ASX:**ALA**

arovella THERAPEUTICS

monsoon communications

Monsoon Twilight Briefing

November

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Arovella's strengths

Off-the-Shelf iNKT Cell Platform

Developing off-the-shelf iNKT cell therapies to target blood cancers and solid tumour cancers

Lead Product Advancing to Clinic

ALA-101, a potential treatment for CD19-expressing blood cancers, progressing to Phase 1 clinical trials, expected to commence in 2024

Addressing Key Unmet Need

Our iNKT cell platform is well positioned to solve key challenges that hamper the cell therapy sector

Strong Leadership Group

Leadership team and Board have proven experience in drug development, particularly cell therapies

Strategic Acquisitions

Focused on acquiring innovative technologies that strengthen our cell therapy platform and align with our focus areas

Unique Value Proposition

Arovella is among few companies globally developing an iNKT cell therapy platform

About Cell Therapy

Cell Therapy has revolutionised blood cancer treatment

CAR-T cells have demonstrated their curative potential in blood cancers

The Cell Therapy market is expected to reach

$61.2 billion

by 2030[1]

Cure

CAR-T cells have demonstrated ability to **cure haematological cancers**

Strong Sales

40-60%

Patients relapse post-CAR-T therapy[2]

Product	Approval Year	2022 Revenue
YESCARTA (axicabtagene ciloleucel)	2017	US$1160m[3]
KYMRIAH (tisagenlecleucel)	2017	US$536m[4]
Abecma (idecabtagene vicleucel)	2021	US$388m[5]

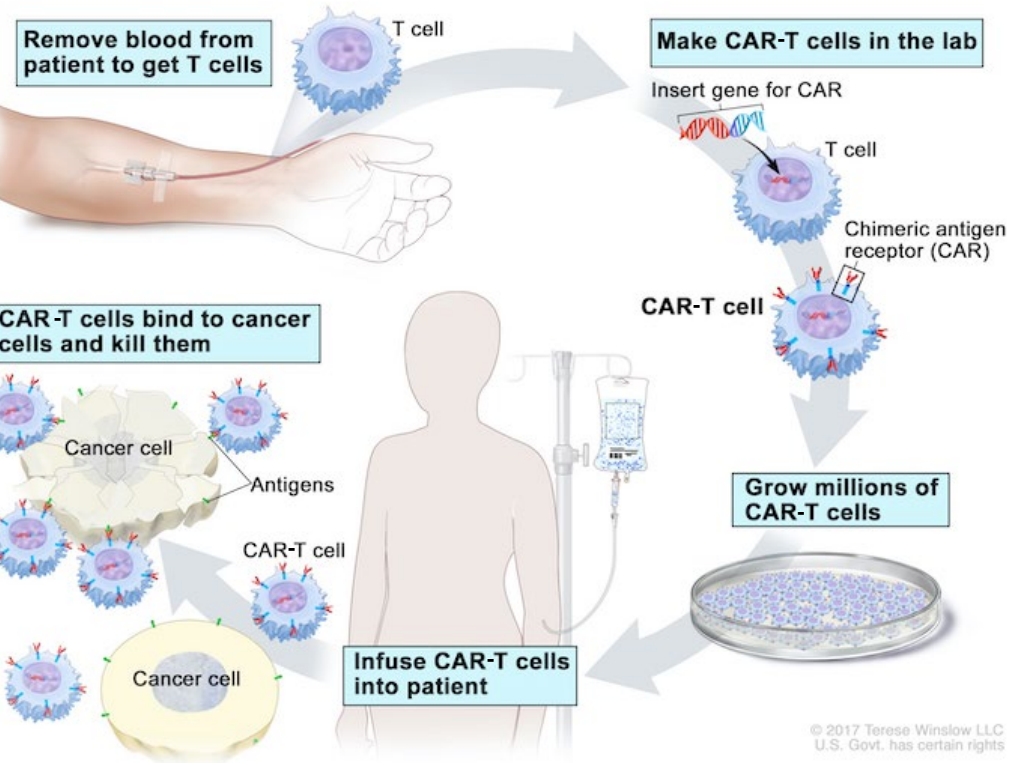
1. *https://www.businesswire.com/news/home/20230529005130/en/Global-Cell-Therapy-Market-Report-2023-Advancements-in-Biotechnology-Drives-Growth---ResearchAndMarkets.com*
2. *Zinzi et al., 2023 Pharmacological Research - 10.1016/j.phrs.2023.106742*
3. *https://s29.q4cdn.com/585078350/files/doc_financials/2022/q4/GILD-Q4-FY22-Earnings-Press-Release-2-February-2023.pdf*
4. *https://www.novartis.com/sites/novartis_com/files/q4-2022-media-release-en.pdf*
5. *https://bioprocessintl.com/bioprocess-insider/therapeutic-class/bms-sees-car-t-sales-rocket-in-line-with-increased-capacity/#:~:text=For%20the%20full%20year%202022,%2487%20million%20the%20year%20prior*

Emily Whitehead - **Celebrating 10 years of CAR-T cell therapy**

https://emilywhiteheadfoundation.org/10-years-of-car-t/

How original CAR-T cell therapies work

CAR-T cell therapy is personalised medicine



T cells = immune cell

T cells are a common type of immune cell that fight infections and can help fight cancer.

T cells from patient 'reprogrammed'

To generate autologous CAR-T cells, T cells are taken from a patient with blood cancer and 'reprogrammed' to produce a Chimeric Antigen Receptor (CAR). The CAR can recognise cancer cells through a target antigen.

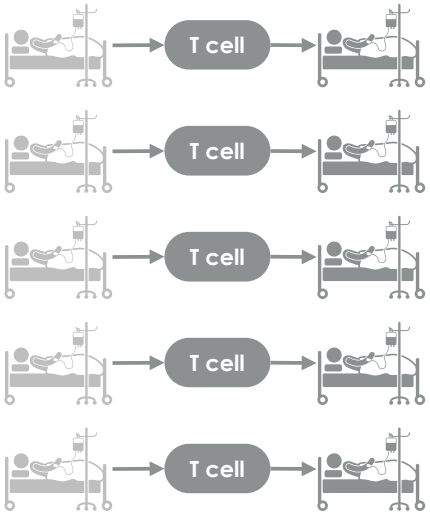
CAR-T cells find & kill tumour cells

CAR-T cells are administered to the patient to find and kill the tumour cells. Once the CAR binds to a tumour cell, the CAR-T cell is activated to kill the tumour cell.

https://www.ohsu.edu/sites/default/files/2021-04/CAR%20TcellTherapy7-700px.jpg

CAR-T cell therapies pose challenges

The current supply chain results in very high costs



T cells must originate from the patient

Each manufacturing batch is patient-specific

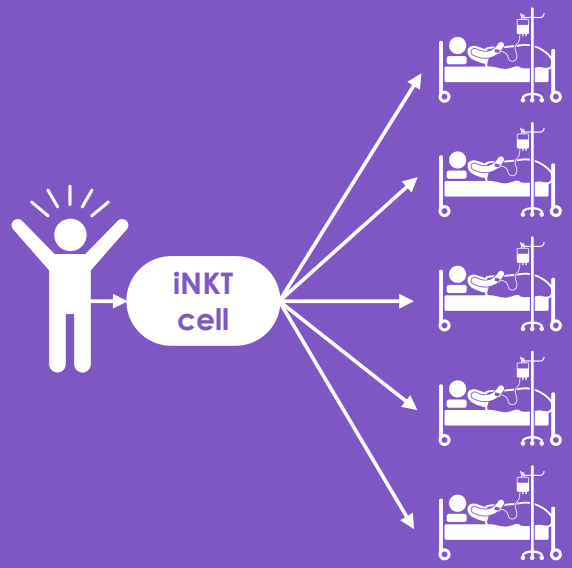
Manufacturing & supply chain costs are high = High drug pricing (>US$500k per patient)

T cells can be compromised due to disease = Potential reduction in efficacy

Limited centres can collect and manufacture = Limits patient access

Arovella's **off-the-shelf CAR-iNKT** cell platform

with potential for improved efficacy



Allogeneic

A single healthy donor batch = treatment for multiple patients

CAR-T cell therapies pose challenges

The manufacturing time can block patient access

4-6 weeks manufacturing time

Patient must wait for therapy to be manufactured

Patient may die waiting for treatment = Time is an issue for patients with aggressive disease

Manufacturing run failures can occur = Further increasing the time to treatment (and cost)

Arovella's **off-the-shelf CAR-iNKT** cell platform

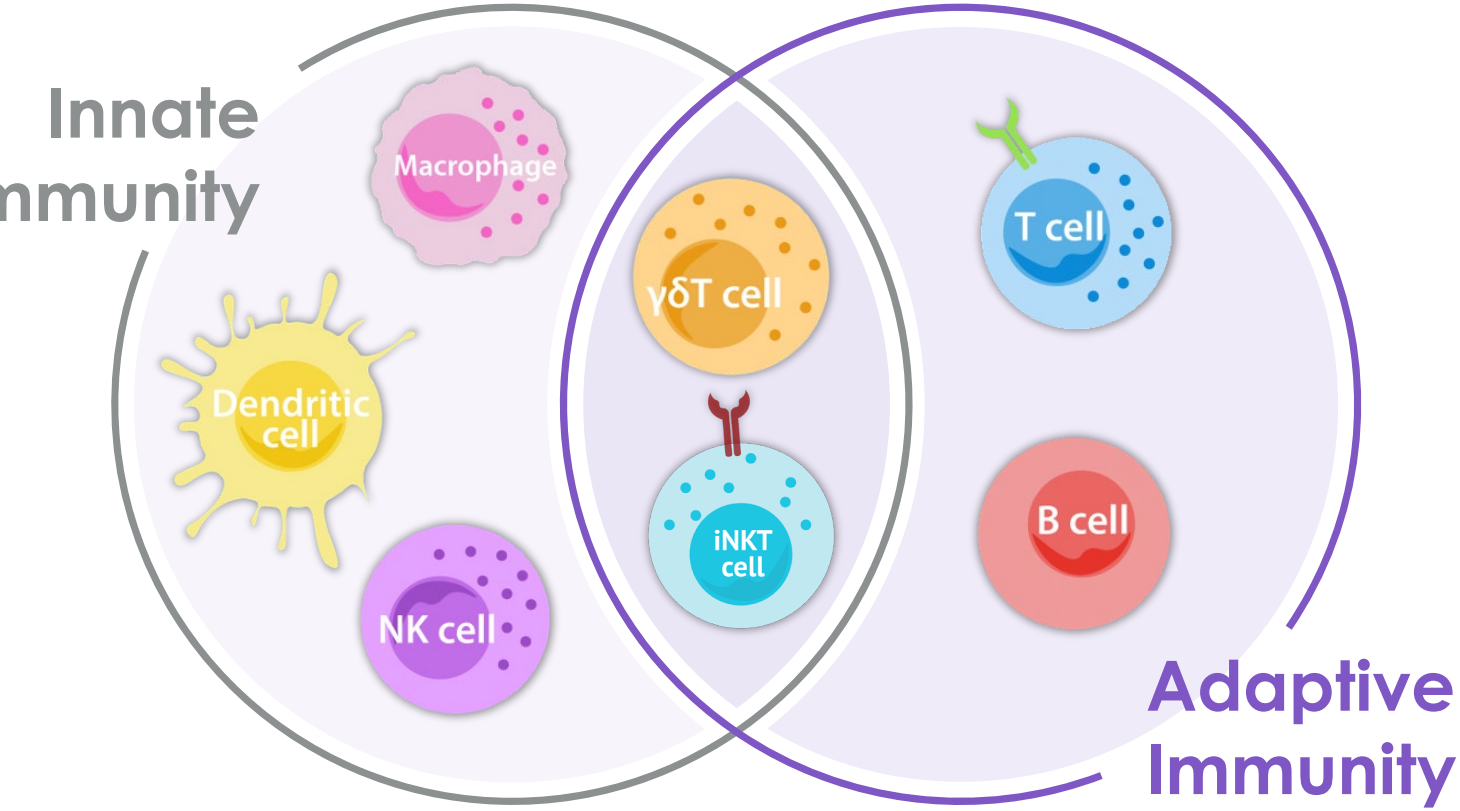
with potential for improved efficacy

1 week

Patients ready to dose within 1 week

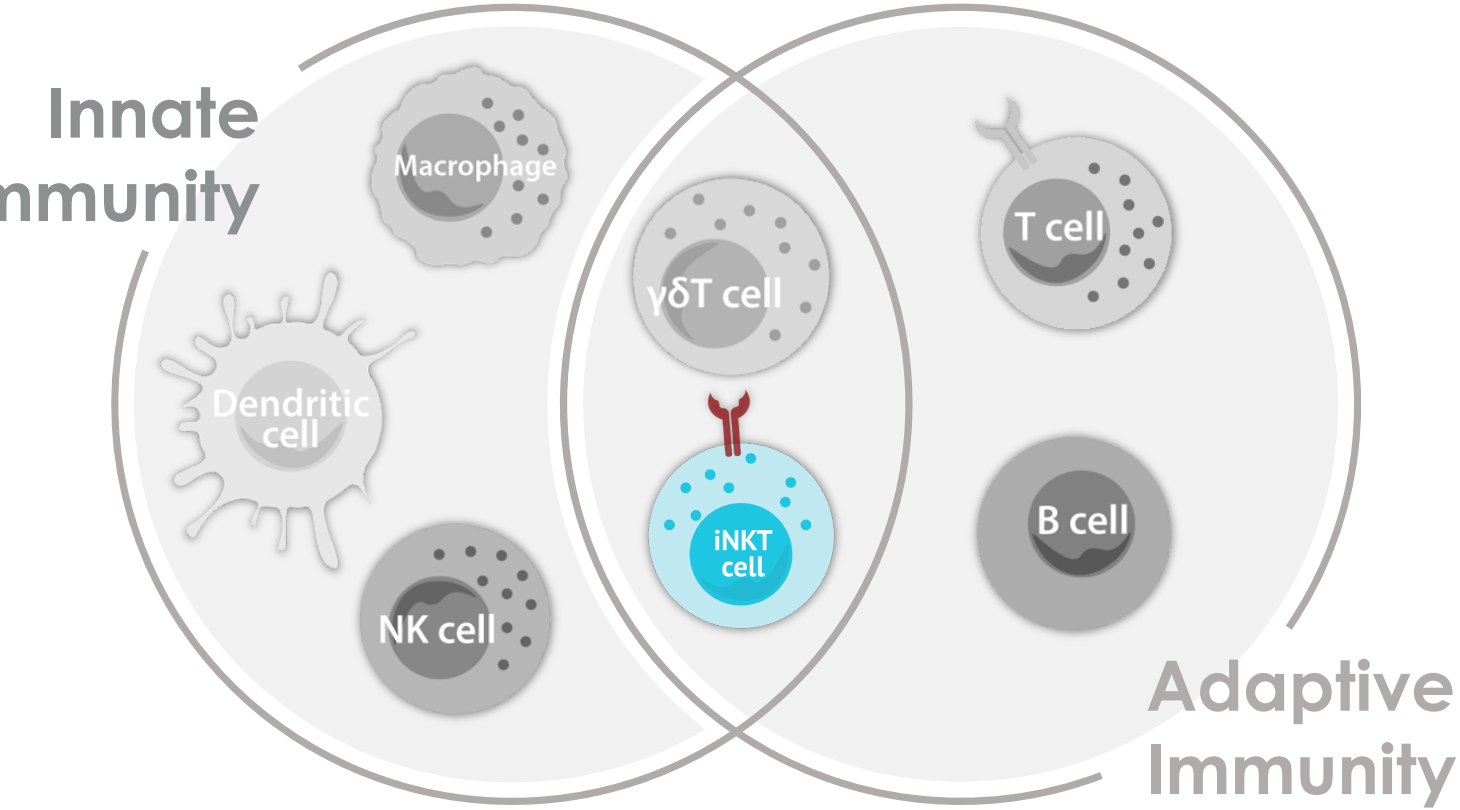
Introducing invariant Natural Killer T (iNKT) cells

Bridging the innate and adaptive immune system



iNKT cells represent a next-generation cell therapy

Properties make them ideal for use in cell therapy



Strong safety profile

- Don't cause graft versus host disease (GvHD)

Front line of the human immune system

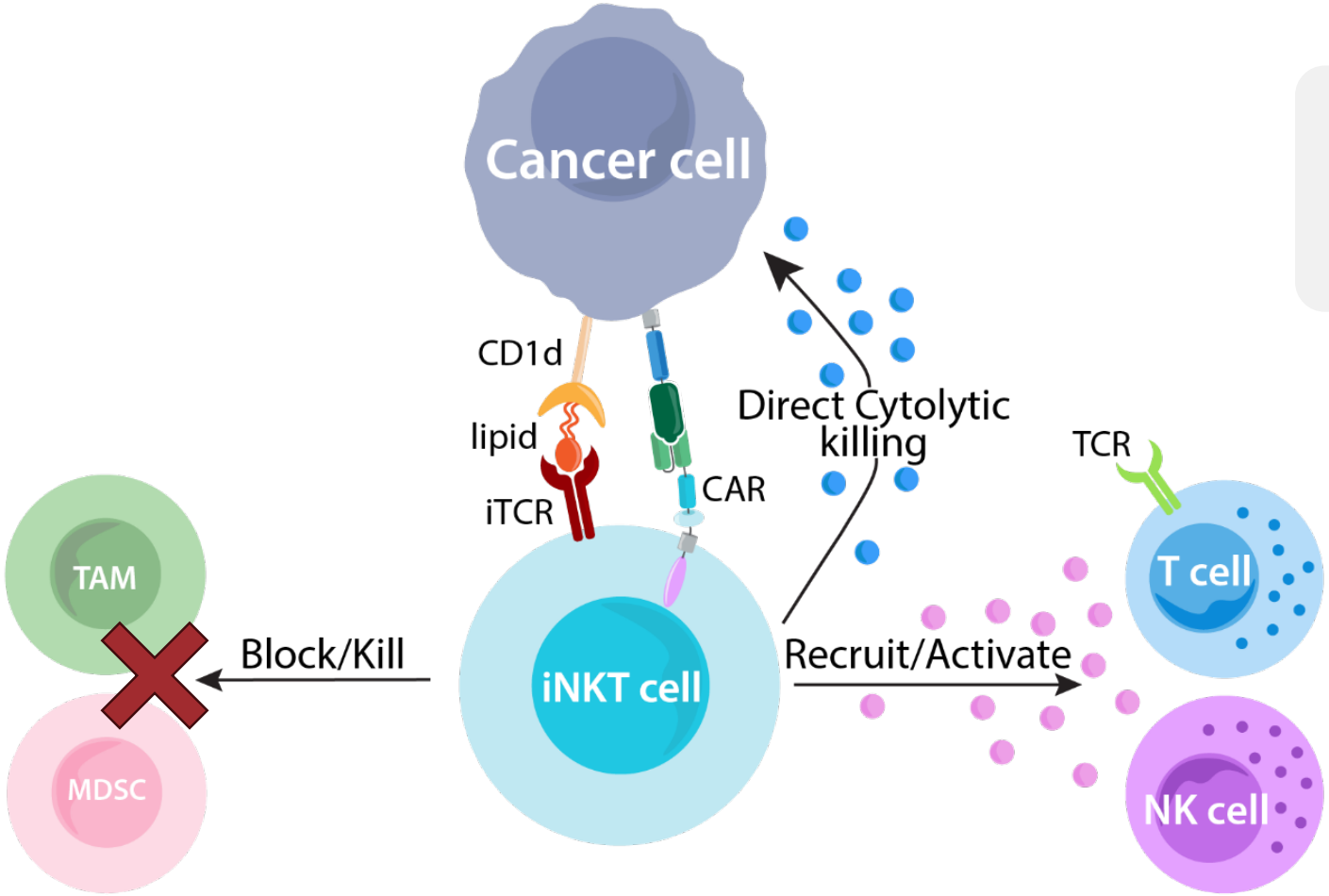
- Bridge innate & adaptive immune responses
- Contain both T cell & NK cell killing mechanisms
- Naturally target & kill cancers that express CD1d

Multiple anti-cancer properties

- Shape the tumour microenvironment by blocking/killing pro tumour cells (TAMs/MDSCs)
- Infiltrate tumours & secrete signaling molecules to activate other immune cells to kill tumour cells

CAR-iNKT cells have multiple ways to kill cancer cells

Also recruit 'good' immune cells and block 'bad' immune cells



TAM	Tumour Associated Macrophage
MDSC	Myeloid Derived Suppressor Cell
CAR	Chimeric Antigen Receptor
NK	Natural Killer

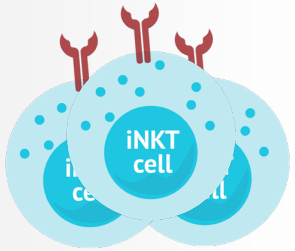
CAR-iNKT cell therapy production advantages

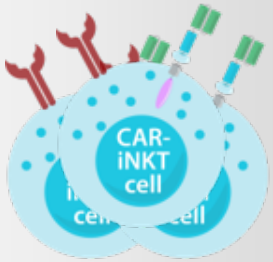
Off-the-shelf manufacturing advantages

MANUFACTURING

Collect Healthy Donor Blood

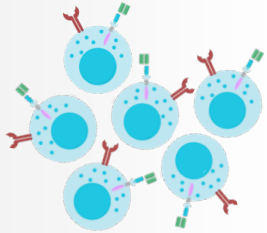
Isolate iNKT cells





Engineer iNKT cells to produce a CAR

Expand to grow billions of CAR-iNKT cells

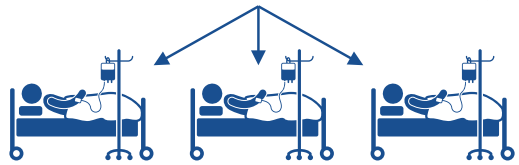


Vial and freeze CAR-iNKT cells

TREATMENT

Thaw CAR-iNKT cells

Dose eligible patients



Healthier starting material
Potentially better efficacy

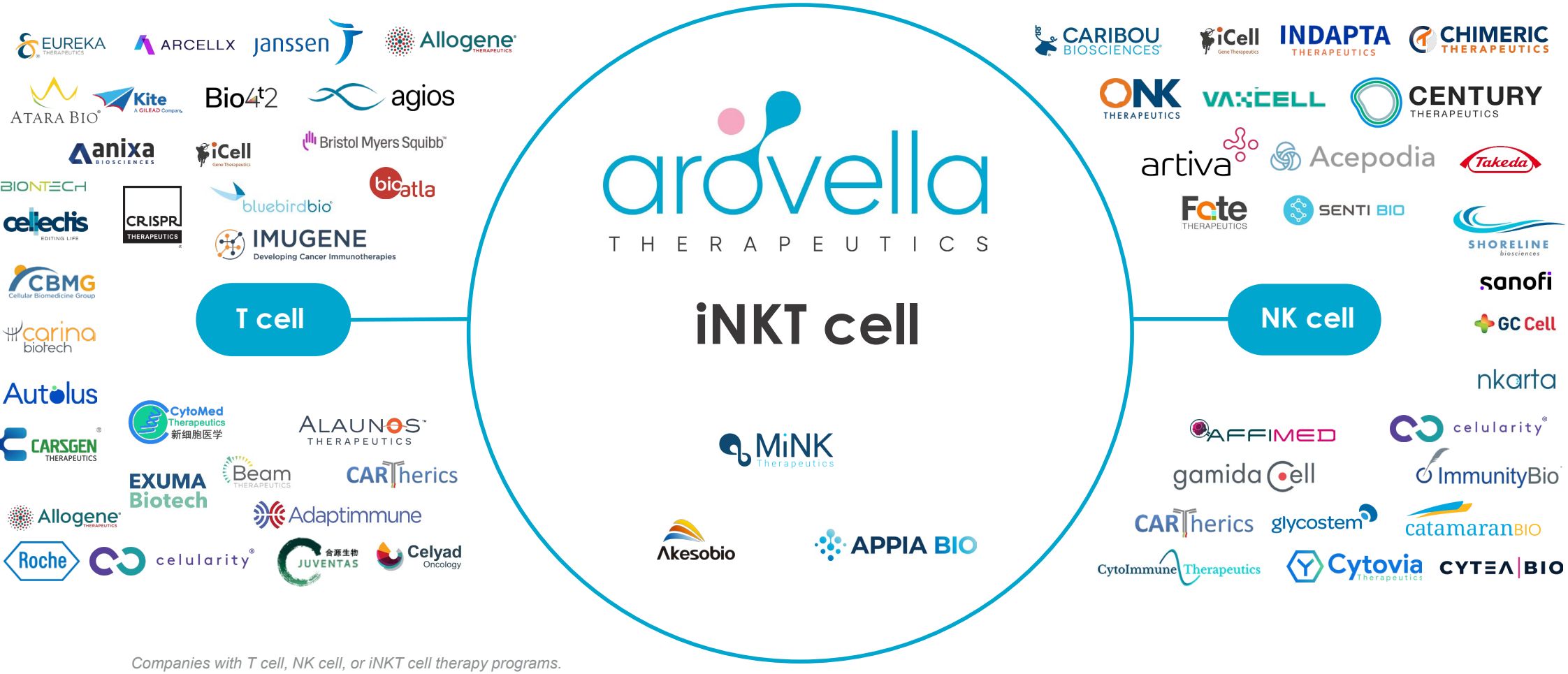
Scalable manufacturing with reduced costs
Reach more patients

Faster access to treatment
Improved outcomes for aggressive cancers

Removes risk of manufacturing run failure

A differentiated position

T cell and NK cell sectors are competitive



Companies with T cell, NK cell, or iNKT cell therapy programs.
Source: Company analysis based on public information

About ALA-101 (CAR19-iNKT cells)

A next generation **off-the-shelf** cell therapy for CD19+ cancers

CD19+ hematological malignancies

Targeting CD19+ blood cancers

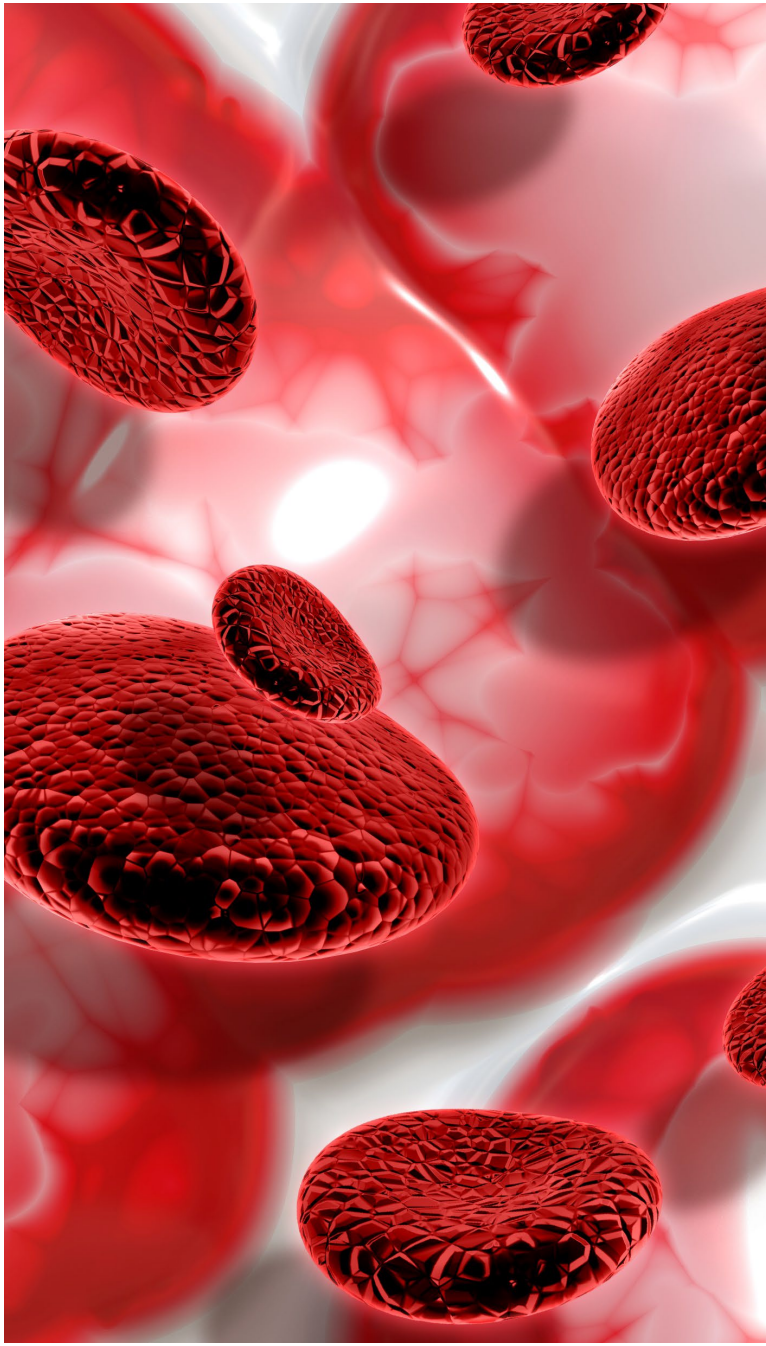
CD19+ lymphomas and CD19+ leukemias

>140k cases in the US in 2023[1,2]

>40k deaths[1,2] in the US in 2023

CAR-T products are moving to second line therapy

No allogeneic cell therapy approved to date for blood cancers

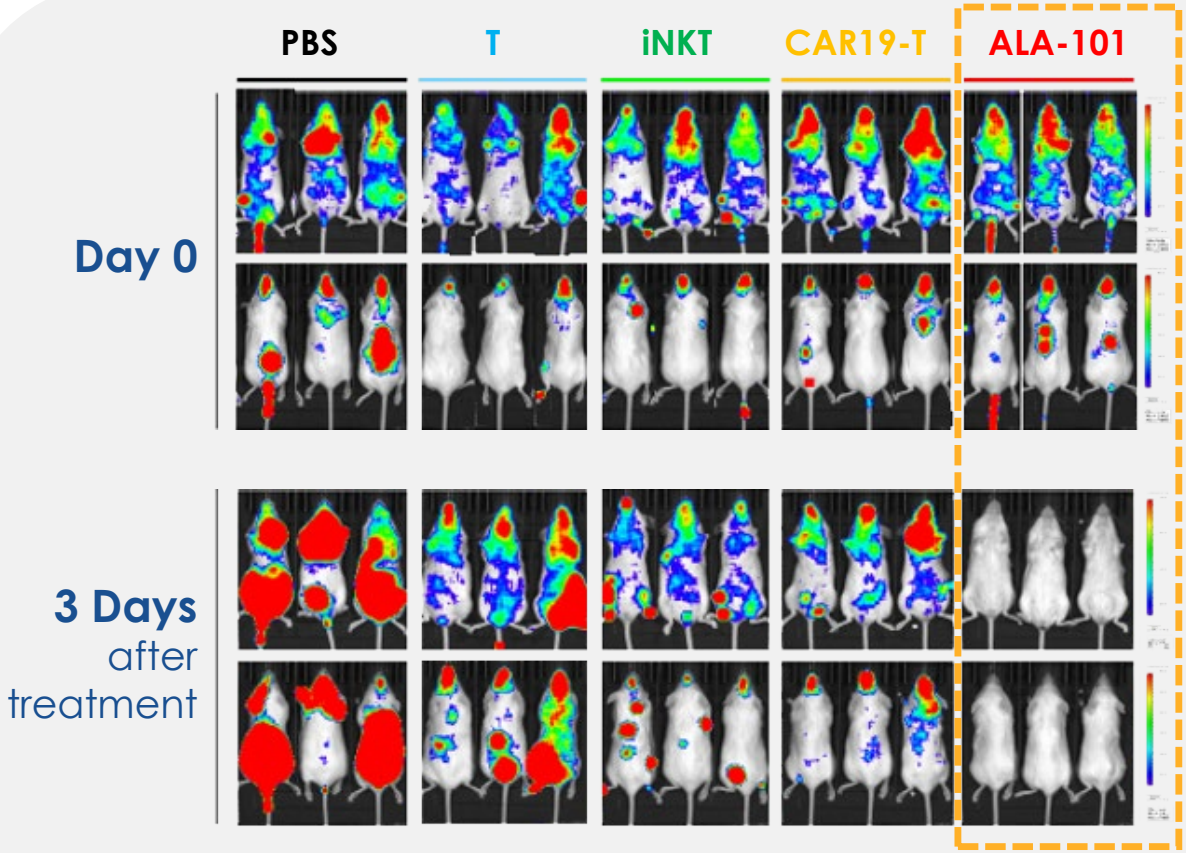


1. https://seer.cancer.gov/statfacts/html/nhl.html; 2. https://seer.cancer.gov/statfacts/html/leuks.html

ALA-101: enhanced tumour killing in vivo

ALA-101 rapidly eradicates tumour cells in mice

- Tumour cells expressing CD19 and CD1d were intravenously delivered into mice
- Mice were treated with:
  - PBS (saline)
  - Unmodified T cells (T)
  - Unmodified iNKT cells (iNKT)
  - CAR19-T cells
  - ALA-101
- After three days, ALA-101 resulted in significant regression of tumour cells
- In all other treatments, we observed strong tumour cell persistence
- ALA-101 displays swift action

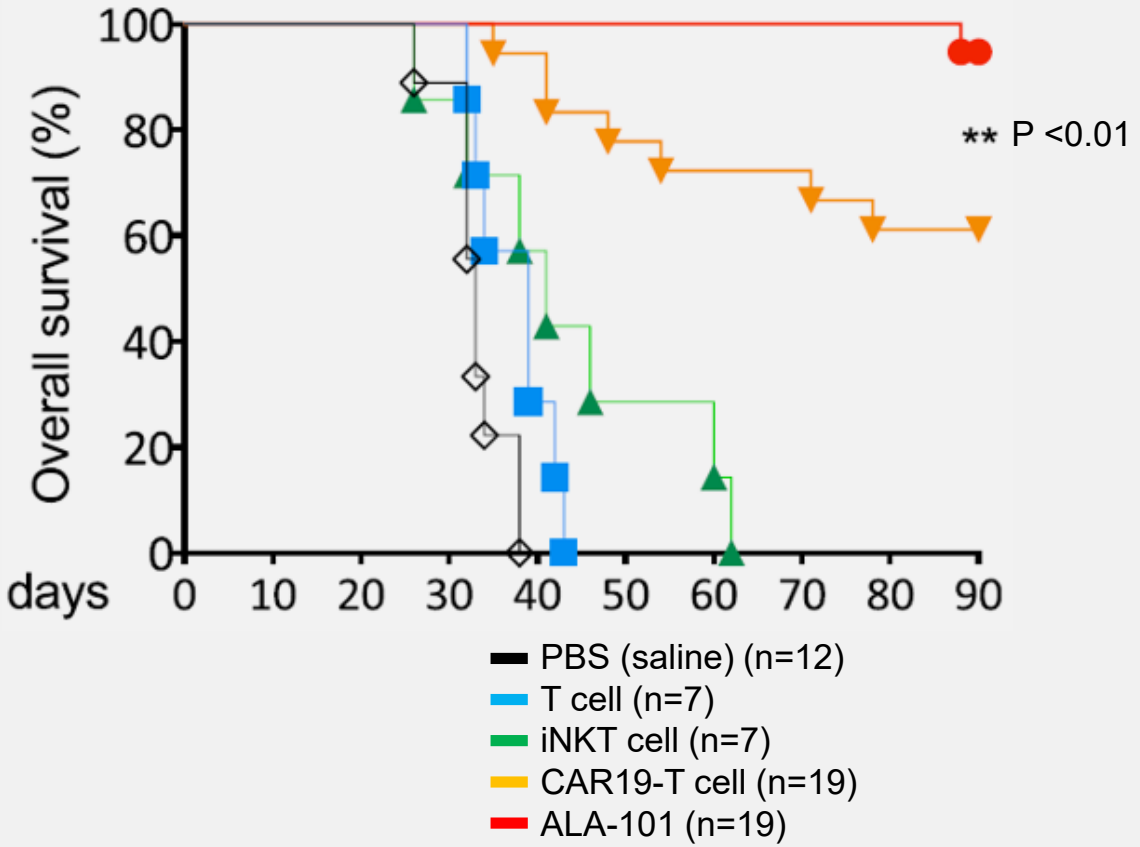


Rotolo *et al.*, Cancer Cell (2018)

ALA-101: next generation cell therapy

ALA-101 significantly increased survival in mice versus treatment with CAR19-T cells

- Tumour cells expressing CD19 and CD1d were intravenously delivered into mice
- Mice were treated with:
  - PBS (saline)
  - Unmodified T cells (T)
  - Unmodified iNKT cells (iNKT)
  - CAR19-T cells
  - ALA-101
- After 90 days, only mice treated with CAR19-T cells or ALA-101 remained alive
- 1.5x more mice treated with ALA-101 remained alive after 90 days relative to CAR19-T cells
- ALA-101 has the potential to be an effective, off-the-shelf cell therapy for the treatment of CD19-expressing cancers

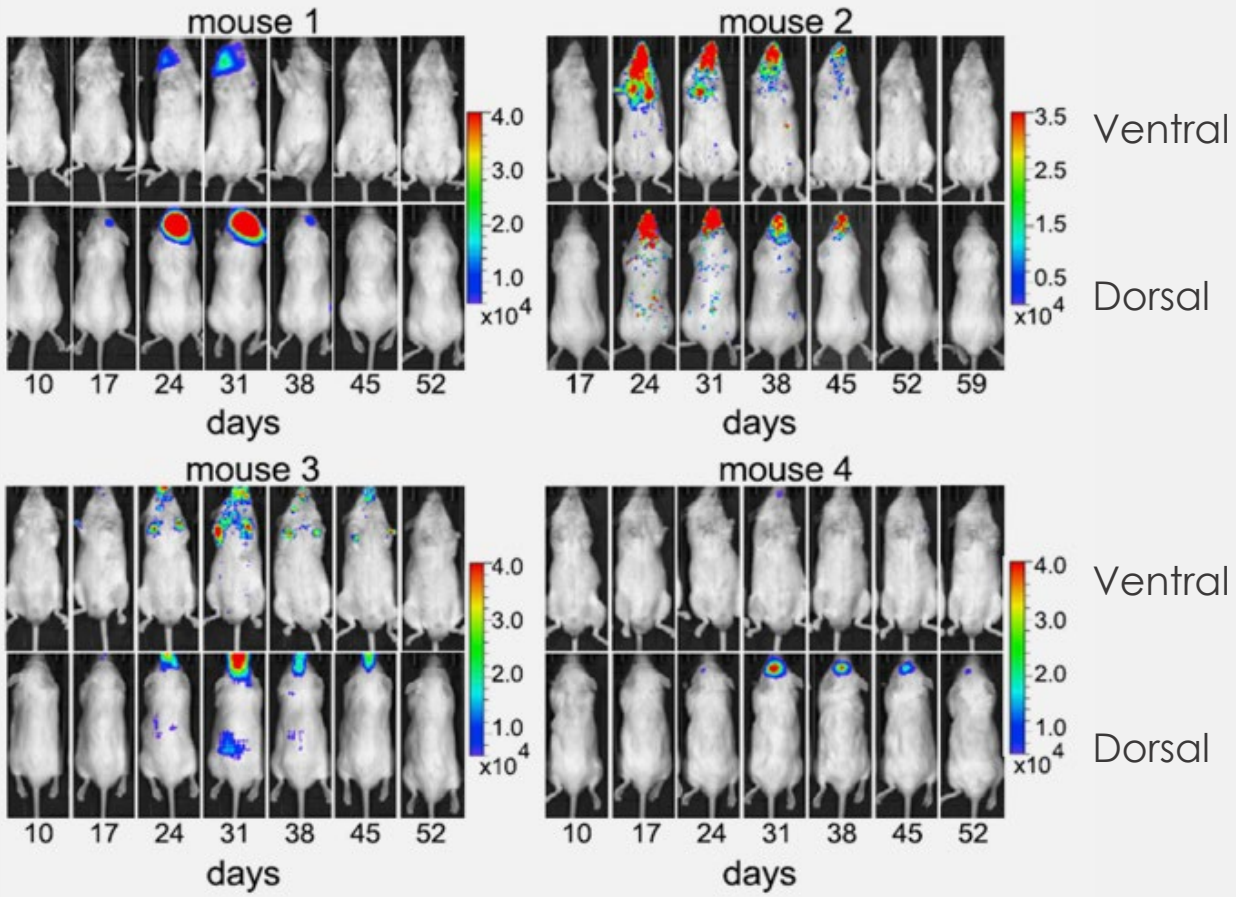


Rotolo *et al.*, Cancer Cell (2018)

ALA-101: spontaneous secondary remission

ALA-101 activity may persist to eradicate tumour cells following relapse

- Four mice treated with ALA-101 had the cancer return to the brain
- In all four mice, the cancer was eliminated a second time with no additional dosing
- This provides evidence that CAR19-iNKT cells can survive and continue to protect against cancer cells *in vivo*
- Potential to use ALA-101 to treat central nervous system lymphoma or brain metastases



Rotolo *et al.*, Cancer Cell (2018)

Progress towards first-in-human clinical trials

ALA-101 data confirms activity and off-the-shelf capability

Potent Antitumour Activity

Demonstrated efficacy of ALA-101 against CD19+ ymphomas and leukemias. Proof-of-concept data generated with clinical-design lentiviral vector in animal models using thawed, “off-the-shelf” ALA-101.

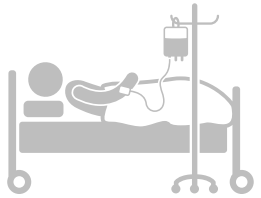
Expected to be Safe

iNKT cells have been shown in clinical trials not to cause graft versus host disease (GvHD) and the CD19 targeting CAR (FMC63) is a validated targeting agent in approved cell therapies.

Multiple Dose Manufacturing

ALA has demonstrated that its manufacturing process can produce a high number of CAR+ cells with potent cell killing properties and has commenced production of GMP-grade lentivirus for CD19 CAR expression.

Phase 1 Clinical Trial



iNKT cells to target solid tumours

Arovella is implementing its strategy to target and kill solid tumours – 90% of newly diagnosed cancer cases[1]

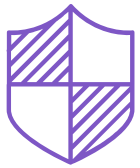
1. *https://www.cancer.gov/types/common-cancers*

Arovella's strategies to combat solid tumours

Arovella is using three approaches to expand the iNKT cell platform into solid tumours

License novel cancer targets

Identify and license new targets that are expressed in multiple cancers to incorporate into Arovella's iNKT cell therapy platform



Armour iNKT cells

Enhance the performance of iNKT cells by equipping iNKT cells with novel armouring technologies

Create unique partnerships

Create partnerships to use novel combination therapies with synergistic effects

Manufacturing CLDN18.2-iNKT cells

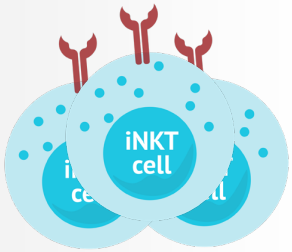
STRATEGY 1

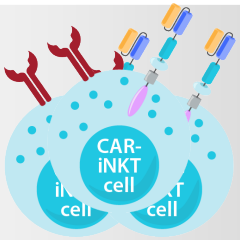
Generation of CLDN18.2-iNKT cells will leverage existing manufacturing process

MANUFACTURING

Collect Healthy Donor Blood

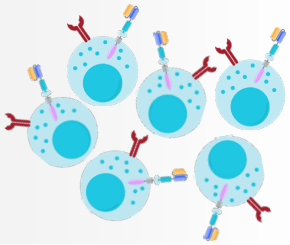
Isolate iNKT cells





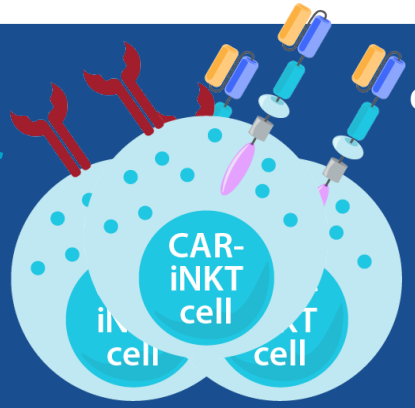
Engineer iNKT cells to produce a CLDN18.2 CAR

Expand to grow billions of CAR-iNKT cells



Vial and freeze CAR-iNKT cells

Arovella will use its **proprietary manufacturing process** to create CLDN18.2-iNKT cells



CLDN18.2 CAR

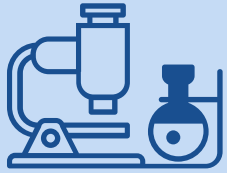
Introducing Claudin 18.2 (CLDN18.2)

A promising solid tumour target

CLDN18.2 overexpression has been

identified in several types of cancers

- gastric cancer **(GC)**
- gastroesophageal junction cancer **(GEJC)**
- pancreatic cancer **(PC)**
- esophageal cancer **(EC)**
- ovarian adenocarcinoma **(OAC)**
- lung cancers **(LC)**



Validated target

with first monoclonal antibody expected to be **approved in 2024**

Gastric cancer

market alone expected to reach **$10.7 billion** by 2031[1]

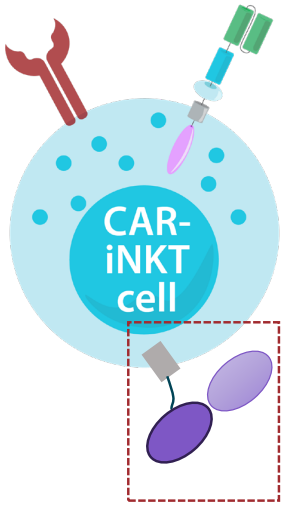
1. https://www.alliedmarketresearch.com/gastric-cancer-market-A74458#:~:text=The%20global%20gastric%20cancer%20market,cells%20lining%20of%20the%20stomach

“Armouring” iNKT cells

STRATEGY 2

Cytokine technology enhances activity of iNKT cells in solid tumours

Cytokine technology



Cytokine technology

Adding specialised cytokines to iNKT cells can **increase persistence of the cells** *(how long they last in the body)* and increase anti-tumour activity

Exclusive option

with University of North Carolina for cytokine technology developed by Prof. Gianpietro Dotti

Cytokine technology is incorporated into the lentiviral vector and **does not require changes to the manufacturing process**

iNKT cells + cytokine technology

Expand more and survive for longer
than CAR-iNKT cells lacking the cytokine

10x more circulating CAR-iNKT cells
4 weeks after treatment in a mouse model

Superior anti-tumour activity
compared to CAR-iNKT cells lacking the cytokine

75%+
of mice treated with CAR-iNKT cells *containing the cytokine* were **alive at 61 days**

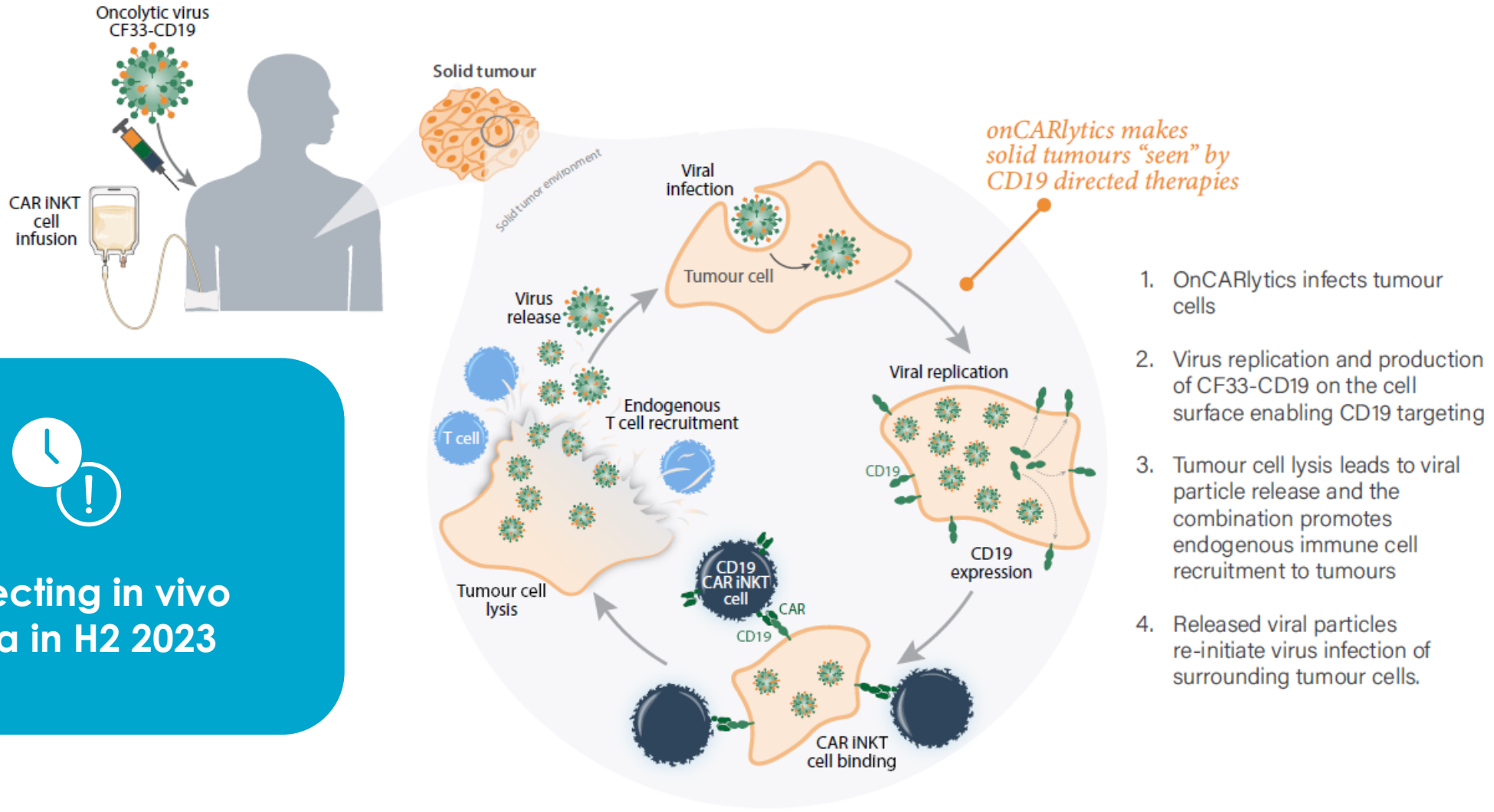
VS

0%
of mice treated with CAR-iNKT cells lacking the cytokine **were alive at 49 days**

ALA-101 & Imugene's onCARlytics

STRATEGY 3

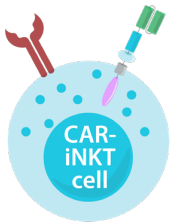
Imugene's onCARlytics platform may make solid tumours sensitive to ALA-101



1. OnCARlytics infects tumour cells
2. Virus replication and production of CF33-CD19 on the cell surface enabling CD19 targeting
3. Tumour cell lysis leads to viral particle release and the combination promotes endogenous immune cell recruitment to tumours
4. Released viral particles re-initiate virus infection of surrounding tumour cells.

Expecting in vivo data in H2 2023

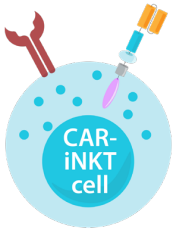
Arovella's expanding pipeline



CD19-CAR

CD19-CAR

Oncolytic virus
CF33-CD19



Novel Targets

Introduction of CLDN18.2

ALA-101

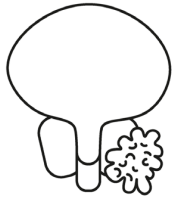
ALA-101 + onCARlytics

CLDN18.2

Cytokine Technology

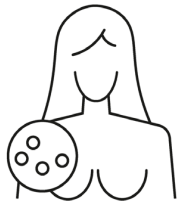
Non-Hodgkin's Lymphoma

Head and Neck Cancer



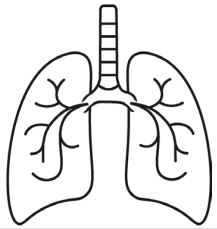
Prostate Cancer

Brain Metastases

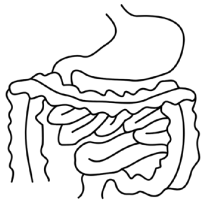


Triple negative breast cancer

Pancreatic Cancer



Lung Cancer



Gastric Cancers

Milestones for FY2024

	June 2023	December 2023	June 2024
ALA-101	▪ Complete process optimisation and scale-up in preparation for cGMP manufacture ▪ Complete production of cGMP lentiviral vector ▪ Finalise clinical trial plan for Phase 1 study	▪ Complete cGMP manufacture for Phase 1 clinical trials ▪ Complete preparatory activities for Phase 1 study, including submission of regulatory dossier, engagement with clinical sites and KOLs	
iNKT Cell Therapy Platform	▪ Confirm the activity of ALA-101 cells when combined with Imugene's onCARlytics to target solid tumours in animal models ▪ In-licence cytokine technology currently under option (pending due diligence)	▪ Initiate proof-of-concept testing for CLDN18.2-iNKT cells to expand iNKT platform for treatment of solid tumours	

Expect to advance ALA-101 to Phase 1 first-in-human clinical trial during 2024

Dose escalation Phase 1 study in patients with CD19+ blood cancers

Continue to enhance the platform and expand the pipeline

Expand the use of the iNKT platform to treat solid tumours

cGMP – Current Good Manufacturing Practice; KOLs – key opinion leaders

Financial overview

Financial Snapshot

ASX CODE	ALA
Market capitalisation[1]	$81.5 million
Shares on issue	906.31 million
52-week low / high[1]	$0.020 / $0.105
Cash Balance (September 30 2023)	$5.32 million
R&D tax rebate received 20 November 2023	$1.95 million

Major Shareholders

Shareholder	Ownership (%) [1]
THE TRUST COMPANY (AUSTRALIA) LIMITED	59,397,161 (6.66%)
RICHARD JOHN MANN	50,905,657 (5.71%)
UBS NOMINEES PTY LTD	20,620,196 (2.31%)
BLACKBURNE CAPITAL PTY LTD	18,325,000 (2.05%)
DYLIDE PTY LTD	15,666,666 (1.76%)

1. *As of 8 November 2023*

Recent cell therapy transactions[1]

Date	Type of deal	Acquirer/Licensee	Target/Licensor	Cell Type	Stage	Upfront (US$M)	Milestones (US$M)	Total deal value (US$M)
Nov-23	Collaboration and investment	AstraZeneca	cellectis	Not specified	Platform	$25	$70-220 per product	
Aug-23	Licence[2]	IMUGENE Developing Cancer Immunotherapies	PRECISION BIOSCIENCES	T Cell	Phase 1b	$21	$206	$227
Aug-23	Strategic investment (ROFR) [3]	astellas	POSEIDA THERAPEUTICS	T Cell	Phase 1	$25	$0	$25
May-23	Licence	janssen	CBMG Cellular Biomedicine Group	T Cell	Phase 1b	$245	*undisclosed*	
Jan-23	Acquisition	AstraZeneca	neogene THERAPEUTICS	T Cell	Phase 1	$200	$120	$320
Oct-22	Development collaboration[4]	GILEAD	ARCELLX	T Cell	Phase 2	$225	*undisclosed*	
Sep-22	Research collaboration	Genentech A Member of the Roche Group	ArsenalBio	T Cell	Preclinical	$70	*undisclosed*	
Aug-22	Licence & strategic collaboration	Roche	POSEIDA THERAPEUTICS	T Cell	Phase 1	$110	$110	$220
Sep-21	Development collaboration	Genentech A Member of the Roche Group	Adaptimmune	T Cell	Preclinical	$150	$150	$300
Aug-21	Research collaboration	GILEAD	APPIA BIO	iNKT Cell	Preclinical	*undisclosed*	*undisclosed*	$875
May-21	Acquisition	Athenex	kuur THERAPEUTICS	iNKT Cell	Phase 1	$70	$115	$185
Jun-21	Acquisition	eterna	Novellus THERAPEUTICS	Multiple	Preclinical	$125	$0	$125
Dec-19	Acquisition	astellas	XYPHOS	Multiple	Preclinical	$120	$545	$665

1. *See Slide 33 for deal references*
2. *Cellectis will receive a US$220m equity investment from Astra Zeneca plus tiered royalties. Milestones are payable for 10 products*
3. *Precision is eligible for double digit royalties on net sales and $145 million in milestone payments and tiered royalties for additional programs*
4. *Poseida also received a US$25m equity investment from Astellas*
5. *Arcellx also received a US$100m equity investment from Gilead*

Summary

Novel allogeneic CAR-iNKT cell platform

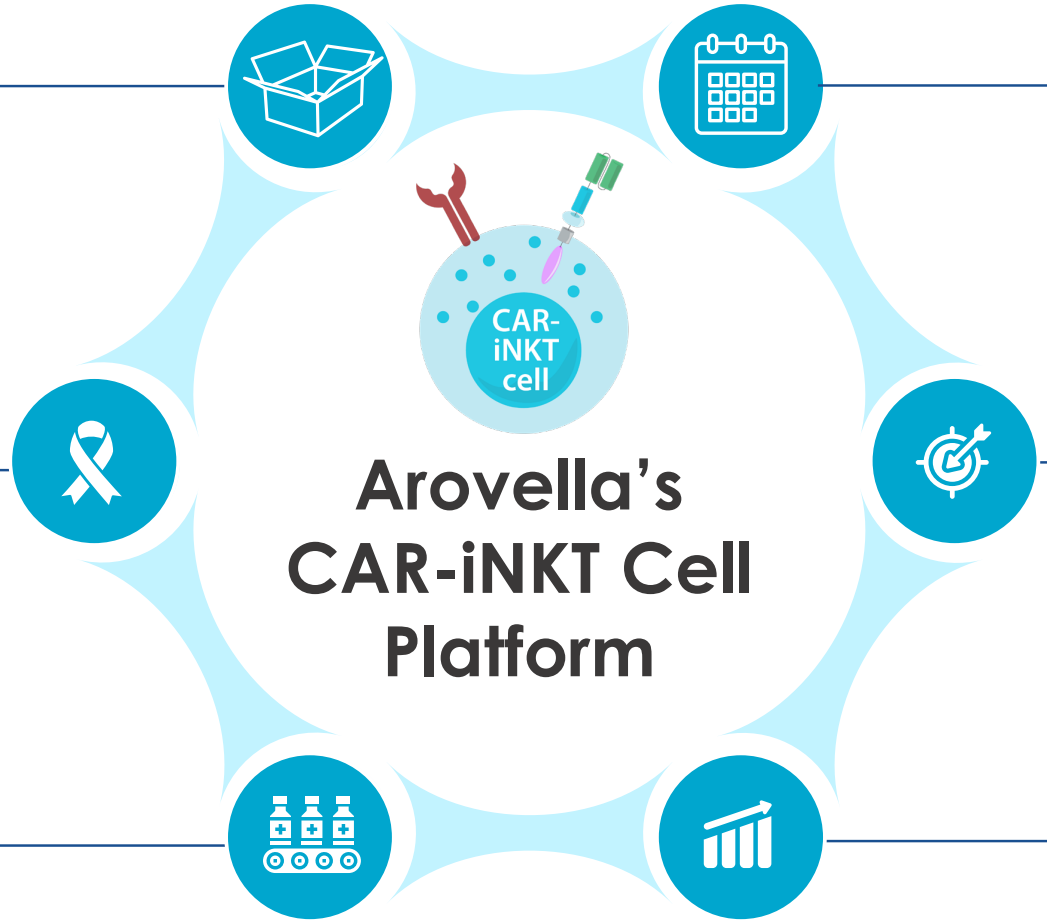
NKT cells serve as an excellent platform to develop allogeneic, or “off-the-shelf”, cell therapies to treat cancer

Improved manufacturing logistics

Allogeneic CAR-iNKT cells will significantly improve ogistics and increase patient access

AR-iNKT cells have multiple anticancer properties

AR-iNKT cells have multiple anti-cancer properties that may support enhanced efficacy over other immune cell types



Lead product progressing to clinical trials

ALA-101, a potential treatment for CD19-expressing blood cancers, is being progressed to Phase 1 clinical trials, expected to commence in 2024

Arovella has an expanding pipeline

Arovella continues to expand the iNKT cell platform to potentially treat solid tumours

Arovella is poised for growth

Arovella is developing a cutting-edge CAR-iNKT cell therapy platform, with an expanding pipeline and a strong leadership team

ASX:ALA

arovella
THERAPEUTICS

Thank You

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CEO & Managing Director

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Cell Therapy Deal References

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