Phio PHARMACEUTICALS

DEVELOPING THE NEXT GENERATION
of immuno-oncology therapeutics

September 2021

www.phiopharma.com | Ticker: PHIO (NASDAQ)

Forward Looking Statements

This presentation contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. Words such as “believes,” “anticipates,” “plans,” “expects,” “indicates,” “will,” “intends,” “potential,” “suggests” and similar expressions are intended to identify forward-looking statements. These statements are based on Phio Pharmaceuticals Corp.’s (the “Company”) current beliefs and expectations. Such statements include, but are not limited to, statements about the impact to our business and operations by the ongoing coronavirus pandemic, the development of our product candidates, the expected timing of certain developmental milestones (including timing or likelihood of regulatory filings and approvals), results from our preclinical and clinical studies, potential partnership opportunities, and the success of any such opportunities, the Company’s competition and market opportunity and pro forma estimates. The inclusion of forward-looking statements should not be regarded as a representation by the Company that any of its plans will be achieved. Actual results may differ from those set forth in this presentation due to risks and uncertainties in the Company’s business, including those identified under “Risk Factors” in the Company’s most recently filed Annual Report on Form 10-K and in other filings the Company periodically makes with the U.S. Securities and Exchange Commission. The Company does not undertake to update any of these forward-looking statements to reflect a change in its views or events or circumstances that occur after the date of this presentation.

Immuno-oncology

Unmet Need

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Immuno-oncology: Definition and key unmet needs

Immuno-oncology is the science of harnessing a patient's immune system to better recognize and attack cancer cells, through:

Cell therapy
e.g. CAR-T adoptive cell therapy (ACT)

Unmet need

- Limited activity in solid tumors
- Cost

Systemic immune stimulating therapy
e.g. checkpoint inhibitors

Unmet need

- High rate of non-responders & relapse
- Immune related adverse events

Solutions include:

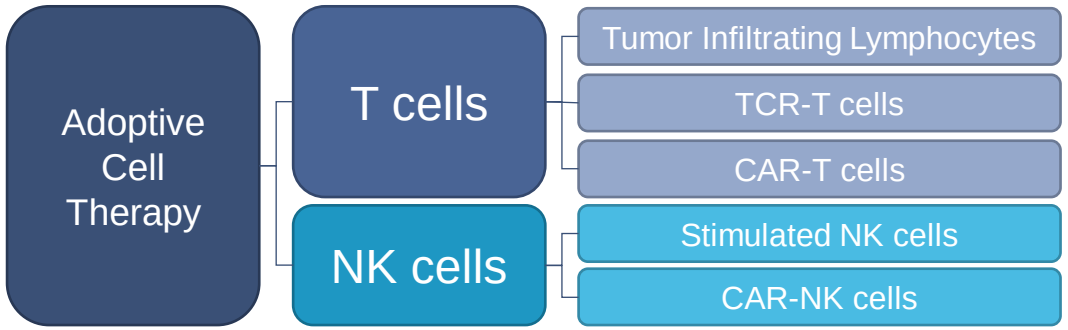
"Reprogramming" cells for ACT

- Activate the otherwise dysfunctional immune cells

"Reprogramming" tumor microenvironment

- Remove the barriers of the tumor immune microenvironment

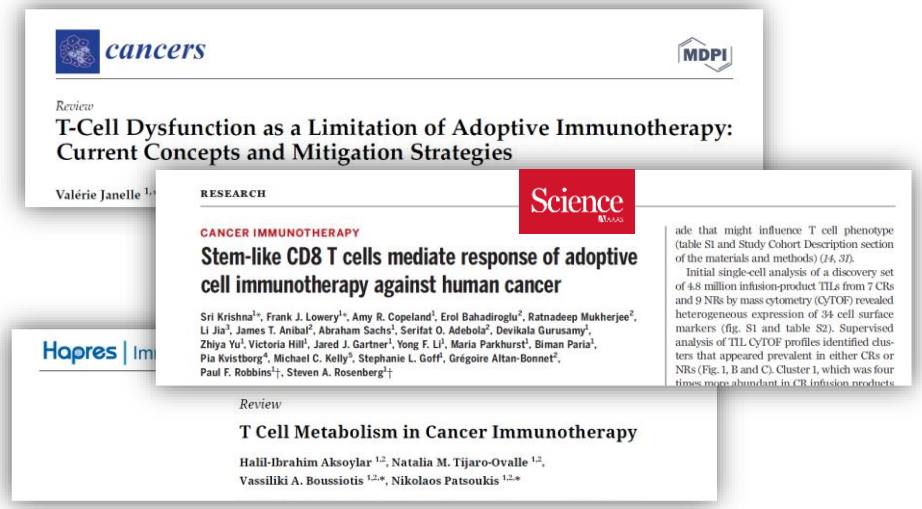
Various adoptive cell therapies share similar issues



Regardless of source / lineage, manufacturing manipulations often lead to dysfunctional features including:

- Terminal differentiation
- Exhaustion
- Senescence
- Suboptimal metabolism

"Dysfunctional features induced during laboratory-based manipulations of immune products prior to adoptive cell transfer has a determining effect on outcomes"


cancers
MDPI
Review
T-Cell Dysfunction as a Limitation of Adoptive Immunotherapy: Current Concepts and Mitigation Strategies
Valérie Janelle
RESEARCH
Science
CANCER IMMUNOTHERAPY
Stem-like CD8 T cells mediate response of adoptive cell immunotherapy against human cancer
Sri Krishna, Frank J. Lowery, Amy R. Copeland, Erol Bahadiroglu, Ratnadeep Mukherjee, Li Jia, James T. Anibal, Abraham Sachs, Serifat O. Adebola, Devikala Gurusamy, Zhiya Yu, Victoria Hill, Jared J. Gartner, Yong F. Li, Maria Parkhurst, Biman Paria, Pia Kvistborg, Michael C. Kelly, Stephanie L. Goff, Grégoire Altan-Bonnet, Paul F. Robbins, Steven A. Rosenberg
Hapres
Review
T Cell Metabolism in Cancer Immunotherapy
Halil-Ibrahim Aksoylar, Natalia M. Tijaro-Ovalle, Vassiliki A. Boussiotis, Nikolaos Patsoukis

Alter cell phenotype:
- Checkpoints & co-inhibitory signals
- Metabolic programing
- Epigenetic programing

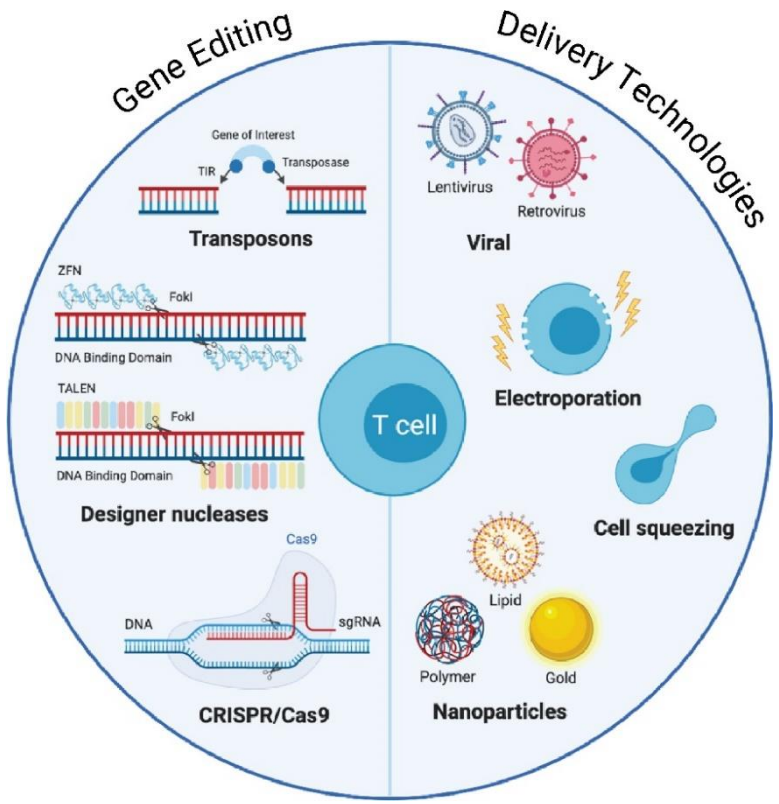
Combination therapies
- Immunomodulation
  - Immune cells
  - Tumor cells

During manufacturing

After manufacturing

Current reprogramming strategies for immune cells in ACT

Gene editing approaches



Graphic from: Atsavapranee E.S. et al., *EBioMedicine* 2021;67:103354.

Gene editing suitability

"permanent modifications are not always required or even desired"

- ✓ Receptor (CAR, TCR)
- ? Built-in checkpoint inhibition
- ✘ Optimize cell metabolism
- ✘ Optimize cell differentiation (e.g. T_{CM}, T_{SCM})
- ✘ Combinations of the above

Gene editing issues[1]

Transposons:
- Inefficient plasmid delivery
- Not suitable for gene disruption

Zinc Finger Nucleases:
- Complex protein engineering for multiple target genes

TALEN:
- Inefficient delivery
- Complex protein engineering for multiple target genes

CRISPR
- Less specific
- Risks of off-target mutagenesis and immunogenicity
- Inefficient *in vivo* delivery
- Low efficiency for targeting multiple genes

[1]Atsavapranee E.S. et al., *EBioMedicine* 2021;67:103354.

INTASYL™

to improve cells used in adoptive cell therapy

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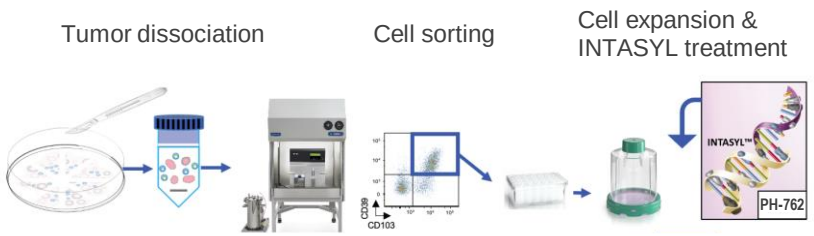
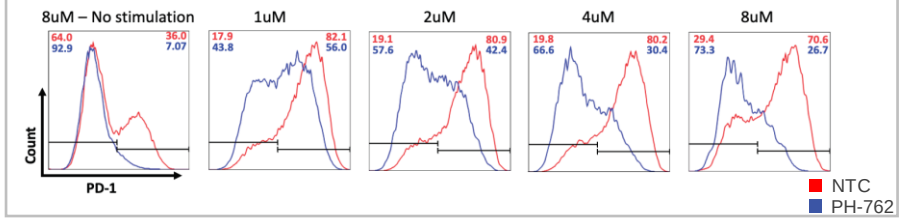
INTASYL in ACT: Increased activation and cell killing with human TILs

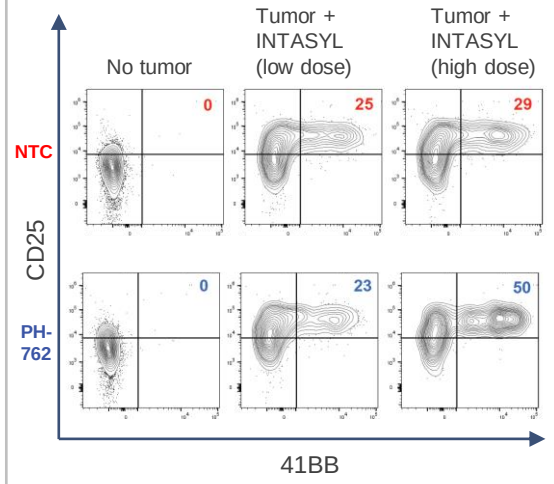
Using PH-762 during the rapid expansion of enriched fraction of tumor-reactive T cells ($CD39^+CD103^+CD8^+$)



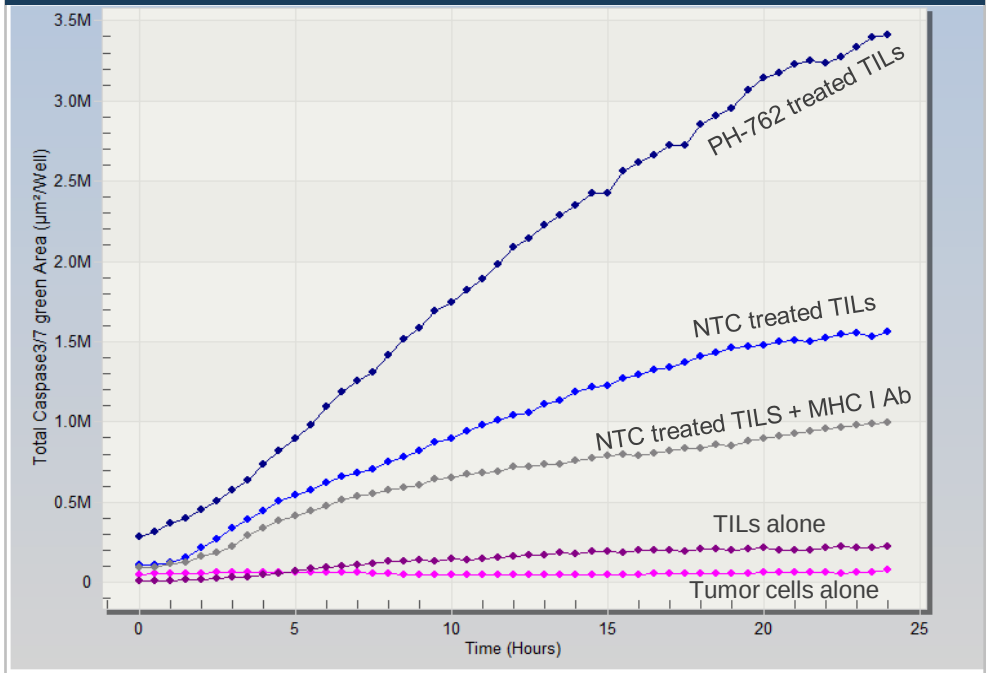
PD-1 protein knock-down by PH-762 is dose dependent

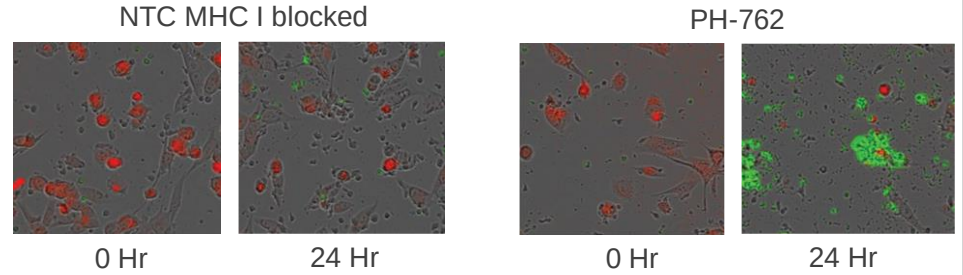


TILs treated with PH-762 express high levels of activation markers



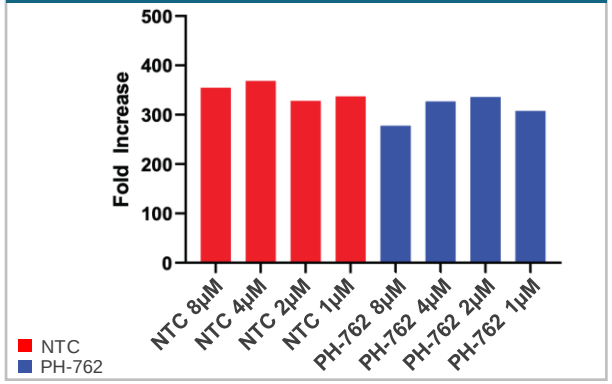
TILs treated with PH-762 efficiently kill autologous tumor cells



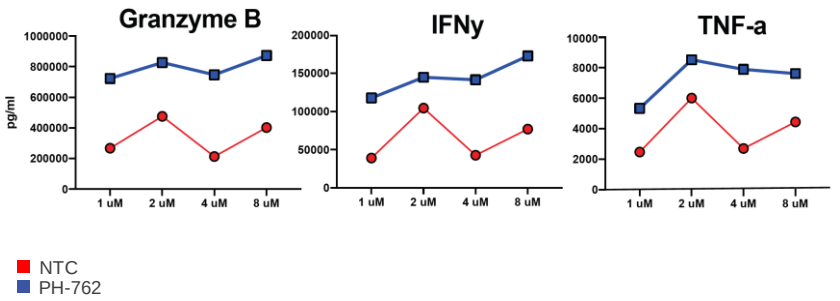


Autologous tumor cell killing measured with Incucyte cell imaging system. Tumor cells are labeled with Cytolight Rapid Red and cell killing is measured by Caspase 3/7 (green staining).

PH-762 does not negatively impact T cell proliferation during rapid expansion



TILs treated with PH-762 produce high levels of effector cytokines



Data courtesy of AgonOx, Inc.: Thalhofer et al, *Journal for ImmunoTherapy of Cancer* 2020, 8; DOI: 10.1136/jitc-2020-SITC2020.0172

NTC = non targeting control; MHC I Ab = MHC Class I blocking antibody

PH-762 empowered TILs: clinical study design

Study concept:

Use of PH-762 in Tumor Infiltrating Lymphocytes

Objectives:

To determine:

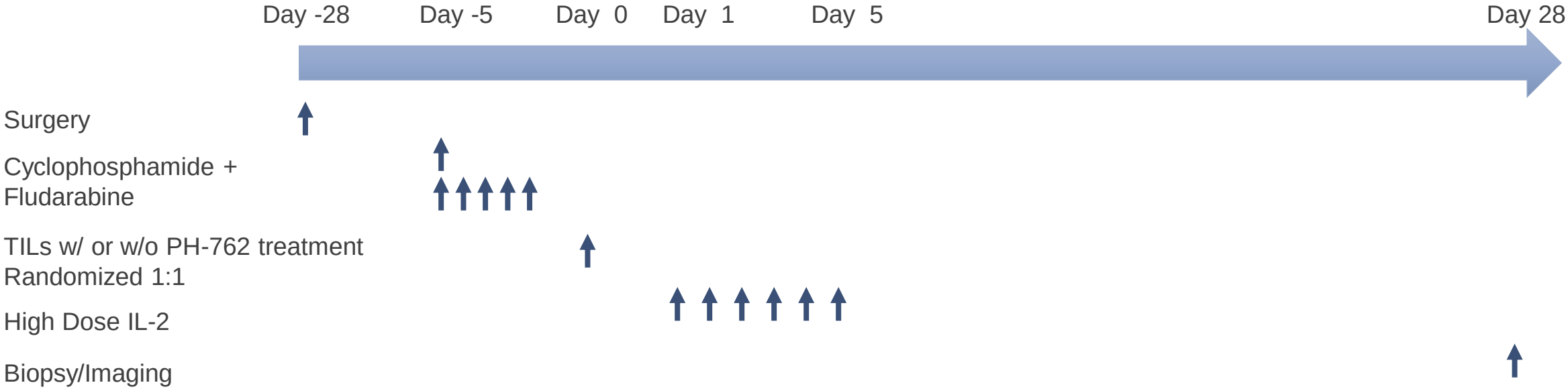
- Safety and efficacy of untreated TILs and PH-762 treated TILs

Patients:

- Basket trial design (melanoma patients and other indications suitable for TIL therapy)

Therapy:

- TIL therapy under established protocols using
  - TILs treated ex vivo with PH-762, or
  - untreated TILs



INTASYL

as direct therapeutic to reprogram the tumor micro-environment

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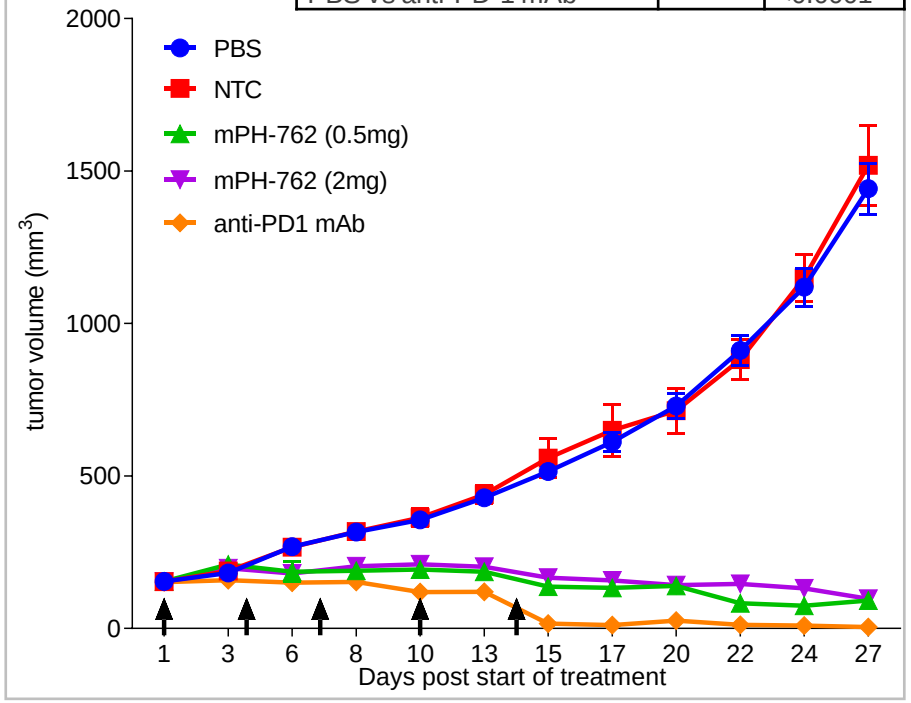
Direct therapeutic use of PH-762: strong anti-tumor activity *in vivo*

Direct treatment with PH-762 gives strong anti-tumor activity *in vivo*

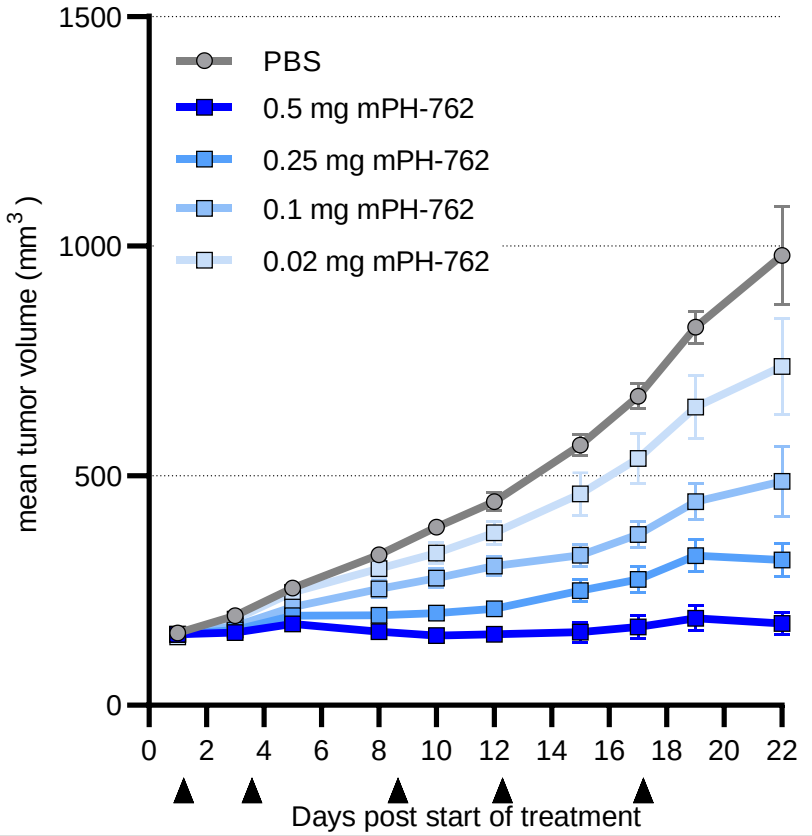
Hepa 1-6 tumor-bearing mice were treated with INTASYL targeting mouse PD-1 (mPH-762) intratumorally on Days 1, 4, 7, 10 and 14

PBS vs NTC	ns	0.9943
PBS vs mPH-762 (0.5 mg)	****	<0.0001
PBS vs mPH-762 (2 mg)	****	<0.0001
PBS vs anti-PD-1 mAb	****	<0.0001

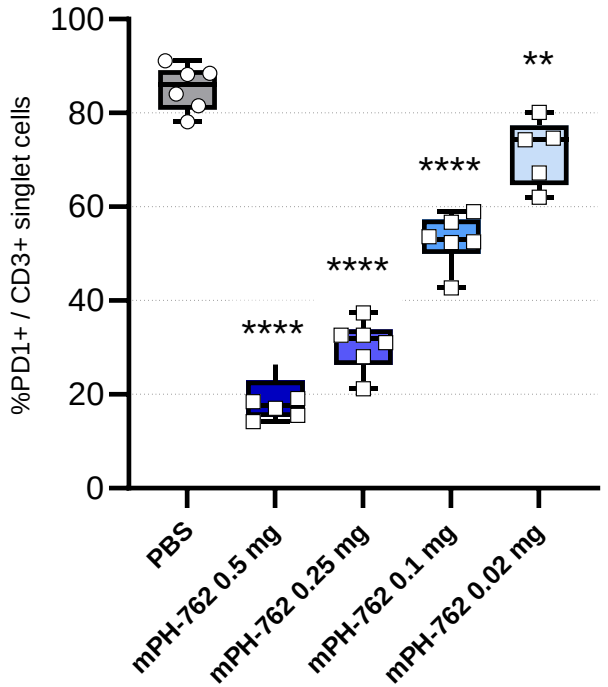


Direct treatment with PH-762 allows a tight dose response

Hepa 1-6 tumor-bearing mice were treated with INTASYL targeting mouse PD-1 (mPH-762) intratumorally on Days 1, 3, 9, 12 and 17



PH-762 treatment results in powerful PD-1 silencing *in situ*



NTC = non targeting control

Direct therapeutic use of PH-762: clinical study design

Protocol title:

Dose Escalation Study to Evaluate the Safety, Tolerability and Clinical Activity of Neoadjuvant Use of PH-762 Administered by Intratumoral Injection in Subjects with Advanced Resectable Melanoma

Objectives:

To determine:

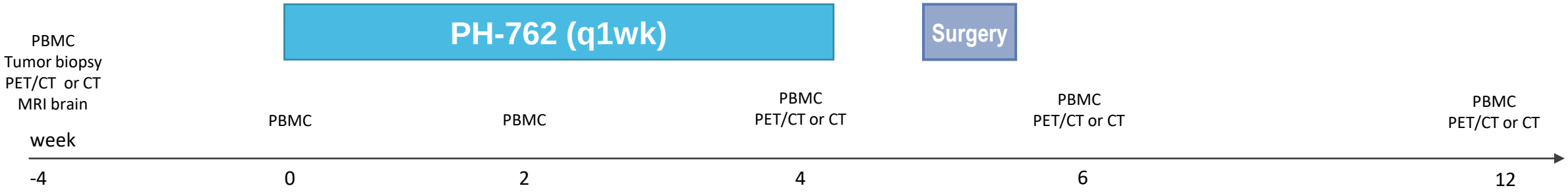
- Safety of PH-762 (IT use)
- Recommended dose in next clinical study
- Immunological response (e.g. immune infiltrate)
- Pathological response
- Pharmacokinetic parameters

Patients:

- Stage IIIB/IIIC or stage IV resectable, oligometastatic (less than or equal to 3 sites of disease, excluding bone and CNS) melanoma

Therapy:

- Neoadjuvant use of PH-762 through intratumoral injection (1x week for 4 weeks)
- Surgical resection (4 weeks after PH-762 treatment)



INTASYL Technology
(self-delivering RNAi)

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INTASYL features are ideally suited for ACT and direct therapeutic use

Therapeutic Characteristics

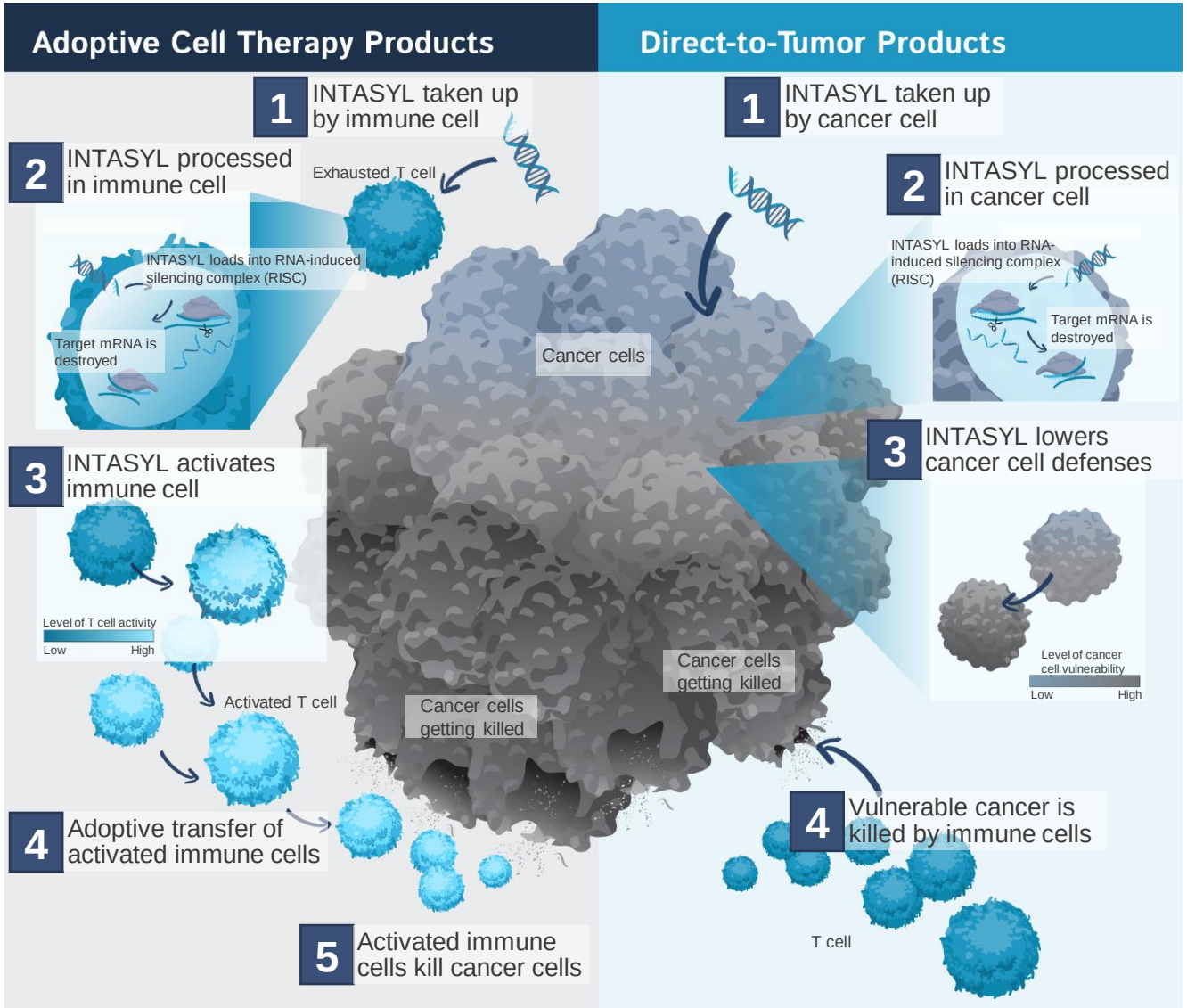
- Single chemically-modified RNA compound with drug-like properties
- Potent, stable, specific
- Efficient cellular uptake and gene silencing
- Rapid lead identification and optimization

Efficacy / Safety

- Robust, long lasting *in vivo* efficacy
- Demonstrated safety and efficacy in human clinical trials (> 100 subjects)

Delivery

- No delivery formulation required
- Delivery not limited to a specific cell type



INTASYL: No delivery tools or complex formulations required

INTASYL results in spontaneous cell uptake, with more potent and concentration-dependent gene silencing compared to competitor RNAi

INTASYL

Cellular uptake **700x** >

Competitor RNAi

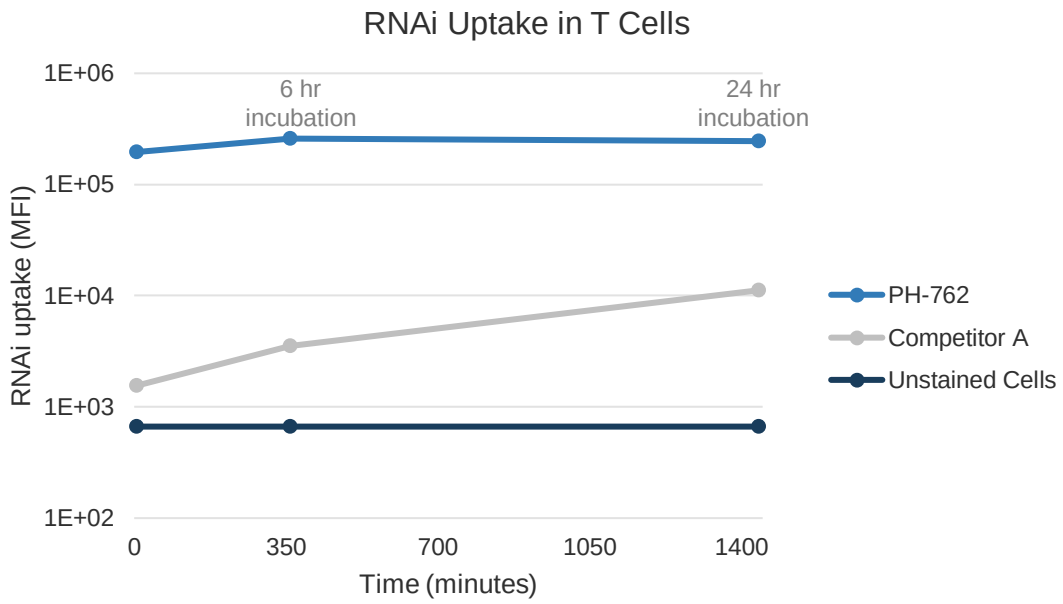
INTASYL

Cellular uptake **13x** >

Competitor RNAi

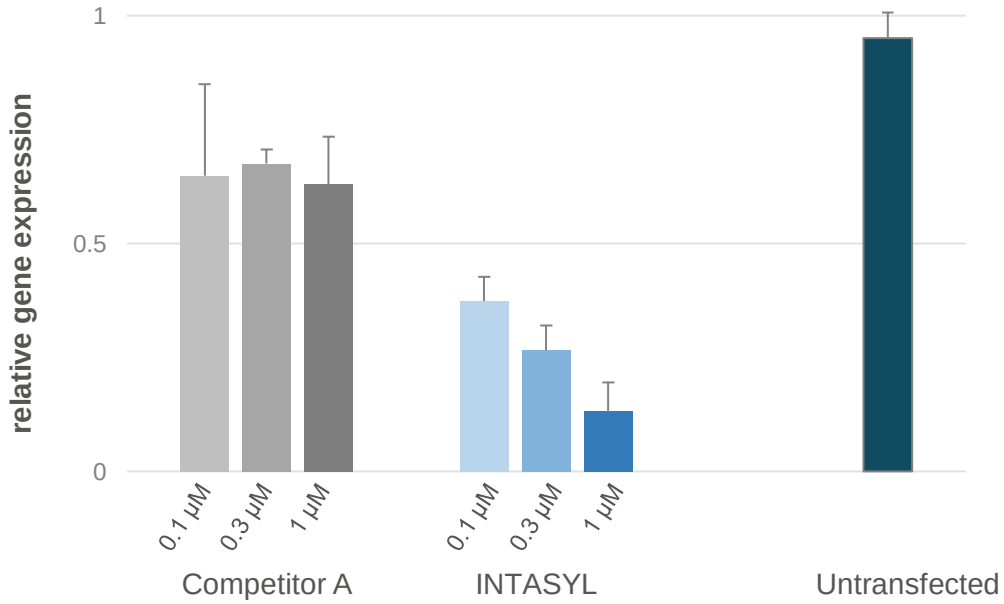
24hr uptake in T cells

Superior cellular uptake of INTASYL vs. Competitor RNAi



72hr Target mRNA Expression in T cells

Superior silencing of INTASYL vs. Competitor RNAi

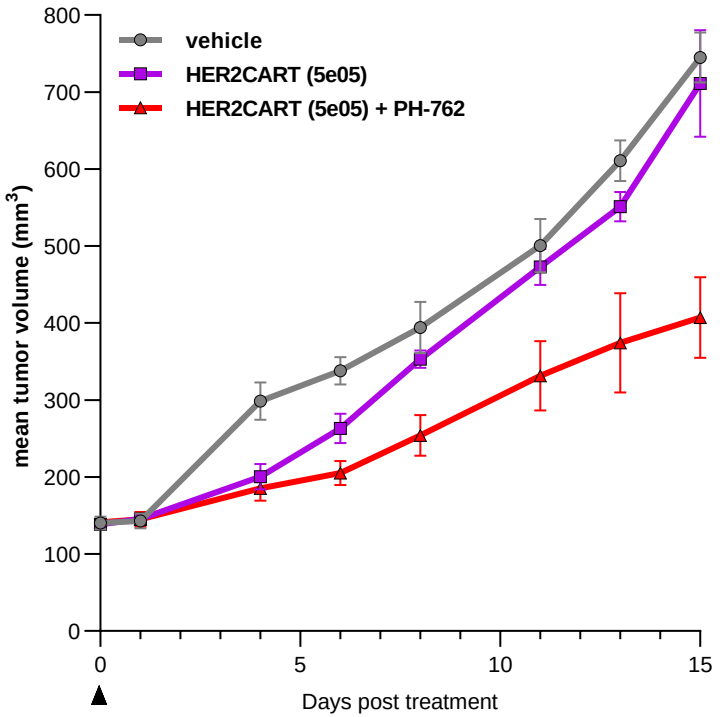


INTASYL: Use in ACT is not limited to a specific cell type

CAR T cells

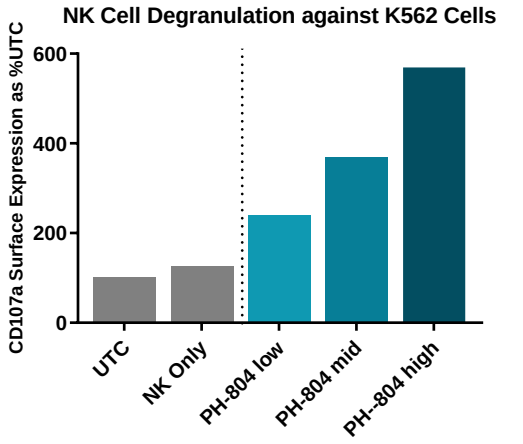
The *in vivo* tumor cell killing of suboptimal dose of CAR T cells can be significantly improved by INTASYL PH-762

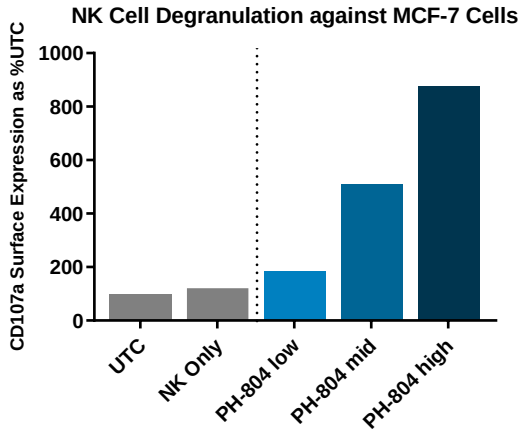
Adoptive cell therapy with HER2 CAR T cells pre-treated with mPH-762 results in increased *in vivo* tumor cell killing (SC SKOV3 in NCG mice)



NK cells

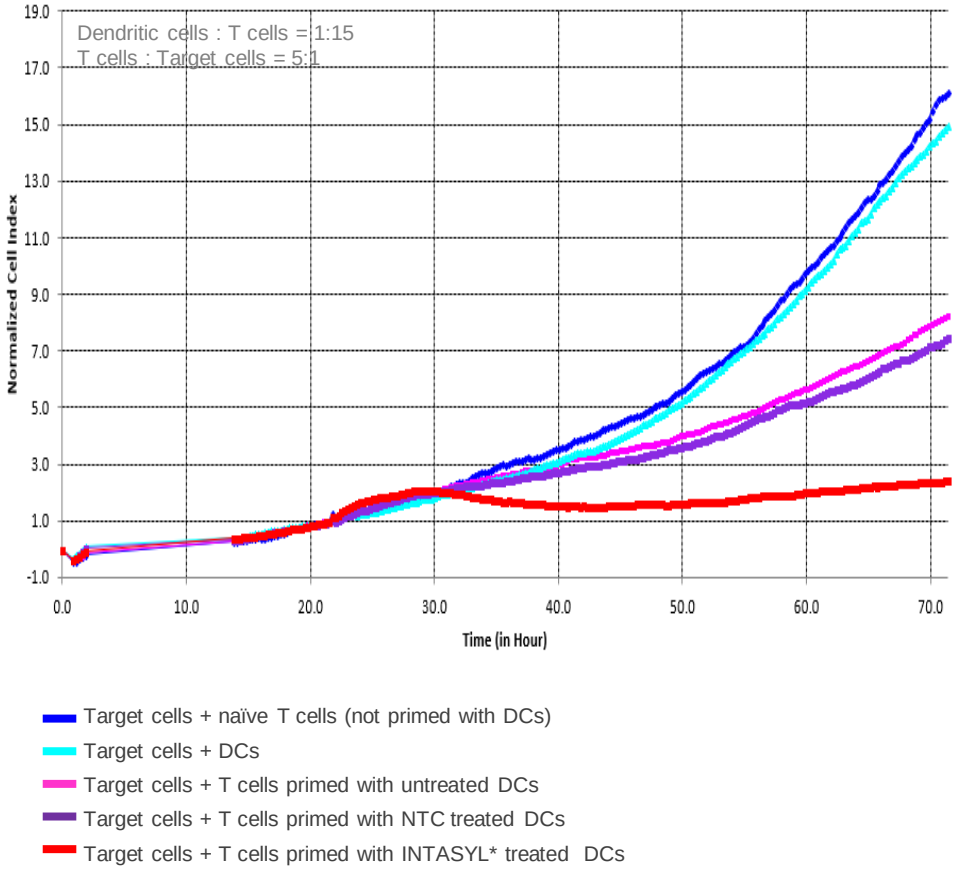
INTASYL PH-804 increases the tumor cell killing potential of NK cells





Dendritic cells

Using INTASYL* to activate DCs resulting in significant impact on T cell priming and killing



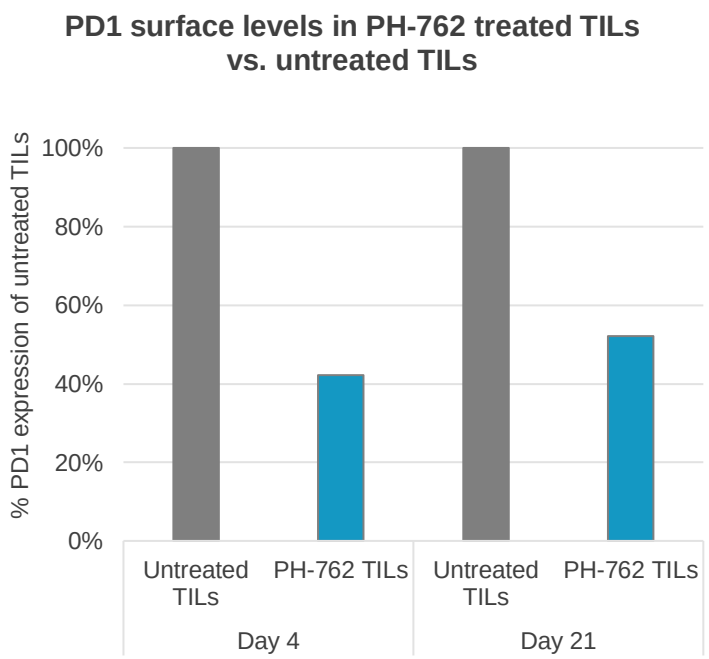
Data courtesy of S. Roersma, Maastricht University

*) undisclosed target

INTASYL: Duration of *in vivo* effect in ACT is long enough for efficacy

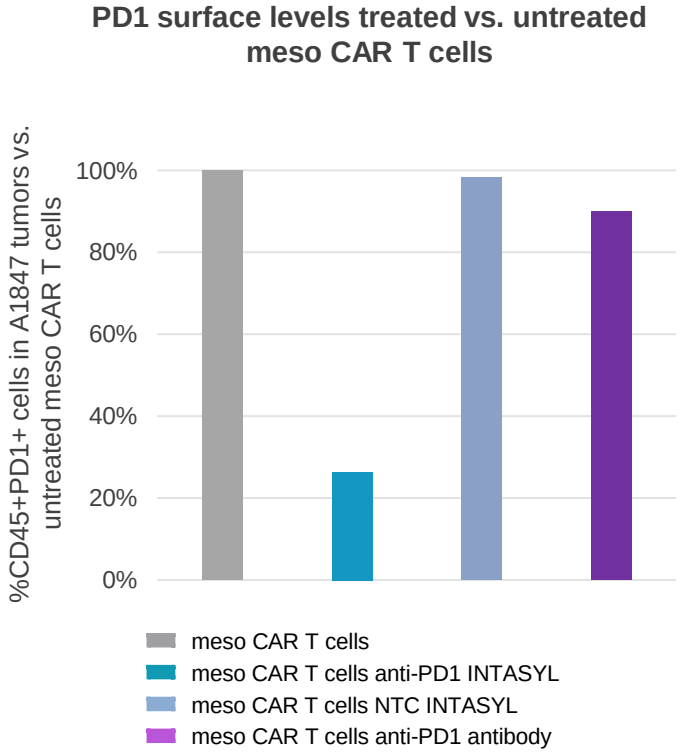
Long *in vivo* effect of INTASYL-empowered cells in ACT

Significant silencing INTASYL 3 weeks after adoptive transfer of TILs in hIL-2 mouse *in vivo* model



- Humanized mouse model of melanoma (patient derived xenograft)
- TILS were pre-treated *ex vivo* and injected via IV injection in mice
- Blood samples were taken and human CD45-expressing cells were extracted and analyzed for PD-1 expression by flow-cytometry
- Results show INTASYL induced PD-1 silencing present after for at least 3 weeks *in vivo*

Significant INTASYL silencing 1 month after adoptive transfer in CAR T *in vivo* model

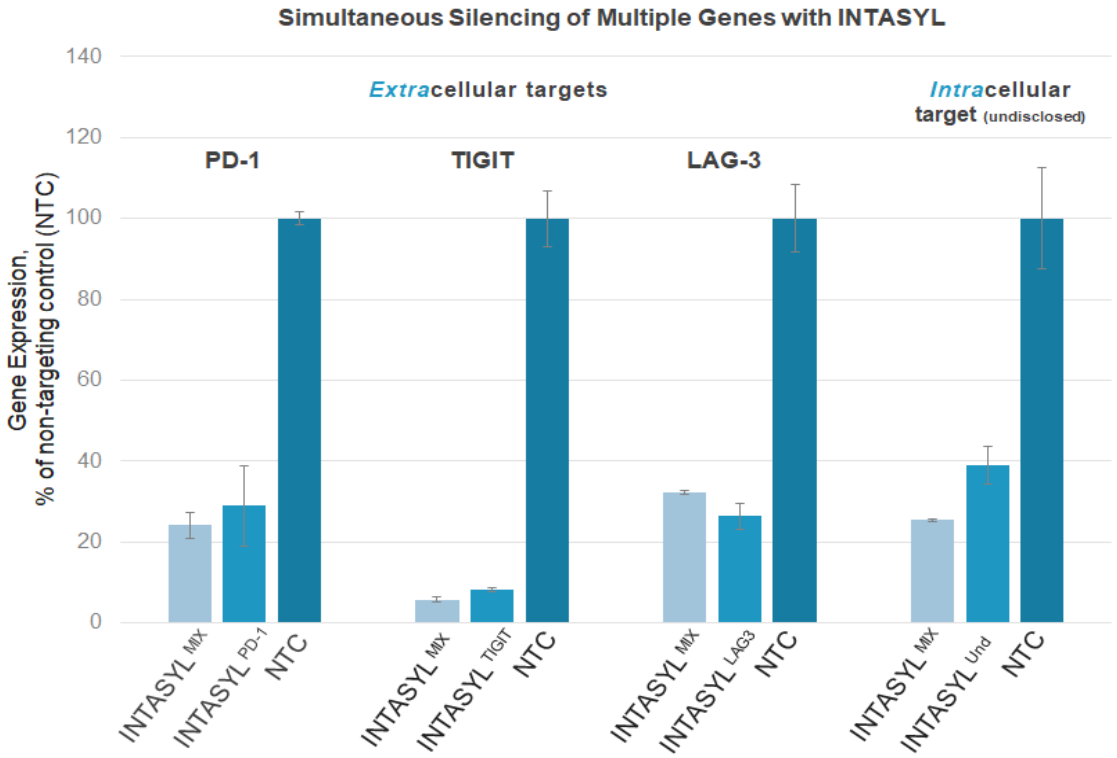


- Mouse xenograft model of ovarian cancer
- Meso CAR T-cells were pre-treated *ex vivo* and injected into human ovarian cancer tumors in mice
- Tumors harvested after one month and human CD45-expressing cells were extracted and analyzed for PD-1 expression by flow-cytometry
- Results show INTASYL induced PD-1 silencing present after 1 month *in vivo*

NTC = non targeting control

INTASYL: Highly specific, easy to modulate, able to hit multiple genes

Use towards different genes without loss of efficiency and efficacy



INTASYL efficiency is high
Frequency of silencing of all three genes in one T cell is high:

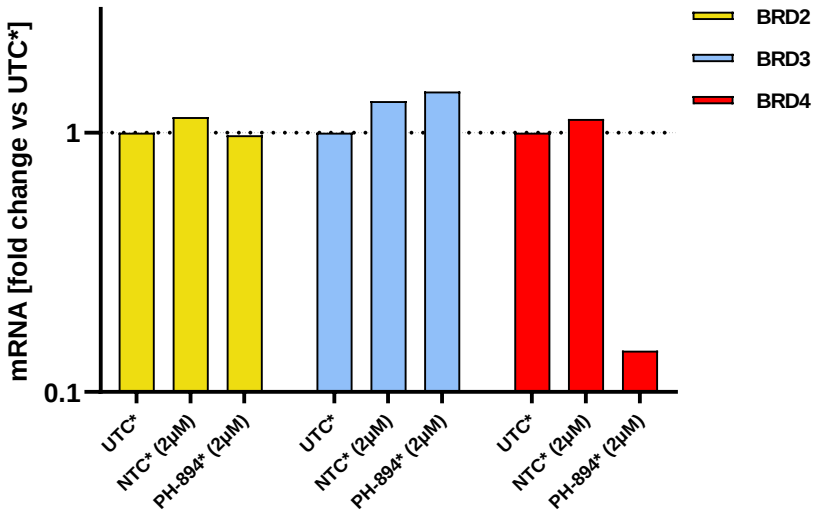
~100%
regardless of number of gene targets

CRISPR efficiency is much lower
Frequency of silencing of all three genes in one T cell is low[1]:

- Cells having one edit: 40%
- Cells having two edits: 20%
- Cells having three edits: 10%

Highly specific, even towards isoforms and individual proteins within a protein family

PH-894 is selective and only silences BRD4, not other protein family members



The bromodomain and extraterminal (BET) protein family (incl. BRD2, BRD3, BRD4) are epigenetic readers that regulate gene transcription with structural similarities but different function. Considering implication of BRD4 in cancer, inhibition of BRD4 without impacting other members is required.

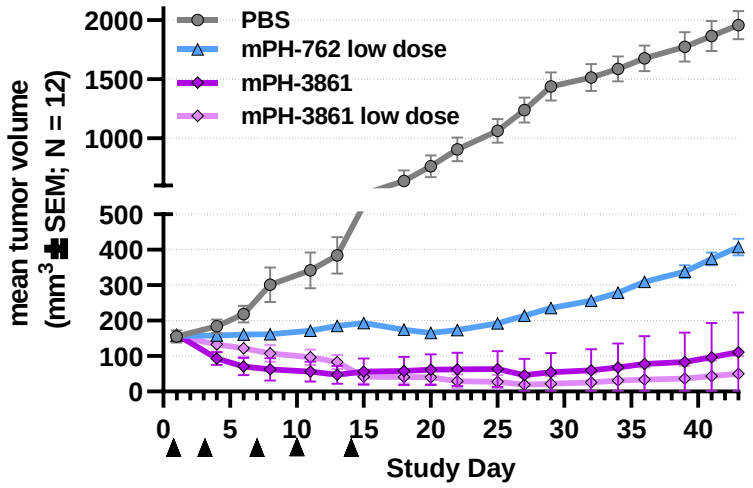
NTC = non targeting control
UTC = untreated control

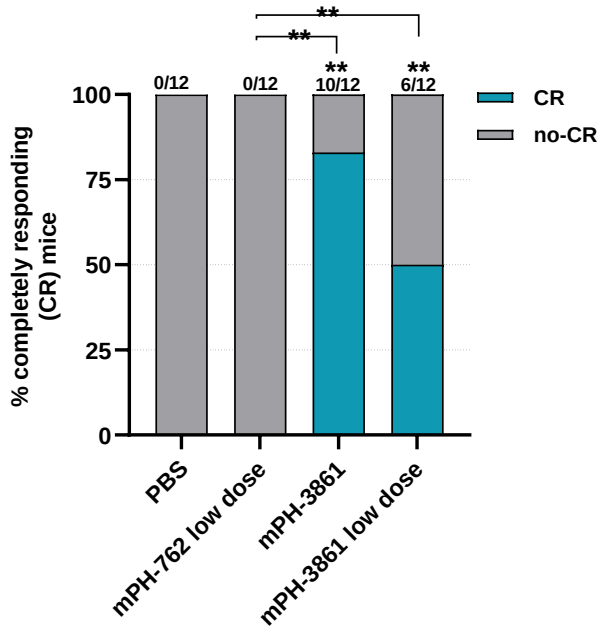
[1] Stadtmauer et al. Science 367: 1001 (2020)

INTASYL: Powerful direct therapy by targeting multiple genes

Dual targeting INTASYL of multiple genes with potential target synergy results in better *in vivo* tumor control

The ability to silence multiple genes, without additional complexity or loss of efficiency, allows for potent drugs to be developed





- Hepa 1-6 model of local treatment with dual targeting INTASYL mPH-3861
- INTASYL mPH-3861 targets
  - PD-1
  - BRD4
- Compared to mPH-762 monotherapy at suboptimal doses, mPH-3861 resulted in
  - stable complete response (CR) of 83% (10/12) of treated Hepa1-6 tumors
  - enhanced tumor control

INTASYL direct therapy has systemic & long-lasting effect

TME administration	**Distant effects,** i.e. systemic anti-tumor immunity against non-injected tumor sites	**Long term** systemic anti-tumor immunity

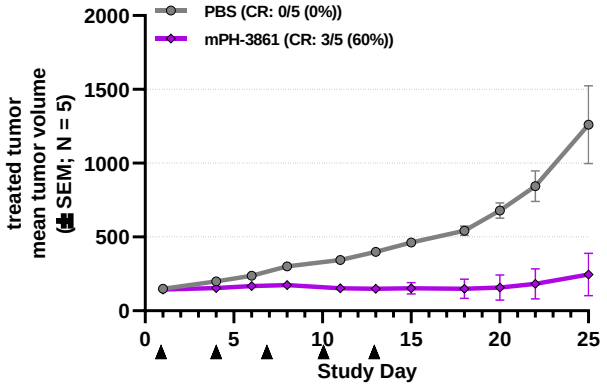
Local priming
Local administration to trigger local reaction and tumor specific immunity

Distant effects
Systemic anti-tumor immunity against non-injected tumor sites

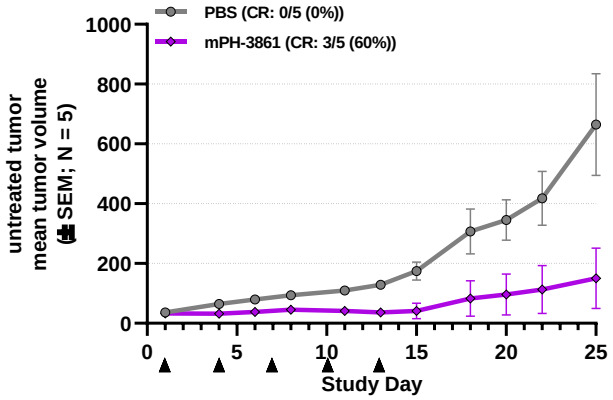
Picture after: Marabelle *et al*., Annals of Oncology, 28(suppl 12), 2017

Mice bearing Hepa 1-6 tumors receiving local INTASYL treatment rejected local, treated and **distant, untreated tumor**

Treated

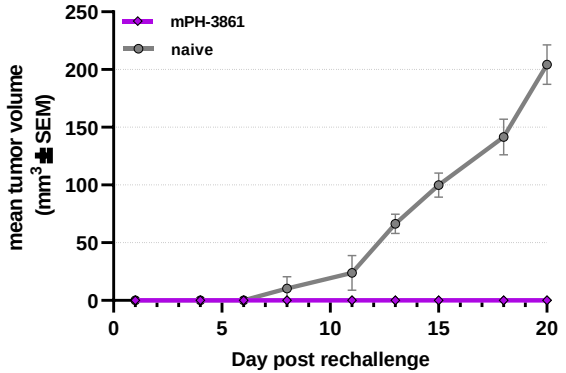


Untreated



Mice previously bearing Hepa 1-6 tumors **previously cured** by local INTASYL treatment rejected a second Hepa 1-6 rechallenge **~2.5 months after treatment**, without any re-treatment.

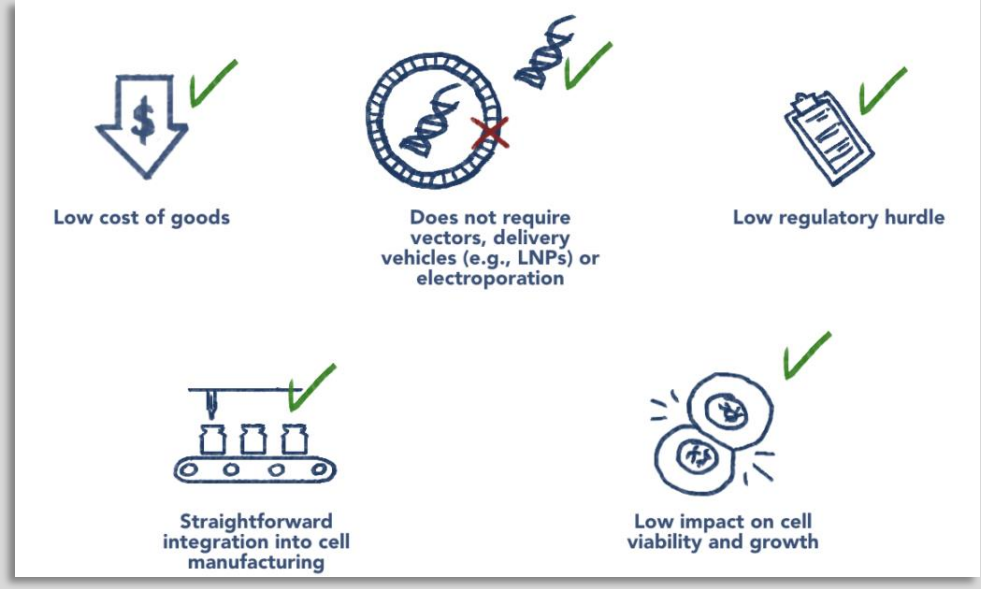
Rechallenge



INTASYL: Lower (manufacturing) complexity and cost

Especially in ACT, as compared to genetic engineering, INTASYL is easy and cost effective

- **Direct cost reduction with INTASYL:**
  - ~10-fold lower COGs INTASYL vs. AAV
  - no vectors & delivery tools required
  - no equipment or media changes



- **Indirect cost reduction with INTASYL:**
  - 100% cell reprogramming efficiency
  - no negative impact of cell growth / survival
  - superior ability to silence multiple genes at once, no selection needed of cells with successful edits
  - no risk of permanent off target toxicity, therefore no need for “safety switches”
  - no need for long-term follow up of clinical trial patients (as is required with gene therapies)

INTASYL
pipeline programs

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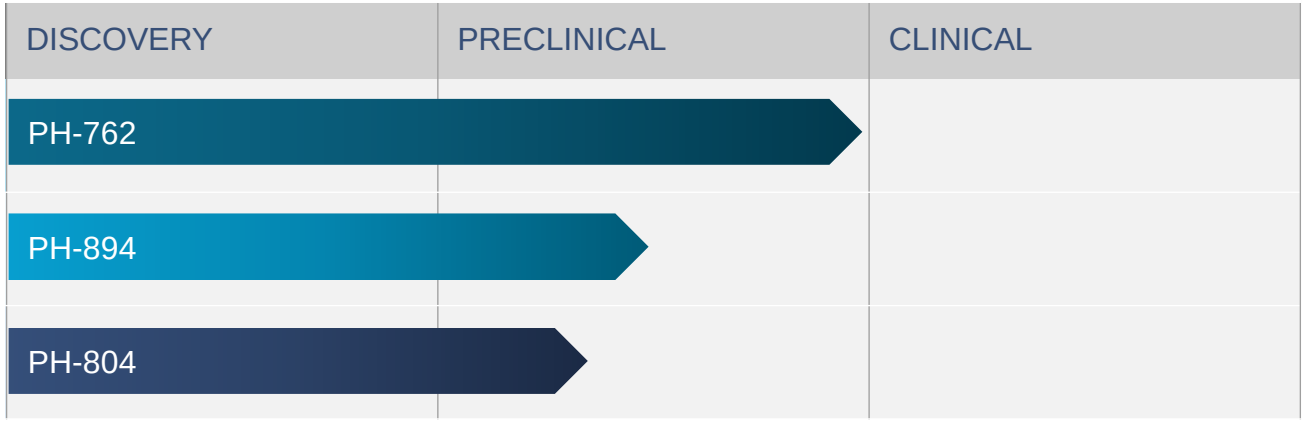
Pipeline of Phio INTASYL Immuno-Oncology Therapeutics

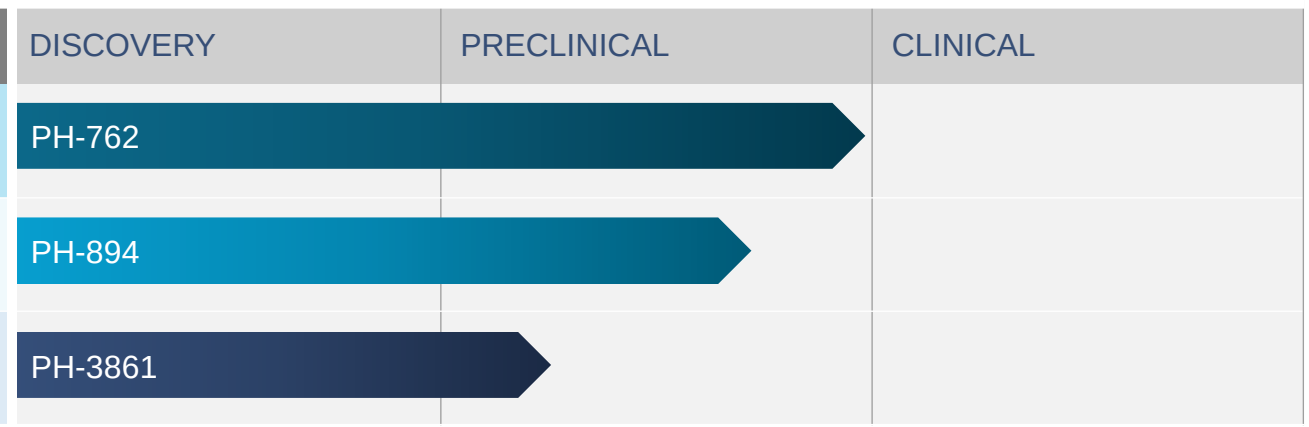
INTASYL to improve cell therapy – reprogram cells for adoptive cell therapy (ACT)

INTASYL	MECHANISM	INDICATION
PH-762	Enhanced T cell activation and tumor cell killing through PD-1 Silencing	Melanoma (+ others)
PH-894	Enhanced T cell activation and tumor cell killing through BRD4 Silencing	Solid tumors
PH-804	Enhanced NK cell activation and tumor cell killing through TIGIT Silencing	Various



INTASYL use as direct therapeutic – reprogram the tumor micro-environment (TME)

INTASYL	MECHANISM	INDICATION
PH-762	*"In situ"* T cell activation and tumor cell killing through PD-1 Silencing	Melanoma (+ others)
PH-894	"*In situ*" T cell activation and tumor cell killing through BRD4 Silencing	Solid tumors
"Dual-Targeting"	"*In situ*" immune cell activation and tumor cell killing through gene Silencing	Various Solid tumors

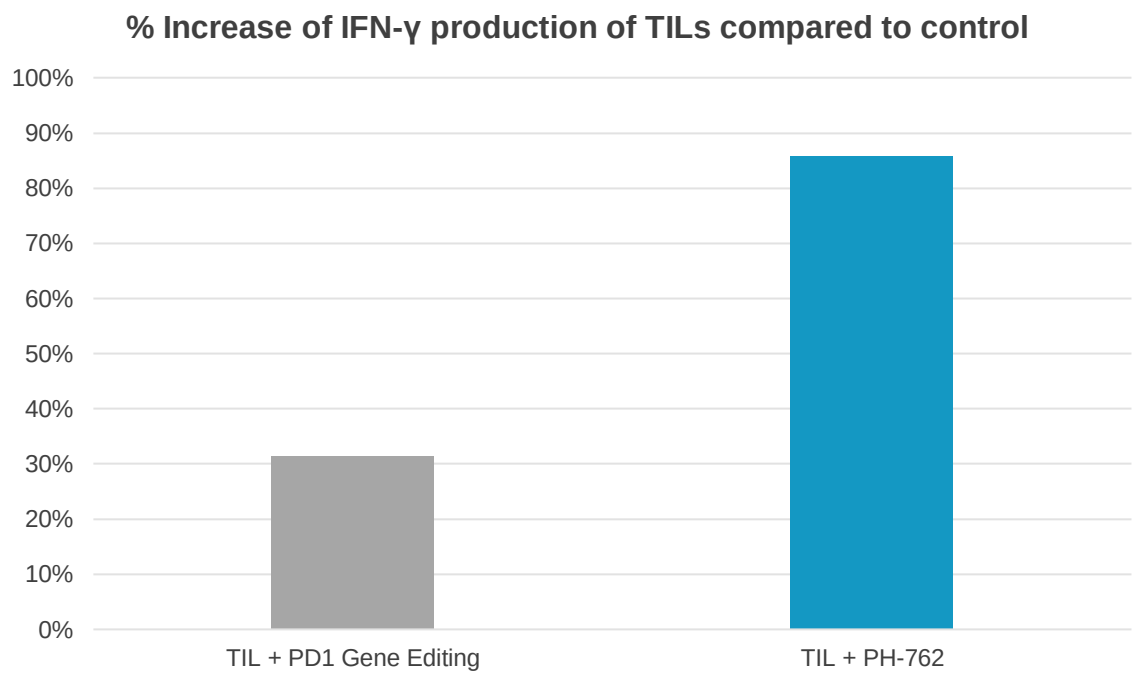


Various additional opportunities & compounds towards other immune cell function / exhaustion / metabolism targets are in discovery research stage.

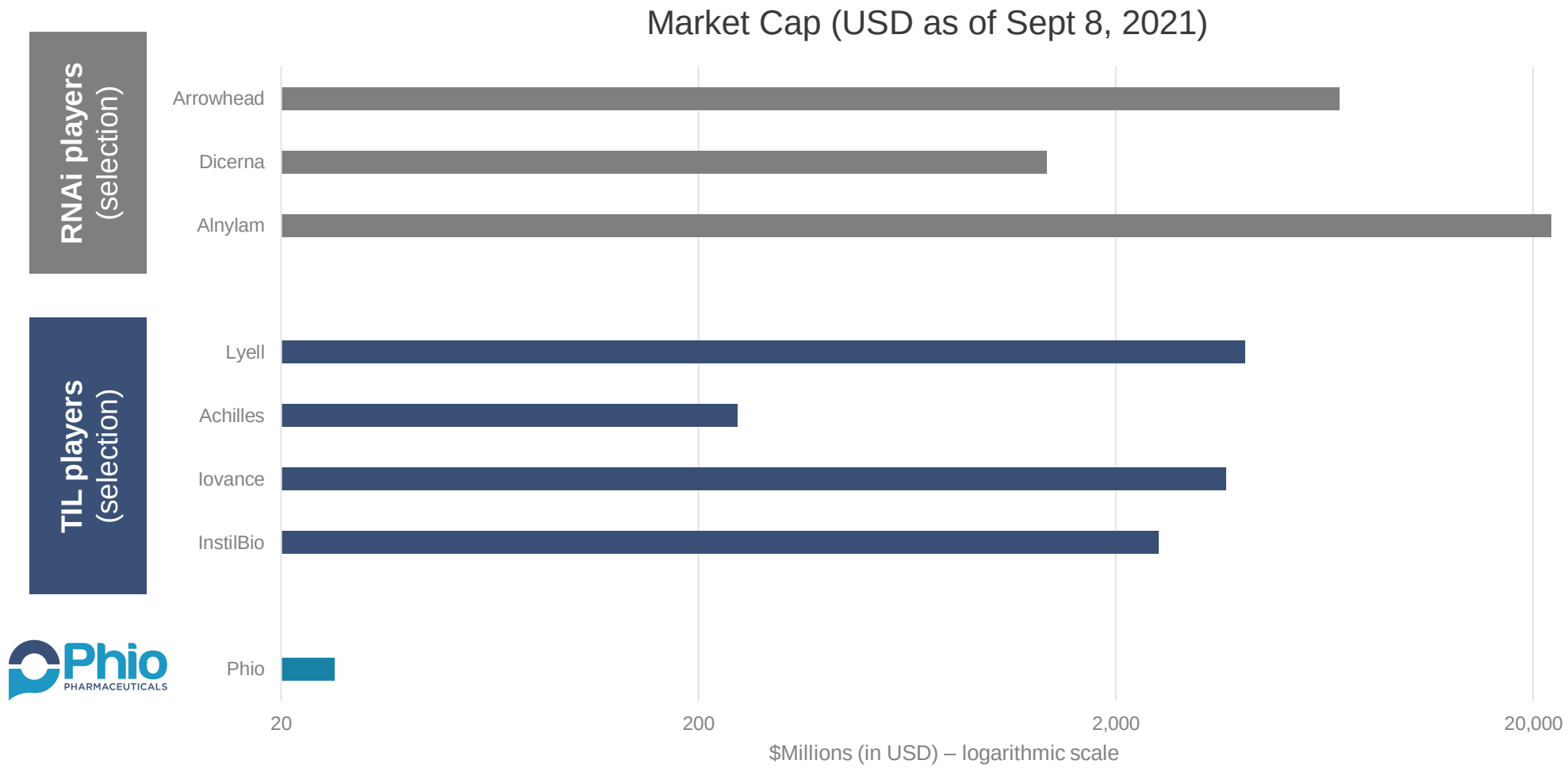
How do our development efforts compare?

INTASYL treated TILs have a more pronounced and more consistent PD1 protein reduction as compared to gene edited TILs (competitor platform)

INTASYL treated TILs display a more pronounced increase in activity as compared to gene edited TILs (competitor platform)



Phio valuation potential



Financial Overview

Snapshot	
Cash (a/o 8/31/2021)	$27.1M
Burn rate	$3.3M / quarter
Cash runway	Q2 2023
Common shares outstanding (a/o 8/31/2021)	13.5M
Market Cap (a/o 8/31/2021)	$28.2M

Recent & Future Milestones

1H 2021	**Partnering:** PH-762 in ACT	☑
2H 2021	**Data:** Publications on PH-762, PH-894 and PH-804	☑
1Q 2022	**Clinical:** Start of PH-762 IT* clinical study	☐
2Q 2022	**Clinical:** Start of PH-762 ACT* clinical study	☐
2H 2022	**Clinical:** Start of PH-894 IT* clinical study	☐

*) high reliance on CROs and other services providers and suppliers some of which are impacted by coronavirus pandemic; full extent of impact is not yet known

THANK YOU