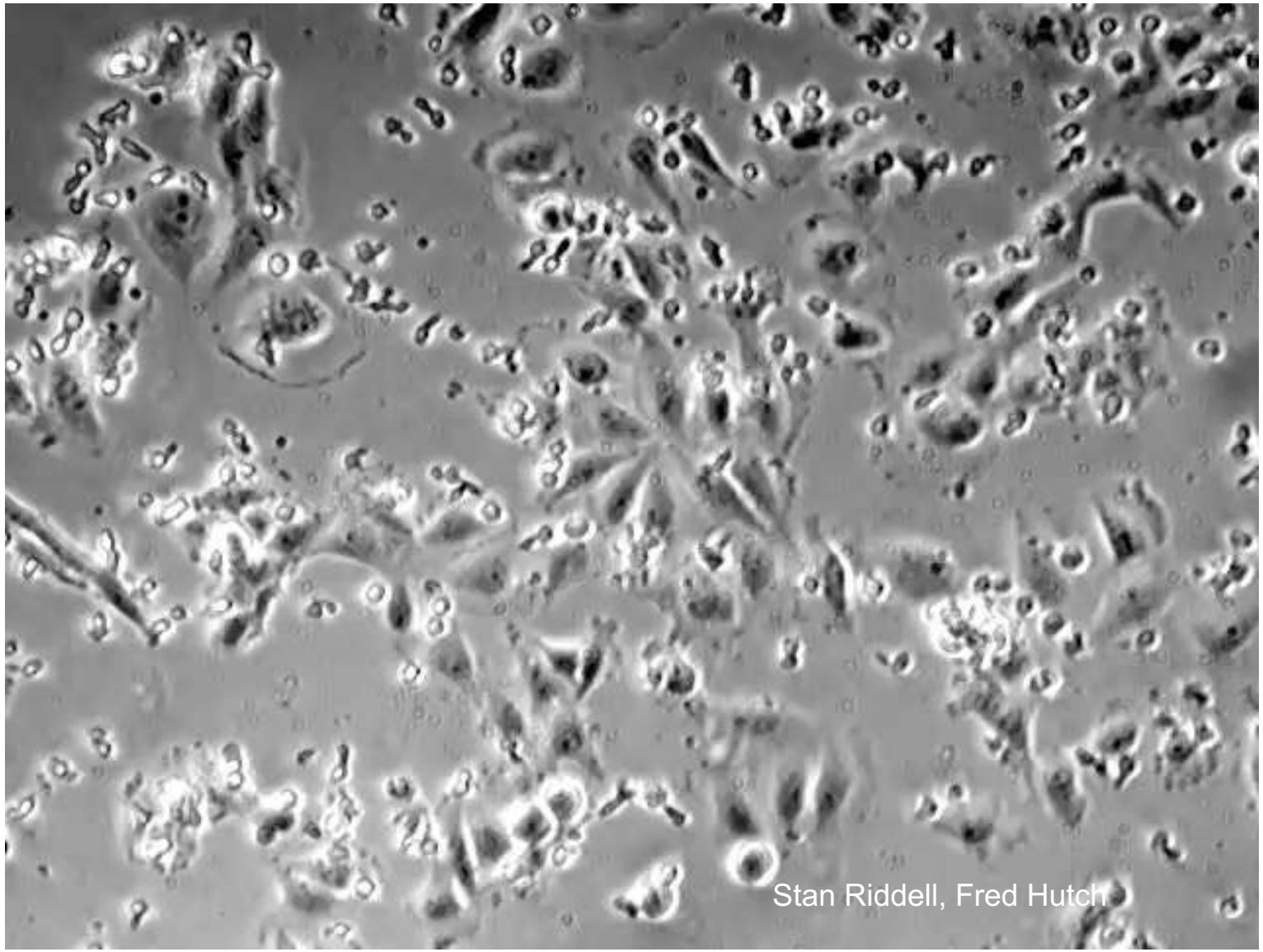
T cells critical for transplant cures—dramatic increase in success

CAR-T therapy: an overview

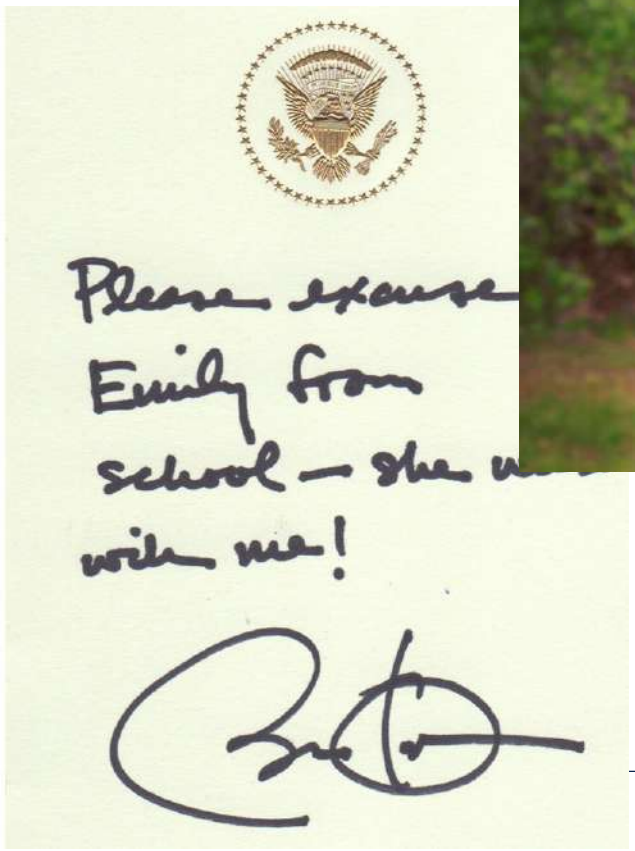


CAR T WORKING GROUP

In vivo killing of cancer cells with CAR-T cells (S. Riddell)



Emily Whitehead: CAR-T Patient #1



2022

CAR-T therapy: a breakthrough therapy for lymphoma

ORIGINAL ARTICLE

Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma

S.S. Neelapu, F.L. Locke, N.L. Bartlett, L.J. Lekakis, D.B. Miklos, C.A. Jacobson, I. Braunschweig, O.O. Oluwole, T. Siddiqi, Y. Lin, J.M. Timmerman, P.J. Stiff, J.W. Friedberg, I.W. Flinn, A. Goy, B.T. Hill, M.R. Smith, A. Deol, U. Farooq, P. McSweeney, J. Munoz, I. Avivi, J.E. Castro, J.R. Westin, J.C. Chavez, A. Ghobadi, K.V. Komanduri, R. Levy, E.D. Jacobsen, T.E. Witzig, P. Reagan, A. Bot, J. Rossi, L. Navale, Y. Jiang, J. Aycock, M. Elias, D. Chang, J. Wiezorek, and W.Y. Go

Neelapu SS, et al. *N Engl J Med.* 2017 Dec 28;377(26):2531-2544.

ZUMA-1: Patient Characteristics

Characteristic	DLBCL (n=73)	TFL/PMBCL (n=20)	All Patients (n=93)
Median age (range), years	59 (25-76)	58 (28-76)	59 (25-76)
Age ≥60 years, n (%)	36 (49)	9 (45)	45 (48)
Male, n (%)	47 (64)	15 (75)	62 (67)
ECOG performance status 1, n (%)	48 (66)	8 (40)	56 (60)
Median number of prior therapies (#)	3 (1-7)	4 (2-12)	3 (1-12)
IPI 3-4, n (%)	32 (44)	9 (45)	41 (44)
Disease stage III/IV, n (%)	64 (88)	15 (75)	79 (85)
Refractory subgroup, n (%)*			
Refractory to 2nd or later-line therapy	56 (77)	16 (80)	72 (77)
Relapse post-ASCT	15 (21)	4 (20)	19 (20)

*2 patients had primary refractory status

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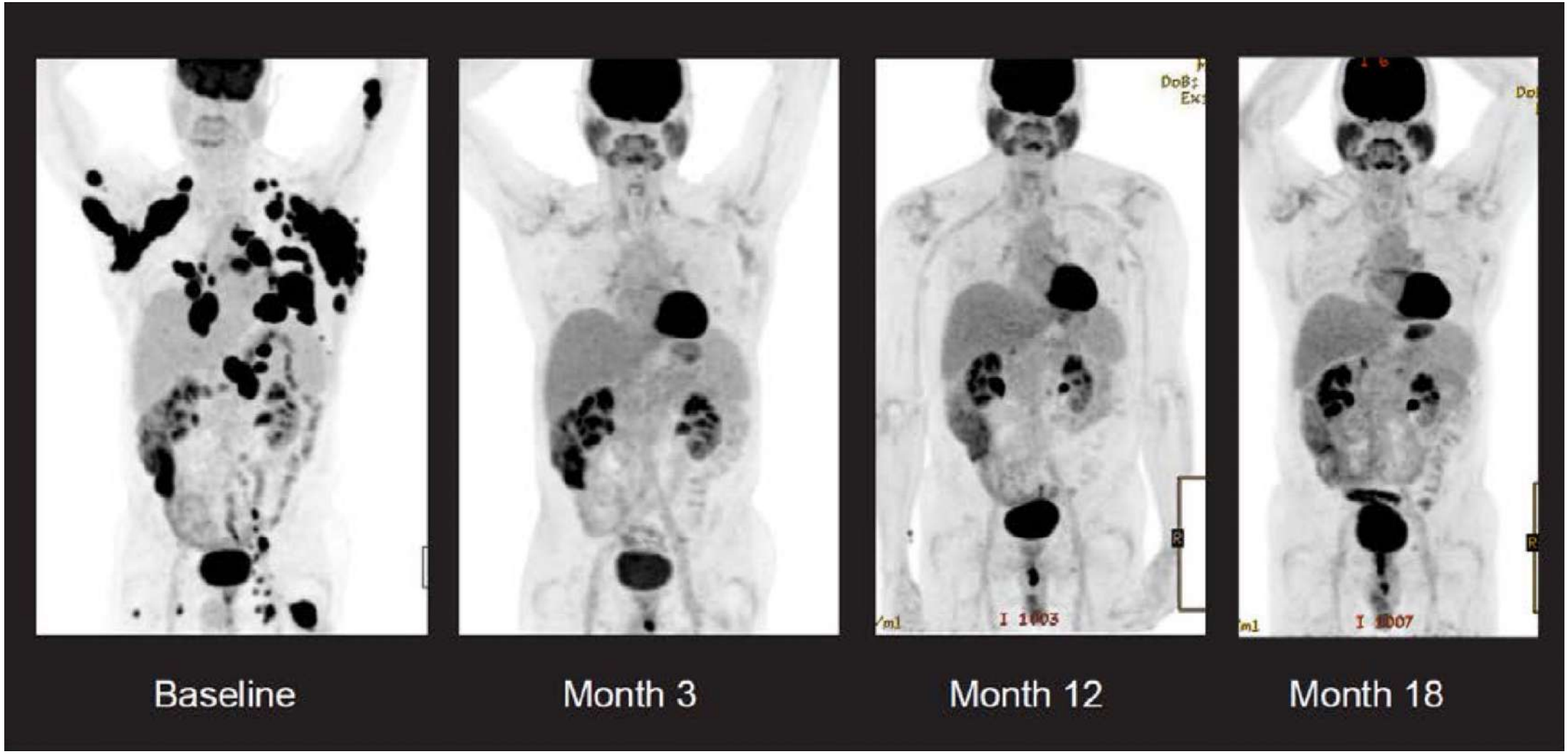
ZUMA-1 Met Primary Endpoint of ORR in Combined Group

Best Response	ZUMA-1 Phase 2					
	DLBCL		TFL/PMBCL		Combined	
	ORR (%)	CR (%)	ORR (%)	CR (%)	ORR (%)	CR (%)
mITT[b]	n = 77		n = 24		n = 101	
	82	49	83	71	82	54

aInferential testing when 92 axi-cel–dosed patients had 6 mo of follow-up. ORR 82%, *P*<0.0001. bmITT (modified intention-to-treat) set of all patients dosed with axi-cel.

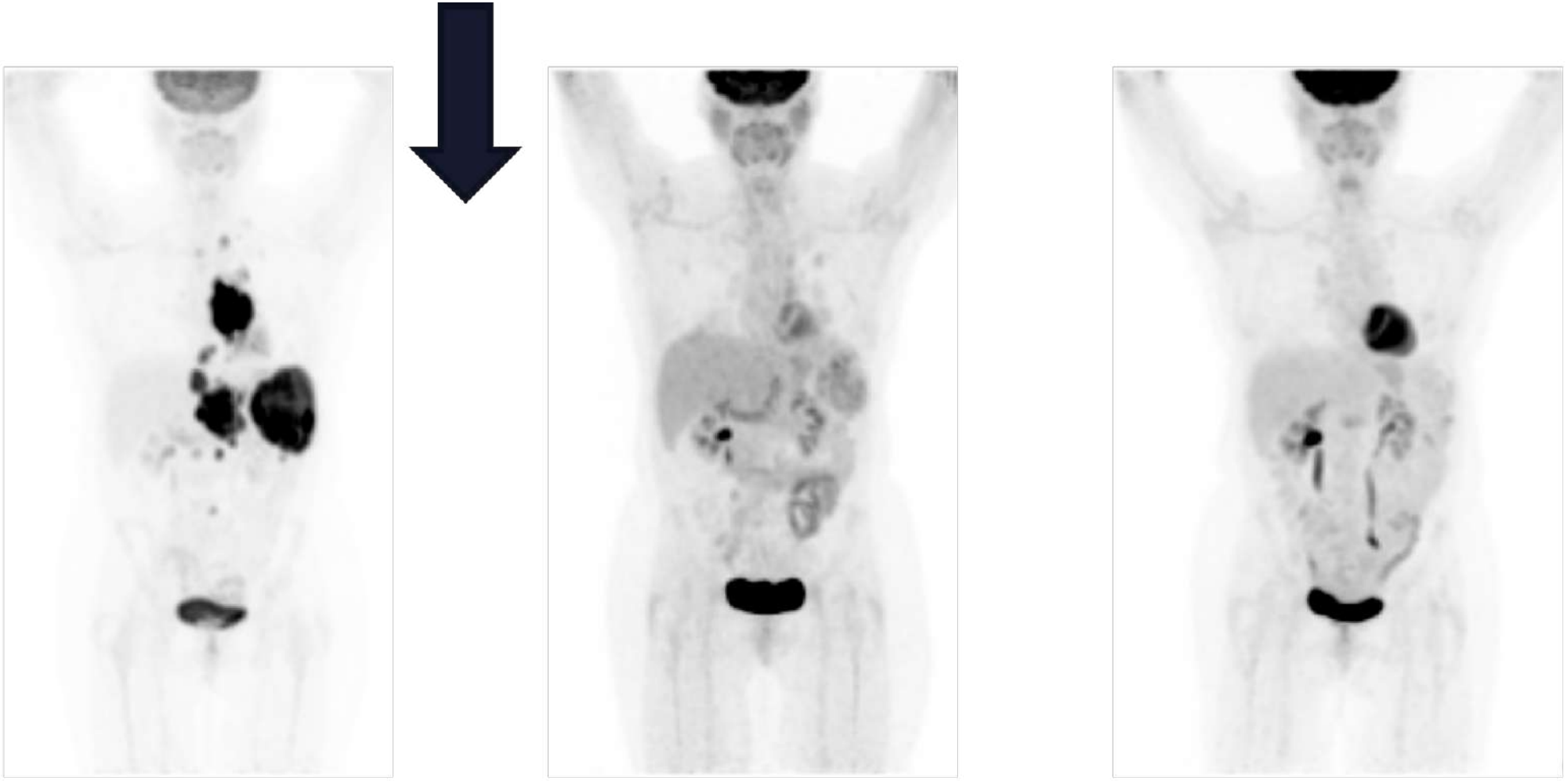
CR, complete response; DLBCL, diffuse large B cell lymphoma; ORR; objective response rate; PMBCL; primary mediastinal B cell lymphoma; TFL, transformed follicular lymphoma.

Cure of refractory lymphoma with CAR-T therapy (axi-cel)



Neelapu, et al., NEJM December 2017

CAR-T therapy after six prior lines of therapy



December 2015 February 2016 April 2016

Images by
Lazaros Lekakis, MD

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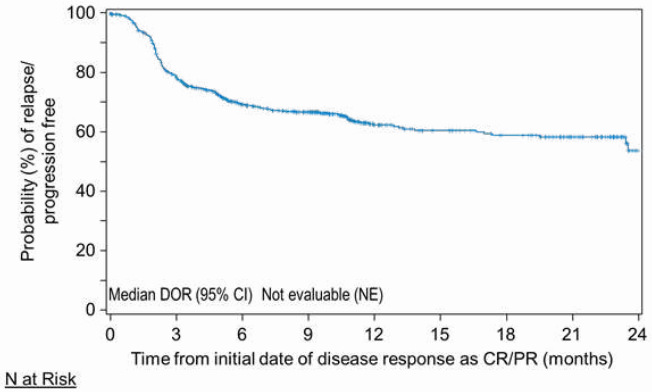
Comparable data between the CIBMTR and the pivotal trials: Axi-cel

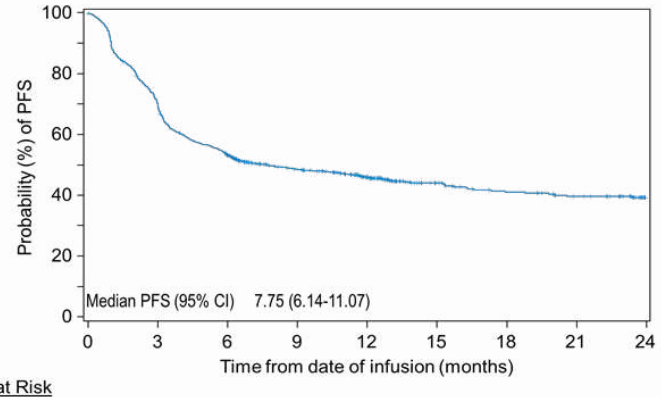
Axi-cel PASS - CIBMTR



N at Risk

All subjects	834	623	426	353	157	123	107	78	10

Patients who did not achieve CR/PR as best response during the follow-up period were excluded.



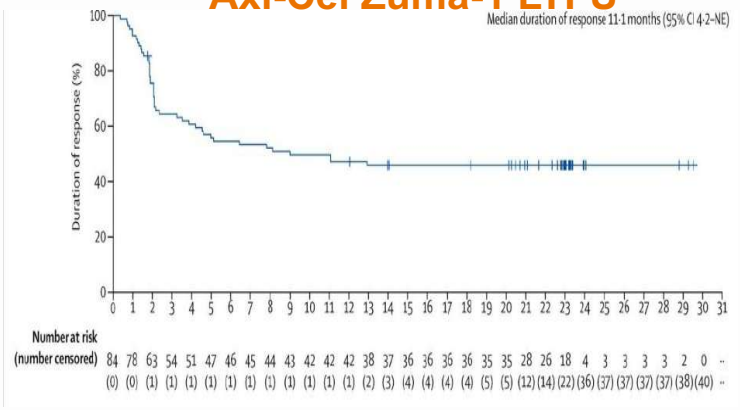
N at Risk

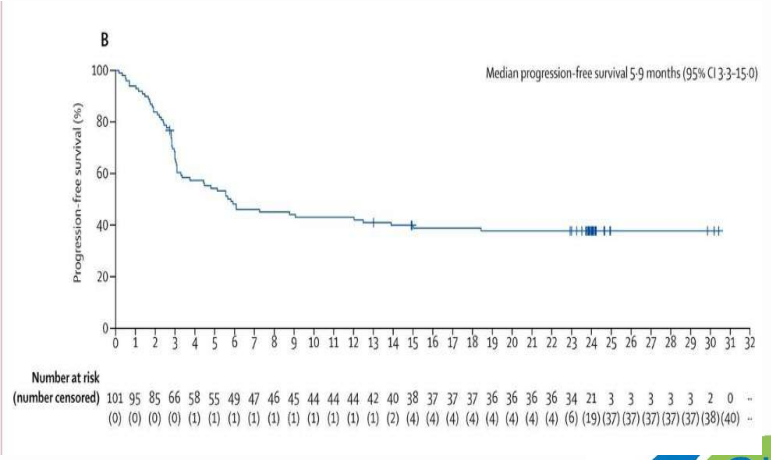
All subjects	1174	823	610	426	323	138	121	110	65

Duration of response

Progression-free Survival

Axi-Cel Zuma-1 LTFU





Jacobson C. et al ASCO 2021, Locke F et al Lancet Oncology 2019

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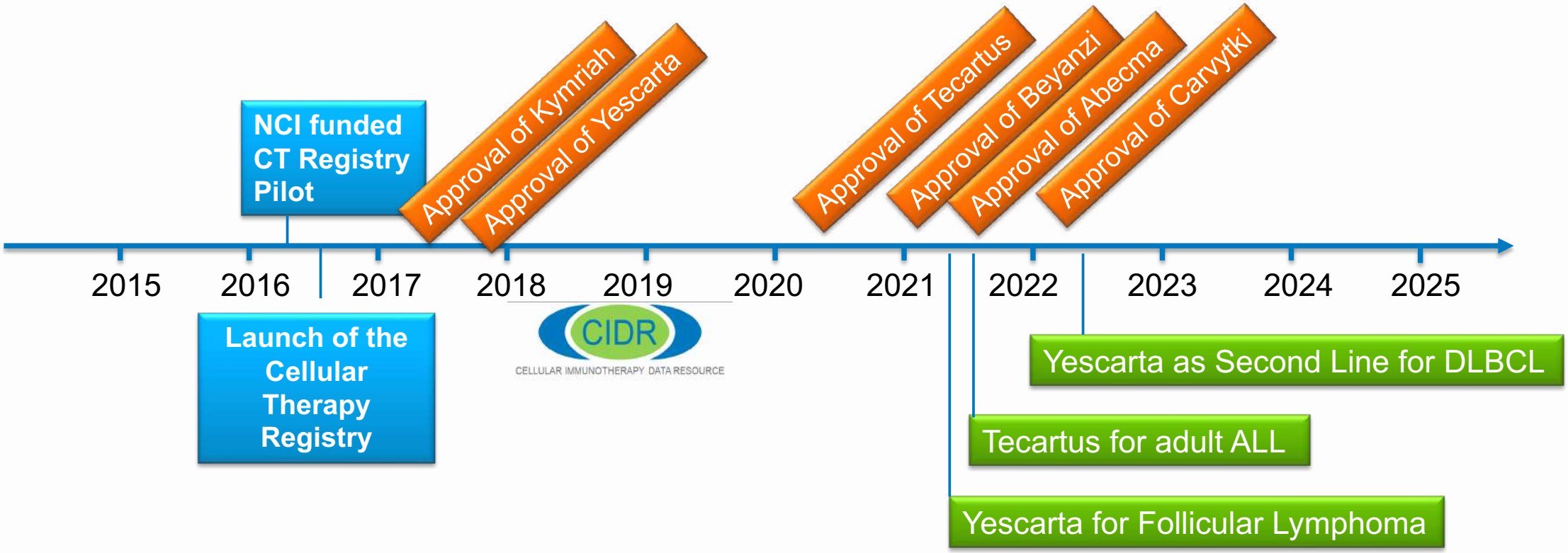
The Development of the Registry Parallel to the Expansion of the Field of Cellular Immunotherapy



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Cellular Immunotherapy Registry at a Glance

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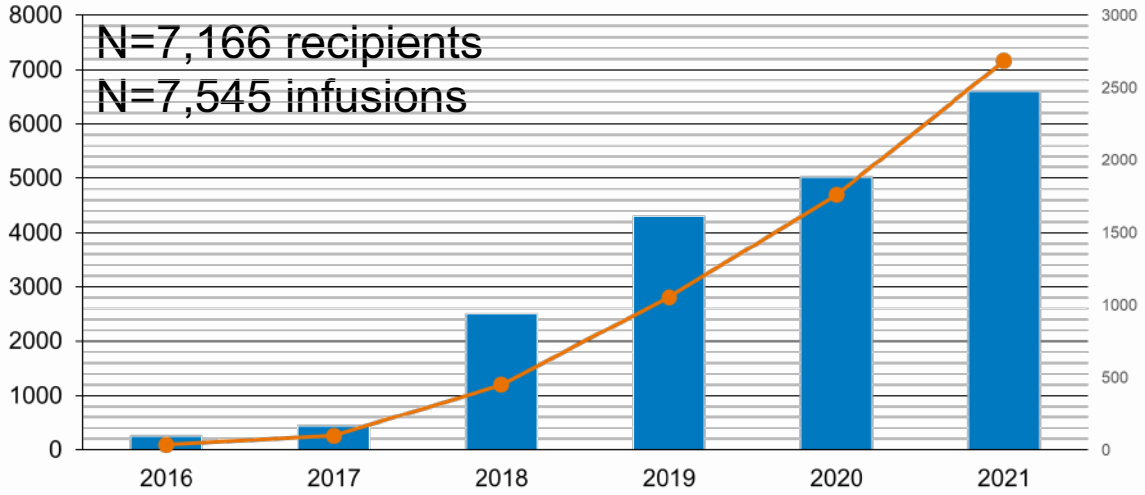

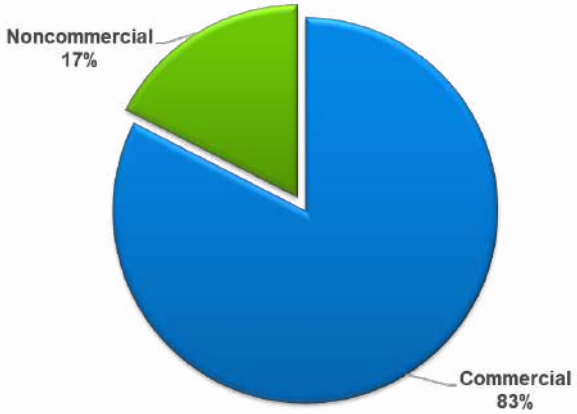

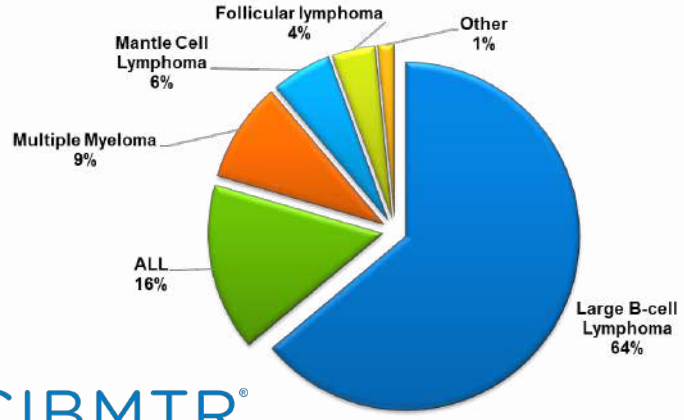

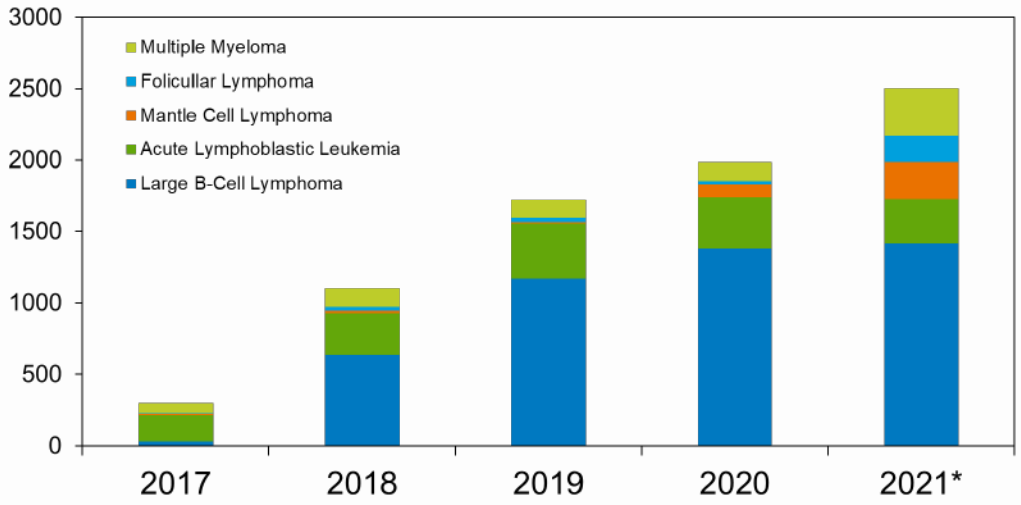

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What about earlier lines of lymphoma therapy?

CD19 CAR T-cells in DLBCL: Earlier Lines

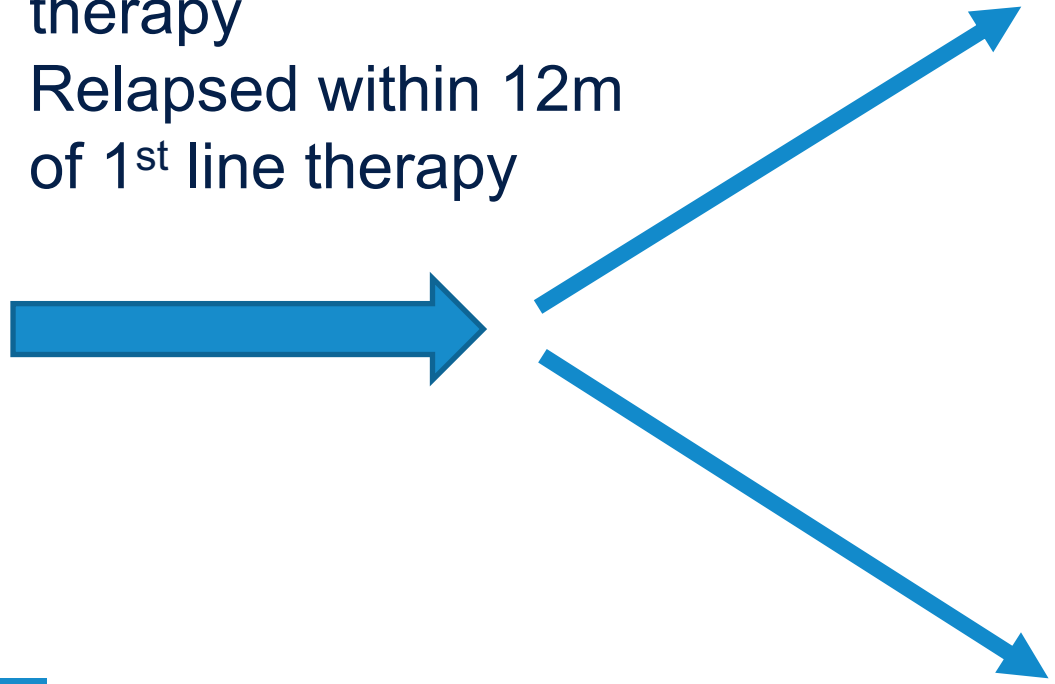
ZUMA-7
Axi-cel

BELINDA
Tisa-cel

TRANSFORM
Liso-cel

High Risk DLBCL:

- Refractory to 1st line therapy
- Relapsed within 12m of 1st line therapy



CAR T

Salvage/ Auto

Is CAR-T therapy the 2nd line DLBCL standard?

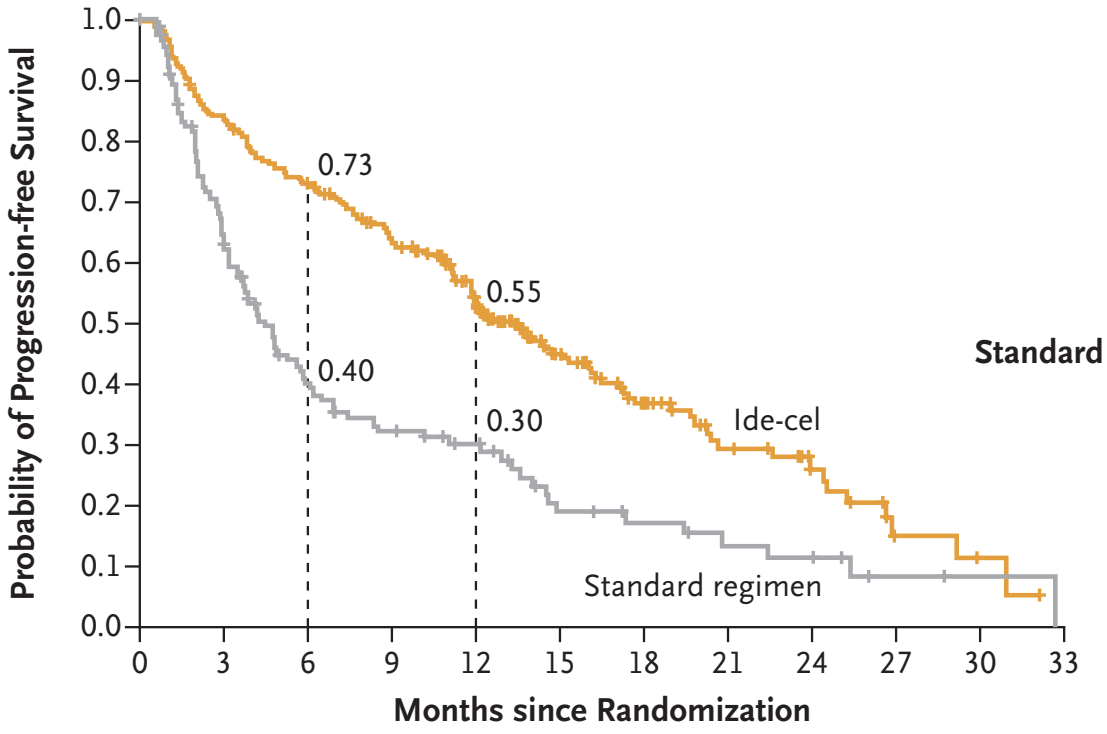
- Two of three RCTs favored CAR-T therapy in the second line setting (ZUMA-7 and TRANSFORM)
- RCTs demonstrated traditional salvage therapies are suboptimally effective (<40% achieved PR and had AutoSCT)
- Additional RCTs would be helpful (but are unlikely)
- *CAR-T therapies are 2nd line standard for patients with early relapse*

What about fourth line? First line?

- Long-term results of all three commercial products suggest only 30-40% cure rates
- Trials of second CAR-T infusions (including targeting CD19/22 or CD19/20) demonstrate ≤30% ORR
- We need better therapies following CAR-T failure, including those that target different antigens (or combinations)
- First-line studies of newly diagnosed lymphoma promising (ZUMA-12, Neelapu, *Nat Med* 2022) but additional data, RCTs needed

Emerging data in myeloma

Ide-cel is superior to SOC in R/R myeloma, but not curative



No. at Risk												
Ide-cel	254	206	178	149	110	62	40	22	14	4	2	0
Standard regimen	132	75	42	32	25	13	10	7	6	2	1	0

	Median Progression-free Survival (95% CI)
	mo
Ide-cel	13.3 (11.8–16.1)
Standard Regimen	4.4 (3.4–5.9)

Hazard ratio for disease progression or death, 0.49 (95% CI, 0.38–0.65)
P<0.001

Rodriguez-Otero, *NEJM,* 2023

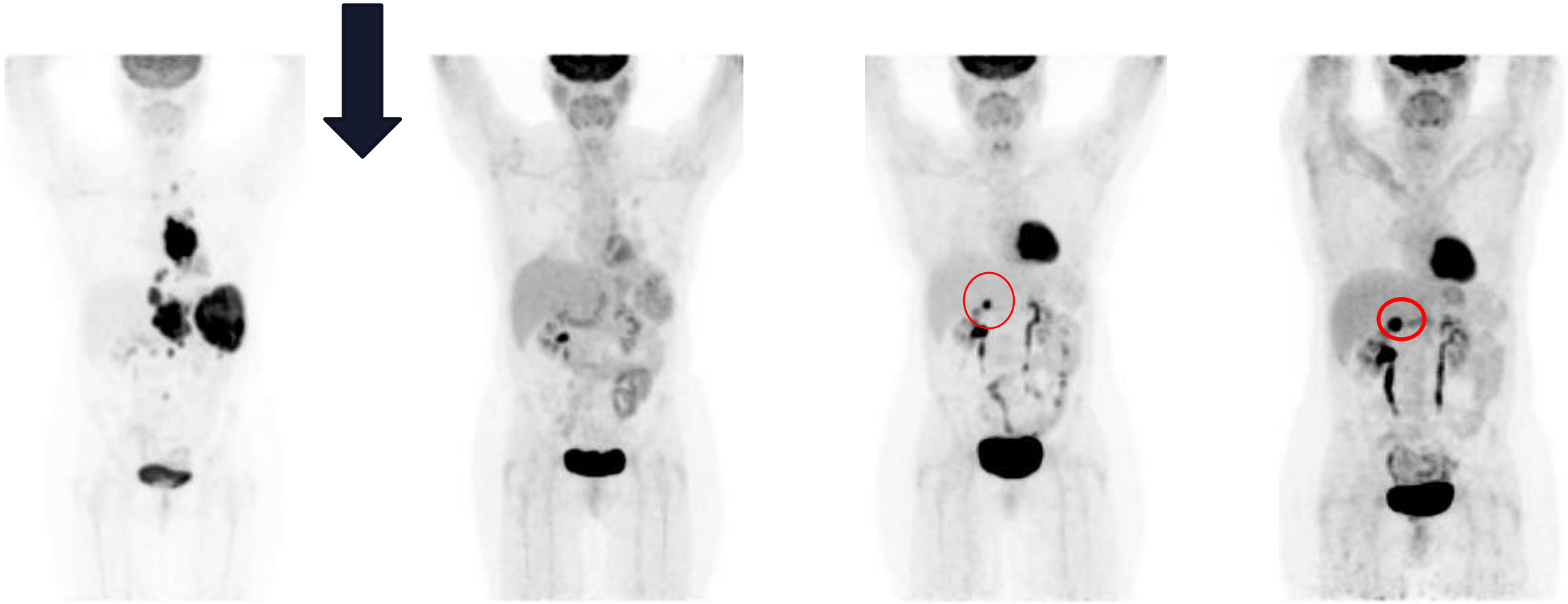
RCT of ide-cel vs. standard regimens in R/R myeloma

- Overall, ide-cel outperformed other SOC regimens in this population
- However, no plateau suggesting curative potential evident in PFS curves
- When progression did occur, BCMA (target) downregulation was NOT seen, in contrast to frequent target loss in CD19 CAR-T treatment failures

Rodriguez-Otero, *NEJM,* 2023

Can we predict cellular therapy failures?

Localized relapse of refractory lymphoma after CAR-T therapy

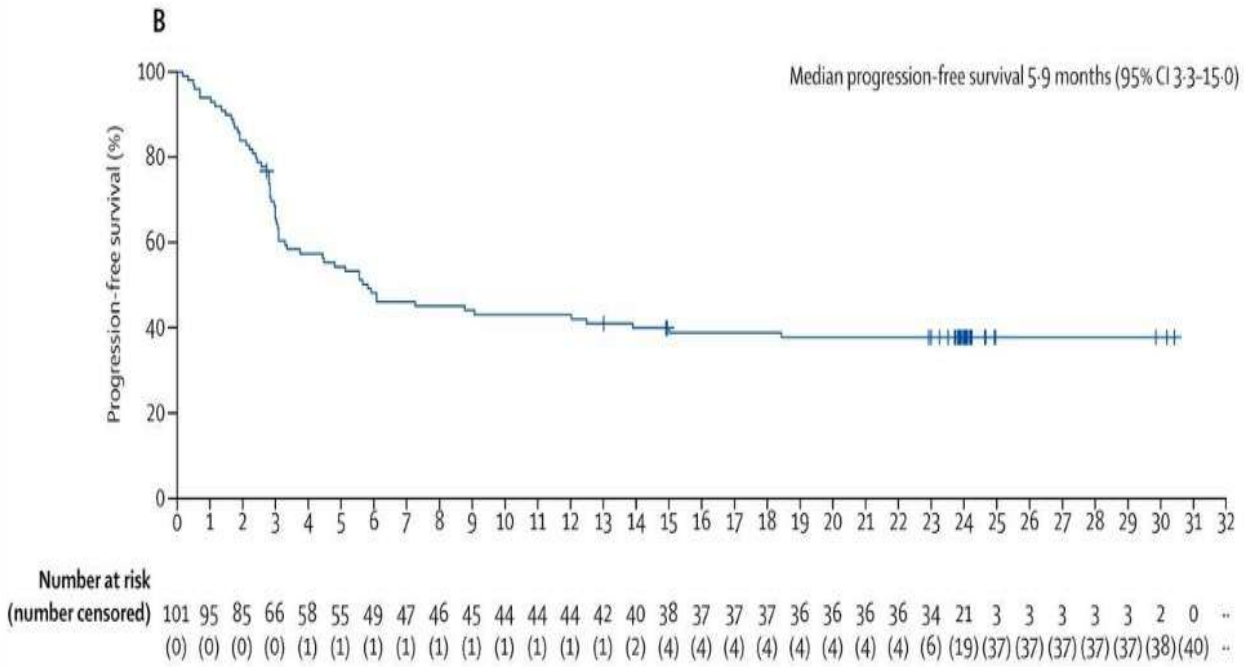


December 2015 February 2016 July 2016 August 2016

Image courtesy of Lazaros Lekakis, MD., University of Miami

Most patients receiving CD19+ CAR-T therapy relapse

Progression-free Survival



Jacobson C. et al ASCO 2021, Locke F et al Lancet Oncology 2019

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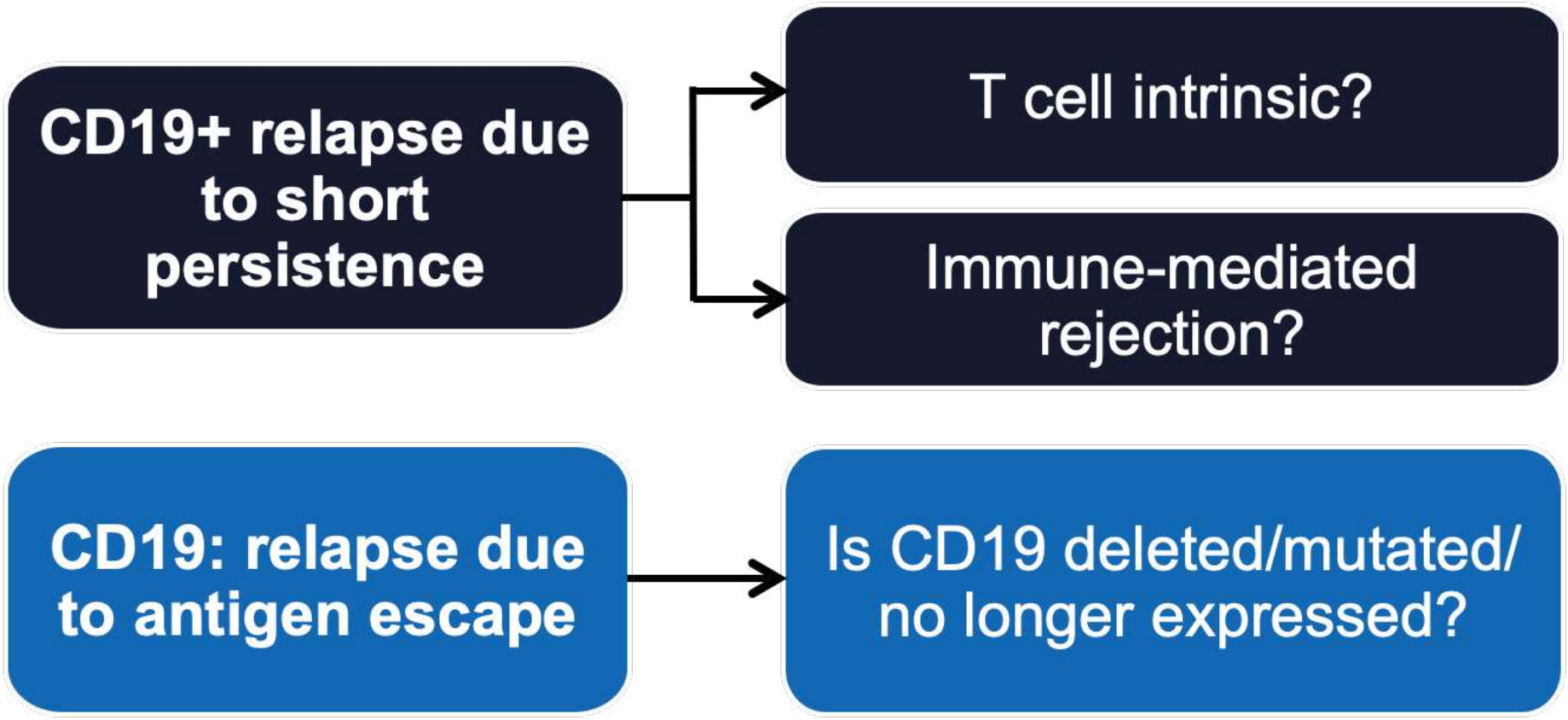
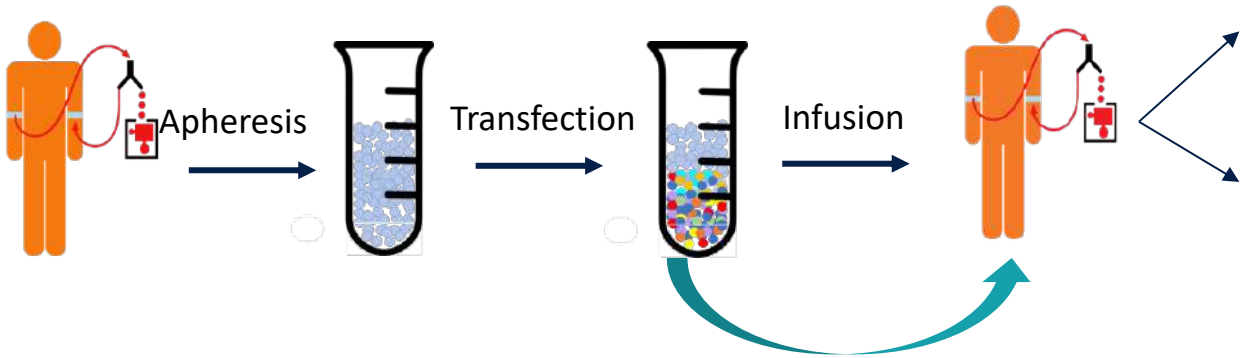
Mechanisms of relapse after CD19 CAR-T therapy

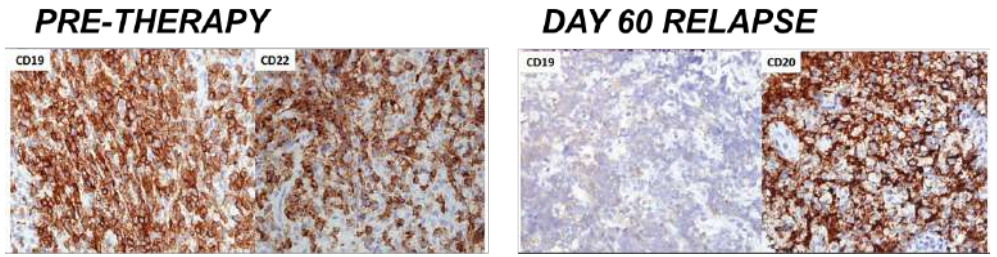


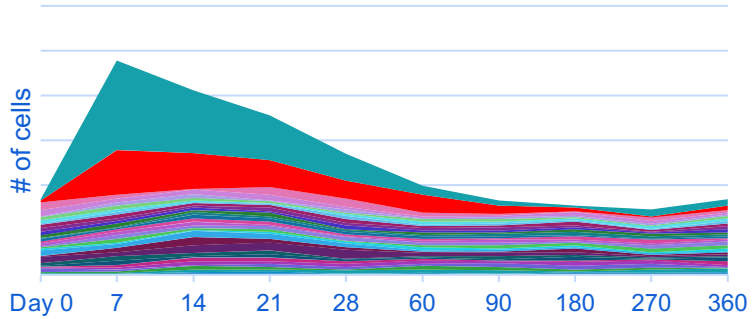
Optimizing CAR-T Therapy: Model by Spiegel and Miklos

Patient **CAR-T Product**



Tumor Biology:
- Tumor Antigen Density
- Tumor microenvironment





CAR-T Product Fitness:
- Patient T cell fitness
- CAR-T construct
- CAR-T manufacturing

CAR-T Pharmacokinetics and Pharmacodynamics
- Characterize which CAR-T localize to tumor
- Immune Phenotype of CAR-T blood expansion

from Spiegel and Komanduri, *Blood Feb 17, 2022*

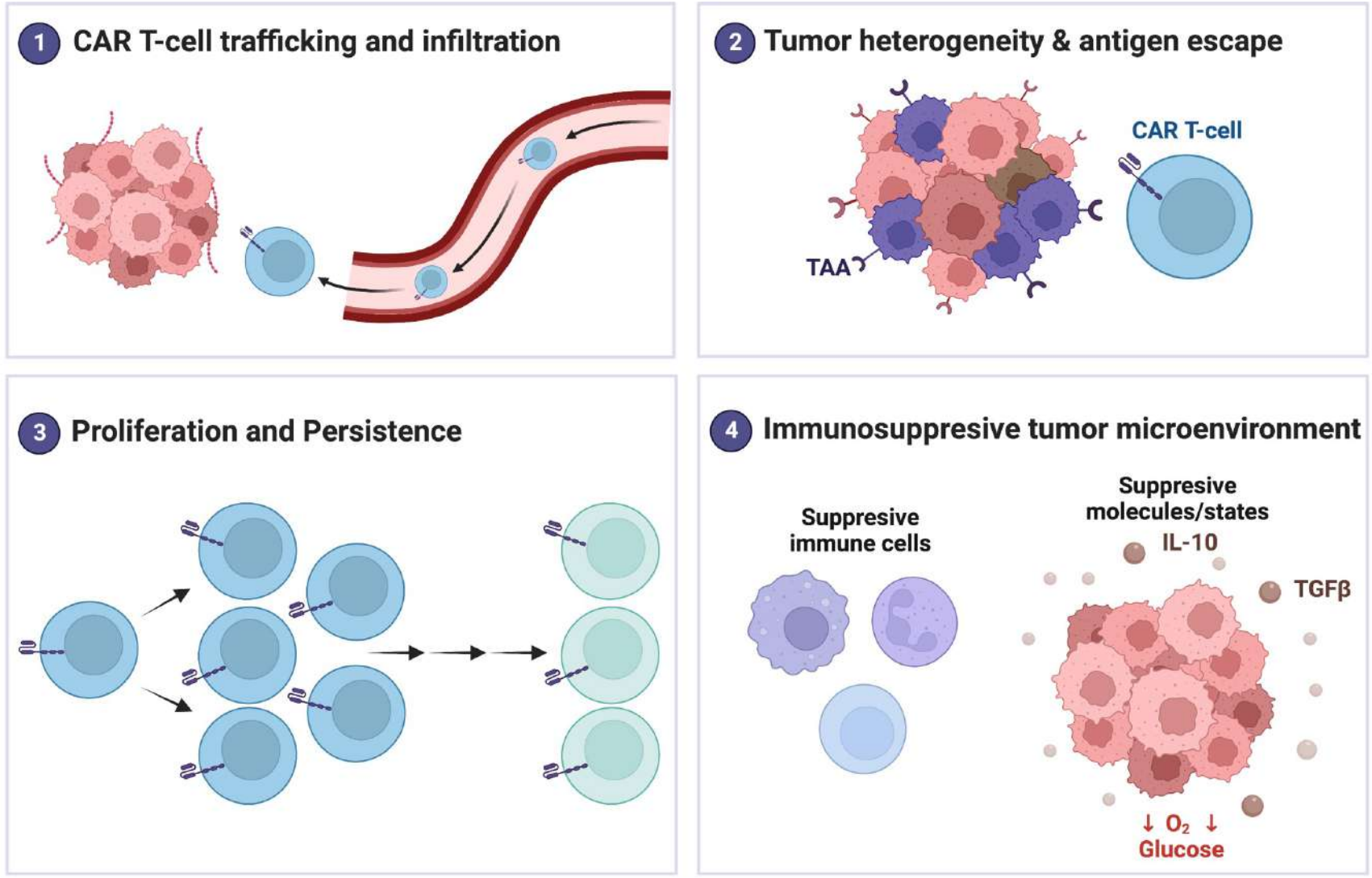
Solid tumor T cell therapies: challenges

Solid tumor targets

Antigen	Cancer	Phase	ID
EGFR	Lung, liver, stomach	Phase 1/2	NCT03179007, NCT03525782
HER2	Central nervous system tumor, pediatric glioma	Phase 1	NCT03500991
EGFR806	Central nervous system tumor, pediatric glioma	Phase 1	NCT03179012
Mesothelin	Ovarian, cervical, pancreatic, lung	Phase 1/2	NCT01583686
PSCA	Lung	Phase 1	NCT03198052
MUC1	Advanced solid tumors, lung	Phase 1/2	NCT03179007, NCT03525782
Claudin 18.2	Advanced solid tumor	Phase 1	NCT03874897
EpCAM	Colon, pancreatic, prostate, gastric, liver	Phase 1/2	NCT03013712
GD2	Brain	Phase 1	NCT04099797
VEGFR2	Melanoma, brain	Phase 1	NCT01218867
AFP	Hepatocellular carcinoma liver cancer	Phase 1	NCT03349255
Nectin4/FAP	Nectin4-positive advanced malignant solid tumor	Phase 1	NCT03932565
CEA	Lung, colorectal, gastric, breast, pancreatic cancer	Phase 1	NCT02349724
Lewis Y	Advanced cancer	Phase 1	NCT03851146
Glypican-3	Liver	Phase 1	NCT02932956
EGFRIII	Glioblastoma and brain tumor	Phase 1	NCT01454596
IL-13Rα2	Glioblastoma	Phase 1	NCT02208362
CD171	Neuroblastoma	Phase 1	NCT02311621
MUC16	Ovarian	Phase 1	NCT02311621
PSMA	Prostate	Phase 1	NCT01140373
AFP	Hepatocellular carcinoma, liver	Phase 1	NCT03349255
AXL	Renal	Phase 1	NCT03393936
CD20	Melanoma	Phase 1	NCT03893019
CD80/86	Lung	Phase 1	NCT03198052
c-MET	Breast, hepatocellular	Phase 1	NCT03060356, NCT03638206
DLL-3	Lung	Phase 1	NCT03392064
DR5	Hepatoma	Phase 1	NCT03638206
EpHA2	Glioma	Phase 1	NCT02575261
FR-α	Ovarian	Phase 1	NCT00019136
gp100	Melanoma	Phase 1	NCT03649529
MAGE-A1/3/4	Lung	Phase 1	NCT03356808, NCT03535246
LMP1	Nasopharyngeal	Phase 1	NCT02980315

EGFR epidermal growth factor receptor, *HER2* human epidermal growth factor receptor 2, *PSCA* prostate stem cell antigen, *MUC1* mucin1, *EpCAM* epithelial cell adhesion molecule, *AFP* alpha-fetoprotein, *FAP* familial adenomatous polyposis, *CEA* carcinoembryonic antigen, *MUC16* mucin16, *PSMA* prostate-specific membrane antigen, *AXL* AXL receptor tyrosine kinase, *DLL3* delta-like 3, *EPHA2* EPH receptor A2, *FRα* folate receptor alpha, *LMP1* Epstein-Barr virus latent membrane protein 1, *MAGE* melanoma antigen gene protein, *DR5* death receptor 5

Challenges to CAR-T cell efficacy/safety in solid tumors



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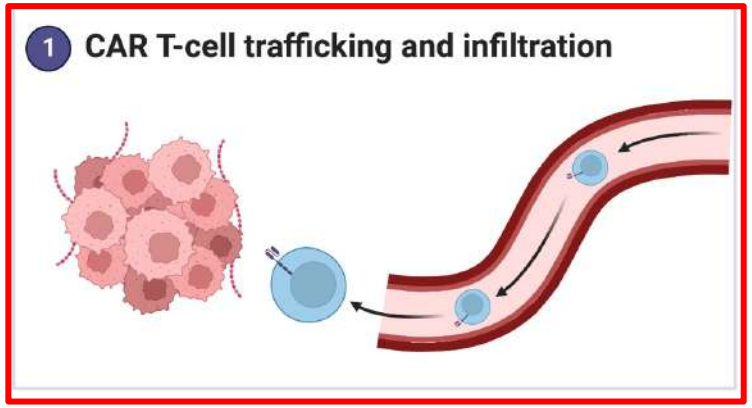
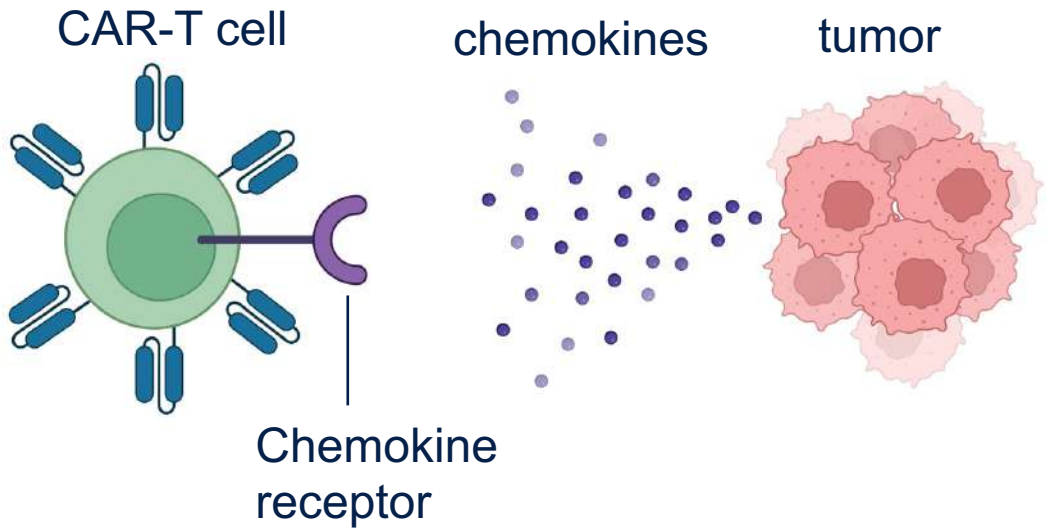
Improving targeting of solid tumor targeted T cells





- Chemokine receptors
- Target tumor stroma/vasculature

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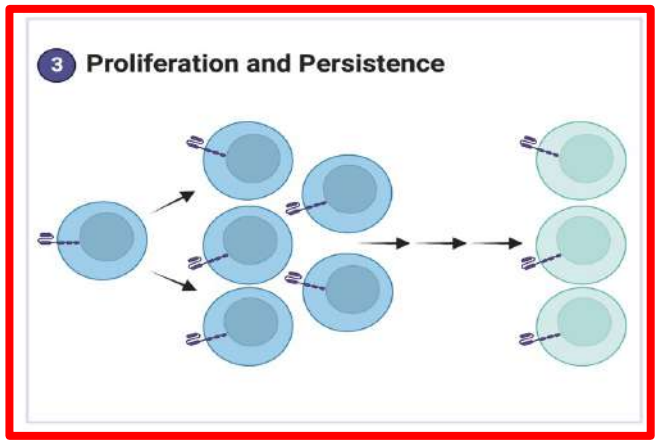
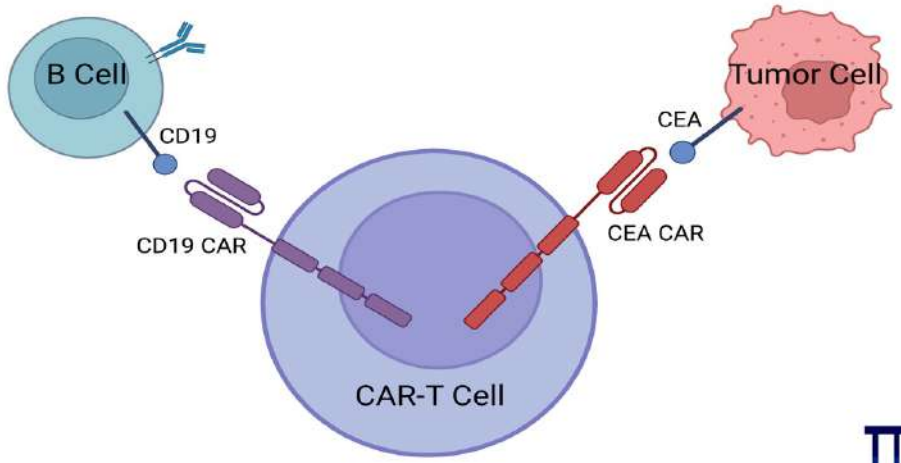
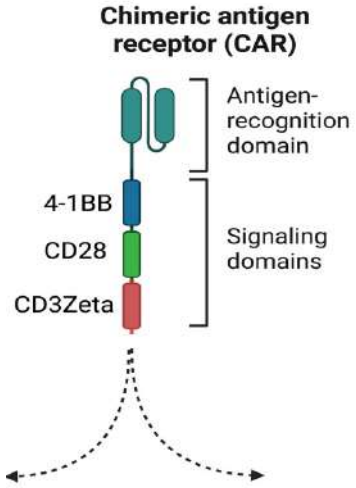
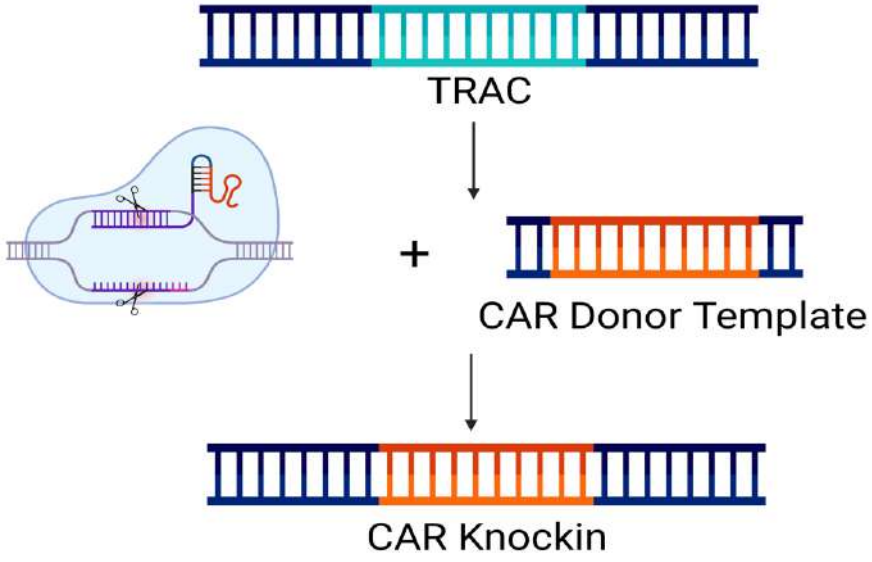
Strategies to improve tumor persistence and proliferation





- Co-stim domains
- Dual targeting
- TRAC KI
- Gene editing (counter exhaustion, metabolic reprogramming)





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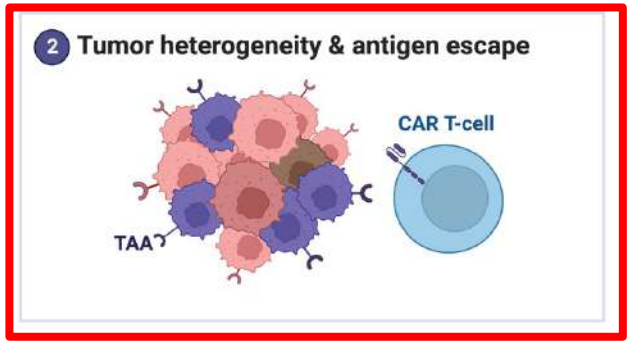
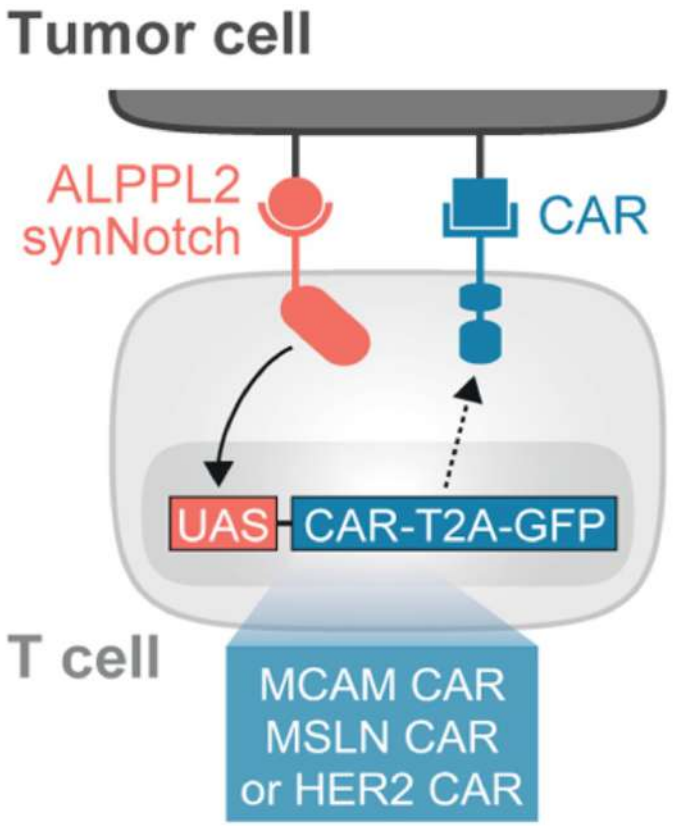
Overcoming the challenge of tumor heterogeneity

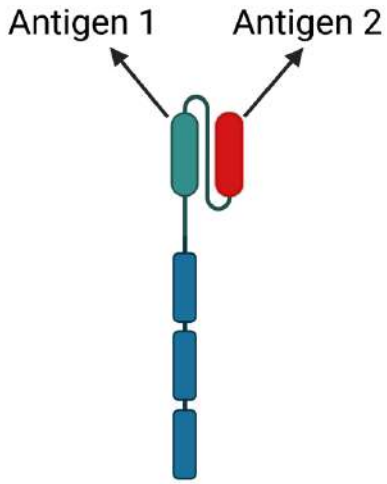


- Bivalent CARs
- Combinatorial antigen recognition with circuits/logic gating

AND Gating



OR Gating



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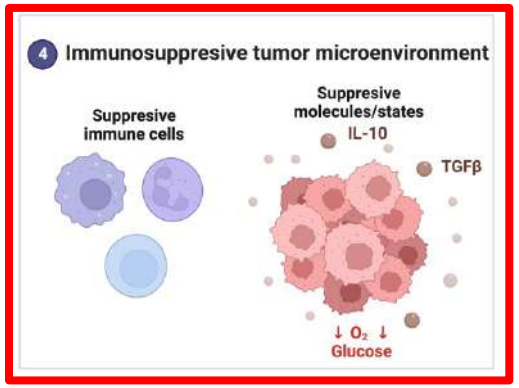
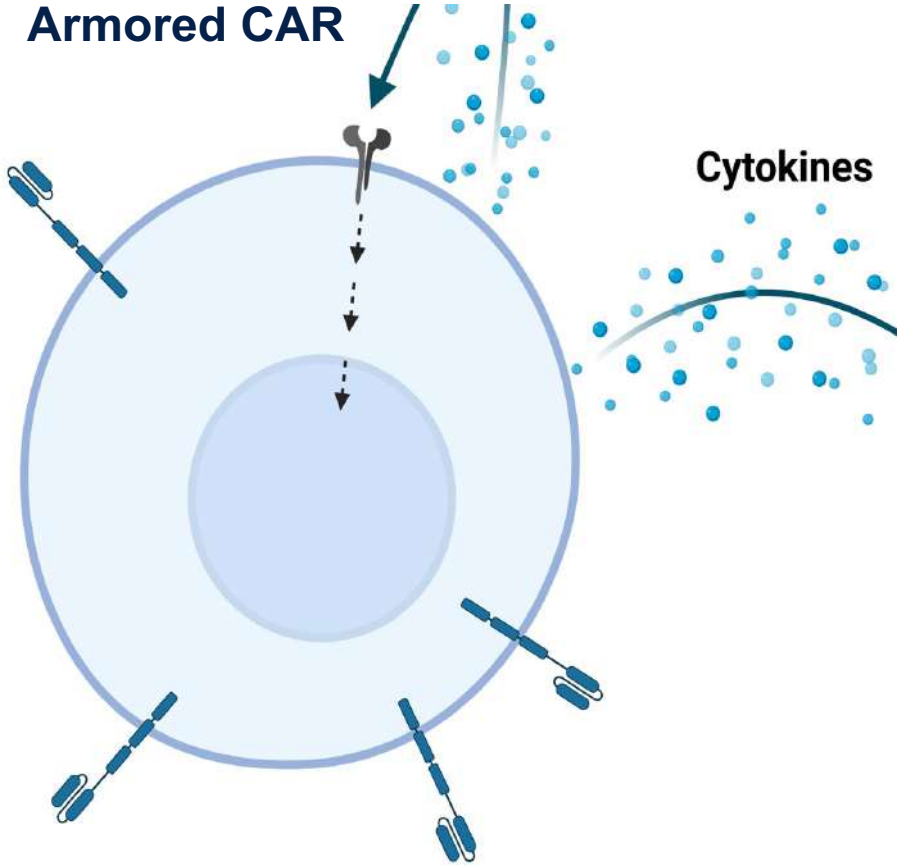
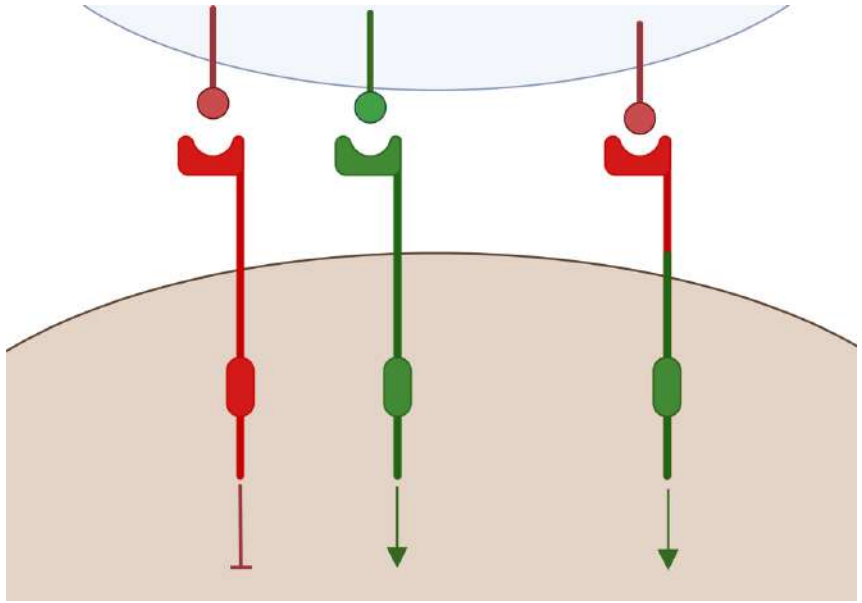
Hyrenius-Wittsten et al. Sci Transl Med, 2021.

Overcoming local immunosuppression







- Switch receptors
- Armored CARs
- Remodel TME
- Gene editing to ignore suppression or withstand metabolic derangements

adapted from slide by Julia Carnevale, MD, UCSF

Solid tumor T cell therapies: directions

- CAR-T cells can induce meaningful radiographic, biochemical, and clinical responses in solid tumors, but are relatively short-lived
- Safety remains an additional barrier to the success of these therapies as non-dispensable cell types (e.g., B cells) are targeted
- Solid tumors pose unique challenges to CAR-T cells, including antigenic heterogeneity and a hostile tumor microenvironment
- Synthetic biology (e.g., cytokines, targeting multiple antigens with logic gating) will improve efficacy and toxicity of CAR-T therapy

Conclusions and future directions

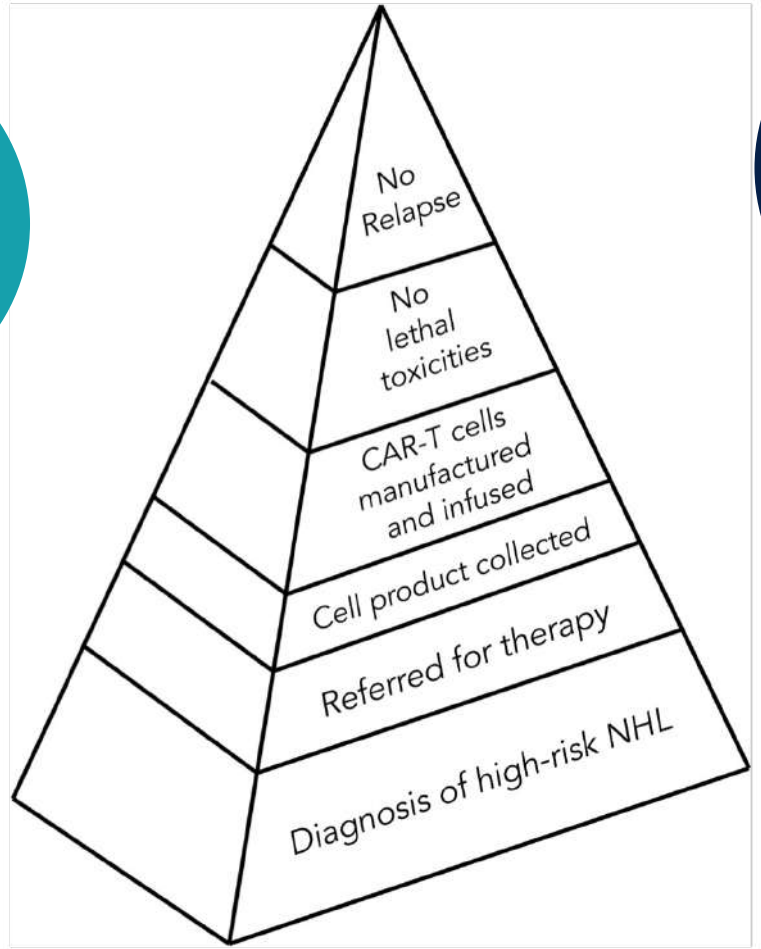
Next steps in T cell therapies

- CAR-T therapies have been transformative for patients with relapsed/refractory pediatric ALL, lymphoma and myeloma; solid tumor successes lie ahead
- Hematology: broader targets, improved manufacturing, allogeneic products
- Solid tumors: Novel strategies to optimize T cell activities in hostile environments and to optimize tumor recognition while minimizing toxicities are being developed and are particularly important as we transition to solid tumor therapies
- We must improve access—even in the US it is estimated that less than 30% of patients who qualify are receiving commercial CAR-T therapies

Improving T cell therapy outcomes

Streamline and scale manufacturing

Better educate patients and referring physicians



Develop new and better therapies

Measure value, advocate for lower cost

Komanduri, *J Clinical Oncology, 2021*

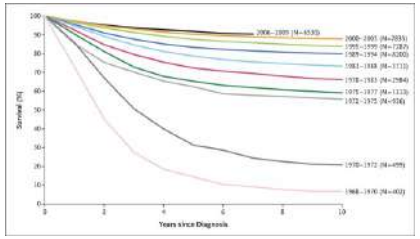
No effective therapies → *Chemotherapy era* → *Stem Cell Transplant era (Combinations of chemotherapy, immunotherapy)* → *Better chemotherapies, advanced stem cell transplants and more effective immunotherapies*

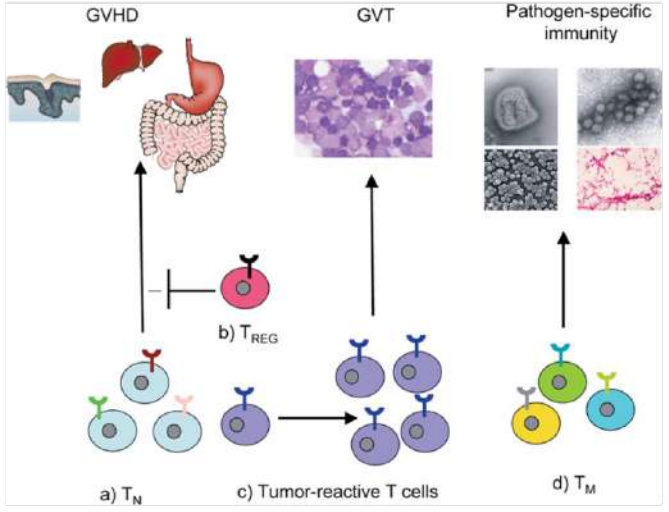
1825

First description of acute leukemia

1960s

Combination chemotherapy + stem cell transplants





1990s

T cells critical for transplant cures—dramatic increase in success

2017

Approval of engineered T cell therapies

Acknowledgements

Slides: **Jay Spiegel (UM/Sylvester)**
Marcelo Pasquini (MCW/CIDR)
Miguel Perales (MSKCC)
Julia Carnevale (UCSF)

Faculty, Staff and Patients at the University of Miami and UCSF

AVA6000

Phase 1a Clinical Study Update – ALS-6000-101

Dr Andrew Saunders, Medical Advisor

23 February 2023

AVA6000: A FAP-Targeted Next Generation Doxorubicin

Exploiting FAP specificity within the tumour by selectively cleaving AVA6000 & activating doxorubicin at tumour sites to…

- ✓Precisely target FAP-positive solid tumours
- ✓Maximise tumour concentrations
- ✓Limit systemic exposure to heathy tissues & organs
- ✓Increase overall efficacy
- ✓Enhance safety & tolerability

Doxorubicin is a very successful chemotherapy due to its efficacy in fighting a wide range of cancers….but it has limitations

- Injury to non-targeted tissues complicates cancer treatment by limiting therapeutic dosages & diminishes the quality of patients' lives during and after treatment
- The heart is a preferential target and cumulative doses above 450mg/m^2 increase risk of heart damage dramatically
- Improving tolerability increases patients' ability to continue treatment and improves cancer outcomes

Hypothesis: Using the pre|CISION linker to mask doxorubicin until it reaches the tumour site where FAP removes the linker and activates doxorubicin within the tumour environment. Systemic concentrations of doxorubicin are lowered substantially while tumour concentrations are increased, sparing healthy tissues and organs.

Phase 1 & 2 Study Designs

AVA6000 in Patients with Advanced, Metastatic Solid Tumours

Phase 1a

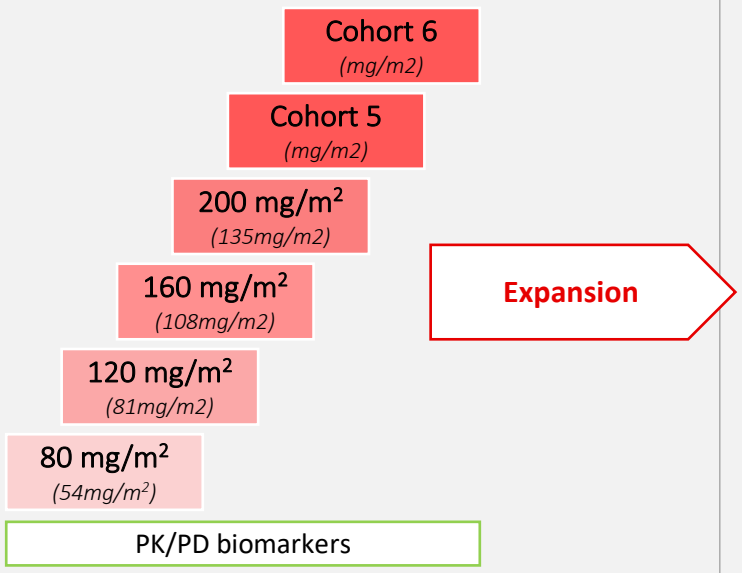
Key Eligibility Criteria
- Locally Advanced, Metastatic Selected Solid Tumours

Endpoints
DLTs, Safety, Tolerability & Cardiac Safety
PK profiles for Cycle 1 & 2
Optional biopsies (AVA6000/Dox levels)
Biomarker assessments
Tumour assessments

Centres
5 UK
2 US

Expand into additional centres for Phase 1b

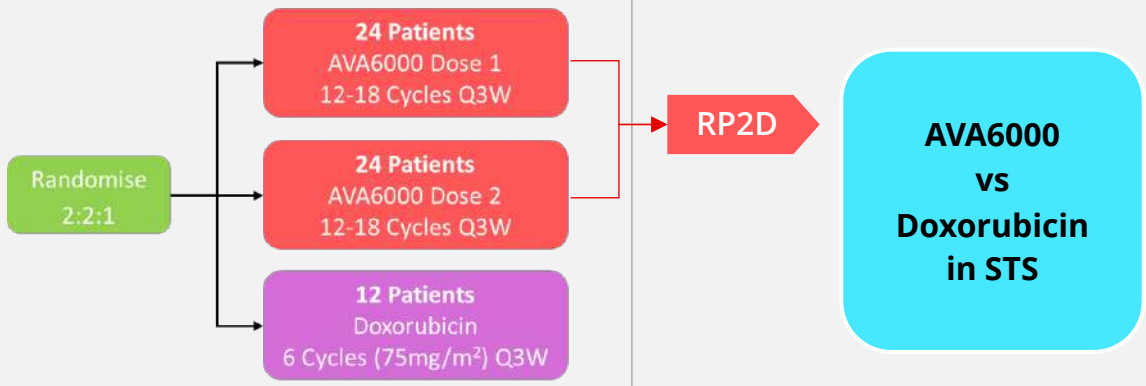
Phase 1a: Dose Escalation



Phase 1a Endpoints
Primary: Safety, MTD, PK, RP2D
Secondary: ORR, DOR
Design: PK-Guided Dose Escalation (3+3)

- ***PK-guided dosing:*** *cumulative systemic exposure of released doxorubicin guides dose escalation decisions*
- *19 patients in four dose cohorts have received an IV dose of AVA6000 every 3 weeks until disease progression, unacceptable toxicity, or other discontinuation criteria were met*

Phase 1b: Dose Expansion



Phase 1b Endpoints
Primary: Safety
Secondary: ORR, DOR, PFS, Pop PK
Design: Open, randomised, parallel group, doxorubicin comparator

- Advanced, metastatic Soft Tissue Sarcoma
- 60 randomised patients
- 2 AVA6000 dose levels for Phase Ib
- Tumour Biopsies in a subset of pts
- Population PK

Phase 2

AVA6000 vs Doxorubicin in STS

Phase 2 Endpoints
Primary: PFS
Secondary: Safety, OS, ORR, DOR
Design: Open, randomised, parallel group, doxorubicin comparator

- Advanced, metastatic Soft Tissue Sarcoma
- 120 randomised patients
- RP2D AVA6000

Overview of Clinical Study ALS-600-101

Phase 1 Dose Escalation of AVA6000 across a range of solid tumours known to be FAP +ve

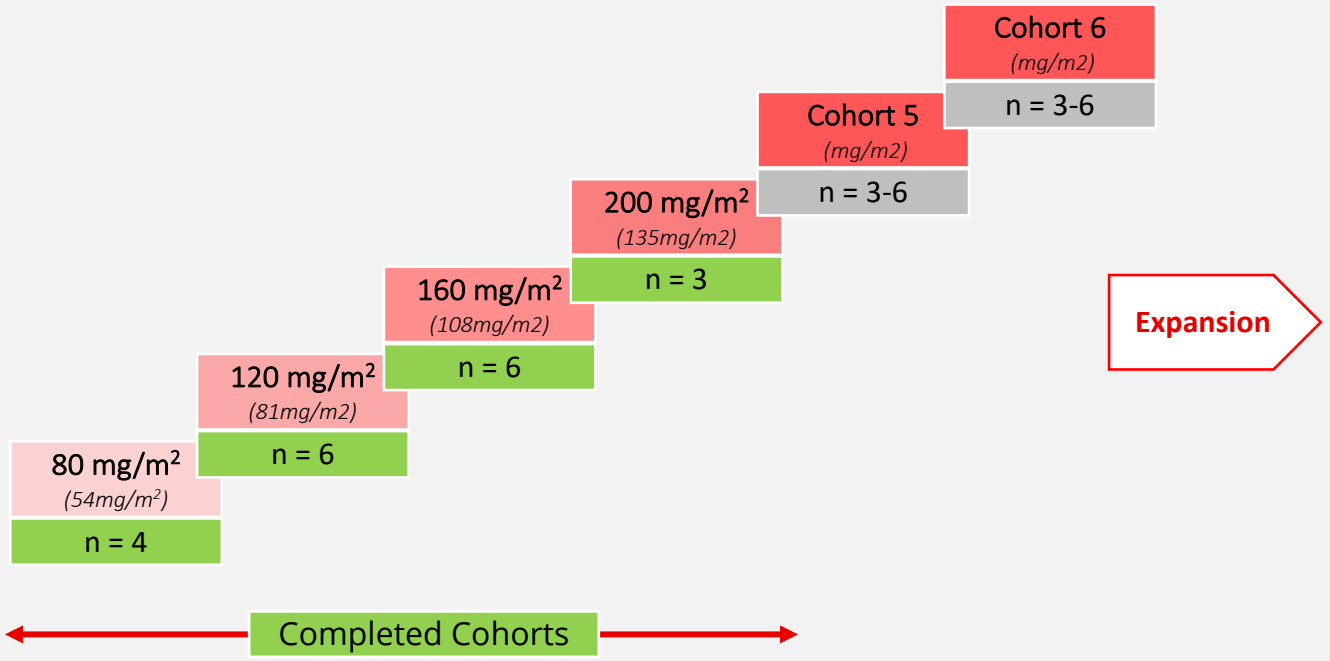
Interim Data Supports AVA6000 Mechanism

- 19 patients dosed across 4 AVA6000 cohorts
  - Median (range) = 2 Cycles (1-8 Cycles)
- AVA600 has a modest and predictable safety profile
- The most frequent adverse events were grade 1-2 nausea, fatigue & decreased appetite
- PK data indicate systemic levels of doxorubicin are considerably lower compared to standard 75mg/m^2 doxorubicin
  - Maximal concentrations of doxorubicin reduced by 80-90%
  - Exposure (AUC) reduced by 60-90%
- PK exposure data suggest that AVA6000 may have the potential to be used for 12-18 cycles depending on dose
- Tumour biopsies across 3 cohorts confirm higher concentrations of doxorubicin compared to systemic levels at same timepoint

Ongoing Phase 1 Dose Escalation Study in metastatic solid tumours (ALS-6000-101): ClinicalTrials.gov Identifier: NCT04969835

AVA6000 Dose Regimen - 3 weekly cycles

(Doxorubicin Equivalent Dose)



PK-guided dosing: *cumulative systemic exposure of released doxorubicin guides dose escalation decisions*

PK/PD biomarkers

Site Initiations Ongoing

Patient Demographics & Baseline Characteristics

Study ALS -6000-101

	80mg/m² (n=4)	120mg/m² (n=6)	160mg/m² (n=6)	200mg/m² (n=3)
Median Age (range), years	58 (56-71)	58 (30-76)	63 (50-73)	63 (53-72)
Female, n (%) Male, n (%)	3 (75) 1 (25)	2 (33) 4 (66)	0 (0) 6 (100)	1 (33) 2 (66)
Race, n (%) White Asian Black Other	 3 (75) 1 (25) 0 0	 5 (83) 0 (0) 0 (0) 1 (17)	 6 (100) 0 0 0	 3 (100) 0 0 0
ECOG PS, n (%) 0 (Capable of normal activity) 1 (Restricted in strenuous activity)	 2 (50) 2 (50)	 1 (17) 5 (83)	 3 (50) 3 (50)	 1 (33) 2 (66)
Tumour Types, n Colorectal Pancreatic Ovarian Soft Tissue Sarcoma Oesophageal	 2 1 1 0 0	 5 1 0 0 0	 1 3 0 1 1	 3 0 0 0 0
Prior lines of anticancer therapy, median (range)	4 (1-7)	3 (2-4)	3 (0-6)	5 (4-8)
Anthracycline Prior Treatment n (%)	2 (50)	0	0	0

AVA6000 Safety Profile (80-200 mg/m^2 Q3W)

Treatment-Related Adverse Events

	Cohort 1 80mg/m^2 (N = 4)	Cohort 2 120mg/m^2 (N = 6)	Cohort 3 160mg/m^2 (N = 6)	Cohort 4 200mg/m^2 (N =3)	Total (N=19)
Dose Limiting Toxicity	0	1	0	0	1 (5%)
Subjects ≥ Grade 3	0	0	1	1	2 (11%)
Neutropenia	0	0	0	1	1 (5%)
Lymphopenia	0	0	0	1	1 (5%)
Mouth ulceration	0	0	1	0	1 (5%)
Subjects Grade 1-2	3	5	6	3	17 (89%)
Neutropenia	0	1	0	1	2 (11%)
Anaemia	1	1	1	0	3 (16%)
Platelet Count Decreased	1	0	0	0	1 (5%)
Heart Failure	0	1	0	0	1 (5%)
Fatigue	0	2	3	1	7 (37%)
Nausea	1	2	2	3	8 (42%)
Decreased appetite	0	2	1	1	4 (21%)
Alopecia	0	1	1	2	4 (21%)

- Overall AVA6000 has a modest and predictable safety profile
- 2 patients had Grade 3 related AEs
  - Neutropenia & lymphopenia (1 pt); mouth ulceration (1 pt)
- Most frequent adverse events were nausea, fatigue, decreased appetite & alopecia
- One dose-limiting toxicity (120mg/m^2)
  - Grade 1 heart failure during Cycle 1
- Excluding DLT patient, no patient had AVA6000 related cardiac toxicity
- Classical acute doxorubicin related toxicities were infrequent across the dose range
  - Myelosuppression
  - Alopecia

Safety Profile: AVA6000 vs Doxorubicin

Treatment-Emergent Adverse Event (TEAE)	[1] AVA6000 (80-200mg/m² Q3W) N = 19 Median No. Cycles = 2 (Range 1-8)		[2] Doxorubicin (75mg/m² Q3W) N = 249 Median No. Cycles = 7 (Range 1-8)	
	Any Grade n (%)	Grade ≥3 n (%)	Any Grade n (%)	Grade ≥3 n (%)
Nausea	10 (52.6)	0	166 (66.7)	6 (2.4)
Fatigue	11 (57.9)	0	147 (59)	12(4.8)
Lethargy	4 (21.1)	0	NR	NR
Decreased appetite	4 (21.1)	0	92(36.9)	1 (0.4)
Vomiting	6 (31.6)	1 (5.3)	69 (27.7)	2 (0.8)
Constipation	5 (26.3)	0	87 (34.9)	2 (2.8)
Diarrhoea	4 (21.1)	0	75 (31.1)	3 (1.2)
Abdominal Pain	3 (15.8)	0	53 (21.3)	3 (1.2)
Weight Decrease	2 (10.5)	0	NR	NR
Mucositis	3 (15.8)	1 (5.3)	NR	NR
Stomatitis	1 (5.3)	0	NR	NR
ALT increase	6 (31.6)	0	19 (7.6)	4 (1.6)
AST Increase	4 (21.1)	0	NR	NR
Bilirubin	3 (15.8)	1 (5.3)	NR	NR
Anaemia	6 (31.6)	0	113 (45.4)	31 (12.4)
Neutropenia	2 (10.5)	1 (5.3)	144 (57)	122 (49)
Thrombocytopenia	1 (5.3)	0	62 (24.9)	21 (8.4)
Lymphopenia	2 (10.5)	1 (5.3)	NR	NR
Alopecia	5 (26.3)	0	124 (49.8)	1 (0.4)
Heart Failure	1 (5.3)	0	NR	NR
Dyspnoea	3 (15.8)	0	36 (14.5)	2 (0.8)
Pyrexia	2 (10.5)	0	46 (18.5)	0
Cough	1 (5.3)	0	61 (24.5)	1 (0.4)
Rash	3 (15.8)	0	23 (9.2)	0
Troponin T increase	1 (5.3)	0	NR	NR
Upper respiratory tract Infection	2 (10.5)	0	25 (10)	1 (0.4)
Urinary Tract Infection	1 (5.3)	1 (5.3)	22 (8.8)	1 (0.4)
Arthralgia	1 (5.3)	0	NR	NR

NR = Not Reported

- No Dose related increase in frequency or severity of AVA6000 TEAEs with increasing dose (80, 120, 160 & 200mg/m2)
- AVA6000 Tumour Type heavily pre-treated metastatic CRC (11), Pancreatic (5), STS (1), Ovarian (1) & Oesophageal (1)
- Doxorubicin Tumour Type: first line metastatic soft tissue sarcoma

Common Terminology Criteria for Adverse Events was used to categorize TEAEs. Grades; mild (grade 1), moderate (grade 2), severe or medically significant but not immediately life-threatening (grade 3), life-threatening (grade 4), and death related to TEAE (grade 5).

TEAE: Treatment-Emergent Adverse Events are undesirable events not present prior to medical treatment, or an already present event that worsens either in intensity or frequency following the treatment. TEAEs may therefore be treatment-related or unrelated as assessed by the treating physician.

References

[1] Ongoing Phase 1 Dose Escalation Study in metastatic solid tumours (ALS-6000-101: ClinicalTrials.gov Identifier: NCT04969835

[2] Tap WD, Wagner AJ, Schöffski P, et al. Effect of Doxorubicin Plus Olaratumab vs Doxorubicin Plus Placebo on Survival in Patients With Advanced Soft Tissue Sarcomas: The ANNOUNCE Randomized Clinical Trial. JAMA. 2020;323(13):1266–1276. doi:10.1001/jama.2020.1707

Tumour Biopsy Data

Plasma vs Biopsy Doxorubicin Concentrations

Cohort	AVA6000 (Dox Dose) mg/m²	Patient	DOX Plasma @24h ng/ml	DOX Biopsy @24h		DOX Ratio** Biopsy:Plasma	Biopsy Source
				ng/g	nM		
Cohort 1	80 (54)	101-006 (1st)	4.9	135	248nM	28:1	Liver
		101-006 (2nd)	4.9	43	79nM	9:1	Liver
Cohort 3	160 (108)	103-021*	4.4	376	690nM	85:1	Liver
		103-022*	2.4	270	496nM	113:1	Liver
		102-023*	7.5	875	1607nM	117:1	Liver
Cohort 4	200 (135)	103-017	15.9	553	1015nM	35:1	Liver
		102-018	10.5	1317	2419nM	125:1	Lung

*Preliminary Data
** ng/ml ~ ng/g

Doxorubicin Target Activity	DOX IC50
DNA adduct formation [1]	25nM
Free radical formation/cardiomyocyte apoptosis[1]	100nM
Topoisomerase Inhibition[1]	400nM
In vitro cytotoxicity[2]	30nM-3μM

[1] doi:10.1007/s11095-018-2456-8.
[2] internal data

AVA6000: Phase Ib Study

Clinical Development in Soft-Tissue Sarcoma (Phase 1 to 2)

Development Rationale in Soft Tissue Sarcoma (STS)

- Advanced, Metastatic STS tumours
- Doxorubicin is the only therapy indicated for first-line monotherapy in advanced STS
- No current or near future competition for doxorubicin in 1st line STS
- Conventional doxorubicin has marginal efficacy (18% ORR; 6mth PFS) & Rx limitation due to cumulative dose limit (450mg/m^2 – 6 cycles maximum)
- AVA6000 has potential to safely increase Rx duration beyond 6 cycles (18 weeks) by x2-3 times (12-18 cycles – 36-54 weeks) with increased efficacy

Phase 1a

- *Select 2 AVA6000 dose levels for Phase Ib study*
- *Use PK/PD modelling to identify safe & effective dose from preclinical and emerging clinical* data

Phase 1b

Expansion Design

- Open-label, randomised design
- Metastatic Soft Tissue Sarcoma
- FAP positive tumours
- 2 AVA6000 dose levels selected
- 3 Rx arms (2 x AVA6000 vs Dox)
- N = 60
- Up to 12 -18 cycles of AVA6000
- 20 US & European Investigator Sites

Outcome Measures

- PFS
- RECIST
- AE/Cardiac safety

Randomise 2:2:1

- Mandate biopsies in patient subset
- Population pK

24 Patients
AVA6000 Dose 1
12-18 Cycles Q3W

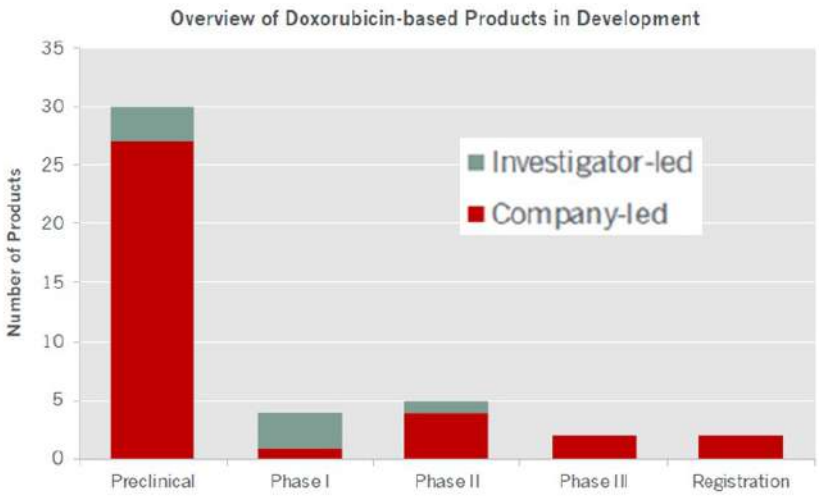
24 Patients
AVA6000 Dose 2
12-18 Cycles Q3W

12 Patients
Doxorubicin
6 Cycles (75mg/m^2) Q3W

Select AVA6000 RP2D Dose for Phase 2

Soft Tissue Sarcoma Drugs in Development

- Modest number of products in clinical development for STS with majority of R&D activity in early stage
- KOLs indicate no serious competition in Soft Tissue Sarcoma indication for 1st Line Therapy

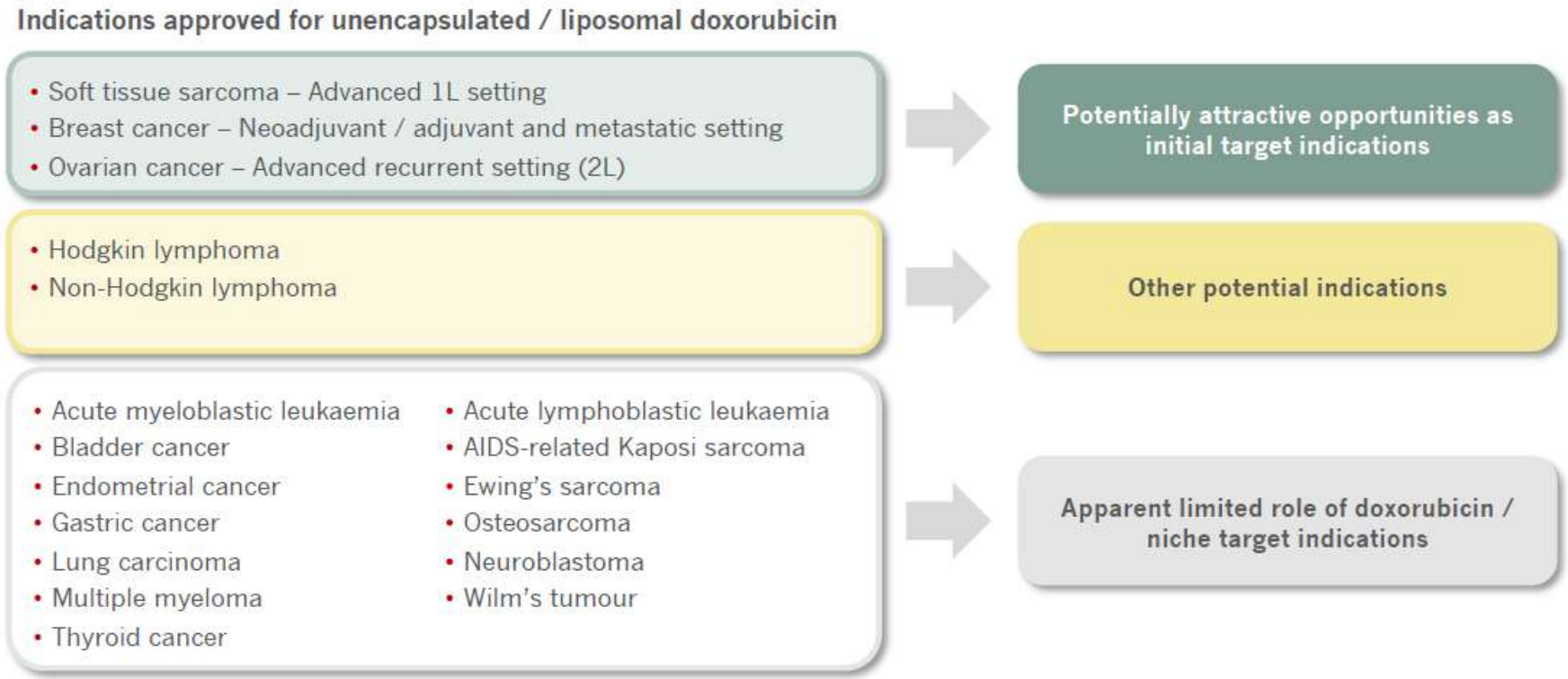


Product	Company	Mechanism	Status/Indication	Comment
Aldoxorubicin	ImmunityBio	Doxorubicin coupled to acid sensitive linker	Ph III Soft Tissue Sarcoma	Failed Phase III study
Fibromun	Philogen	Fully human immunocytokine	Ph. III Soft Tissue Sarcoma	Combination with DOX
Xpovio (selinexor)	Karyopharm Therapeutics	Selective inhibitor of nuclear export protein (XPO1)	Ph. II/III Soft Tissue Sarcoma	Approved in MM/DLBCL & being evaluated for STS
Camsirubicin	Gem Pharma / Monopar Therapeutics	Doxorubicin analog selective inhibition of topoisomerase IIα	Phase II Soft Tissue Sarcoma	Completed Phase II in 2016
Imx-110	Immix Biopharma	Nanoparticle small dose doxorubicin-Curcumin (pan-kinase inhibitor)	Phase I/II	Positive interim data reported in Dec 2018

Market Potential for AVA6000

There is huge potential for an improved next generation doxorubicin product considering:

- The market value being generated by current doxorubicin therapies and the expectation that doxorubicin-based therapies will continue to be a key approach for oncology treatment
- There is considerable scope for improvement on the profile of conventional and liposomal doxorubicin, around both safety / tolerability and efficacy
- There is modest future competitor activity exploring new doxorubicin approaches and few products identified to be in direct competition to AVA6000's approach



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AVA6000 Conclusions

Dose Escalation

- AVA6000 has a modest and predictable safety profile across the dose range (80-200mg/m2)
- PK data for released doxorubicin highlights a positive profile
  - Doxorubicin Exposure (AUC) & Maximal Concentrations (Cmax) substantially reduced across doses
  - Doxorubicin concentrations are higher in tumour biopsies compared to plasma at 24 hrs timepoint
  - Emerging PK profiles offer the opportunity to increase dosing duration & intensity of doxorubicin targeted to the tumour

Confidence in Development Strategy for AVA6000 in 1st Line Soft Tissue Sarcoma (STS)

- Advanced, Metastatic STS tumours are known to be highly FAP positive
- Doxorubicin monotherapy is the only therapy indicated for first-line advanced, metastatic STS
- Large unmet clinical need in STS to improve patients outcomes in difficult to treat tumours
- AVA6000 preferentially targets the tumour environment using FAP specificity to activate doxorubicin
- AVA6000 can safely deliver larger doses of doxorubicin to tumour whilst sparing healthy tissues & organs

Investigators

United Kingdom

Professor Chris Twelves, Chief Investigator
Leeds Teaching Hospitals NHS Trust, Leeds

Professor Udai Banerji
The Royal Marsden NHS Foundation Trust, London

Professor Jeff Evans
The Beatson West of Scotland Cancer Centre, Glasgow

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United States

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Memorial Sloan Kettering Cancer Centre, New York

Dr Lee D. Cranmer
Fred Hutchinson Cancer Centre, Seattle

Avacta®

Current & Future Treatment Strategies for Soft Tissue Sarcoma

William Tap, MD

Chief, Sarcoma Medical Oncology Service

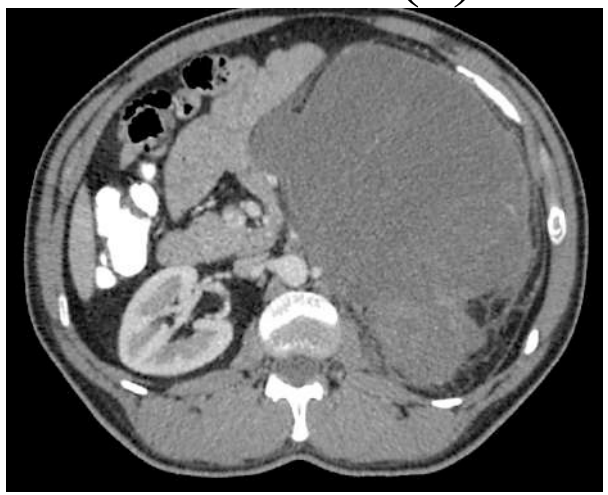
Co-Director Stuart Center for AYA Medicine

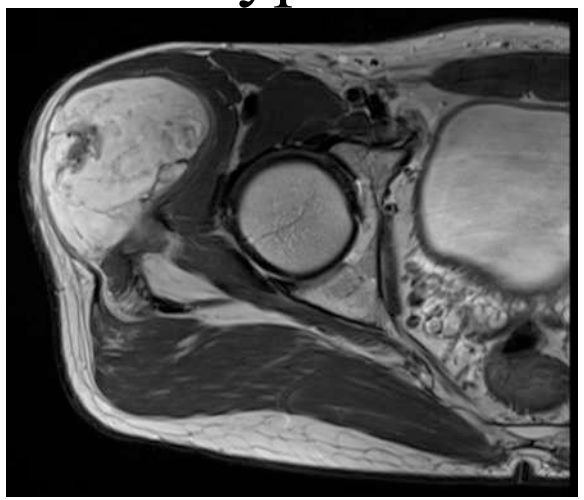
Memorial Sloan Kettering Cancer Center

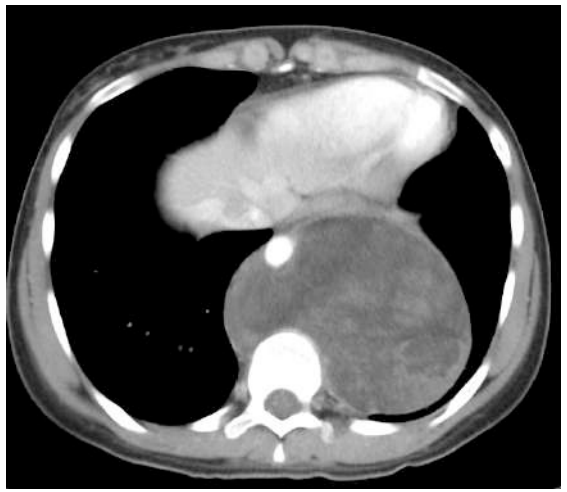
Sarcoma

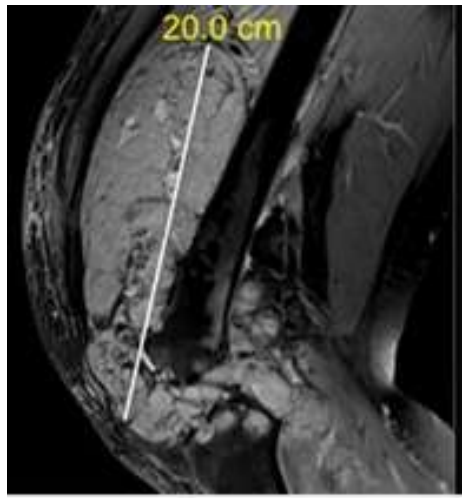
Heterogeneous group of malignancies

- Arise from the bone and soft tissue of individuals of all ages
- 16,000 new cases diagnosed in the United States per year
  - (similar to testicular cancer, esophageal cancer – well defined treatment strategies)
- 100 (?) different subtypes bone and soft tissue sarcoma









How to develop research programs (basic science + clinical) to meet the needs of our patient population?

Memorial Sloan Kettering Cancer Center

Simplest Conceptual Level

Table 3 Biological characteristics of sarcomas by type of associated genetic alterations

Characteristic	Sarcomas with specific genetic alterations	Sarcomas with nonspecific genetic alterations
Karyotypes	Often simple	Usually complex
Translocations	Reciprocal & specific	Nonreciprocal & nonspecific
Average age at diagnosis[a]	27	57
Prevalence of p53 pathway alterations	Relatively low	High
Prognostic impact of p53 pathway alterations	Strong	Weak to moderate
Incidence in p53 mutant or knockout mouse models	Rare, if ever	Common
Incidence in bilateral retinoblastoma and Li-Fraumeni syndrome[b]	Rare	Common
Incidence among radiation-induced sarcomas	Rare	Common

Vol. 9, 1941–1956, June 2003 Clinical Cancer Research

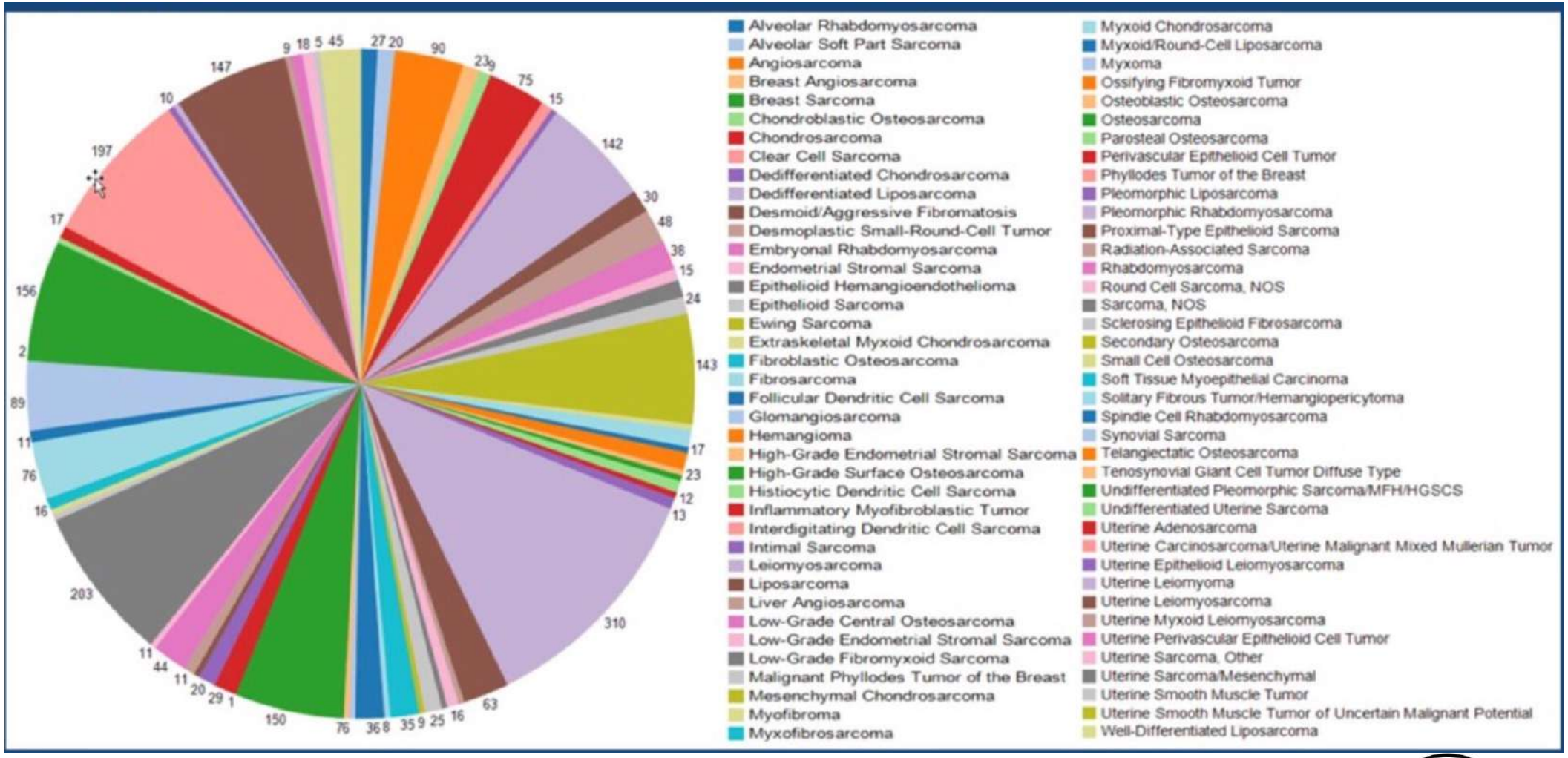
Ewing's Sarcoma
Rhabdomyosarcoma
Synovial Sarcoma
DFSP
Myxoid Round Cell Liposarcoma
ASPS
GIST

Osteosarcoma
Liposarcoma
Myxofibrosarcoma
Leiomyosarcoma
Angiosarcoma
Undifferentiated Pleomorphic

Memorial Sloan Kettering Cancer Center

2020 WHO Classification of Soft Tissue Sarcoma

Twitter



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Sarcomas with fusion genes					
Fusion genes involving TET genes					
	Gene (N-C)	Chromosomal location	Clinical Significance	Proposed function of gene product	Detection Method
Ewings/PNET	*EWSR1- FLI1*	t(11;22)(q24;q12)	Diagnostic	Overexpression of	IHC (FLI1)
	FUS-FEV				
	EWSR1-ZSG				
Desmoplastic Small Round Cell Tumor	*EWSR1- WT1*	t(11;22)(p13;q12)	Diagnosis, therapeutic (PDGF inhibitors)	up-regulates oncogenic factors e.g. *PDGF, IL2Rβ, BAIALP3, TALLA1,MLF1*	IHC (WT1) FISH (EWSR1 break-apart probe) Karyotype
Clear cell sarcoma(CCS)					FISH (EWSR1 break apart probe), PCR
Angiomatoid Fibrous Histiocytoma	*FUS-ATF1*	t(12;16)(q13;p11)	Diagnosis		FISH
	EWSR1-ATF1	t(12;22)(q13;q12)			
	EWSR1-CREB1	t(2;22)(q33;q12)			
Extraskeletal myxoid chondrosarcoma	*EWSR1-NR4A3*	t(9;22)(q22;q12)	Diagnosis		FISH, RT-PCR (NR3A3-EWS fusion)
	TAF2N-NR4A3				
	TCF12-NR4A3				
Low Sarcoma / HSCT	*CREB3L2*	t(11;16)(p11;p11			break-apart probe), RT-PCR
	FUS-CREB3L1				
Fusion genes involving RTK genes					
Congenital mesoblastic nephroma	*ETV6-NTRK3*	t(12;15)(p13;q25)	Diagnosis		FISH, RT-PCR
Congenital fibrosarcoma	*ETV6-NTRK3*	t(12;15)(p13;q25)	Diagnosis		FISH, RT-PCR
Inflammatory myofibroblastic tumor	*TPM3-ALK*	t(1;2)(q			IHC (ALK protein) FISH, RT-PCR
	TPM4-ALK	t(2;19)(			
	CLTC-ALK	t(2;17)(			
	RANBP2-ALK	t(2;2)(p23;q13)			
Fusion genes involving chromatin remodeling genes					
Synovial sarcoma	*SS18-SSX1*	t(X;18)(p11;q11)	Diagnosis,		FISH (SYT
	TLE1 gene				

Endometrial stromal sarcoma	*JAZF1-SUZ12*	t(7;17)(p15;q21)	Diagnosis		RT-PCR
	JAZF1-PHF1	t(			
	EPC1-PHF1	t(			
Fusion genes involving growth factors genes					
Dermatofibrosarcoma protuberans				Up-regulate the expression of *PDGFR*	FISH, RT-PCR
Giant Cell Fibroblastoma	*COL1A1-PDGFB*				FISH, RT-PCR
Other type of fusion genes					
Alveolar Rhabdomyosarcoma	*PAX3*				FISH (*FOXO1A* Break-apart probe), Karyotype, RT-PCR
	FOXO				
	PAX7				
	FOXO				
	PAX3-MLL T7				
Alveolar soft part sarcoma					IHC (TFE3), RT-PCR
Aneurysmal bone cyst	*CDH11-USP6*	t(16;17)	Diagnosis		FISH, RT-PCR
	THRAP3-USP6	t(1;17)			
	CNBP-USP6	t(3;17)			
	OMD-USP6	t(9;17)			
		t(17;17)			
Tenosynovial giant ce tumor	*COL6A3*				
Hemangiopericytoma					
Pericytoma	*ACTB-GLI1*				
Sarcomas with specific oncogenic mutation					
Gastrointestinal Stromal Tumors	KIT o PDGF			Activation Tyrosine ptor	IHC (C-Kit), PCR
Rhabdoid tumor	SMA	22	Diagnosis	LOH	IHC (loss of INI1)
Atypical lipomatous tumor/ Well-differentiated liposarcoma	giant and		Cyclin dependent kinase	FISH (MDM2, *CDK4 amplification*)	
natosis	APC inactivation	Trisomies 8 20 Deletion of			IHC(β catenin)

CDK4i/PARPi/LSDi/bi-specifics
Splice Switch/GAMPER Oligos
CHK1i
cMET/HGF inhibitor
TKIs/Trabectedin
Trabectidin/PI3Ki/NYESO/MAGE(ACT)/ Eribulin
ALK inhibitors
PDGFRi/NYESO/MAGE/BRD9 degraders
Hormonal blockade
PDGFRB inhibitors
RANKL inhibitors
FGFR4 inhibitors?
VEGF/METi/PD-1i
CSF inhibitors
mTOR/TEAD
TKIs/MEK inhibitors
EZH2i
MDM2/CDK4 inhibitors/Eribulin/PD1i
TKIs/GSI/Notchi

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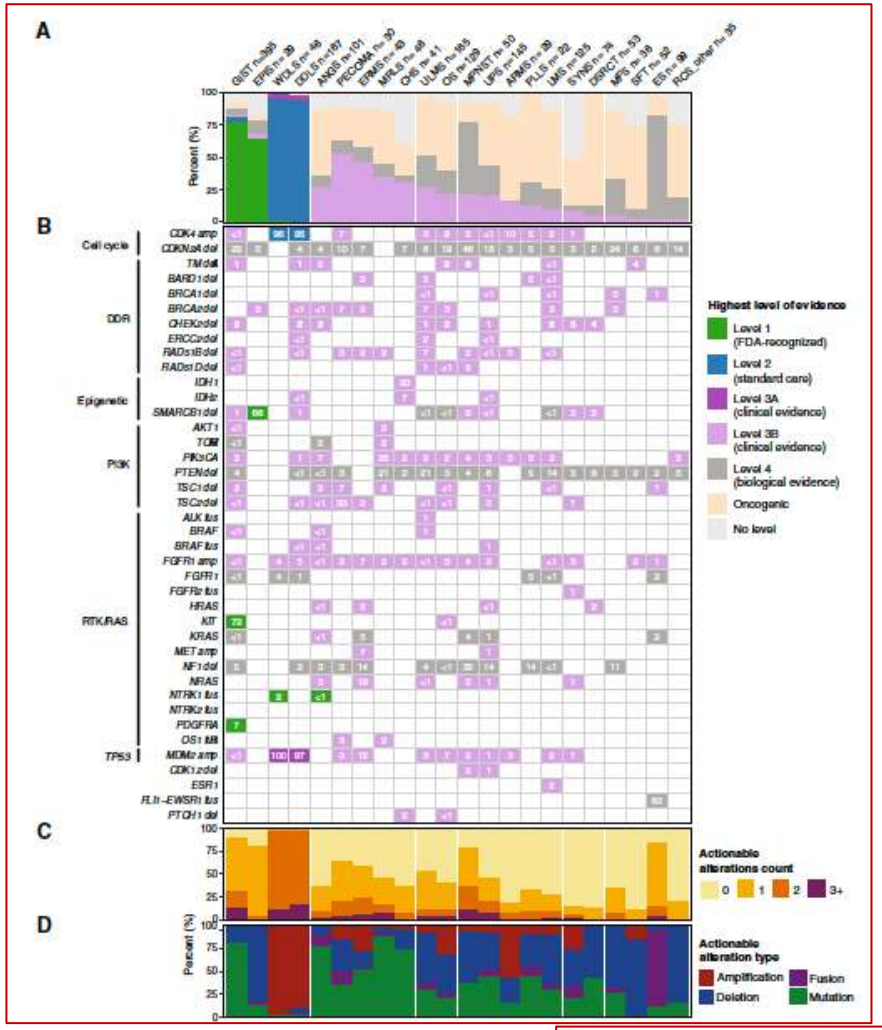
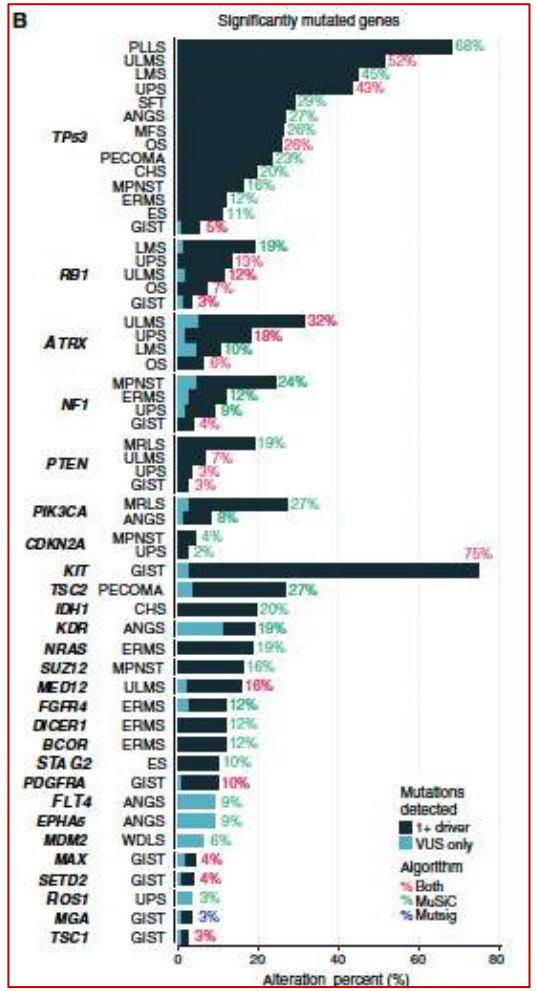
Int J Clin Exp Pathol 2010;3(4):416-429

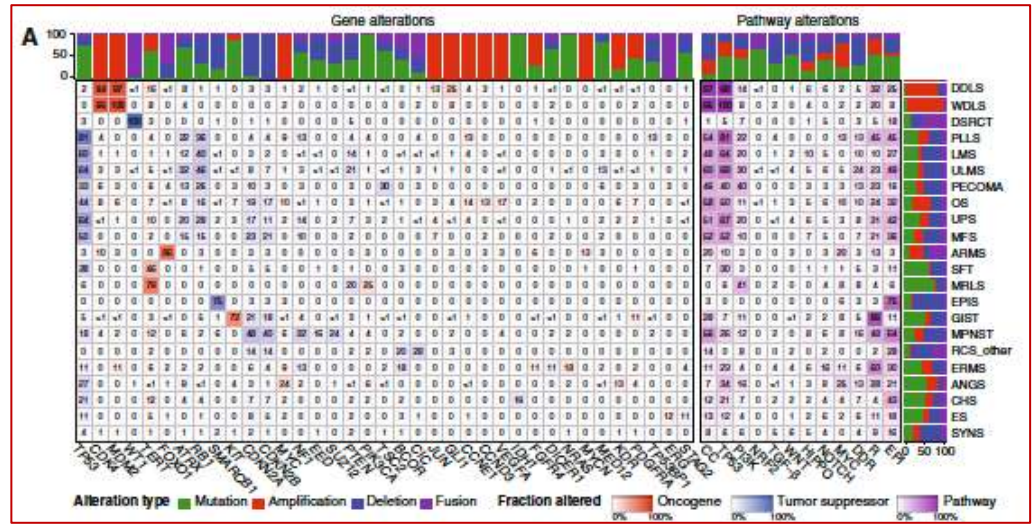
Clinical sequencing of soft tissue and bone sarcomas delineates diverse genomic landscapes and potential therapeutic targets

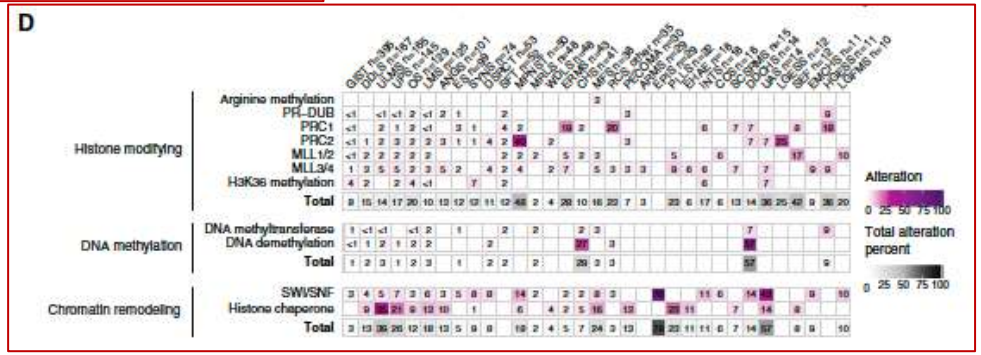
NATURE COMMUNICATIONS | (2022)13:3405

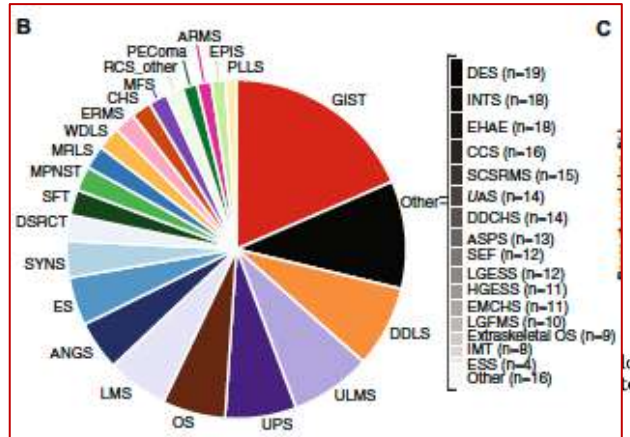
Benjamin A. Nacev[1,2,3,15], Francisco Sanchez-Vega[4,14,15], Shaleigh A. Smith[4,5], Cristina R. Antonescu[6], Evan Rosenbaum[1,2], Hongyu Shi[7], Cerise Tang[6,8], Nicholas D. Socci[5,9], Satshil Rana[6], Rodrigo Gularte-Mérida[4], Ahmet Zehir[6], Mrinal M. Gounder[1,2], Timothy G. Bowler[1], Anisha Luthra[5,10], Bhumika Jadeja[4], Azusa Okada[4], Jonathan A. Strong[4], Jake Stoller[4], Jason E. Chan[1], Ping Chi[1,2,10], Sandra P. D'Angelo[1,2], Mark A. Dickson[1,2], Ciara M. Kelly[1,2], Mary Louise Keohan[1,2], Sujana Movva[1,2], Katherine Thornton[1,2], Paul A. Meyers[11], Leonard H. Wexler[11], Emily K. Slotkin[11], Julia L. Glade Bender[11], Neerav N. Shukla[11], Martee L. Hensley[1,2], John H. Healey[4], Michael P. La Quaglia[4,11,12], Kaled M. Alektiar[13], Aimee M. Crago[4,12], Sam S. Yoon[4,12], Brian R. Untch[4,12], Sarah Chiang[6], Narasimhan P. Agaram[6], Meera R. Hameed[6], Michael F. Berger[5,6,10], David B. Solit[1,2,5], Nikolaus Schultz[7,10], Marc Ladanyi[6,10], Samuel Singer[4,12]✉ & William D. Tap[1,2]✉











Changing Tide…

- Genetic diversity attractive drug development
- Open field application new technology and scientific advancement
- Influx of new agents and trials
- Subtype and disease specific - Potential registration tracts
- Sarcoma as a bridge to other malignancies/markets
- Discovery into mesenchymal biology and the tumor microenvironment

Subclassifications of Sarcoma Based on Treatment

Sarcomas with…

- Genomic alterations with a definitive target and therapy and not responsive to chemo (minority)
  - GIST (KIT/PDGFRA), PEComa (TSC1/2), Chondrosarcoma (IDH1)
- Genomic alterations with target but chemo remains front line
  - Epithelioid sarcoma (SMACB1), Dedifferentiated Liposarcoma (CDK4/MDM2), Synovial Sarcoma (MAGE/NYESO, BRD9d)
- Complex genome, with no or untargetable driver (TP53, RB, NF1), chemo front line
  - Leiomyosarcoma, Undifferentiated Pleomorphic Sarcoma, MPNST

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What is First Line?

Pharmacokinetics and metabolism of adriamycin in man

Clinical Pharmacology and Therapeutics

A pharmacokinetic evaluation of adriamycin and its metabolites was undertaken in cancer patients treated according to an intermittent single high-dosage schedule. The long plasma half-life of adriamycin and metabolites, 26.7 hours, was similar to that of daunorubicin and its metabolites. Long plasma half-life of adriamycin, 16.7 hours, was shorter than that of its metabolites, 31.7 hours. In addition to differences in the metabolism of the two drugs, the cumulative 5 day urinary excretion of adriamycin and its metabolites was only 5.7% of the administered dose in contrast to 23% for daunorubicin and its metabolites. This study establishes that after a single intravenous dose plasma levels of adriamycin are maintained for long periods; it lays a rational foundation for the empirically effective intermittent single high-dosage schedule. That adriamycin undergoes extensive metabolic degradation in patients is described for the first time.

Received for publication Dec. 4, 1972.
Accepted for publication April 3, 1973.

Robert S. Benjamin, M.D., Charles E. Riggs, Jr., and Nicholas R. Bachur, M.D., Ph.D. *Baltimore, Md.*
Biochemistry Section, Baltimore Cancer Research Center, National Cancer Institute

Memorial Sloan Kettering Cancer Center

Adria vs Adria/Ifos

2003-2010 – published 2014

Doxorubicin alone versus intensified doxorubicin plus ifosfamide for first-line treatment of advanced or metastatic soft-tissue sarcoma: a randomised controlled phase 3 trial

*Ian Judson, Jaap Verweij, Hans Gelderblom, Jörg T Hartmann, Patrick Schöffski, Jean-Yves Blay, J Martijn Kerst, Josef Sufliarsky, Jeremy Whelan, Peter Hohenberger, Anders Krarup-Hansen, Thierry Alcindor, Sandrine Marreaud, Saskia Litière, Catherine Hermans, Cyril Fisher, Pancras CW Hogendoorn, A Paolo dei Tos, Winette T A van der Graaf, for the European Organisation and Treatment of Cancer Soft Tissue and Bone Sarcoma Group** *Lancet Oncol 2014; 15: 415–23*

- 455 patients 38 centers; Age </= 60yo; 7 years to enroll
- Adria 75mg/m2 (6 cycles – 4.2 months); Ifos 10grams/m2
- OS primary endpoint
- Median f/u 56 months

- Median OS 12.8 vs. 14.3 HR 0.83 p=0.76
- Median PFS: Adria 4.6 mos; AI 7.4 months
  - HR 0.72; P0.002
- RR 14% (A) v 26% (AI)
- Significant more toxicity with AI

	Doxorubicin group (n=215)	Doxorubicin and ifosfamide group (n=210)
Surgery	44 (20%)	43 (20%)
Chemotherapy	136 (63%)	134 (64%)
Doxorubicin	12 (6%)	27 (13%)
Epirubicin	3 (1%)	1 (<1%)
Ifosfamide	99 (46%)	32 (15%)
Trofosfamide	6 (3%)	13 (6%)
Trabectedin	33 (15%)	37 (18%)
Docetaxel	25 (12%)	34 (16%)
Paclitaxel	5 (2%)	6 (3%)
Gemcitabine	32 (15%)	40 (19%)
Dacarbazine	7 (3%)	18 (9%)
Temozolomide	0 (0%)	1 (<1%)
Pazopanib	14 (7%)	14 (7%)
Eribulin	7 (3%)	11 (5%)
Etoposide	8 (4%)	11 (5%)

Data are n (%).

Table 6: **Post-protocol treatment**

Figure 2: **Kaplan-Meier curves for overall survival (A) and progression-free survival (B)**
HR=hazard ratio.

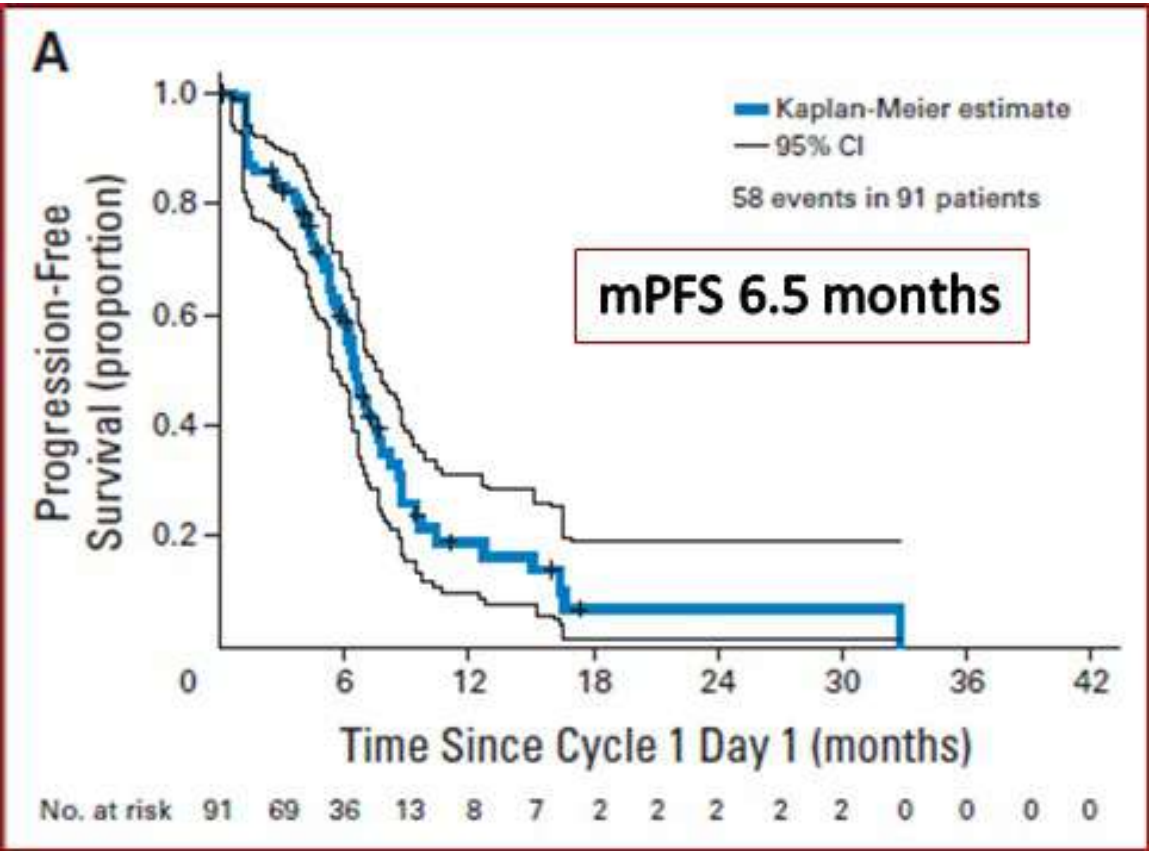
Phase II Study of the Safety and Antitumor Activity of the Hypoxia-Activated Prodrug TH-302 in Combination With Doxorubicin in Patients With Advanced Soft Tissue Sarcoma *J Clin Oncol 32:3299-3306. © 2014*

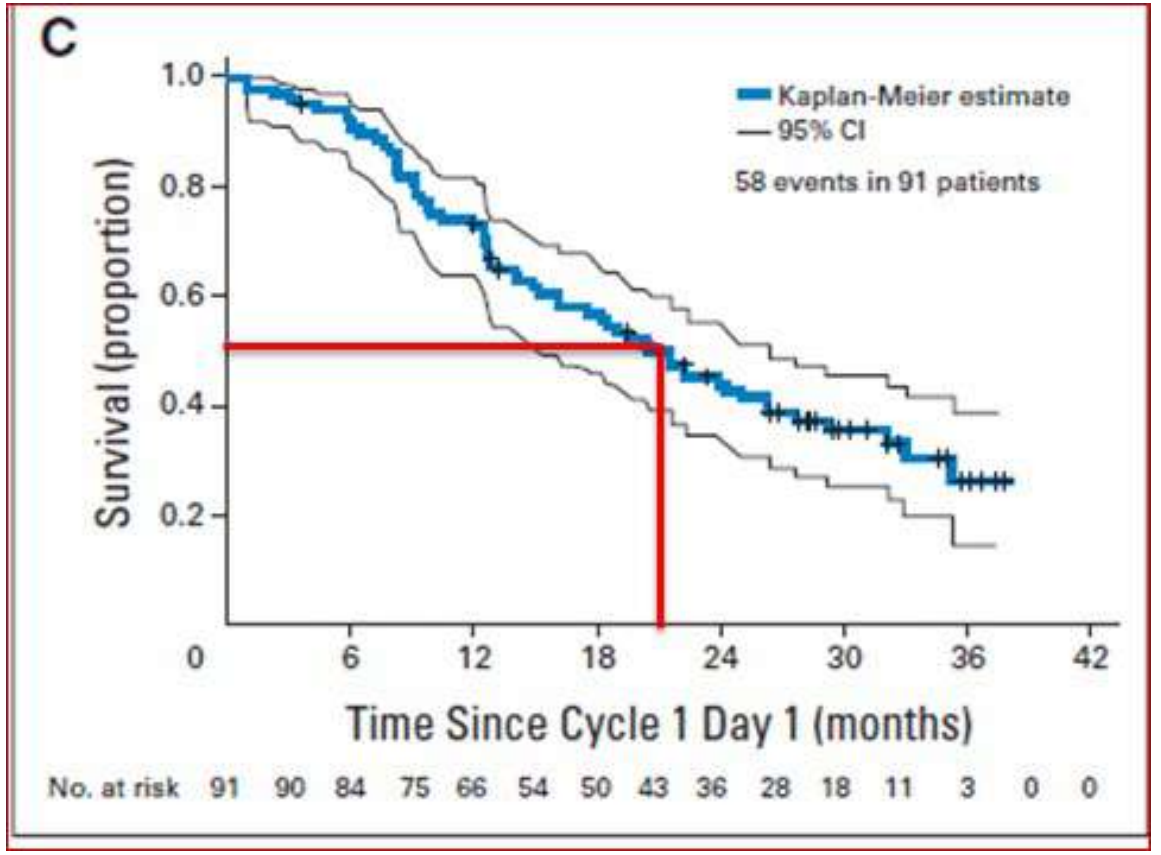
Sant P. Chawla, Lee D. Cranmer, Brian A. Van Tine, Damon R. Reed, Scott H. Okuno, James E. Butrynski, Douglas R. Adkins, Andrew E. Hendifar, Stew Kroll, and Kristen N. Ganjoo

Front line setting
Adria x 6, 18 weeks (4.2 Months)
TH302 (evofosfamide) single agent

Median Overall Survival
Adria/Evo 21.5 m

2-year Overall Survival
Adria/Evo ≈43%





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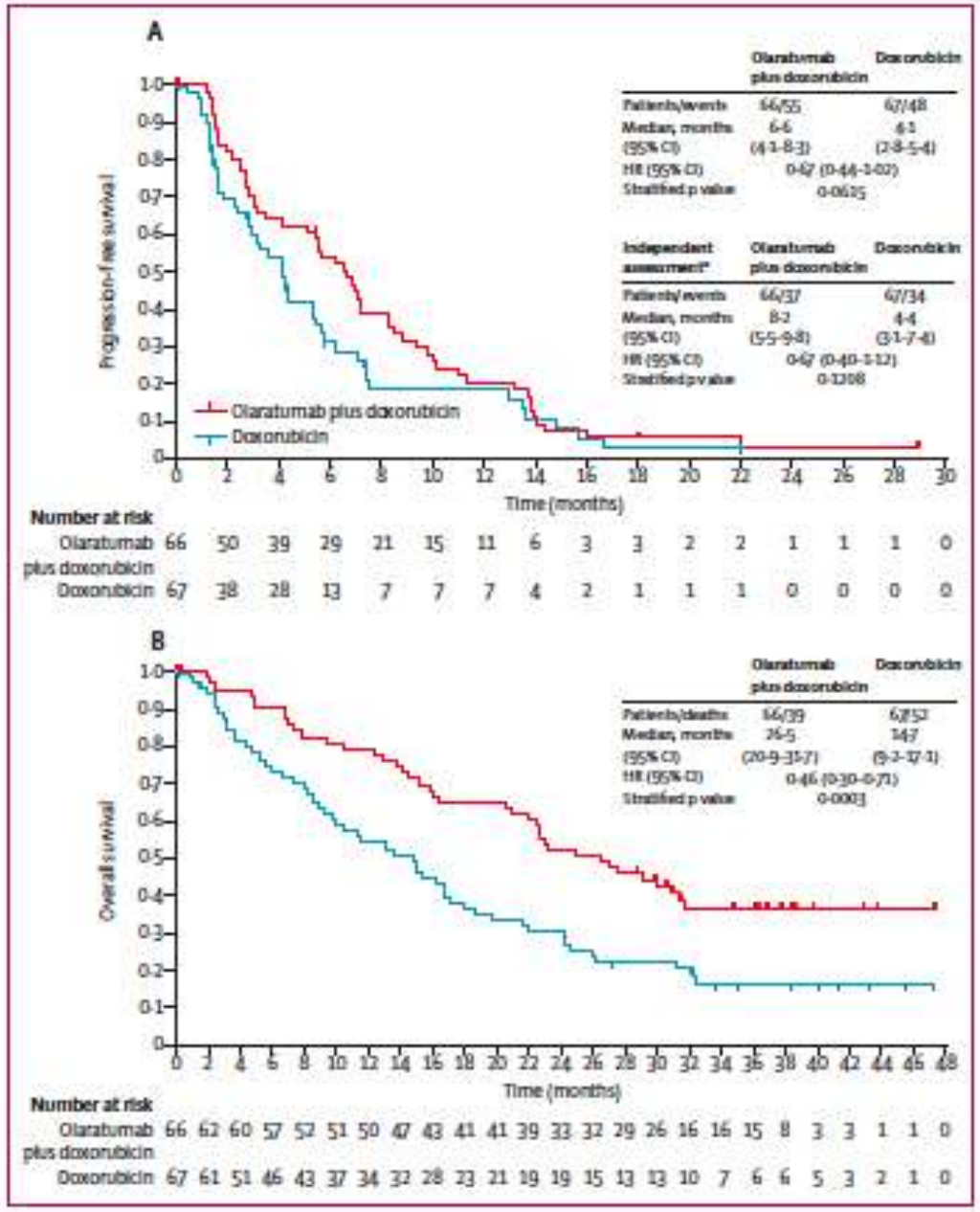
Olaratumab and doxorubicin versus doxorubicin alone for treatment of soft-tissue sarcoma: an open-label phase 1b and randomised phase 2 trial

Lancet 2016; 388: 488–97

William D Tap, Robin L Jones, Brian A Van Tine, Bartosz Chmielowski, Anthony D Elias, Douglas Adkins, Mark Agulnik, Matthew M Cooney, Michael B Livingston, Gregory Pennock, Meera R Hameed, Gaurav D Shah, Amy Qin, Ashwin Shahir, Damien M Cronier, Robert Ilaria Jr, Ilaria Conti, Jan Cosaert, Gary K Schwartz

	Olaratumab plus doxorubicin (n=66)	Doxorubicin (n=67)
Age (years)		
Median (range)	58·5 (22–85)	58·0 (29–86)
Sex		
Men	26 (39%)	33 (49%)
Women	40 (61%)	34 (51%)
Race		
White	55 (83%)	60 (90%)
Black	6 (9%)	5 (8%)
Asian	2 (3%)	2 (3%)
Native Hawaiian or other Pacific Islander	1 (2%)	0
Other	2 (3%)	0
Ethnic origin		
Hispanic or Latino	6 (9%)	2 (3%)
Not Hispanic or Latino	60 (91%)	64 (96%)
Missing	0	1 (2%)
ECOG performance status		
0–1	62 (94%)	63 (94%)
2	4 (6%)	4 (6%)
PDGFRα status*		
Stratification assay		
Positive	58 (88%)	59 (88%)
Negative	8 (12%)	8 (12%)
Exploratory assay (post hoc)†		
Positive	18 (33%)	19 (34%)
Negative	37 (67%)	37 (66%)
Histological type		
Leiomyosarcoma	24 (36%)	27 (40%)
Non-leiomyosarcoma‡	42 (64%)	40 (60%)
Previous treatments		
0	27 (41%)	31 (46%)
≥1	39 (59%)	36 (54%)
Histological type		
Leiomyosarcoma	24 (36%)	27 (40%)
Undifferentiated pleomorphic sarcoma	10 (15%)	14 (21%)
Liposarcoma	8 (12%)	15 (22%)
Angiosarcoma	4 (6%)	3 (5%)
Synovial sarcoma	1 (2%)	2 (3%)
Neurofibrosarcoma	1 (2%)	0
Fibrosarcoma	1 (2%)	0
Other‡	17 (26%)	6 (9%)

Adriamycin 8 cycles (600mg/m2) ; Any line of treatment



PFS 4.2m vs 6.6m

OS 14.7m vs 26.5m

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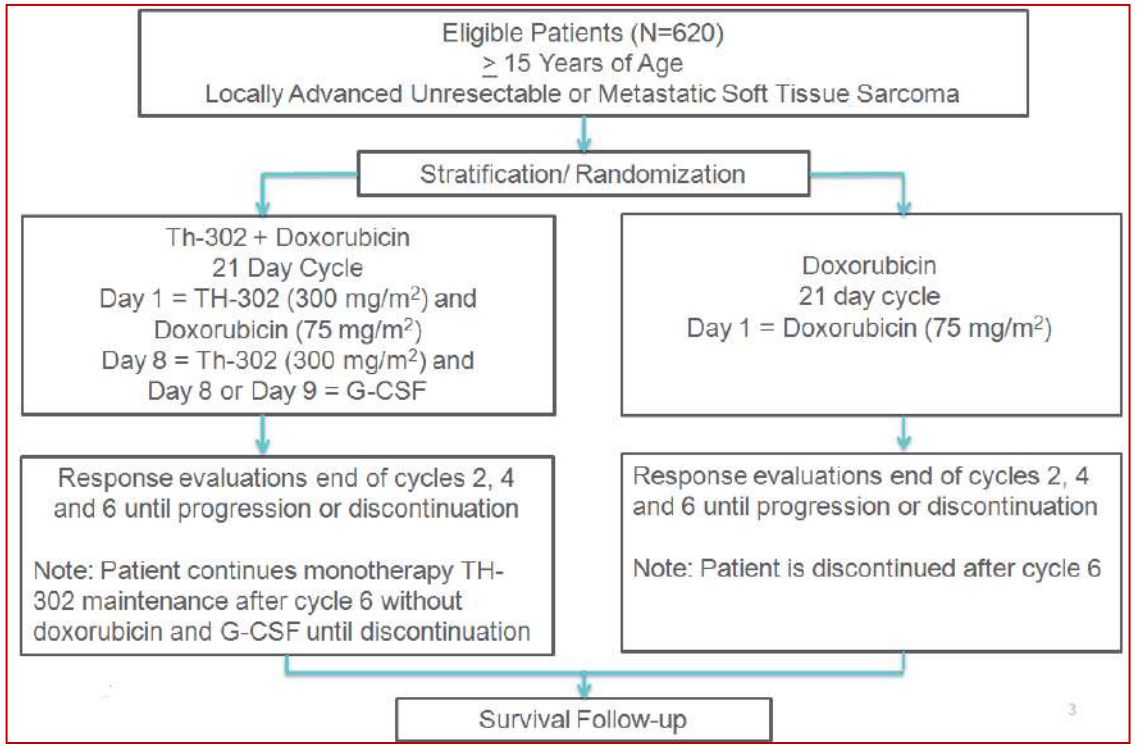
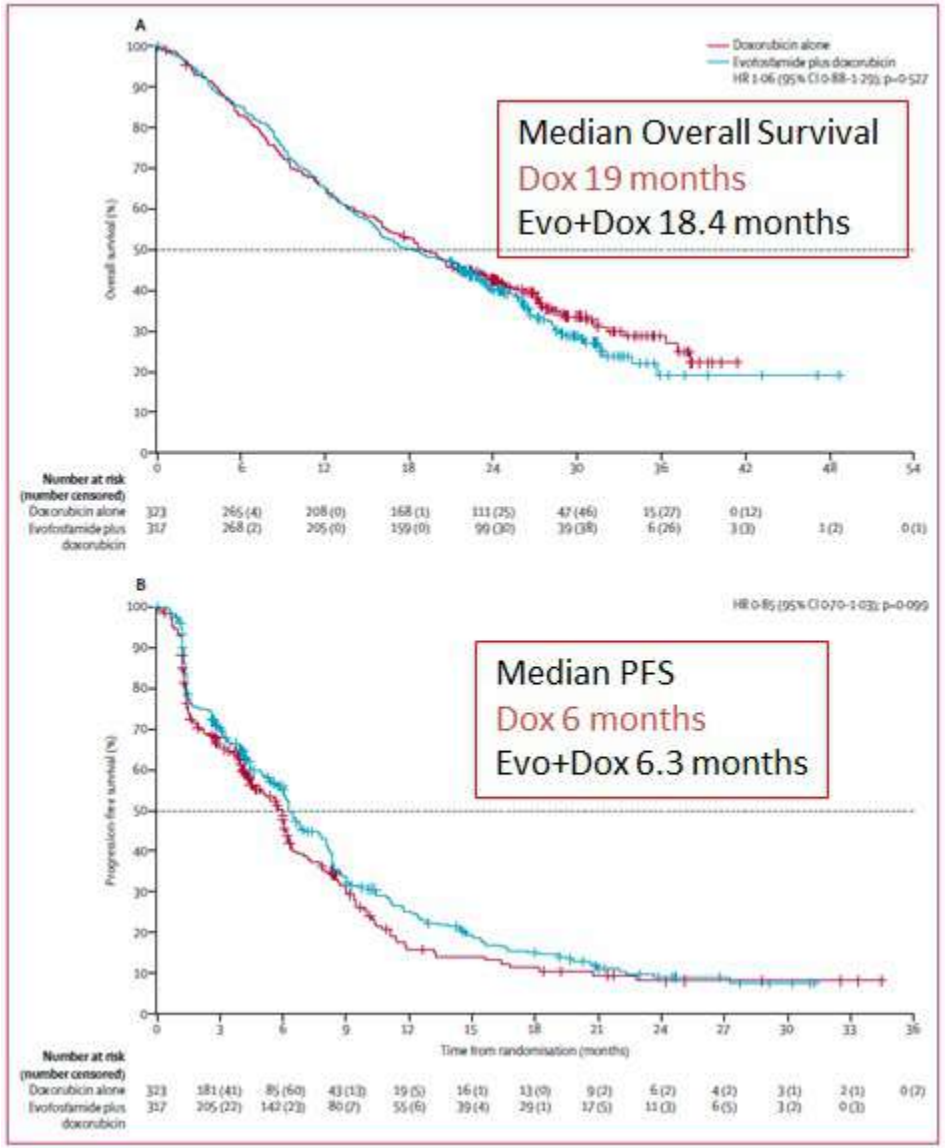
Doxorubicin plus evofosfamide versus doxorubicin alone in locally advanced, unresectable or metastatic soft-tissue sarcoma (TH CR-406/SARC021): an international, multicentre, open-label, randomised phase 3 trial

Lancet Oncol 2017
Published Online June 23, 2017

William D Tap, Zsuzsanna Papai, Brian A Van Tine, Steven Attia, Kristen N Ganjoo, Robin L Jones, Scott Schuetze, Damon Reed, Sant P Chawla, Richard F Riedel, Anders Krarup-Hansen, Maud Toulmonde, Isabelle Ray-Coquard, Peter Hohenberger, Giovanni Grignani, Lee D Cranmer, Scott Okuno, Mark Agulnik, William Read, Christopher W Ryan, Thierry Alcindor, Xavier F Garcia del Muro, G Thomas Budd, Hussein Tawbi, Tillman Pearce, Stew Kroll, Denise K Reinke, Patrick Schöffski

Not blinded; OS primary endpoint
1st line stetting
Evo maintenance component





640 patients
28 months

Contemporary Data Set – Doxorubicin – Front line Setting

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Contemporary Data Set of Doxorubicin Front Line

- Median 6 Cycles – 4.2 months
- 45% of patients required a dose modification
- 10% pts had decrease LVEF >10% or more (EF <55%)
- 30-35% patients had a serious adverse event (neutropenia and anemia)

- 6 months PFS
- 19 months OS
- ORR 18%

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Bolus versus Continuous Intravenous Delivery of Doxorubicin in Soft-Tissue Sarcomas: *Post Hoc* Analysis of a Prospective Randomized Trial (SARC021/TH CR-406)

Lee D. Cranmer[1,2], Yao Lu[3], Rachel S. Heise[3], Karla V. Ballman[3], Elizabeth T. Loggers[1,2], Seth M. Pollack[1,2,4], Michael J. Wagner[1,2], Denise K. Reinke[5,6], Patrick Schöffski[7], and William D. Tap[8]

Clin Cancer Res; 2023

Cardiac tox related to cumulative doxorubicin dose

Subgroup analysis of older patients treated within the randomized phase 3 doxorubicin versus doxorubicin plus evofosfamide (SARC021) trial

Journal of Geriatric Oncology 11 (2020) 463–469

Eugenie Younger [a,b], Karla Ballman [c], Yao Lu [c], Zsuzsanna Pápai [d], Brian A. Van Tine [e], Steven Attia [f], Patrick Schöffski [g], Denise Reinke [h], William D. Tap [c,i], Robin L. Jones [a,j,*]

- No Difference in median OS, PFS, or RR, ≥ 65yo (209 patients)
- Significantly more hematological and Grade ≥ 3 AEs
- No significant difference in cardiotoxicity
- More likely to stop treatment early

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JAMA | Original Investigation

Effect of Doxorubicin Plus Olaratumab vs Doxorubicin Plus Placebo on Survival in Patients With Advanced Soft Tissue Sarcomas
The ANNOUNCE Randomized Clinical Trial

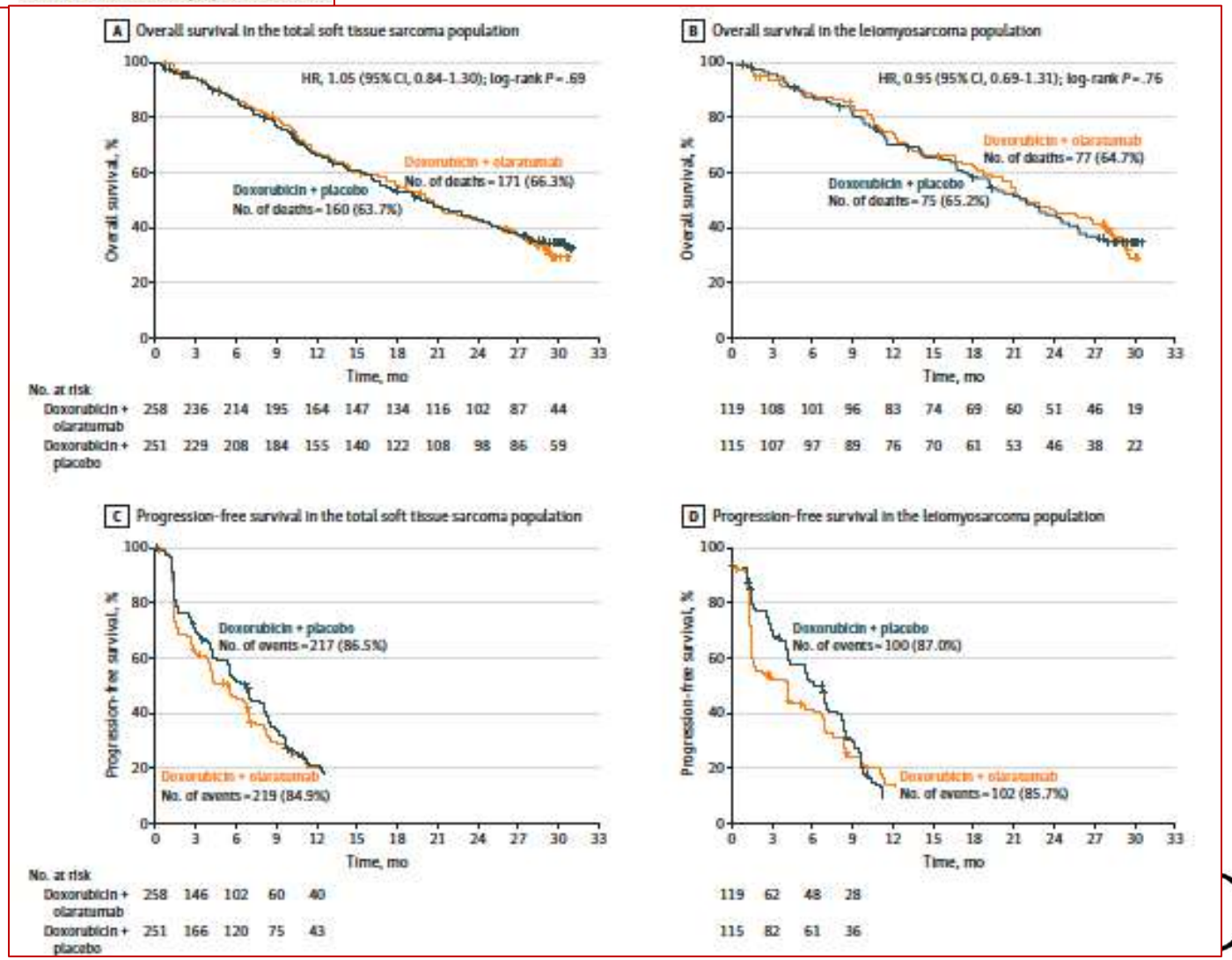
William D. Tap, MD; Andrew J. Wagner, MD, PhD; Patrick Schöffski, MD, PhD, MPH; Javier Martin-Broto, MD, PhD; Anders Krarup-Hansen, MD, PhD; Kristen N. Ganjoo, MD; Chueh-Chuan Yen, MD; Albiruni R. Abdul Razak, MRCPI; Alexander Spira, MD, PhD; Akira Kawai, MD, PhD; Axel Le Cesne, MD; Brian A. Van Tine, MD, PhD; Yoichi Naito, MD; Se Hoon Park, MD, PhD; Alexander Fedenko, MD; Zsuzsanna Pápai, MD, PhD; Victoria Soldatenkova, MS; Ashwin Shahir, MD; Gary Mo, PhD; Jennifer Wright, MD; Robin L. Jones, MD, MBBS, BSc; for the ANNOUNCE Investigators

JAMA. 2020;323(13):1266-1276.

Blinded/Placebo; OS primary endpoint
1st/2nd line stetting
Dual Primary endpoint (STS:LMS)
Olara maintenance component

624 patients
10 months

Characteristic	No. (%) Doxorubicin + olaratumab (n = 258)	Doxorubicin + placebo (n = 251)
Age, median (range), y	57.0 (23-84)	57.0 (20-82)
<65	180 (69.8)	180 (71.7)
≥65	78 (30.2)	71 (28.3)
Sex		
Male	114 (44.2)	99 (39.4)
Female	144 (55.8)	152 (60.6)
Race[a]		
White	186 (72.1)	193 (76.9)
Asian	50 (19.4)	48 (19.1)
Black or African American	12 (4.7)	2 (0.8)
Other[b]	10 (3.9)	8 (3.2)
Hispanic or Latino ethnicity[a]	26 (10.1)	29 (11.6)
Geographic region		
Europe	108 (41.9)	106 (42.2)
North America	88 (34.1)	85 (33.9)
Rest of the world	62 (24.0)	60 (23.9)
EGOG PS[c]		
0 (Capable of normal activity)	153 (59.3)	150 (59.8)
1 (Restricted in strenuous activity)	105 (40.7)	101 (40.2)
Histology		
Leiomyosarcoma	119 (46.1)	115 (45.8)
Liposarcoma	48 (18.6)	43 (17.1)
Pleomorphic sarcoma	34 (13.2)	30 (12.0)
Other[d]	57 (22.1)	63 (25.1)
Duration of disease, median (range), mo	11.3 (0-260)	11.8 (0-192)
Metastatic disease at randomization	216 (83.7)	206 (82.1)
Prior systemic therapies[e]	73 (28.3)	69 (27.5)
Neoadjuvant	1 (0.4)	1 (0.4)
Adjuvant	8 (3.1)	10 (4.0)
Locally advanced	14 (5.4)	9 (3.6)
Metastatic	59 (22.9)	54 (21.5)
Prior radiation therapy	87 (33.7)	85 (33.9)



OS 20.4 v 19.7
STS

OS 21.6 vs 21.9
LMS

PFS 5.4 v 6.8
STS

PFS 4.3 vs 6.9
LMS

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Contemporary Data Set of Doxorubicin 1st/2nd Line

- Median 7 Cycles – 5.3 months; median cumulative dose 483mg/m2
- 6.8 months PFS; 20 months OS; ORR 18%

Prospective Evaluation of Doxorubicin Cardiotoxicity in Patients with Advanced Soft-tissue Sarcoma Treated in the ANNOUNCE Phase III Randomized Trial AC Clin Cancer Res; 27(14)

Robin L. Jones[1,2], Andrew J. Wagner[3,4], Akira Kawai[5], Kazuo Tamura[6], Ashwin Shahir[7], Brian A. Van Tine[8], Javier Martín-Broto[9], Patrick M. Peterson[10], Jennifer Wright[10], and William D. Tap[11]

Median cumulative dose total population - 450mg/m2 (504 pts; 43% (219) received 8 cycles)
Median follow-up of cardiac AEs was 28 weeks
Dexrazoxane more frequently administered higher dose; did not affect treatment efficacy

LVEF deterioration		≥Grade 3 Cardiac Dysfunction (Clinical grade)
40.5%	≤450mg/m2	2%
51.6%	≤450-600mg/m2	3%
56.2%	≥600mg/m2	1.1%

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How Many Variables Confound a Trial?

620-640 randomized participants
80-99 sites, 12+ countries
40+ Disease Entities; intra-subtype variability
Locally Advanced/Metastatic
Variations in clincial behavior
Trial Endpoints, Overall Survival?
Practice/subsequent treatment variability
Maintenance Therapy with Inactive Drugs?
DRUG MOA; Pharmacodynamics
Confounding P1/2 lead in data

True numbers of comparable diseases (In P3; P2 vs P3)
Studying different populations of those diseases in the P2 and P3

Subtype specific trials

- Subtype specific – true understanding subtype
  - Often new disease entities, recently genetically defined
  - Natural history of the disease poorly understood/defined
  - Genomic and clinical variability not ordered
  - Clinical needs patient population need to be defined/measured
  - Meaningful clinical and research outcome measures
  - Unique features drug/technology need to be understood
  - Unknown response or usage patterns for repurposed drugs

- Does our community have the bandwidth for each subtype
  - Early signal finding studies to pivotal efforts
  - Appropriate outcomes measures
  - Novel unique trial designs (redefine our approach)
  - New drugs technology – understanding of biology and MOA
  - Understanding the science
  - What is the correct long-term application
  - Reliance on Pharma and discordant goals
  - Unique Regulatory tracts

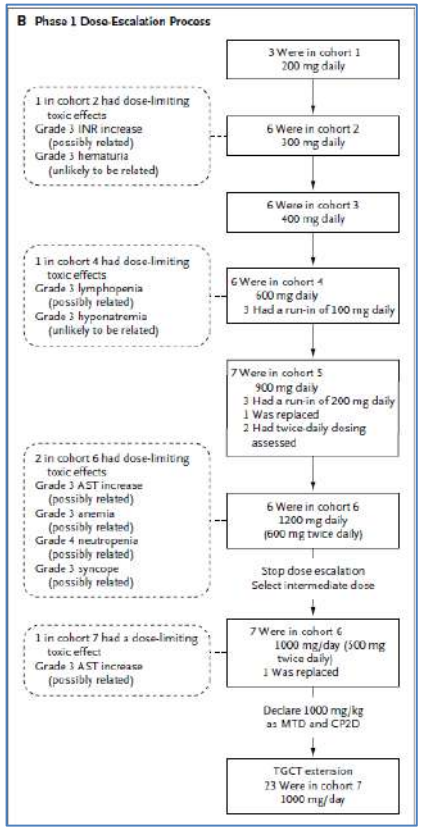
ORIGINAL ARTICLE N Engl J Med 2015;373:428-37.

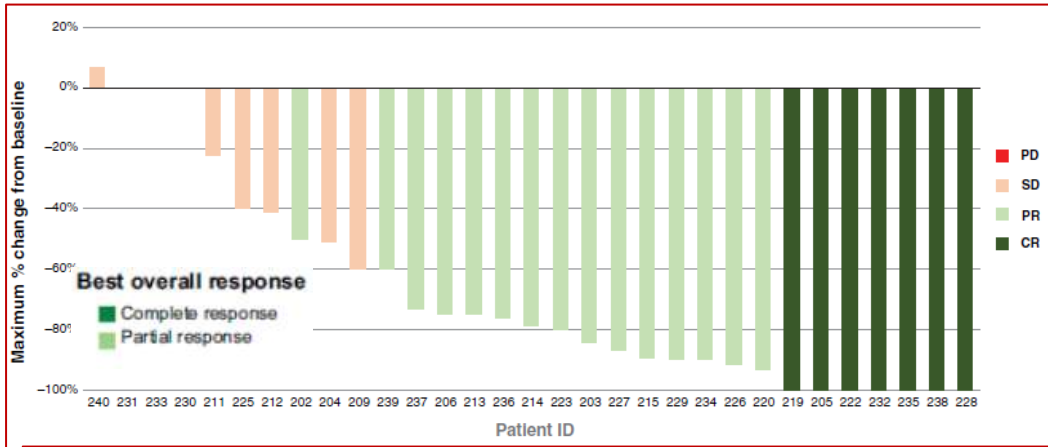
Structure-Guided Blockade of CSF1R Kinase in Tenosynovial Giant-Cell Tumor

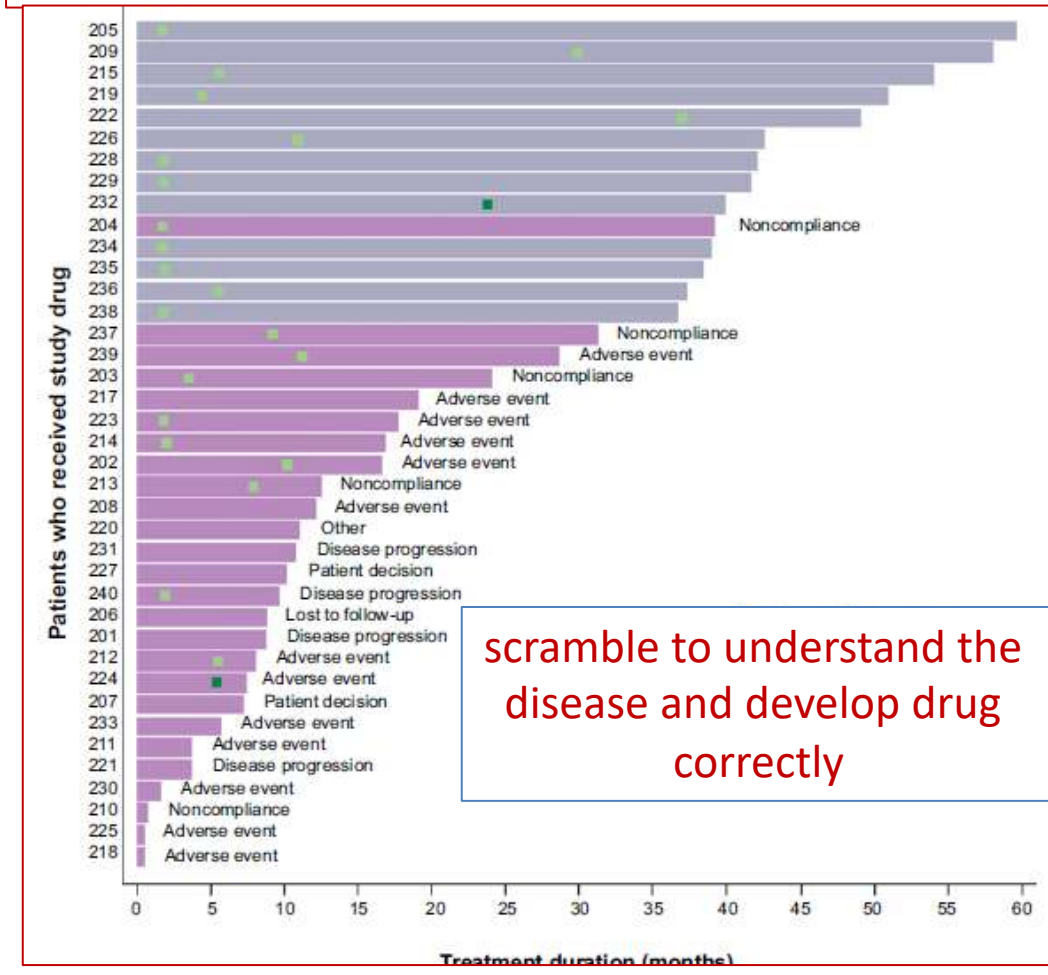
W.D. Tap, Z.A. Wainberg, S.P. Anthony, P.N. Ibrahim, C. Zhang, J.H. Healey, B. Chmielowski, A.P. Staddon, A.L. Cohn, G.I. Shapiro, V.L. Keedy, A.S. Singh, I. Puzanov, E.L. Kwak, A.J. Wagner, D.D. Von Hoff, G.J. Weiss, R.K. Ramanathan, J. Zhang, G. Habets, Y. Zhang, E.A. Burton, G. Visor, L. Sanftner, P. Severson, H. Nguyen, M.J. Kim, A. Marimuthu, G. Tsang, R. Shellooe, C. Gee, B.L. West, P. Hirth, K. Nolop, M. van de Rijn, H.H. Hsu, C. Peterfy, P.S. Lin, S. Tong-Starksen, and G. Bollag

Part 2 Extension, six cohorts:

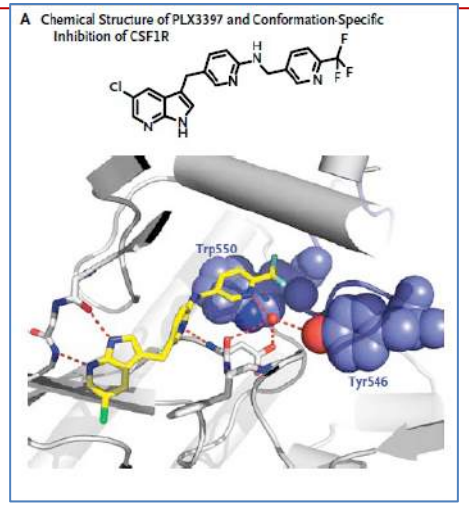
1) Mucoepidermal carcinoma salivary gland
2) Tenosynovial giant cell tumor
3) Gastrointestinal stromal tumor
4) Anaplastic thyroid carcinoma
5) Solid tumors with documented malignant pleural or peritoneal effusions, and
6) Miscellaneous tumor types, with scientific evidence supporting the involvement of CSF1R/KIT signaling in tumorigenesis







scramble to understand the disease and develop drug correctly



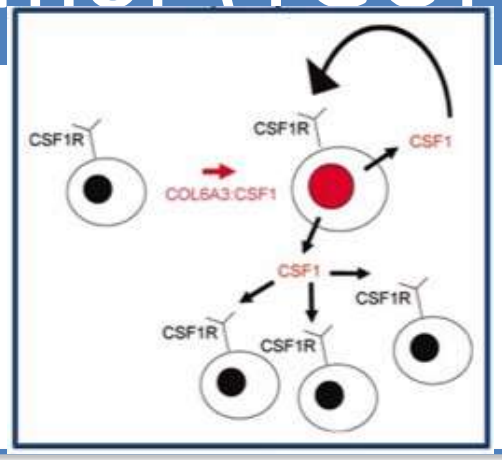
Tumor	Total treatment duration (days)	Best response
GIST	80	SD
GIST	111	SD
GIST	169	SD
GIST	345	SD
MEC	350	SD
Malignant effusion[a]	55	SD
Malignant effusion[b]	263	SD
Malignant effusion[c]	56	SD
Familial schwannomatosis	187	SD
Neurofibromatosis	199	SD
Neurofibromatosis	113	SD
ACC	57	SD
Mesothelioma	150	SD
Pancreatic neuroendocrine tumor	413	SD
Erdheim–Chester disease	494	PR
Mesothelioma	55	SD

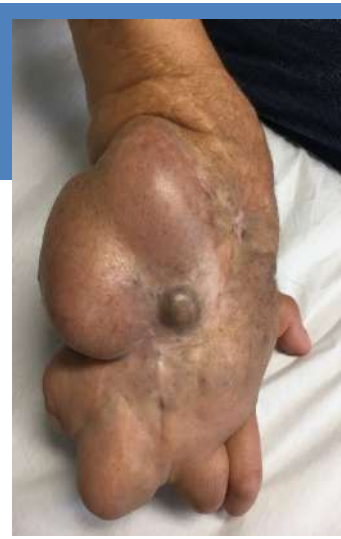
Clin Cancer Res; 28(2) January 15, 2022
PMID: 34713196

Tenosynovial Giant Cell Tumor (TGCT)

High Morbidity

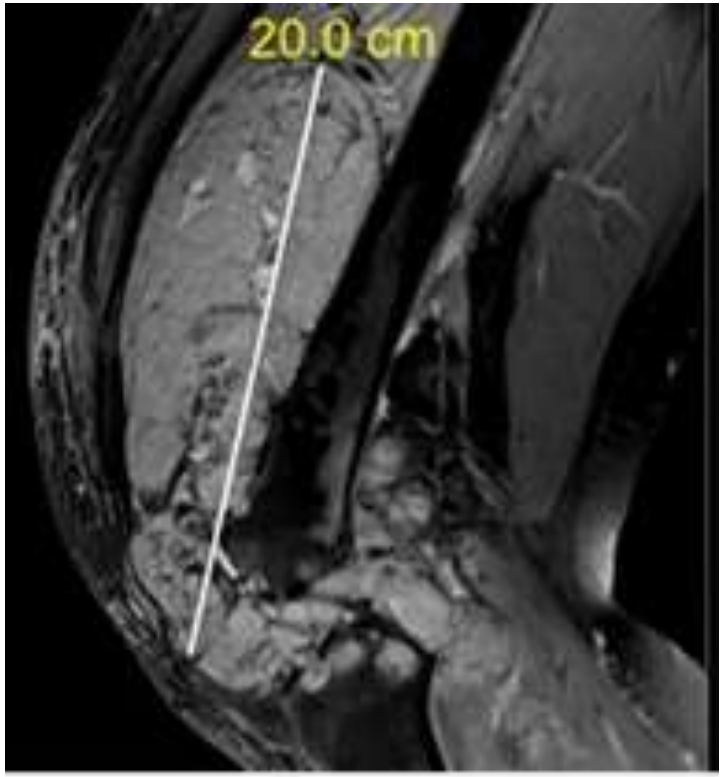
- While usually not metastatic, disease is locally aggressive, and recurrence is common after surgical resection (particularly with Diffuse PVNS)
- Affects young & middle-aged adults of both sexes; no ethnic predisposition; patients are diagnosed in their 30s and 40s; and can live ~40years after diagnosis

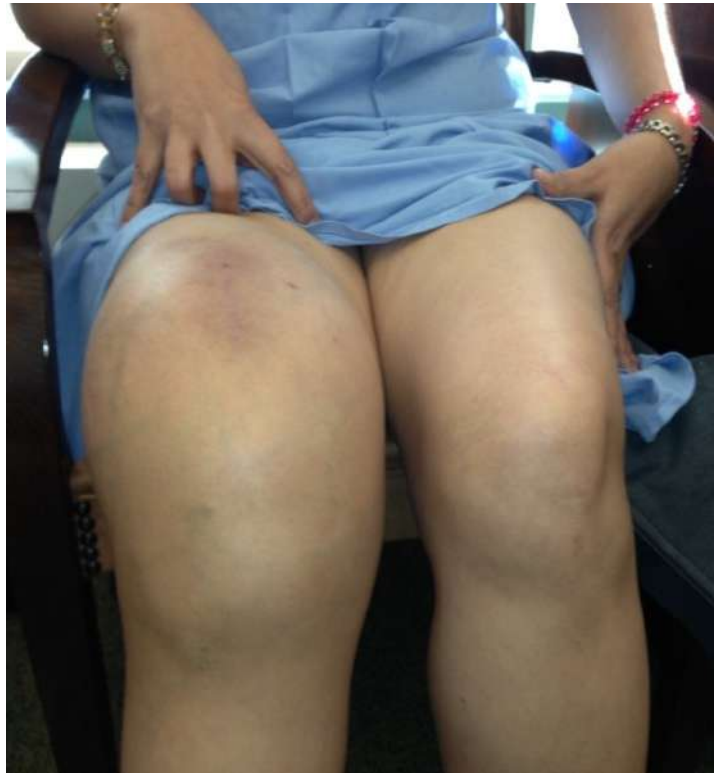




Gross features:

- Collagen deposition
- Subchondral bone erosions
- Repeat hemarthrosis





Clinical features:

- Usually single joint:
  - Swelling
  - Pain
  - ↓ range of motion
  - Stiffness
- Functional impairment
- Narcotic use
- Disability

West, et al. (2006)
PNAS, USA 103, 690-695

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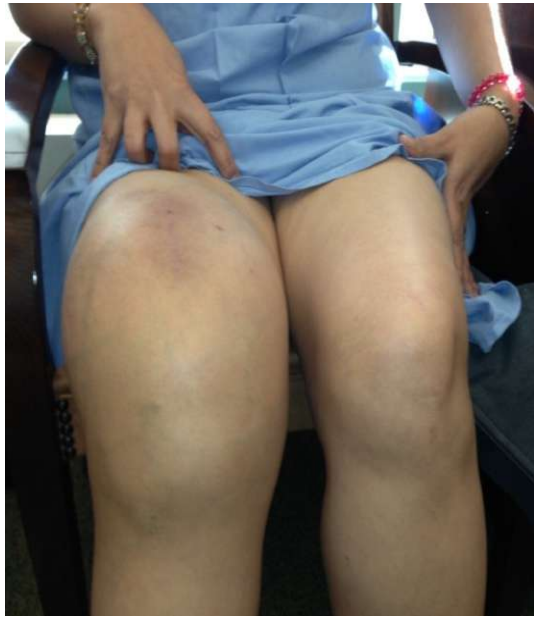
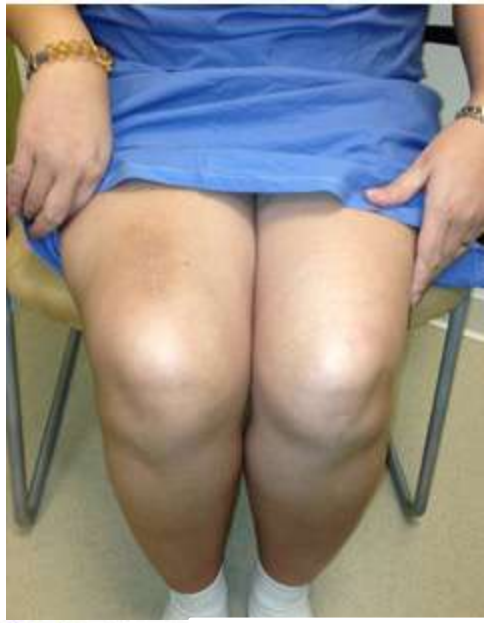
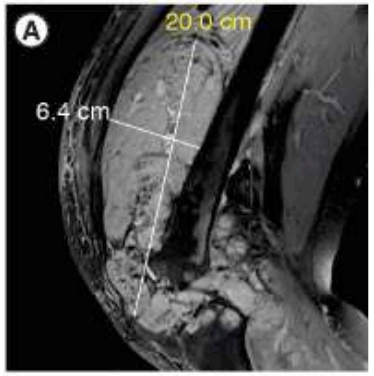
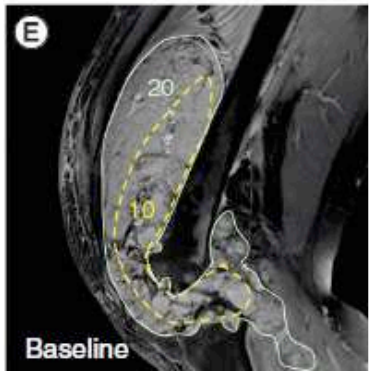






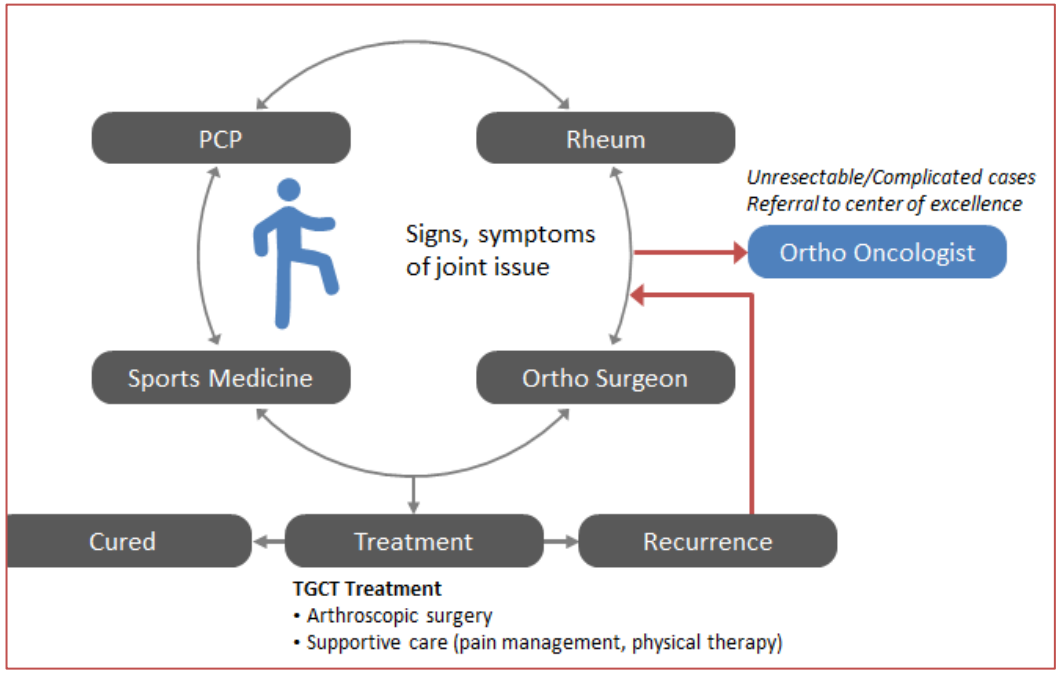


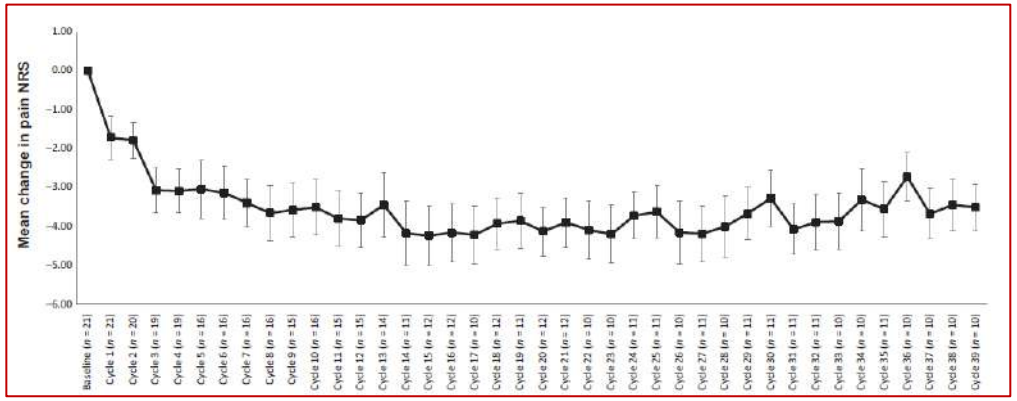
CSF1 receptor inhibition of tenosynovial giant cell tumor using novel disease-specific MRI measures of tumor burden

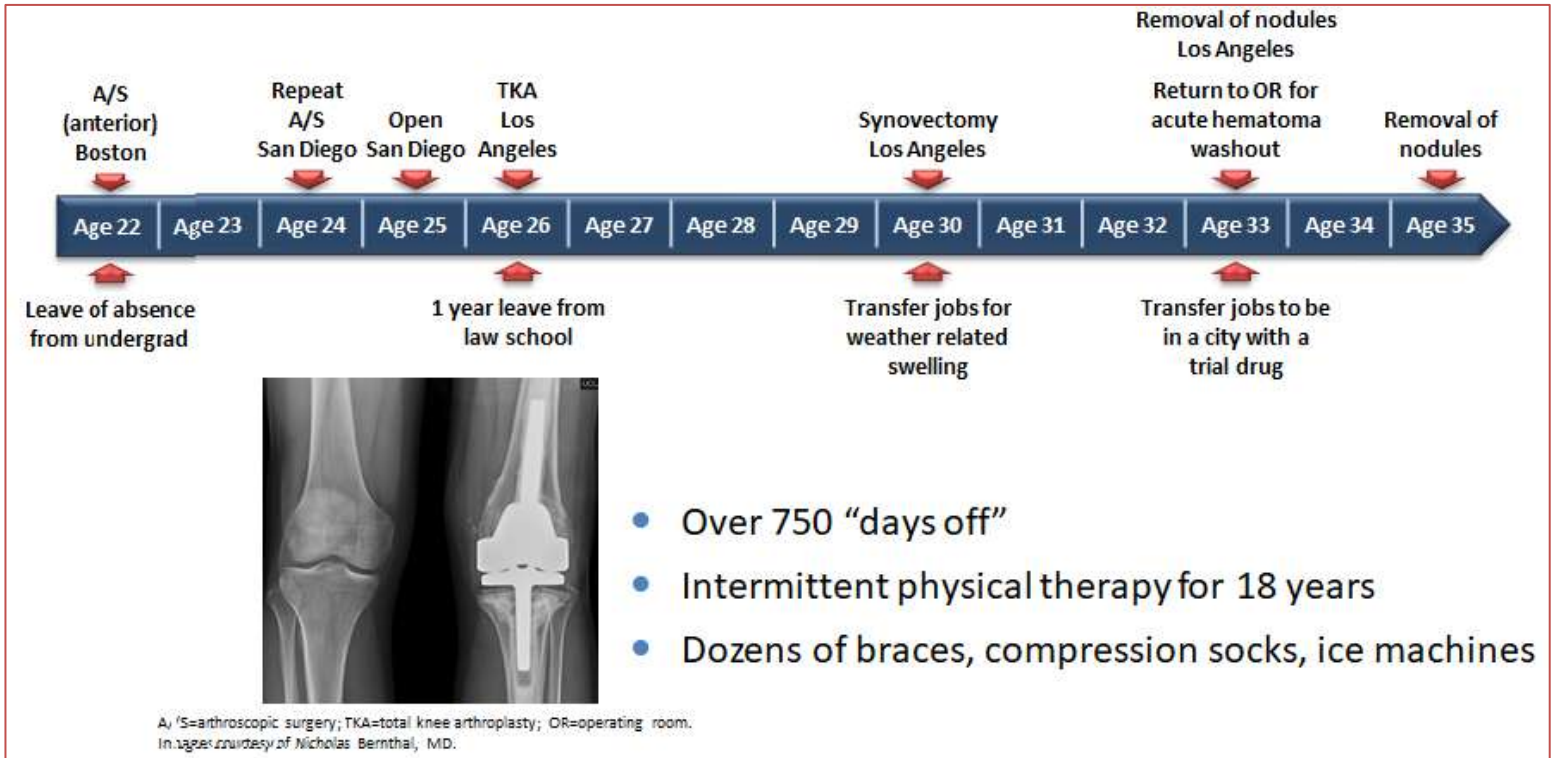
Charles Peterfy*,[1], Yan Chen[1], Peter Countryman[1], Bartosz Chmielowski[2], Stephen P Anthony‡,[3], John H Healey[4], Zev A Wainberg[5], Allen L Cohn[6], Geoffrey I Shapiro[7], Vicki L Keedy[8], Arun Singh[5], Igor Puzanov[9], Andrew J Wagner[7], Meng Qian[10], Mike Sterba[11], Henry H Hsu‡,[11], Sandra Tong-Starksen‡,[11] & William D Tap[4]

Future Oncol. (2022) 18(12), 1449–1459

Memorial Sloan Kettering Cancer Center







The measurement of physical functioning among patients with Tenosynovial Giant Cell Tumor (TGCT) using the Patient-Reported Outcomes Measurement Information System (PROMIS)

Heather L. Gelhorn[1*], Xin Ye[2], Rebecca M. Speck[1], Sandra Tong[3], John H. Healey[4], Susan V. Bukata[5], Richard D. Lackman[6], Lindsey Murray[1], Grant Maclaine[7], William R. Lenderking[1], Henry H. Hsu[3], Paul S. Lin[3] and William D. Tap[4]

Gelhorn et al. Journal of Patient-Reported Outcomes (2019) 3:6

Clinical Therapeutics/Volume ∎, Number ∎, 2016

Patient-Reported Symptoms of Tenosynovial Giant Cell Tumors

Heather L. Gelhorn, PhD[1]; Sandra Tong, MD[2]; Kelly McQuarrie, BS[1]; Christina Vernon, MPH[1]; Jennifer Hanlon, MPH[1]; Grant Maclaine, BMedSc, MBBS, MEc, MA[3]; William Lenderking, PhD[1]; Xin Ye, PhD, MS[4]; Rebecca M. Speck, PhD, MPH[1]; Richard D. Lackman, MD[5]; Susan V. Bukata, MD[6]; John H. Healey, MD[7]; Vicki L. Keedy, MD, MSCI[8]; Stephen P. Anthony, DO[9]; Andrew J. Wagner, MD, PhD[10]; Daniel D. Von Hoff, MD[11]; Arun S. Singh, MD[6]; Carlos R. Becerra, MD[12]; Henry H. Hsu, MD[2]; Paul S. Lin, MD, MBA[2]; and William D. Tap, MD[7]

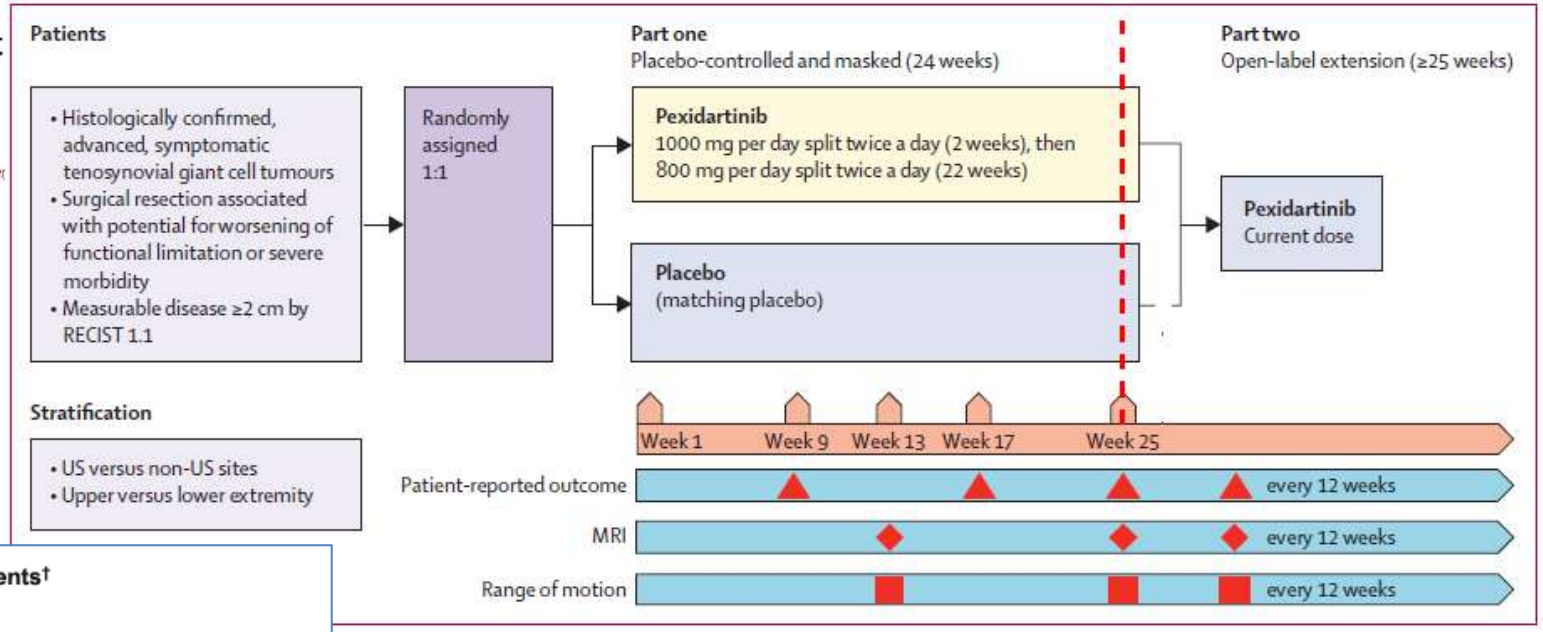
Memorial Sloan Kettering Cancer Center

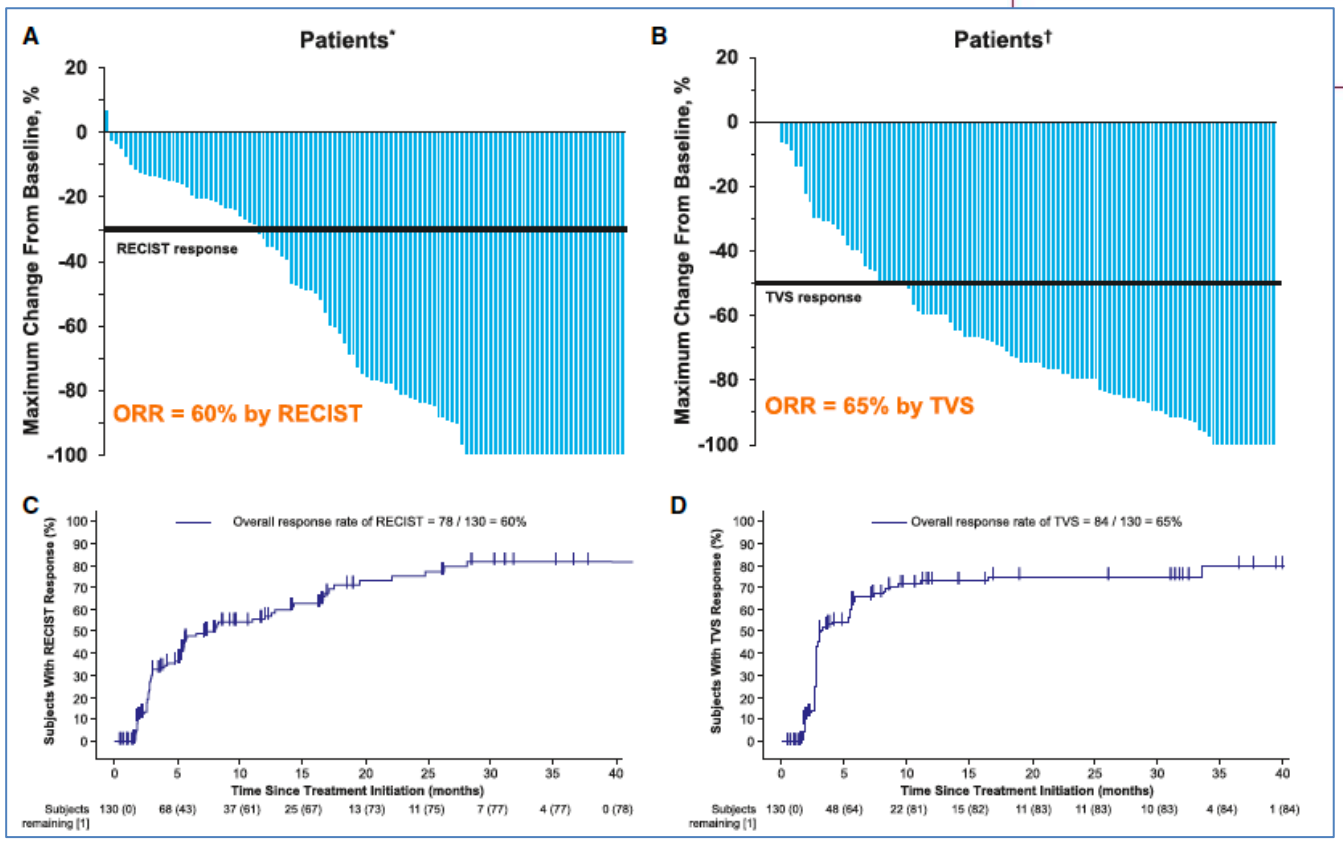
Pexidartinib versus placebo for advanced tenosynovial giant cell tumour (ENLIVEN): a randomised phase 3 trial

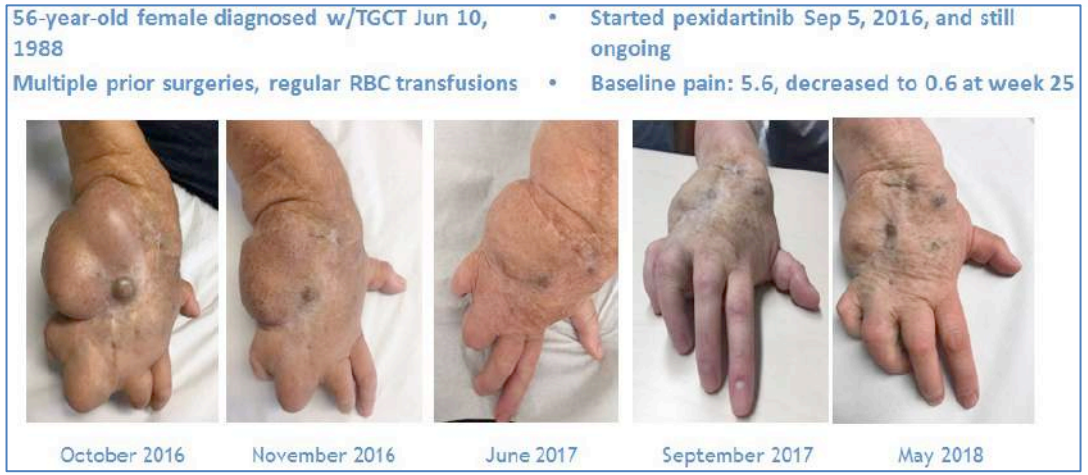
William D Tap, Hans Gelderblom, Emanuela Palmerini, Jayesh Desai, Sebastian Bauer, Jean-Yves Blay, Thierry Alcindor, Kristen Ganjoo, Javier Martín-Broto, Christopher W Ryan, David M Thomas, Charles Peterfy, John H Healey, Michiel van de Sande, Heather L Gelhorn, Dale E Shuster, Qiang Wang, Antoine Yver, Henry H Hsu, Paul S Lin, Sandra Tong-Starksen, Silvia Stacchiotti*, Andrew J Wagner*, on behalf of the ENLIVEN investigators†

Lancet 2019; 394: 478–87

Need for Placebo?
Outcome assumptions?
Based on ORR P1
Doing too much?







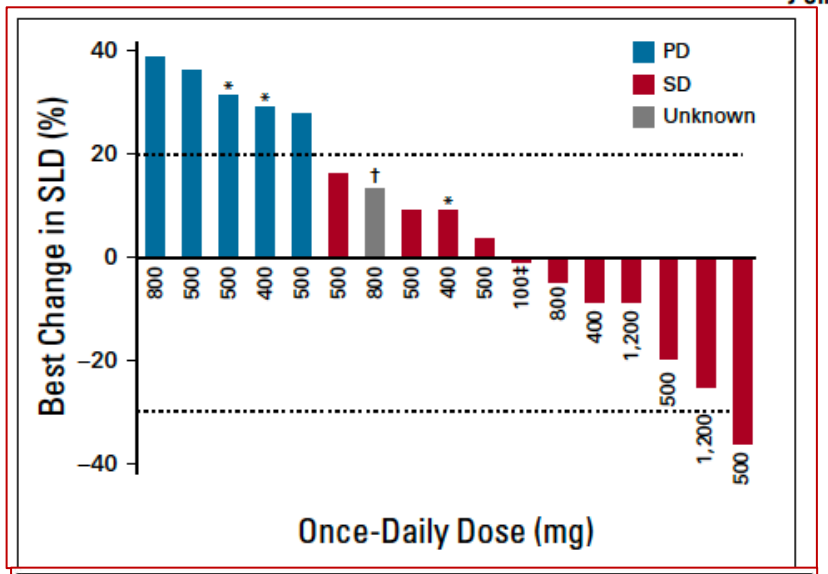
Data Missingness
Reordered endpoints
Rare but dangerous cholestatic hepatotoxicity
Vanishing Bile Duct Syndrome
ODAC and REMS

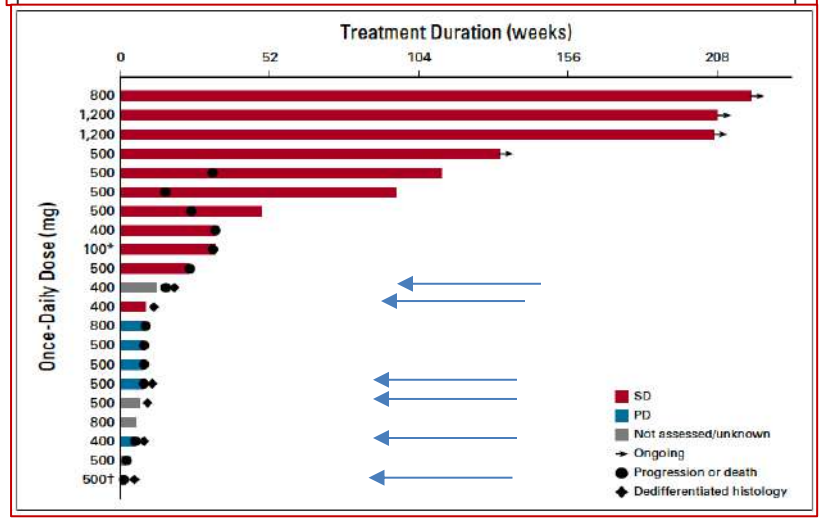
PMID: 33197285

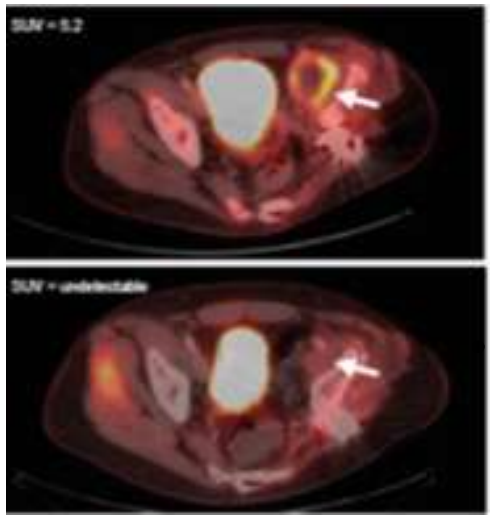
Phase I Study of the Mutant IDH1 Inhibitor Ivosidenib: Safety and Clinical Activity in Patients With Advanced Chondrosarcoma

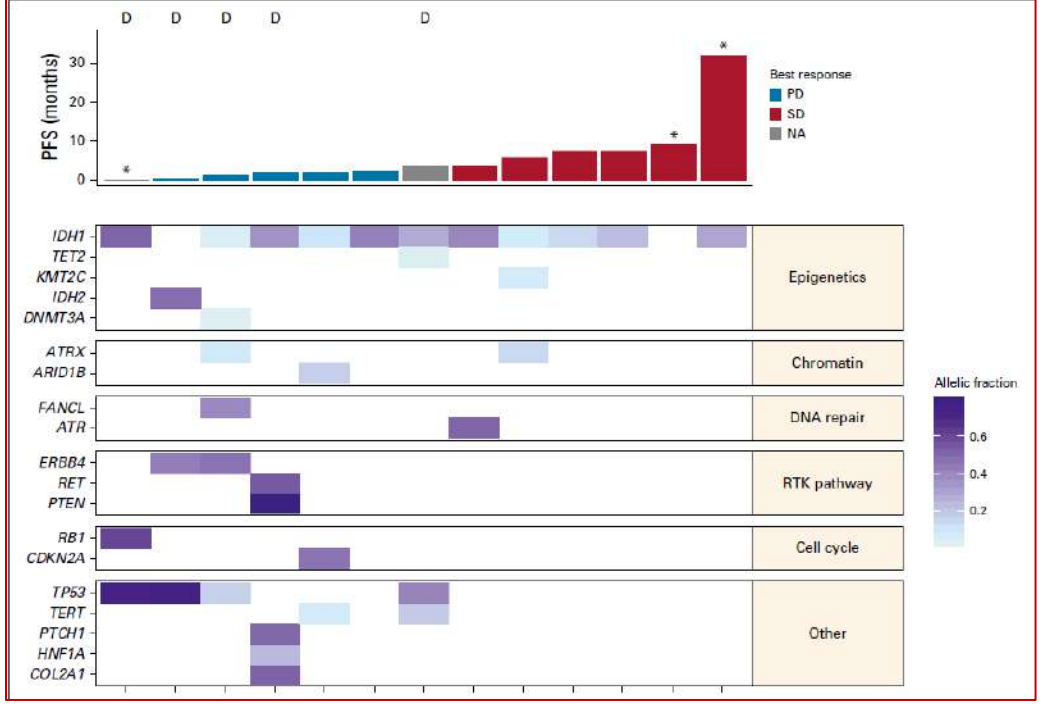
William D. Tap, MD[1,2]; Victor M. Villalobos, MD, PhD[3]; Gregory M. Cote, MD, PhD[4]; Howard Burris, MD[5]; Filip Janku, MD, PhD[6]; Olivier Mir, MD, MPH, PhD[7]; Murali Beeram, MD[8]; Andrew J. Wagner, MD, PhD[9]; Liewen Jiang, PhD[10]; Bin Wu, PhD[10]; Sung Choe, PhD[10]; Katharine Yen, PhD[10]; Camelia Gliser, BS[10]; Bin Fan, PhD[10]; Sam Agresta, MD, MPH[10]; Shuchi S. Pandya, MD[10]; and Jonathan C. Trent, MD, PhD[11]

J Clin Oncol 38:1693-1701. © 2020









NCCN Compendium listed

Molecular and Clinical Variation in Chondrosarcoma

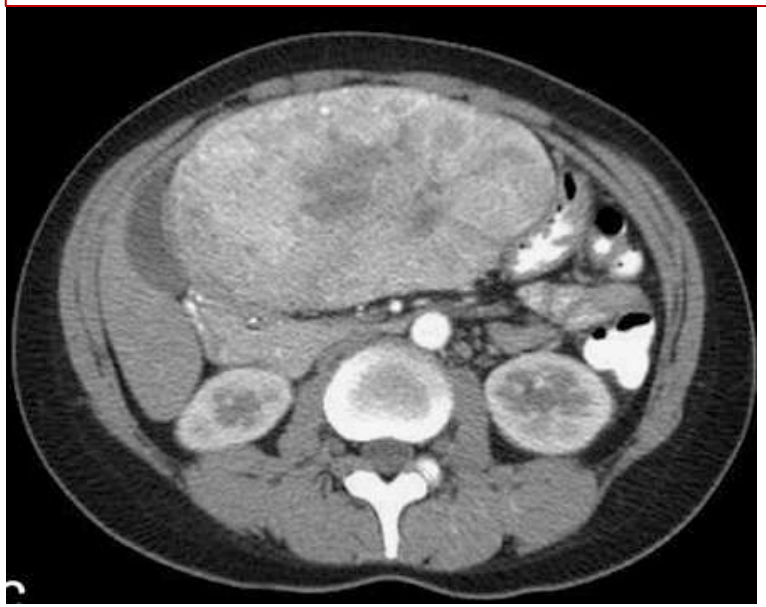
- Conventional vs De-differentiated
- Variable Natural History in Conventional (PFS/OS)
- Large Boney Components (difficult to Image)
- Lack of Utility with RECIST
  - Novel Imaging Technique vs Molecular/Metabolic based outcomes
- Quality of Life Outcomes, Symptoms, PROs
  - Variable locations of disease
- Biology and Clinical Impact of IDH Mutations

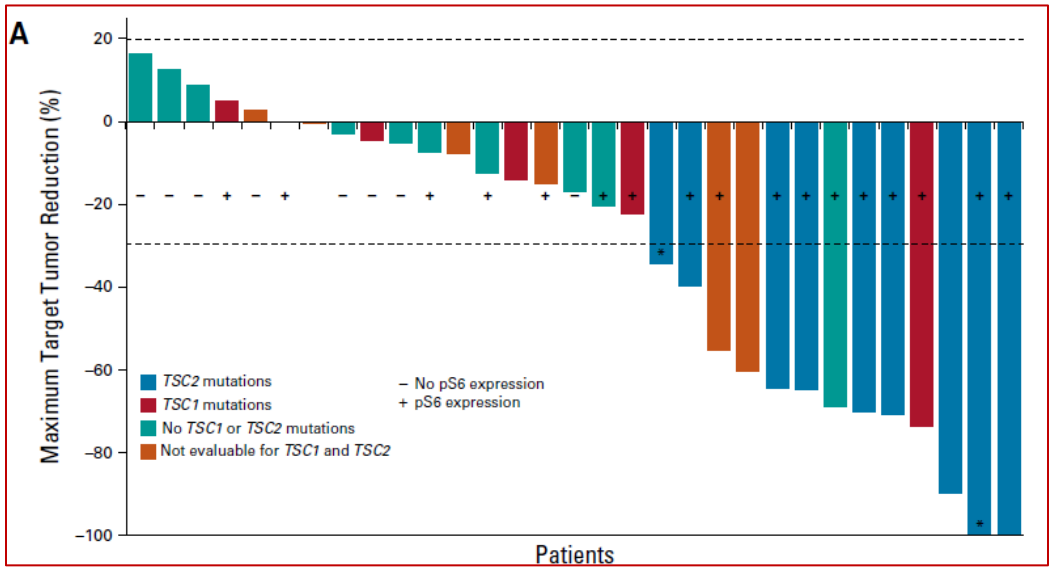
nab-Sirolimus for Patients With Malignant Perivascular Epithelioid Cell Tumors

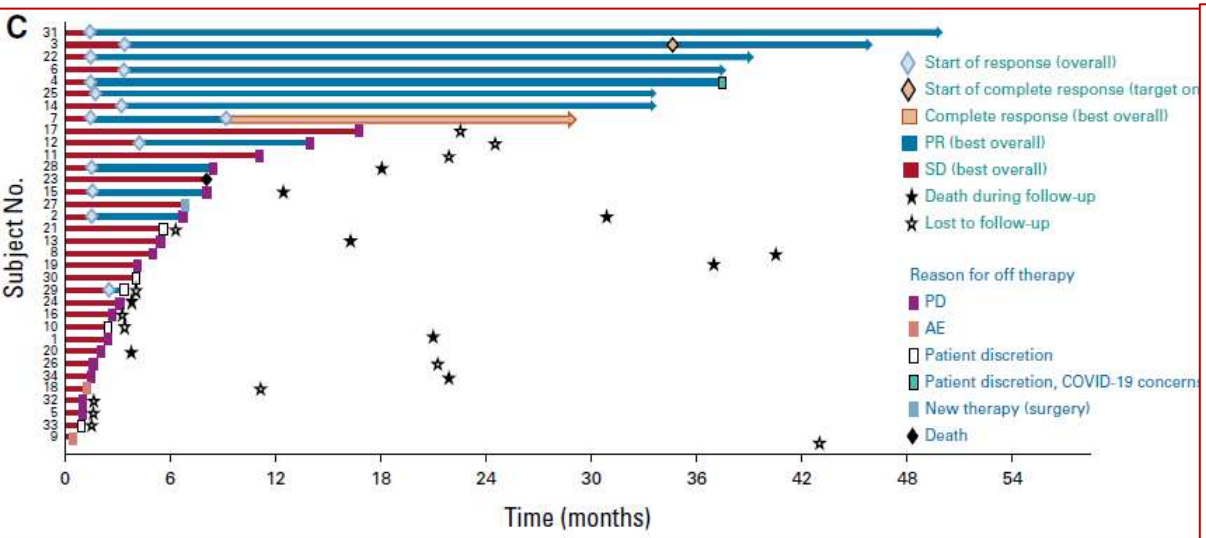
J Clin Oncol 39:3660-3670. © 2021

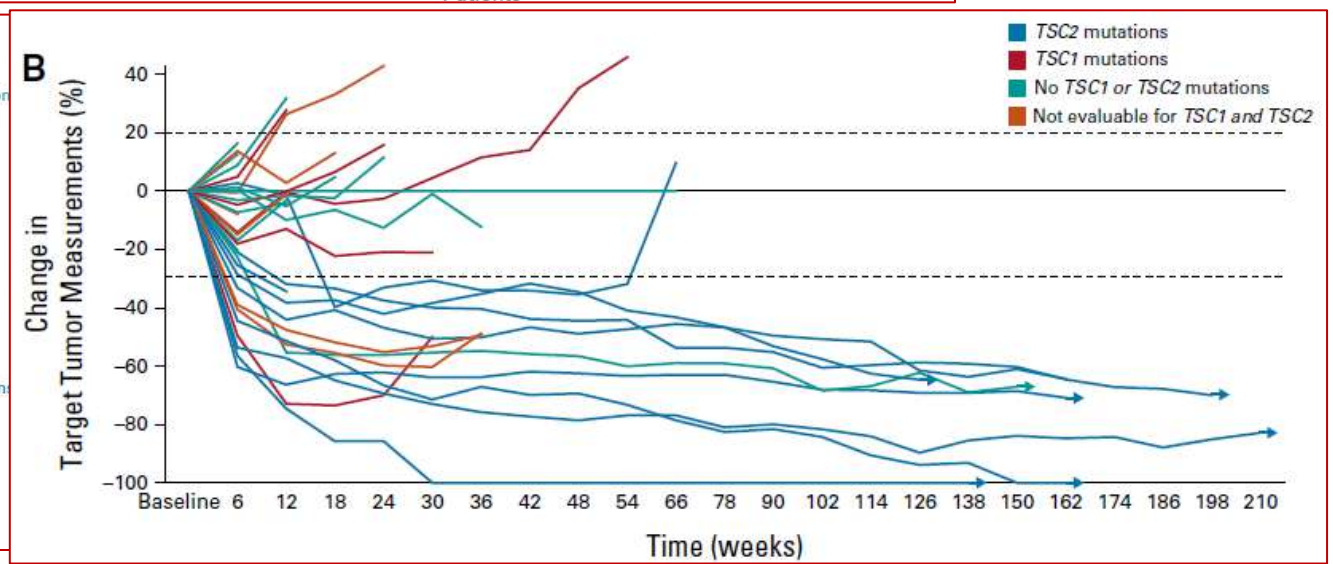
Andrew J. Wagner, MD, PhD[1]; Vinod Ravi, MD[2]; Richard F. Riedel, MD[3]; Kristen Ganjoo, MD[4]; Brian A. Van Tine, MD, PhD[5]; Rashmi Chugh, MD[6]; Lee Cranmer, MD, PhD[7]; Erlinda M. Gordon, MD[8]; Jason L. Hornick, MD, PhD[9]; Heng Du, MD[9]; Berta Grigorian, BS[10]; Anita N. Schmid, PhD[10]; Shihe Hou, PhD[10]; Katherine Harris, DrPH[10]; David J. Kwiatkowski, MD, PhD[9]; Neil P. Desai, PhD[10]; and Mark A. Dickson, MD[11]

ORR 39%
mDOR NR (2.5 years f/u)
mPFS 10 months
mOS 40.8 months





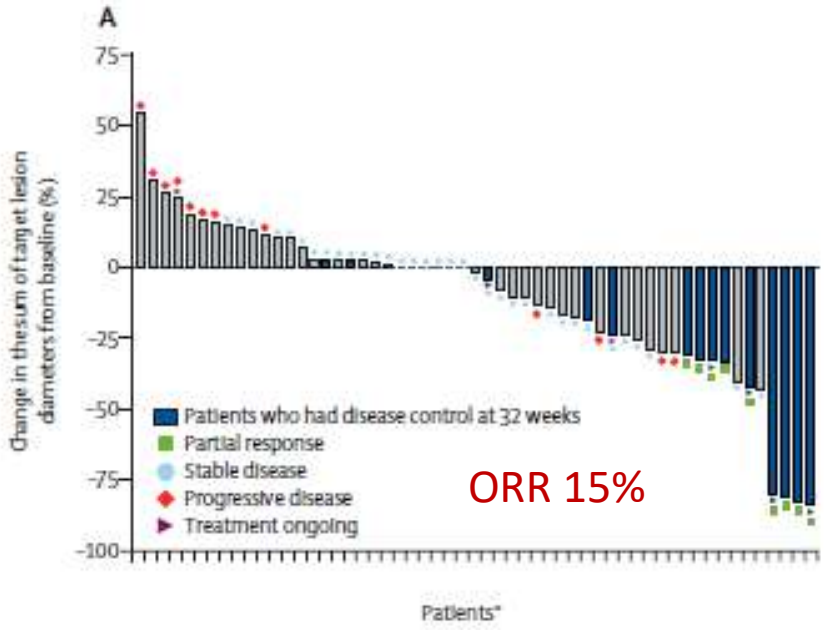




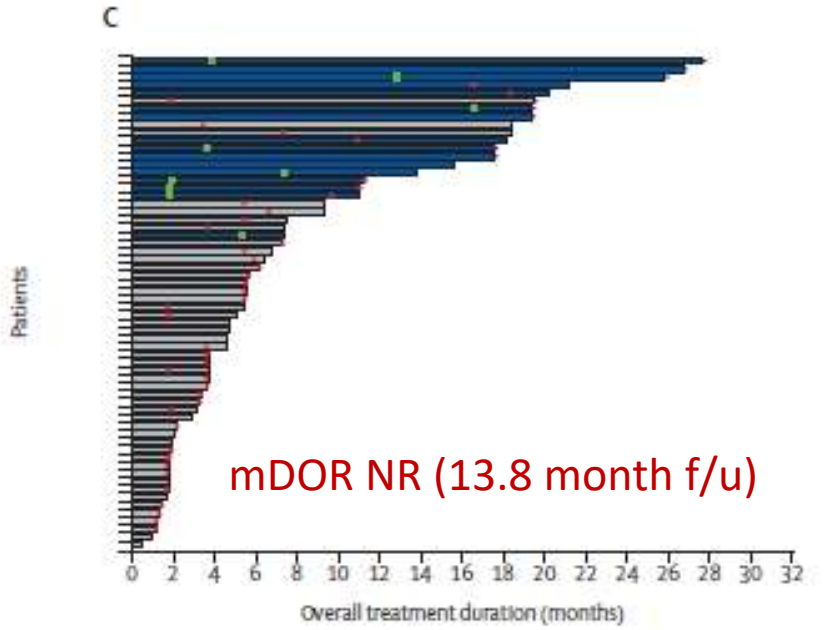
Tazemetostat in advanced epithelioid sarcoma with loss of INI1/*SMARCB1*: an international, open-label, phase 2 basket study

Lancet Oncol 2020; 21: 1423–32

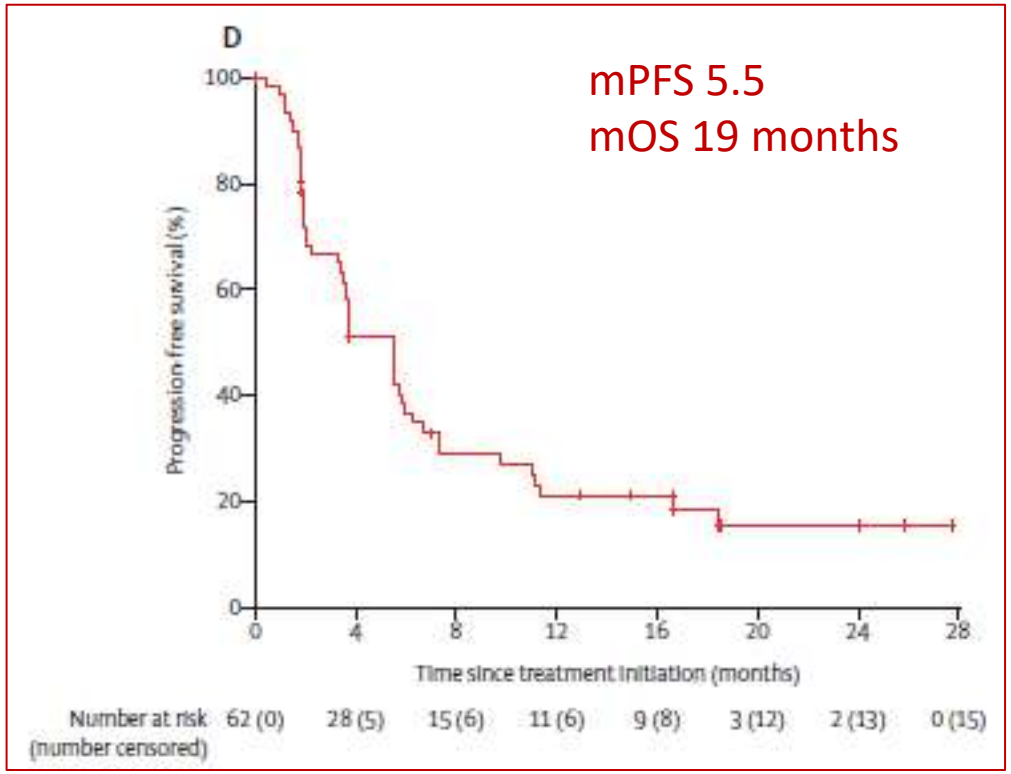
Mrinal Gounder, Patrick Schöffski, Robin L Jones, Mark Agulnik, Gregory M Cote, Victor M Villalobos, Steven Attia, Rashmi Chugh, Tom Wei-Wu Chen, Thierry Jahan, Elizabeth T Loggers, Abha Gupta, Antoine Italiano, George D Demetri, Ravin Ratan, Lara E Davis, Olivier Mir, Palma Dileo, Brian A Van Tine, Joseph G Pressey, Trupti Lingaraj, Anand Rajarethinam, Laura Sierra, Shefali Agarwal, Silvia Stacchiotti



ORR 15%



mDOR NR (13.8 month f/u)



mPFS 5.5
mOS 19 months

FDA ODAC December 18, 2019
11-0 for Accelerated Approval

A Phase 1b/3 trial of tazemetostat plus doxorubicin in the 1st line setting

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"The Pit and the Pendulum"
Clinical Need and Opportunity in Sarcoma

–Need to start with early FOCUSED development

•Single diseases, homogenous presentations

–Understand historical response patterns/outcomes

–Objective measures of disease behavior and impact

–Applicable endpoints and measurements

–Account for practice variations

–Mirror Design and Population in P1 through P3

– Complete Development Strategies to inform correct clinical usage

–Simple Designs

–Incorporating/not over interpreting MOA

–Biomarkers and patient selection

–Correlative work is critical

Memorial Sloan Kettering Cancer Center

THANK YOU

Memorial Sloan Kettering Cancer Center

Avacta®

Targeted Oncology 2030

Panel Discussion

Avacta®

Closing Remarks