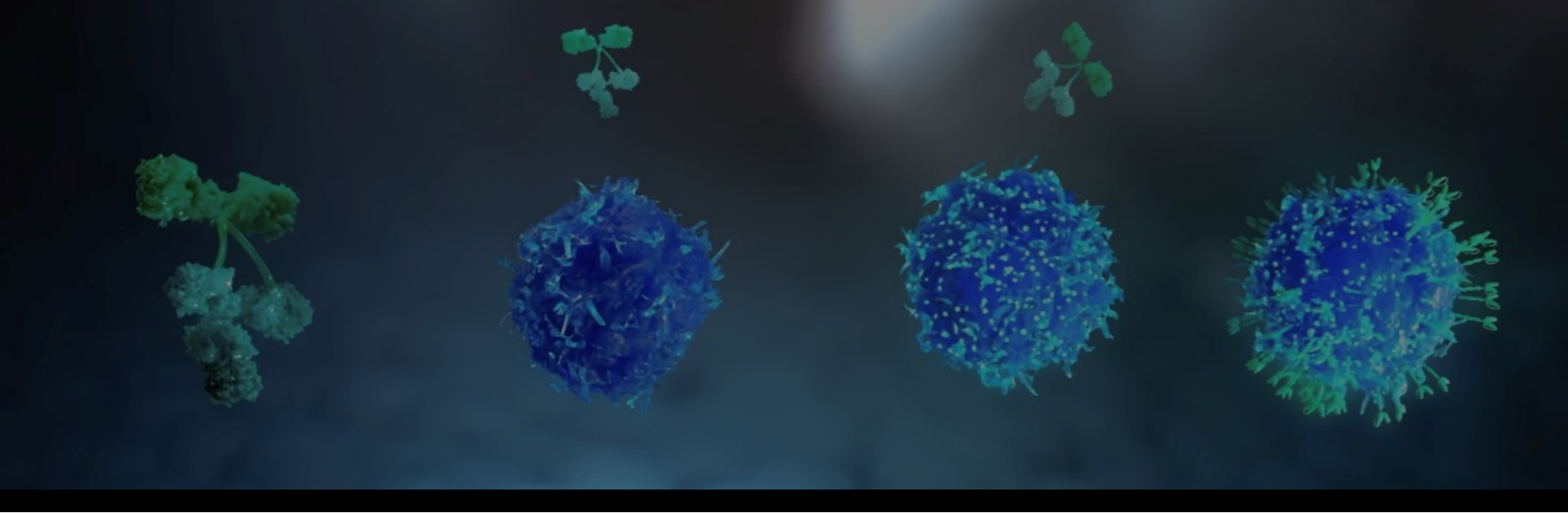


Developing CYT-303 NK Cell Engager Combination Therapies for Hepatocellular Carcinoma

Innate Killer Summit, March 30th 2023

Tony Arulanandam, DVM, PhD
SVP and Head Preclinical R&D
Cytovia Therapeutics

Disclosures and Forward-Looking Statement

- Employee of Cytovia Therapeutics
- Co-Founder NextPoint Therapeutics

This presentation contains forward-looking statements that are based on the company ’s current expectations, assumptions, estimates and projections about the company and the pharmaceutical industry. The company makes no representations about the accuracy of such statements estimates or projections. Forward-looking statements are indicated by words such as: may, will, should, predict, continue, plan, expect, anticipate, estimate, intend, believe, could, goal objectives and similar expressions. Forward-looking statements may include, but are not limited to, statements concerning the company ’s anticipated performance, including revenue and profit expectations; development and implementation of collaborations; benefits provided to collaboration partners by our technology; business mix; revenues and growth in our partner base; market opportunities; competing technologies, industry conditions and trends; and regulatory developments. Actual results may differ materially from the anticipated results due to substantial risks and uncertainties related to the company and the biopharmaceutical industry in which the company operates.

Topics to Cover

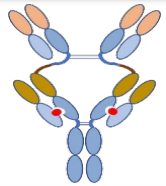
- Cytovia iNK and NK cell engager platforms
- CYT-303 NK cell engager combination therapy options
- Rationale for CY-303 combination with checkpoint inhibition with Atezo + Bev in HCC
- CYT-303 reversal of NK cell dysfunction in HCC serial killing and immunosuppressive TME
- CYT-303 dose response in anti-tumor efficacy HCC tumor models
- CYT-303 pharmacokinetics in normal and tumor bearing mice
- CYT-303 in-vitro immunotoxicity and GLP toxicology
- CYT-303 clinical development plan

Two Platforms Engaging and Empowering NK Cells as Cancer Therapeutics

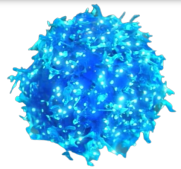
Both Platforms are Applicable to other Immune Cells

First company combining NK cell engager bispecific antibody & gene-edited iPSC-derived NK cell platforms

Flex-NK™ Cell Engager Bispecific Antibody Platform



Gene edited iPSC-Derived NK Cell Platform



Multiple Therapeutic Modality products

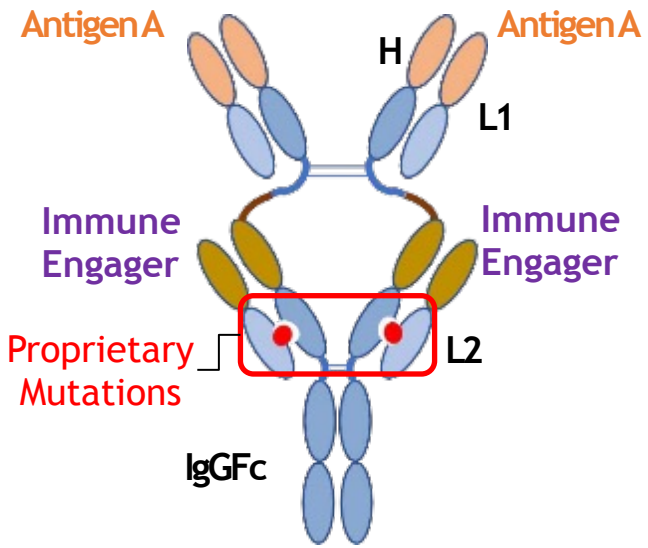
- **Flex-NK™ Cell Engager bispecific antibody**
- **iNK Cell pre-complexed with Flex-NK™ Cell Engager or conventional combo**
- **Edited universal iNK Cell**
- **CAR-iNK Cell**

Current Therapeutic Indications

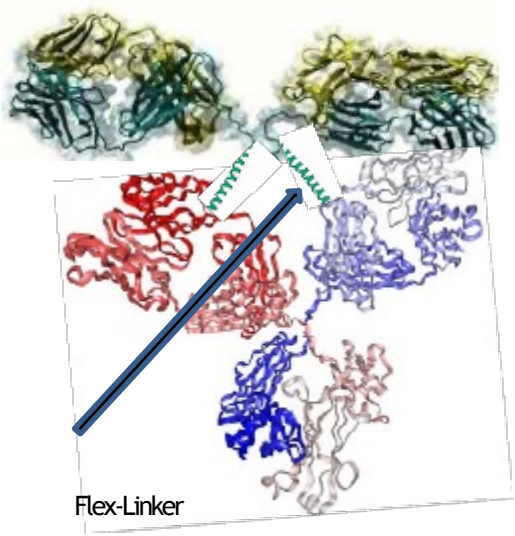
Hepatocellular Carcinoma (HCC)	Other Solid Tumors expressing GPC3	Glioblastoma Multiforme (GBM)	Multiple Myeloma (MM)	Cutaneous T-Cell Lymphoma (CTCL) & other CD38 expressing hematological tumors

Proprietary BsAb Technology Leading to Novel Multifunctional Flex Format

Flex™ Cell Engager multi-specific antibodies help redirect immune cells towards their target and further activate their killing activity at the tumor site



- Flexible linker allowing simultaneous binding to 2 different cells
- Full IgG with Fc allows for a half-life longer than other bispecifics supporting at least weekly administration
- Proprietary mutation ensuring proper alignment of light and heavy chains
- Tetravalent structure for increased affinity and avidity
- Up to 2 years stability
- IP acquired from Cytovia scientific cofounder
- Worldwide patent granted



Jean Kadouche, PhD
Co-founder

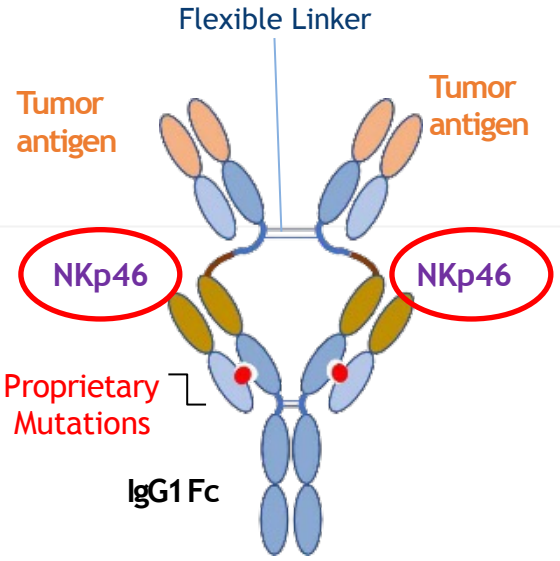
Cytovia Therapeutics

Flex-linker facilitates binding to multiple antigens on different cells

Source: Golay et al. J Immunol 2016

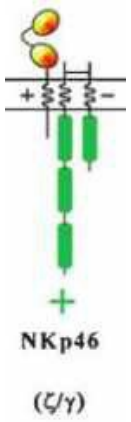
A Differentiated Approach to Engage NK Cells - NKp46 is a preferred activating receptor to induce NK Cell-mediated anti-tumor immunity in solid tumors

Exclusive License from Hebrew University for NKp46 Antibodies



NKp46 has significant benefits as an Activating Receptor*

- Primary driver of NK Cell's "natural cytotoxicity"
- Foundational NCR1 identified as critical for formation of ***NK cell immune synapses*** with target cells
- Potent NK signaling via ITAM subunits CD3 zeta and Fc gamma to activate Zap 70, Syk and PI3K kinases to mediate NK cytotoxicity and cytokine production
- NKp46 shows sustained expression on NK cells in the TME while other activating receptors, such as NKG2D, NKp30, CD16 and NKp44 are therein downregulated or shed in the TME



Prof. Ofer Mandelboim
Hebrew University, Jerusalem

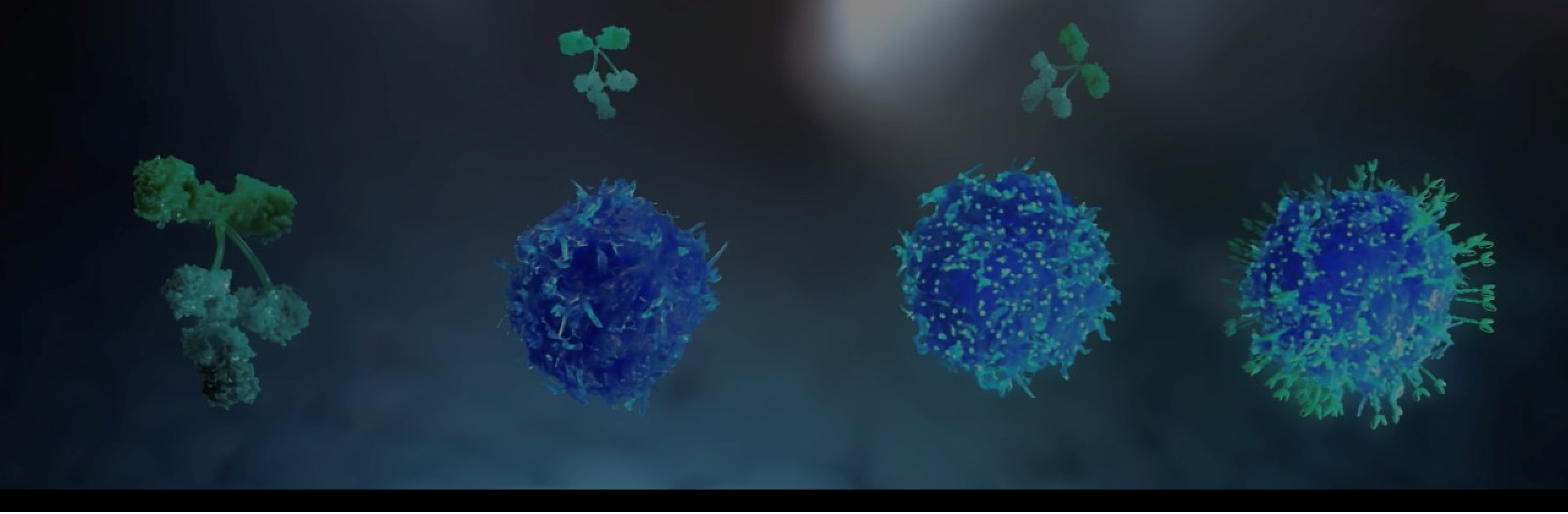
NKp46 Receptor-Mediated Interferon-gamma Production by Natural Killer Cells Increases Fibronectin 1 to Alter Tumor Architecture and Control Metastasis
O. Mandelboim
Immunity Cell Press 2018

Source: Gauthier et al, Cell 2019, 177, 1701-1713

Cytovia Pipeline Supports 2 INDs in 2023 from its GPC3 and CD38 Franchises

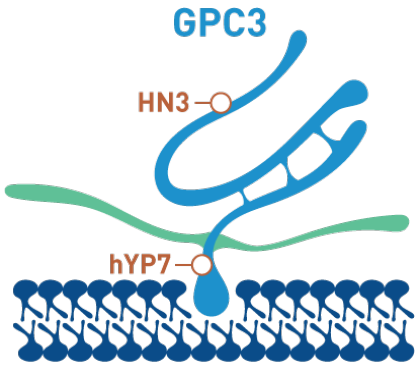
Product Platform	Product Candidates	Indication	Pre-Clinical	Clinical	IND Filings
Flex-NK™ Bispecific Antibodies *(monotherapy & combination with iNK cells)*	CYT-303	HCC	GPC3 Flex-NK™ Bispecific Antibodies		2023
	CYT-103 *(CytoLynx Program)*	HCC	GPC3 Flex-NK™ Bispecific Antibodies Pre-Complexed with iNK Cells		China IIT in 2023
	CYT-338 +/- CYT150	MM, CTCL	CD38 Flex-NK™ Bispecific Antibodies		Monotherapy 2023
	CYT-303 + CYT-150	HCC	GPC3 Flex-NK™ Bispecific Antibodies + Edited iNK Cells		IIT/IND 2024
CAR-iNK Cells	CYT-503	HCC	GPC3 CAR-iNK Cells		IIT/IND 2024
	CYT-538	MM	CD38 CAR-iNK Cells		2025
	CYT-501	GBM	EGFR vIII + WT CAR-iNK Cells		2025

HCC: Hepatocellular Carcinoma
IND: Investigational New Drug
IIT: Investigator-Initiated Trial
MM: Multiple Myeloma
CTCL: Cutaneous T-cell lymphoma
GBM: Glioblastoma Multiforme



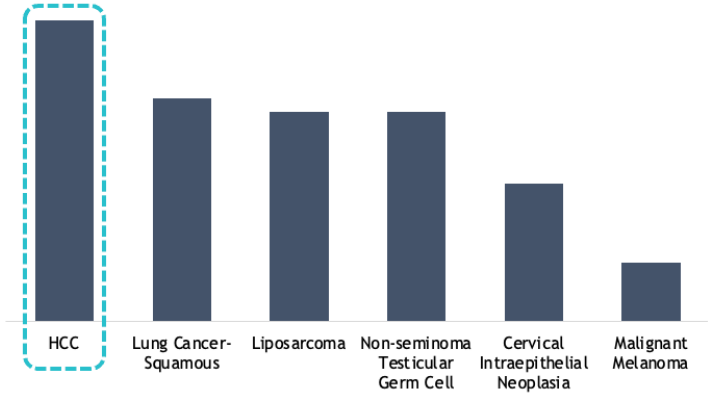
Glypican 3 (GPC3)
HCC & Solid Tumors Franchise

GPC3: A Promising New Therapeutic Target for HCC and Other Solid Tumors

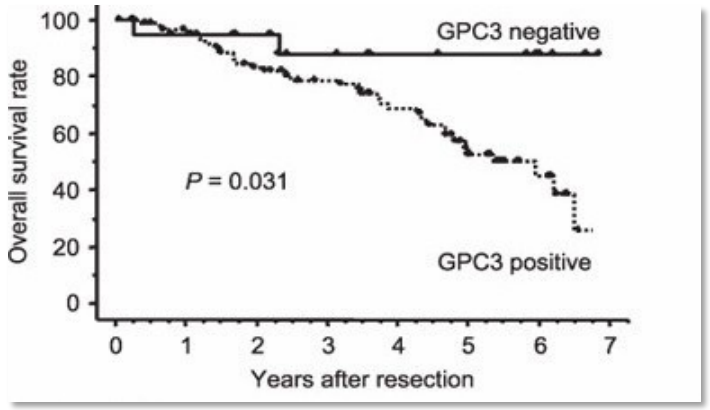


Glypican 3 (GPC3) is an oncofetal antigen expressed on the cell membrane of HCC & other select solid tumors, while predominantly absent in normal tissue.

GPC3 Relative Expression in Solid Tumors



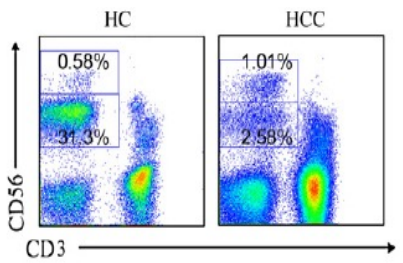
GPC3 Blood Levels Correlate with Severity of Disease



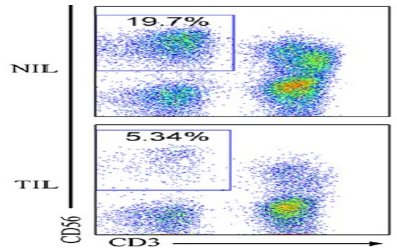
(1) Athenex acquired Kuur Therapeutics in May, 2021
Source: Baumhoer et al., Am J Clin Pathol 2008;129:899-906

NK Cell Status in HCC

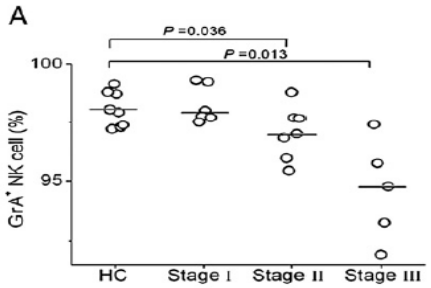
HCC Blood NK cells



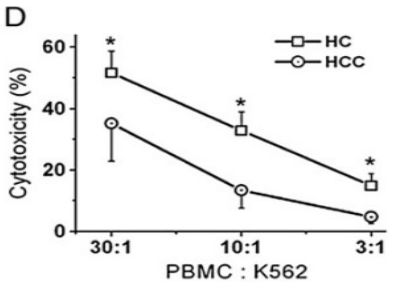
HCC Tumor Infiltrating NK cells



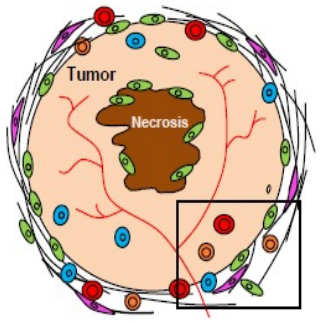
HCC Granzyme A



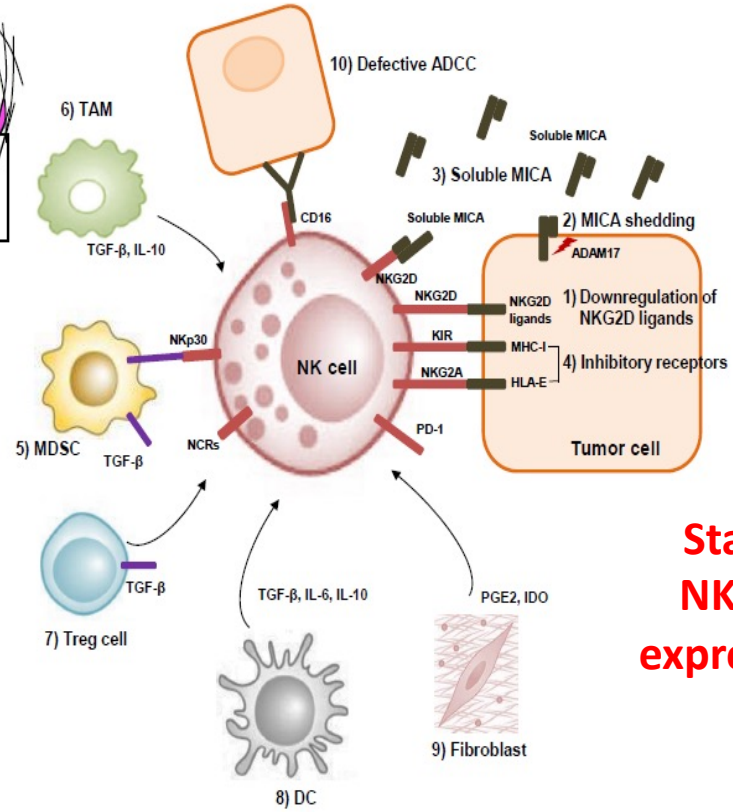
HCC NK Cytotoxicity



HCC NK cell dysfunction mechanisms



High GPC3 expression



Stable NKp46 expression

Cai L et al Clin Immunol 2008
Sung P et al Int J Mol Scien 2018

CYT-303 Bispecific Antibody Combination Therapy Options in HCC

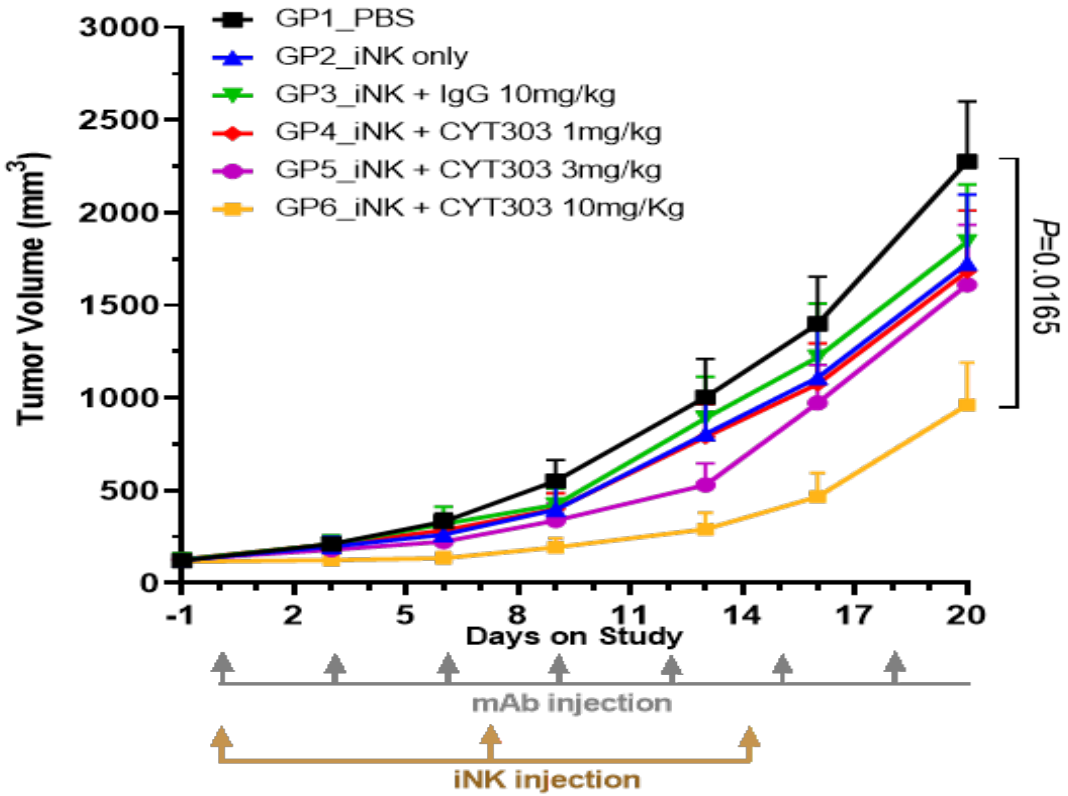
CYT-303
NK engager
For HCC

CYT-303 NK cell engager
combination with iNK CYT-100
or
CYT-303 NK cell engager
precomplexed with iNK CYT-100

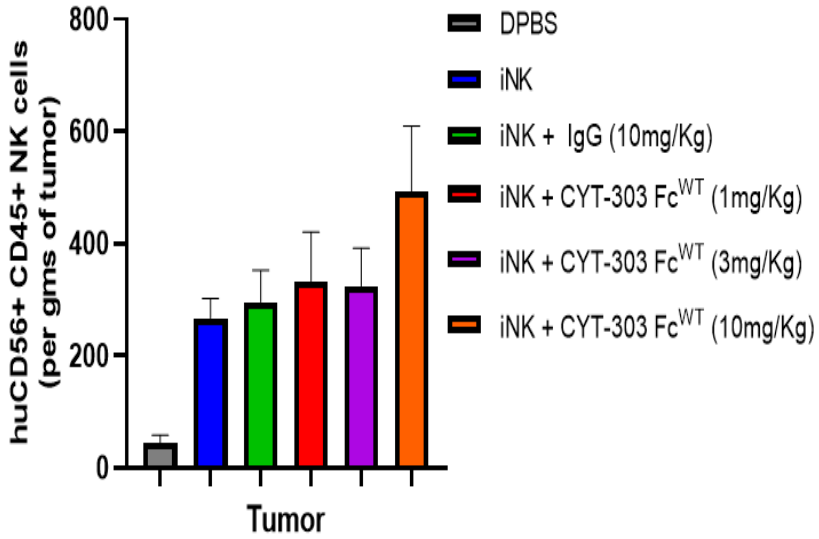
CYT-303 NK cell engager
combination with Atezo +Bev
checkpoint inhibitor refractory
patients (2nd line immunotherapy)

CYT-303 Antibody Combination with iNK Cells Demonstrates Dose-Dependent Anti-Tumor Efficacy in HCC Tumor Models

CYT-303 Tumor Growth Inhibition



PBNK Tumor Infiltration

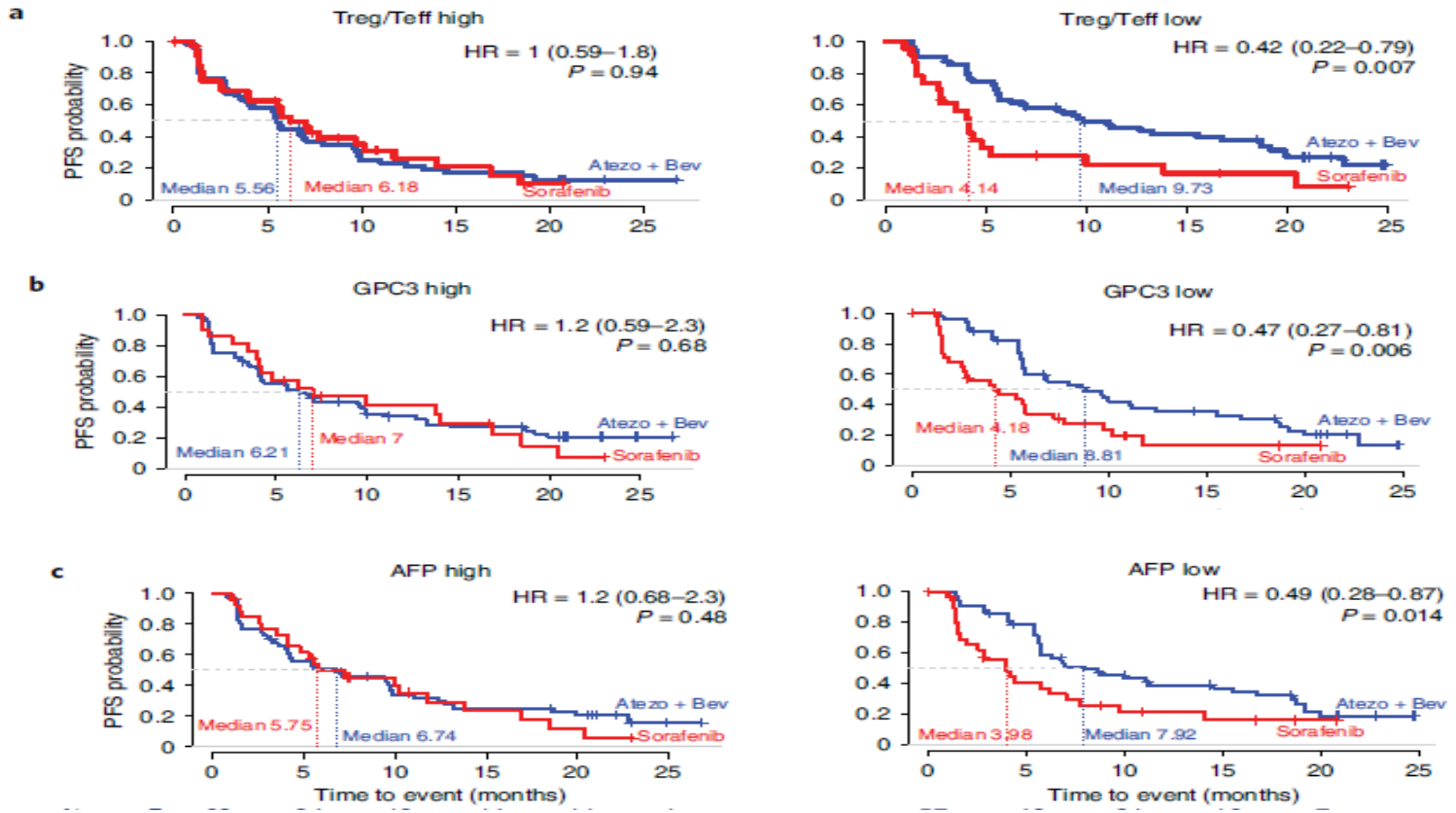


Arulanandam, et al., Abstract 756, Glypican-3 (GPC3) and NKp46 directed FLEX-NK™ cell engager antibody (CYT-303) distributes to tumors and shows dose-dependent tumor growth inhibition in a hepatocellular carcinoma (HCC) mouse model, Ann Oncol 2022 September: 33 (Suppl 7)

Rationale for CYT-303 Combination Therapy with Checkpoint Immunotherapy in HCC

- Retrospective biomarker analysis of Atezo + Bev Imbrave 150 clinical trial in HCC showed high GPC3, AFP and Treg/Teff ratios associated with disease progression.

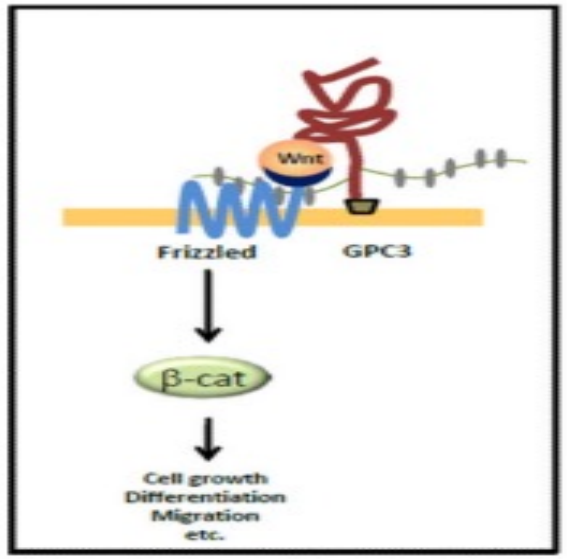
- Since CYT-303 can activate NK cells and reduce HCC tumor burden high GPC3 and AFP levels in HCC can be converted to low GPC3 and AFP signatures associated with response to Atezo + Bev checkpoint



A Xu et al Nat Med 2022 and GO30140 and IMbrave150

GPC3-Mediated Wnt/beta Catenin Signaling is Pro-Tumorgenic and Excludes Immune Cells in HCC

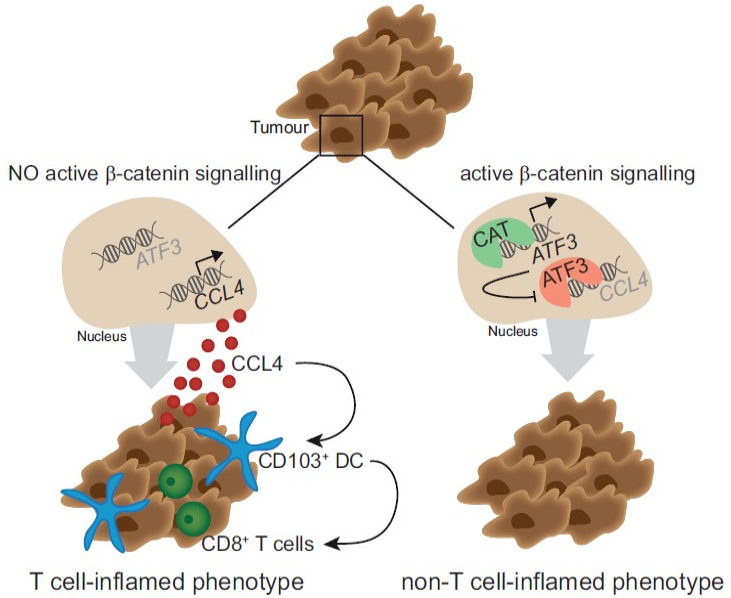
GPC3 induces HCC proliferation via Wnt/beta Catenin pathway



(M Ho et al 2011)

- High tumor GPC3 levels are known to be associated with increased Wnt / beta catenin oncogenic signaling resulting in HCC tumor proliferation

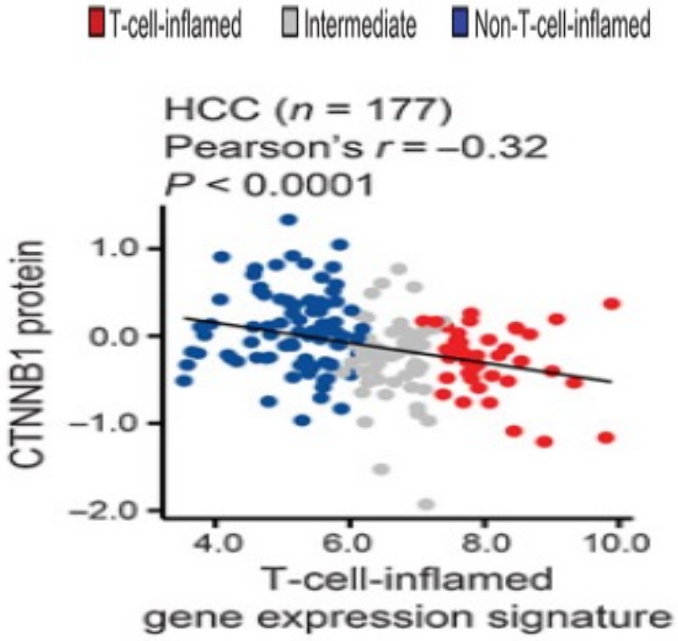
Wnt/beta Catenin activation results in T cell exclusion in TME



(Spranger and Gajewski et al 2015)

- Wnt/beta catenin signaling activates ATF-3 transcription factor that <u>represses</u> chemokine (CCL4) production and DC migration to tumor resulting in T cell exclusion in TME

High beta Catenin associated with Non-inflamed T cells in HCC TME



(Luke and Gajewski et al 2019)

- Increased beta catenin levels show reduced T cell inflamed signatures in HCC and other solid tumors (TCGA data)

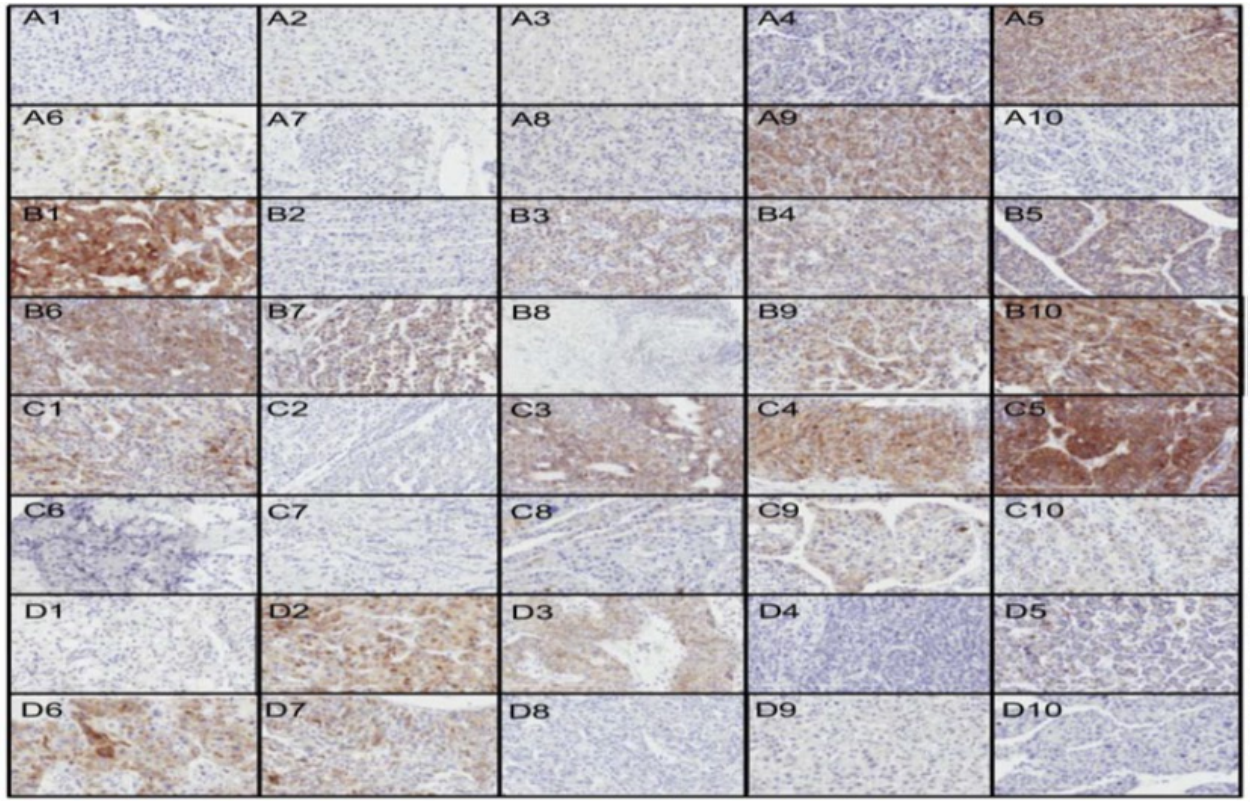
CYT-303 Shows Subnanomolar Binding to Human NKp46 and GPC3

Cross-reactivity against cynomolgus monkey for toxicology studies

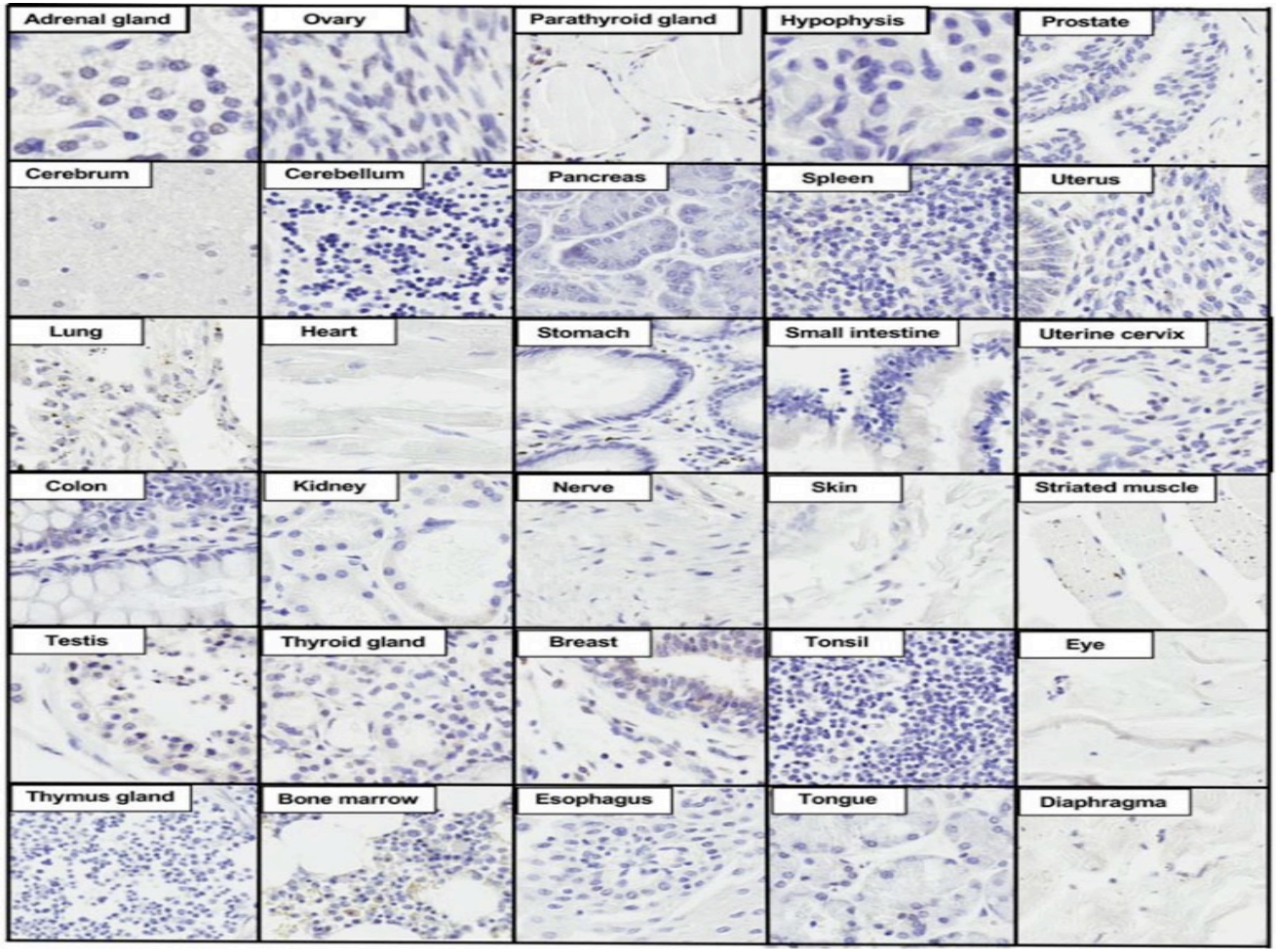
Target	Human Ligands (nM)	Cyno Ligands (nM)	Mouse Ligands (nM)
GPC3	K_D=0.646	K_D=0.273	K_D=0.447
NKP46	K_D= 0.202	K_D= 2910	KD= no binding
CD16	K_D=642 F K_D=147 V	K_D=140	K_D=4980

CYT-303 GPC3 Binder Does Not Show Any Significant Human Tissue Crossreactivity

GPC3 Expression in HCC Tumor Tissues

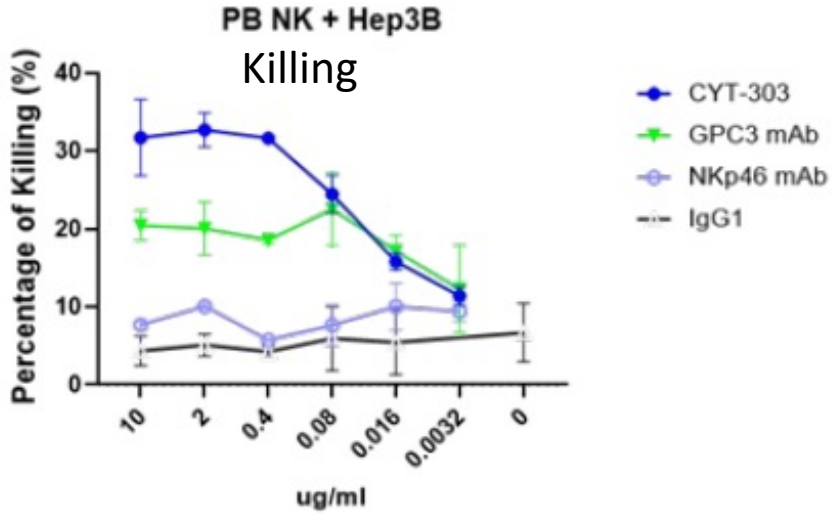


GPC3 Expression in Different Human Normal Tissues

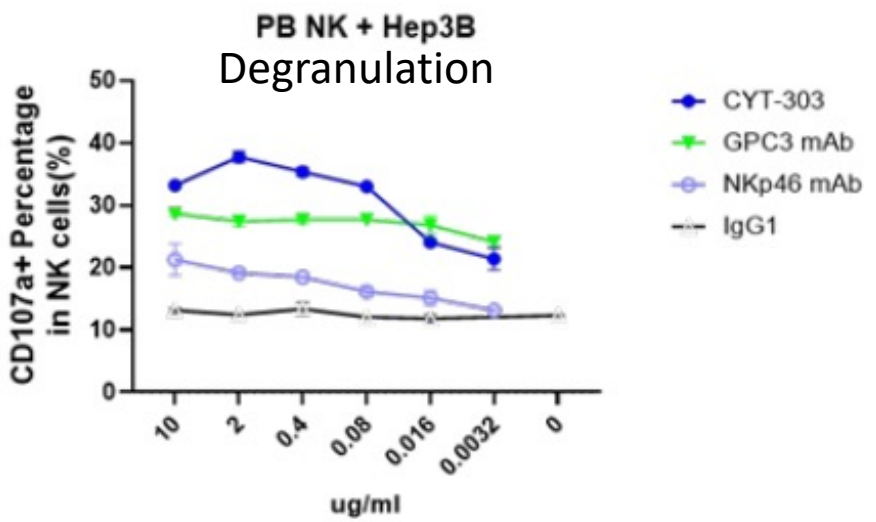


CYT-303 Engager NK Cell Redirected HCC Killing is Superior to GPC3 Monoclonal Antibody

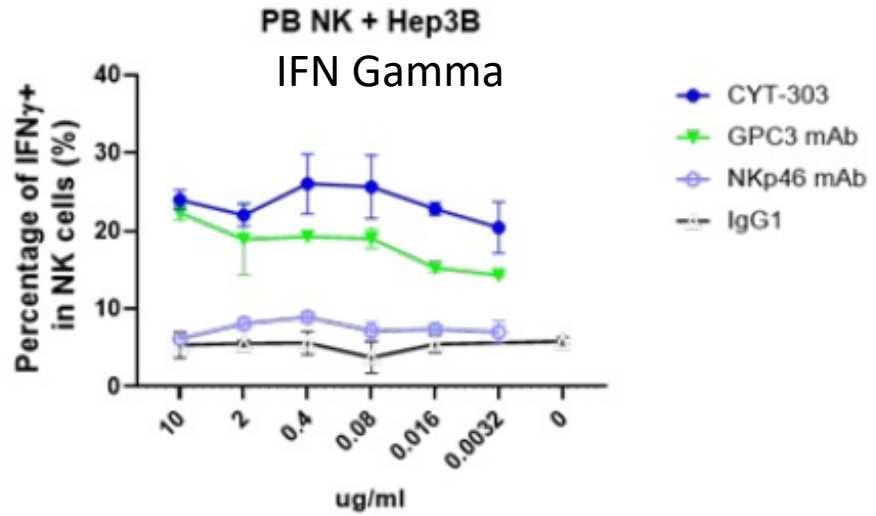
a)



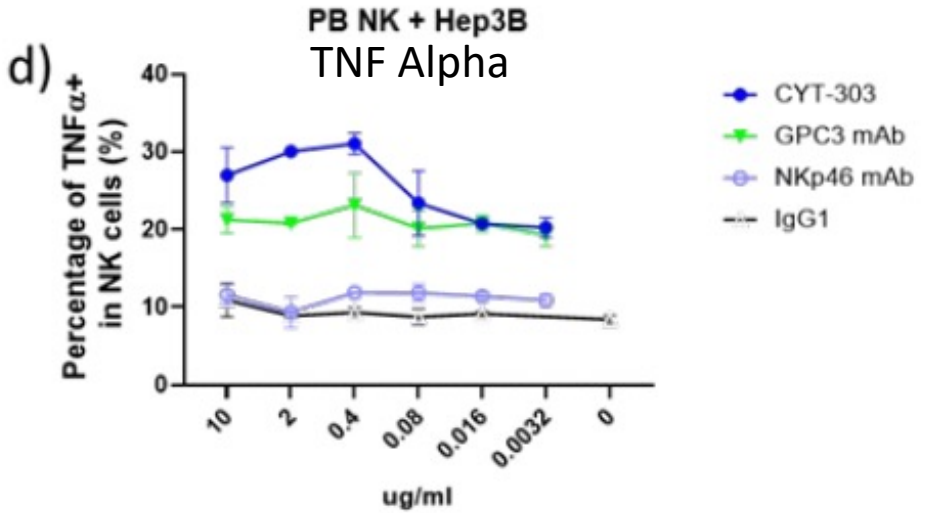
b)



c)



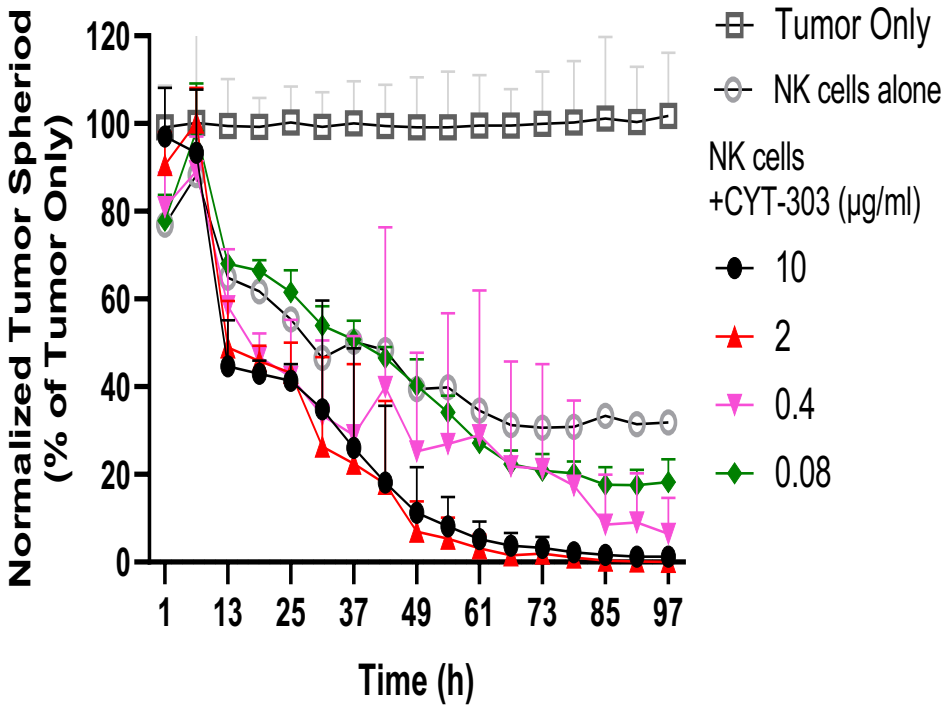
d)



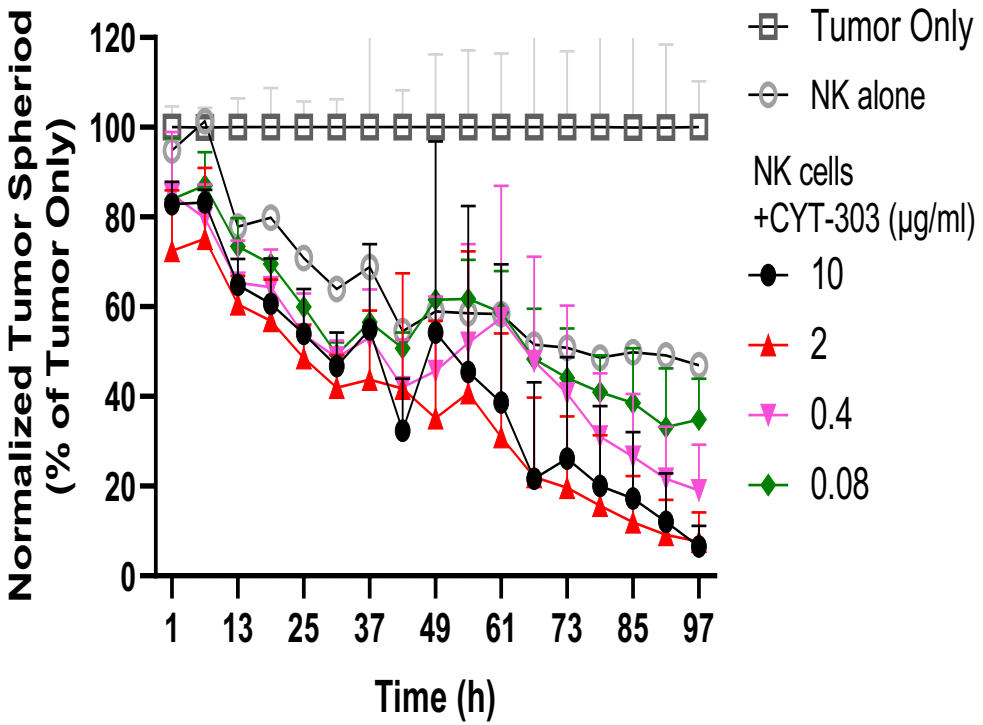
Arulanandam et al, Poster Presentation AACR 2022 #2752
Preclinical Characterization of HLE X NK CD Tetravalent NKp46 Engager Directed Against GPC3 (CYT-303) Alone or in Combination With iPSC DerivedNatural Killer Cells (iNKs) Against Hepatocellular Carcinoma (HCC)

CYT-303 Enhances iNK and PBNK Cytolysis of HCC Tumor Spheroids

iNK CYT-100 killing

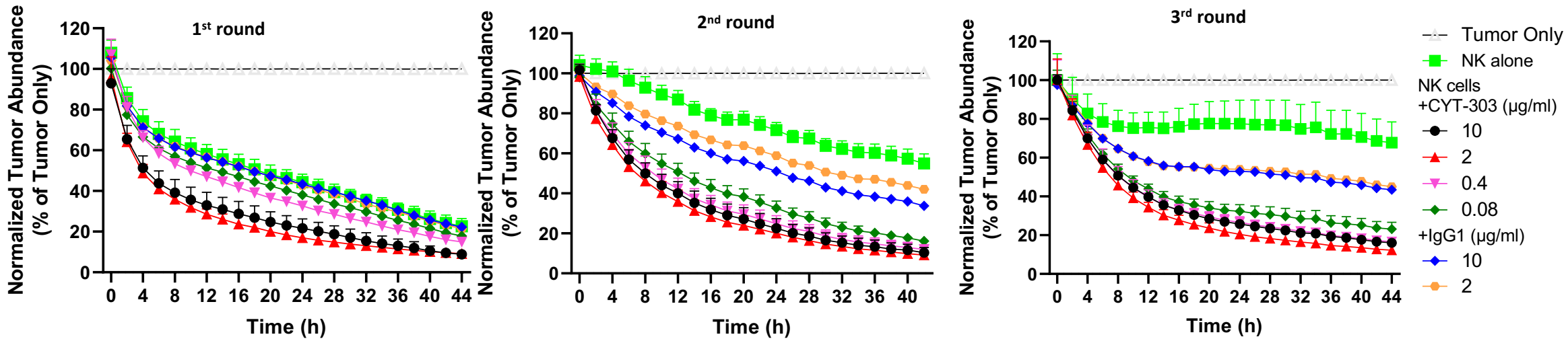


PBNK killing



Liang Lin et al. Preclinical characterization of CYT-100 iPSC derived NK cells alone and in combination with CYT-303 NK cell engager for hepatocellular carcinoma (HCC), SITC Poster presentation 2022 #177

CYT-303 Enhances HCC Tumor Killing & Reverses Dysfunction of PBNK Cells During Serial Killing



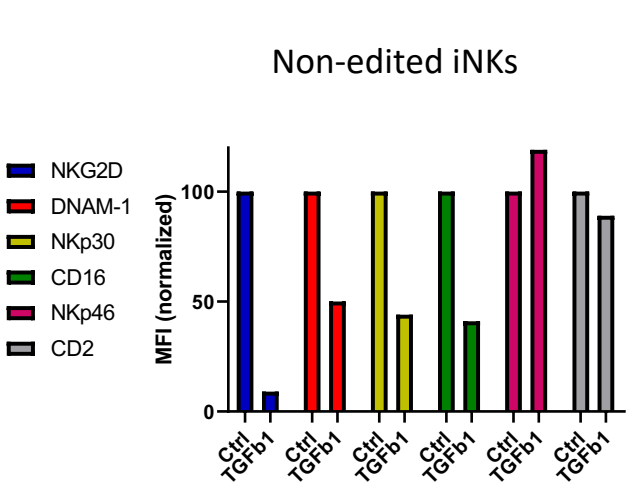
E/T ratio 1:2

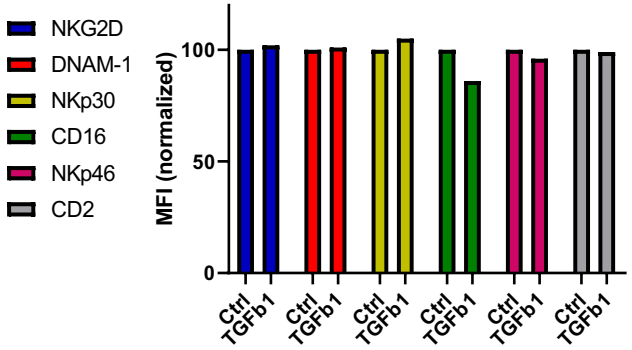
→ **PBNK cells alone showed gradual reduction in serial killing of Hep3B tumors suggesting dysfunction of these cells over time**

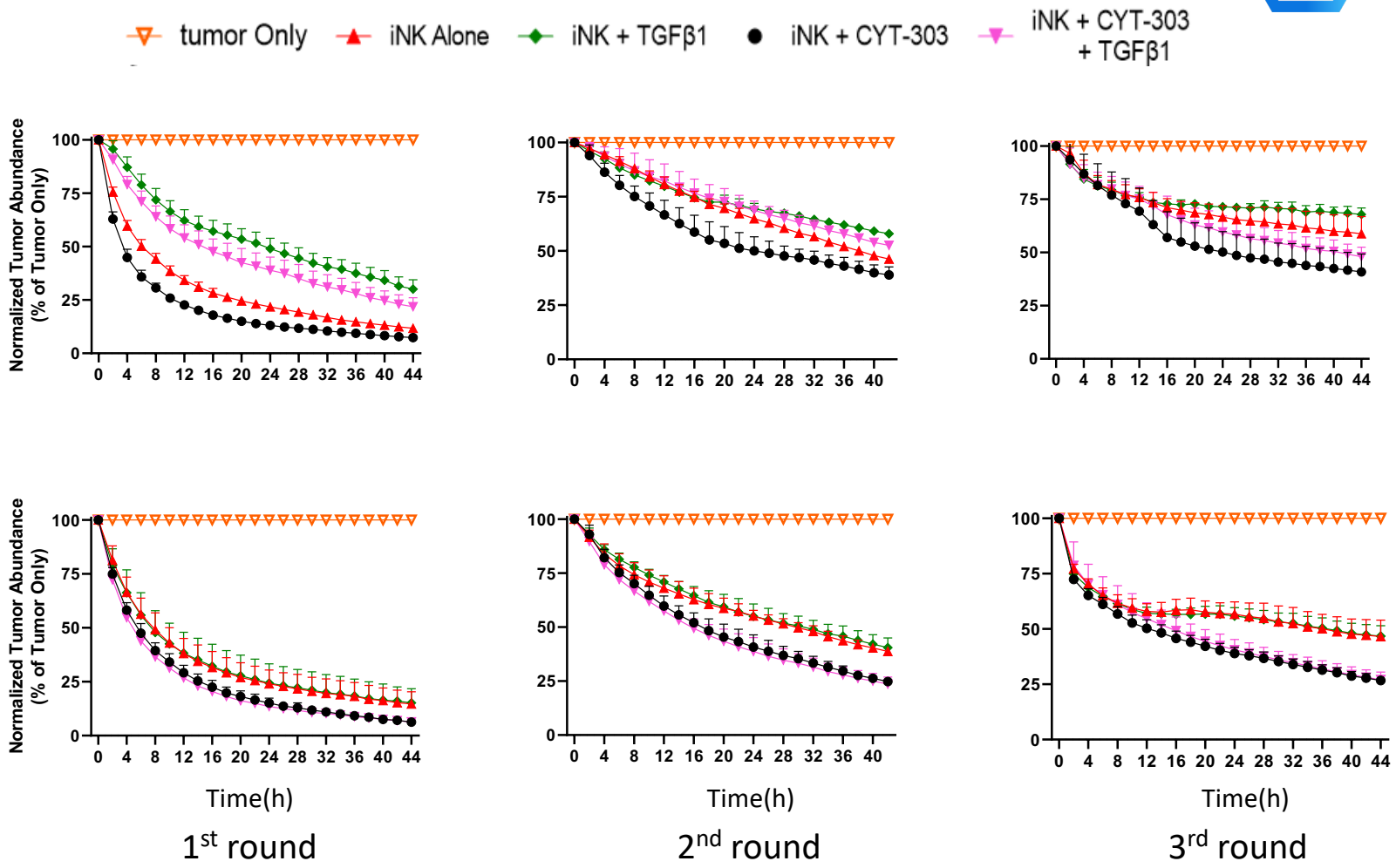
→ **CYT-303 reversed dysfunction of PBNKs and enhanced serial killing of Hep3B tumors in a dose dependent manner**

Liang Lin et al, Preclinical characterization of CYT-100 iPSC derived NK cells alone and in combination with CYT-303 NK cell engager for hepatocellular carcinoma (HCC), SITC poster presentation 2022 #177

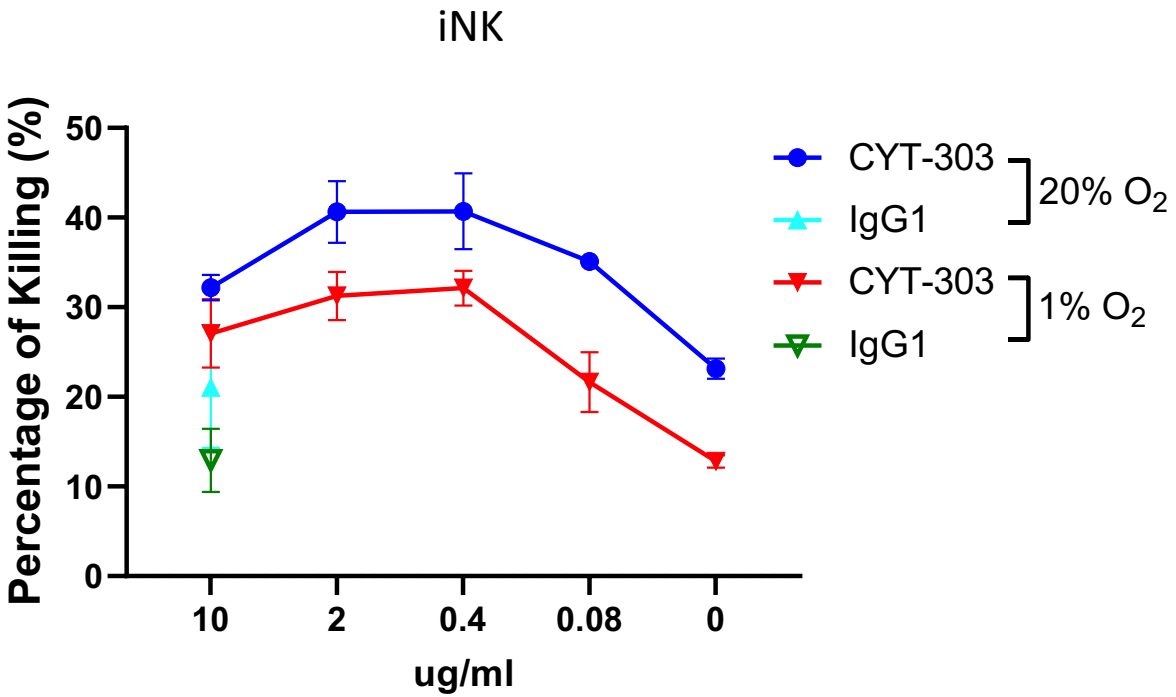
CYT-303 Enhances Killing & Reverses Dysfunction of iNK Cells During Serial Killing Even in the Presence of TGFβ

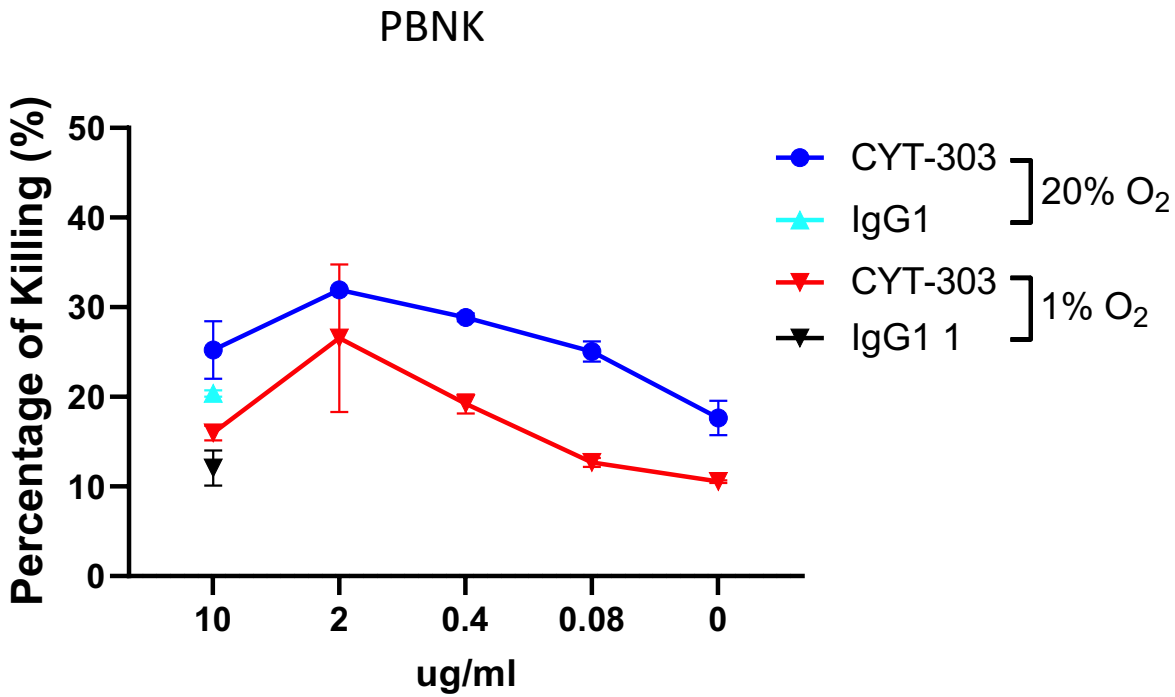






CYT-303 Reverses Hypoxia-Induced PBNK Dysfunction to Kill HCC Tumors



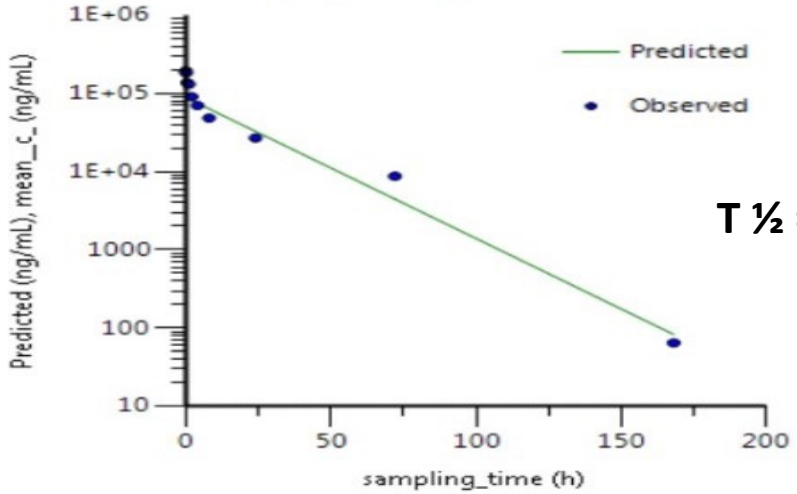


CYT-303 Pharmacokinetics in Mouse

→ *In addition to FcRn binding antibody half life is dependent on amino acid sequences and % mannose content due to clearance by mannose receptors*

CYT-303 Flex NK engager

- NCA – 2h-168h (6 points)

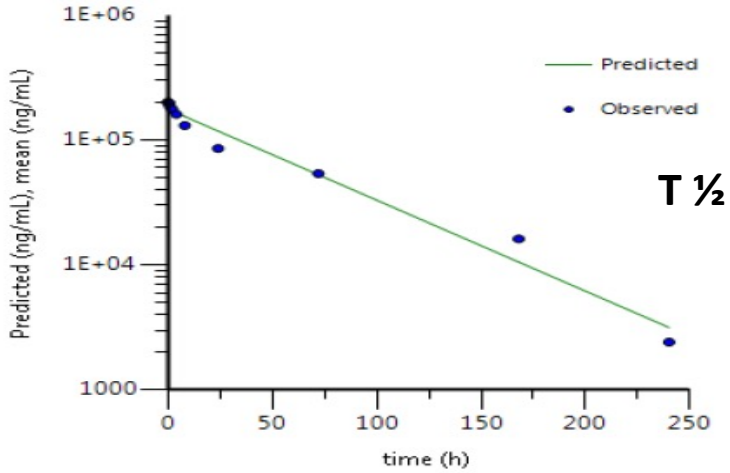


T ½ = 17 hrs

Parameter	Unit	Estimate_data 1
AUC(0-t)	*ng*h/mL*	2531406
AUC(0-inf)	*ng*h/mL*	2532968
DNAUC	*h*kg*ng/mL/mg*	253297
T1/2	*h*	17
MRT	*h*	28
CL	*mL/h/kg*	3.9
VSS	*mL/kg*	112

CYT-338 Flex NK engager

- **NCA:** 0.08h-240h (10 points)

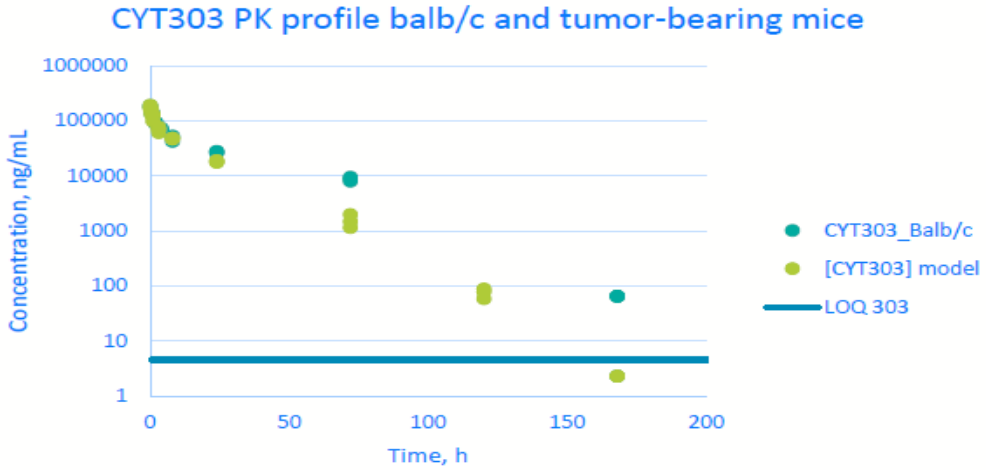


T ½ = 41 hrs

Parameter	Unit	Estimate
AUC(0-t)	*ng*h/mL*	10399858
AUC(0-inf)	*ng*h/mL*	10543701
DNAUC	*h*kg*ng/mL/mg*	1054370.1
T1/2	*h*	41.34
MRT	*h*	61.66
CL	*mL/h/kg*	0.95
VSS	*mL/kg*	58.48

Source: data on file

CYT-303 Single Dose PK in Normal and Tumor-Bearing Mice Showing Some Evidence of TMD

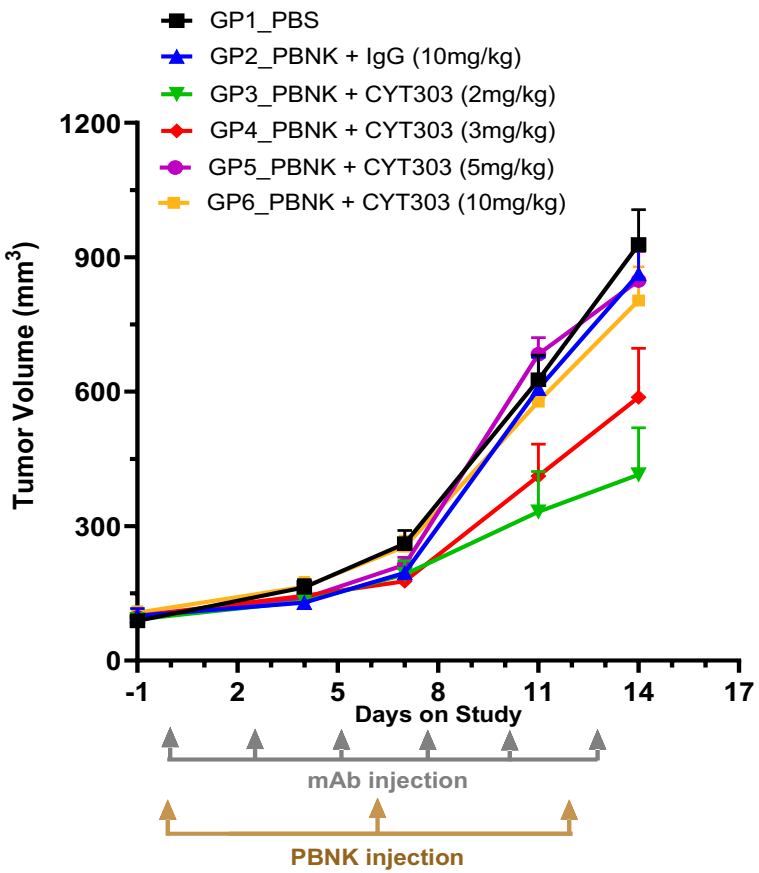


NCA analysis WNL		CYT303 estimate	
Parameter	Unit	Balb/c	Tumor-bearing mice
AUC(0-t)	*ng*h/mL*	2529406	1654265
AUC(0-inf)	*ng*h/mL*	2529884	1654303
DNAUC	*h*kg*ng/mL/mg*	252988	165430
T1/2	*h*	14	11.4
MRT	*h*	28	14.8
CL	*mL/h/kg*	4.0	6.0
VSS	*mL/kg*	111	89.5

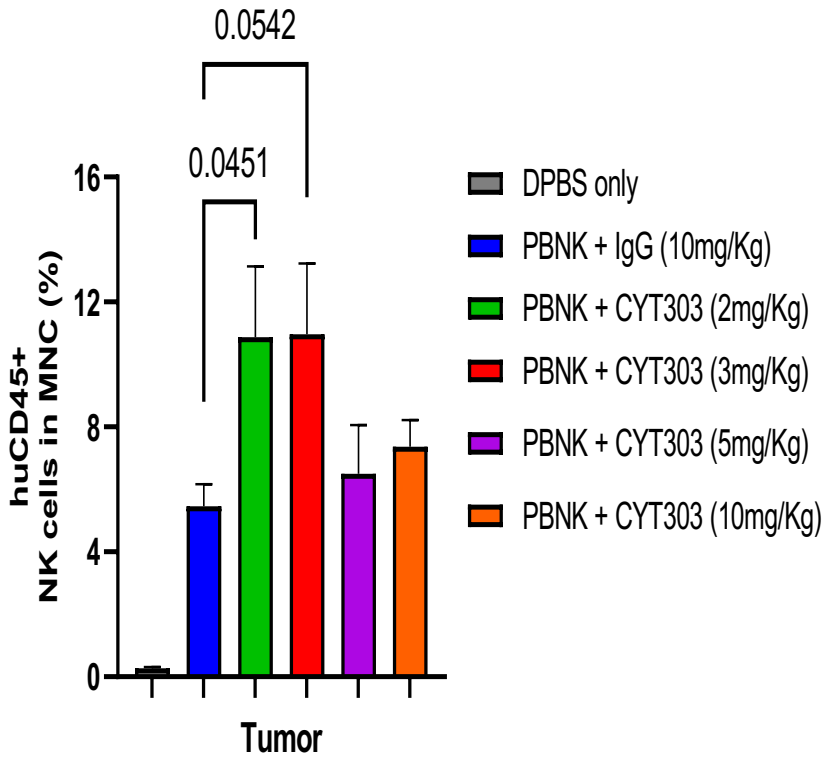
Source: PK study report form Onco-design

CYT-303 Anti-HCC Tumor Dose Response Correlates with Increased PBNK Trafficking from Blood to the Tumor

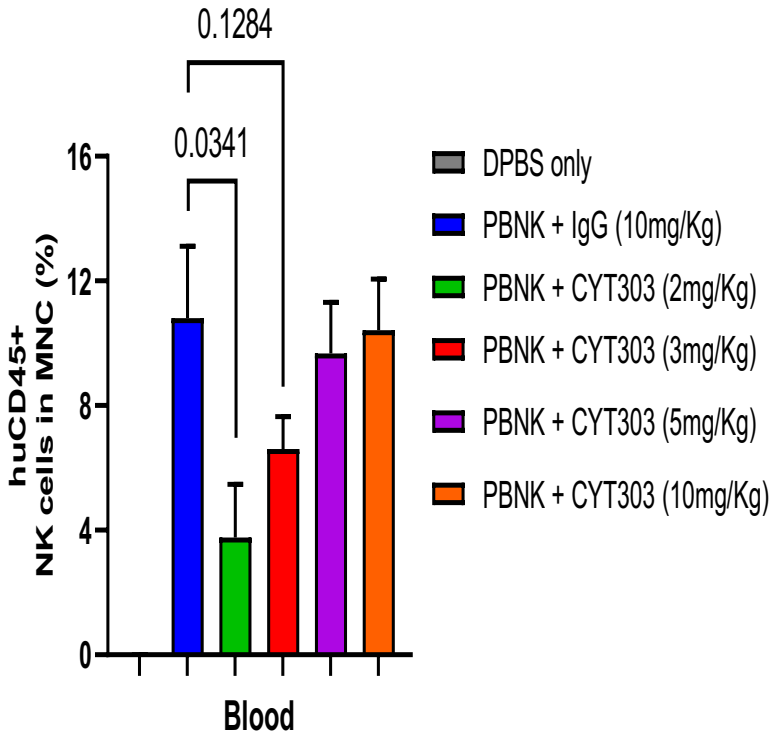
CYT-303 Tumor Growth Inhibition



PBNK Tumor Infiltration



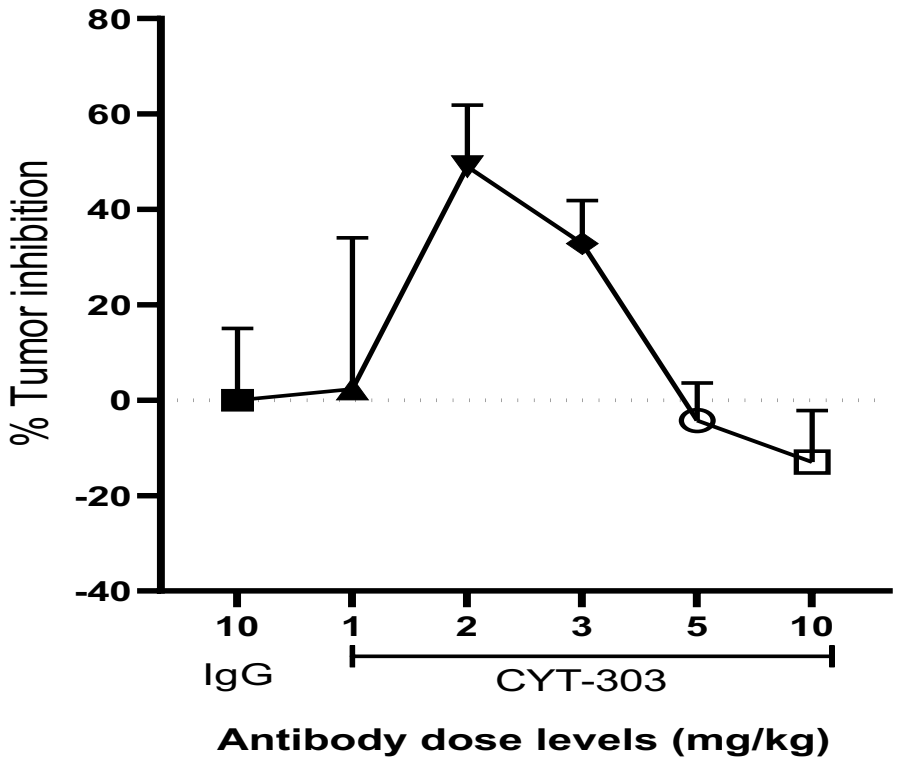
PBNK Pharmacodynamics in blood



CYT-303 Dose Response is Representative of Immune Synapse in PBNK Humanized HCC Tumor Model

-

CT-2 & 8



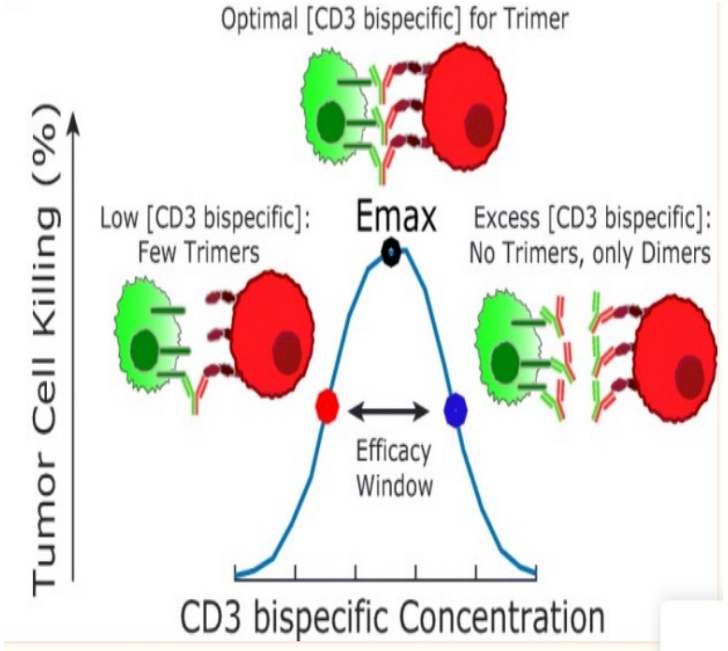


Illustration of MOA for bell shape activities for engagers

Source: Study report to be generated

CYT-303 Does Not Show Any Human Cytokine Release or Immunotoxicity In-Vitro

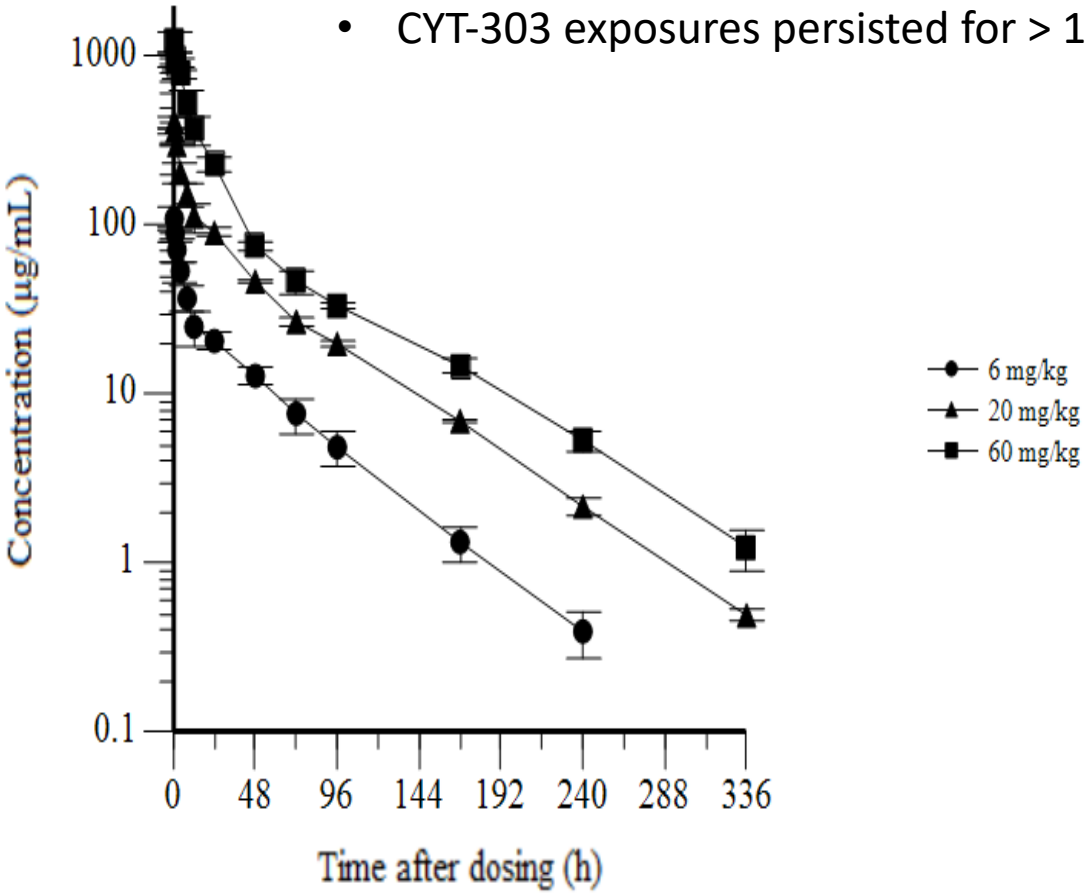
- CYT-303 showed no significant cytokine release in human PBMCs whilst the positive control TGN1412 super agonist anti-CD28 and anti-CD3 mAbs showed robust cytokine release

- CYT-303 did not show any NK cell fratricide whilst Anti-CD38 Daratumuab readily induced fratricide

- CYT-303 did not show any depletion of immune cell subsets including T. NK, B and monocytes while Daratumuab readily induced depletion of NK cells and monocytes

CYT-303 Pharmacokinetics in Cynomolgus Monkeys Supports Weekly Dosing in Clinical Trials

- CYT-303 was well tolerated and showed no evidence for any treatment related cytokine release
- CYT-303 showed dose liner pharmacokinetics parameters with a T ½ of 39-47 hrs
- CYT-303 exposures persisted for > 1 week supporting weekly dosing in clinical trials



Pharmacokinetic parameters of CYT-303 are shown in the following table.

Dose (mg/kg)	C_{max} (μg/mL)	$AUC_{0\text{-}168h}$ (μg·h/mL)	T_{max} (h)	$T_{1/2}$ (h)	Vdss (mL/kg)
6	109 ±16.9	1910 ±286	0.500	39.0 ±1.48	136 ±13.5
20	408 ±26.9	7740 ±302	0.500	44.3 ±0.651	118 ±8.39
60	1240 ±175	19800 ±1530	0.500	47.6 ±3.11	115 ±20.6

Data represent the mean ±SD of three animals.

4-Week Toxicity Study with CYT-303 in Cynomolgus Monkeys with a 6-Week Recovery following Once Weekly IV infusion (GLP)

Study objective: To evaluate the toxicity , safety pharmacology, PK and immunogenicity of CYT-303 following 4 weekly doses.

Group	Test and Control Articles	Dose Level (mg/kg)	Dose Volume (mL/kg)	Concentration (mg/mL)	Necropsy	Number of Animals (Animal No.)	
						Males	Females
1	Control*	-	5	-	Terminal Recovery	3 2	3 2
2	CYT-303	6	5	1.2	Terminal	3	3
3	CYT-303	20	5	4	Terminal	3	3
4	CYT-303	60	5	12	Terminal Recovery	3 2	3 2

Results:

- Well tolerated and no treatment related toxicitys
- No evidence for cytokine release (based on cytokine measurements and clinical pathology assessments)
- CYT-303 dose dependent increases in Cmax and AUC's were observed following the first and last dose and no evidence for accumulation was observed. CYT-303 exposures were maintained throughout the 4- week duration of the study.
- ADA occurred in 1 /22 animals (6 mg/kg group) and as expected was associated with reduced CYT-303 levels in this animal.
- ***NOAEL in the study was the highest dose administered in the study = 60 mg/Kg.***

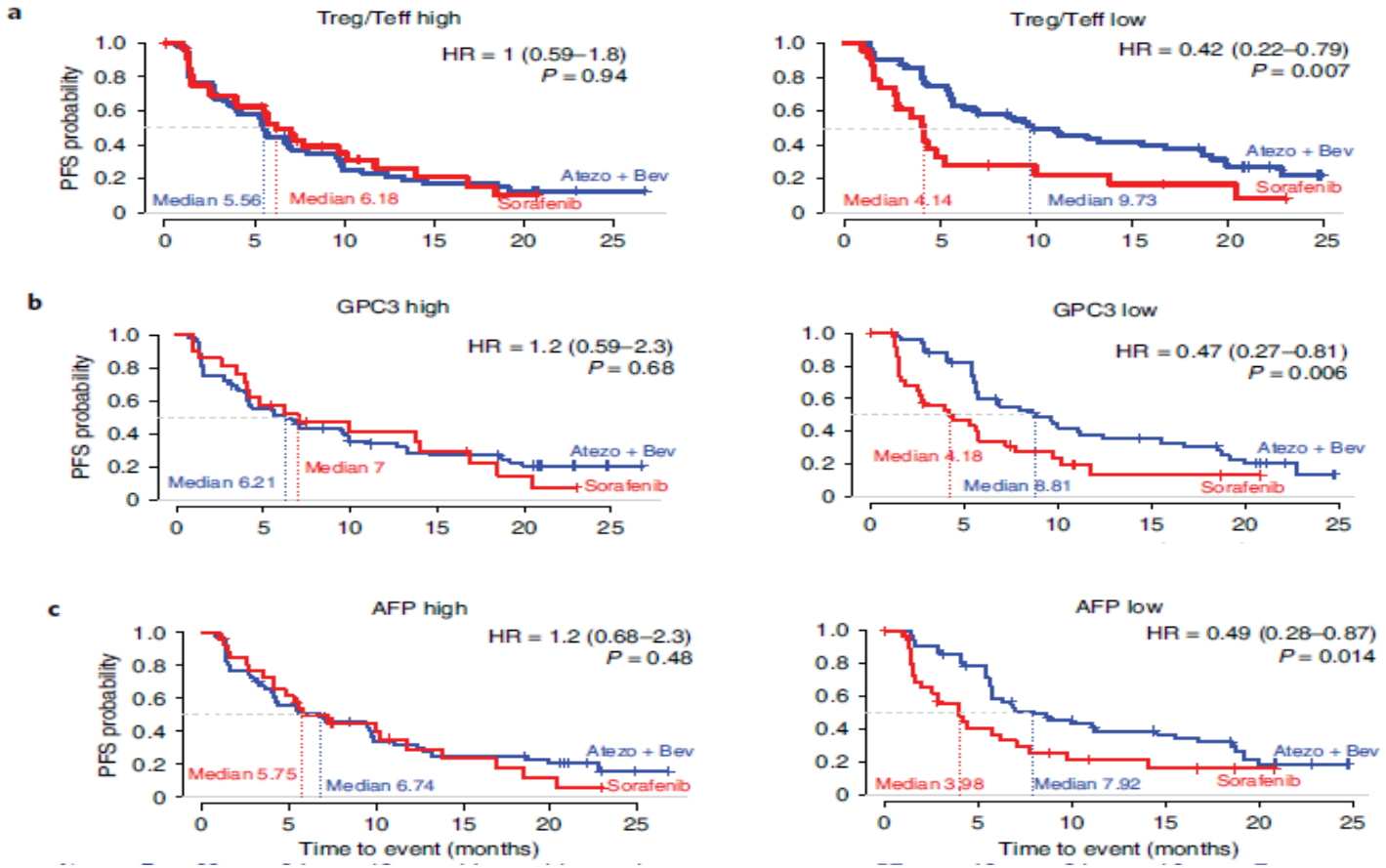
Conclusion:

- The results from the tox studies together with efficacy in tumor models support a PAD (pharmacologically active dose) based approach for first in human dosing in clinical trials.

Rationale for CYT-303 Combination Therapy with Check Point Immunotherapy

Retrospective Biomarker Analysis of Atezo + Bev First Line HCC Immunotherapy Approval

- Since CYT-303 can activate NK cells and reduce HCC tumor burden high GPC3 and AFP levels can be converted to low GPC3 and AFP signatures that are responsive to Atezo + Bev first line immunotherapy

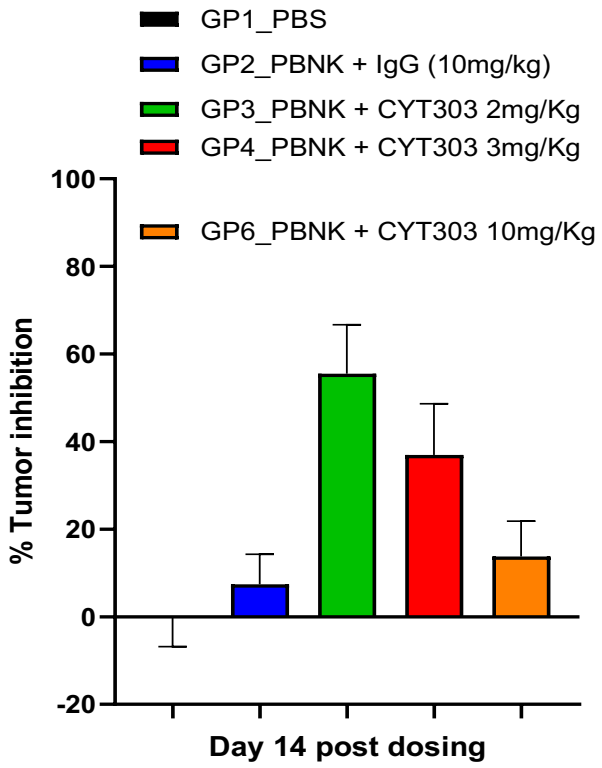


A Xu et al Nat Med 2022 and GO30140 and IMbrave150

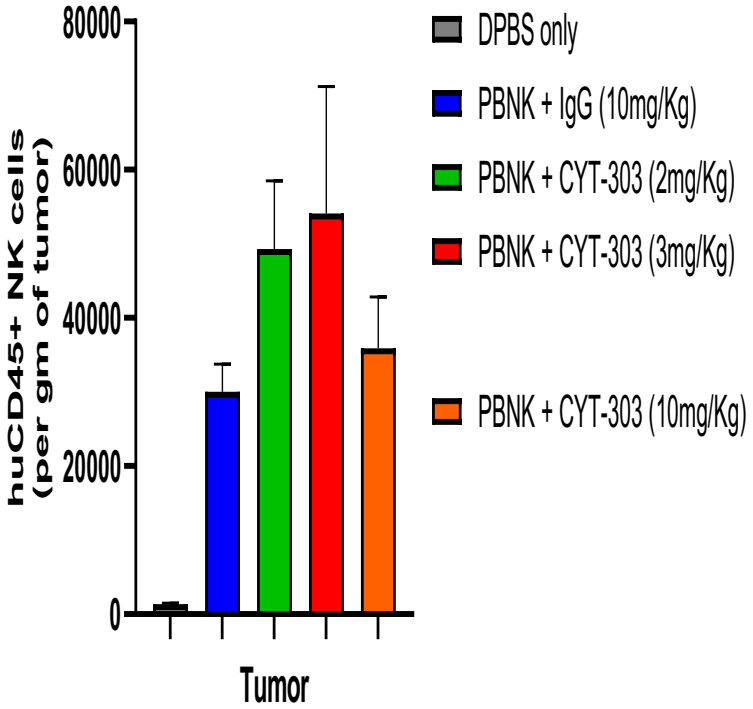
CYT-303 Activates NK Cells and Reduces HCC Tumor Burden and Blood AFP Levels:

Converts Non Responder Atezo + Bev Signature → Responder Atezo + Bev Signature

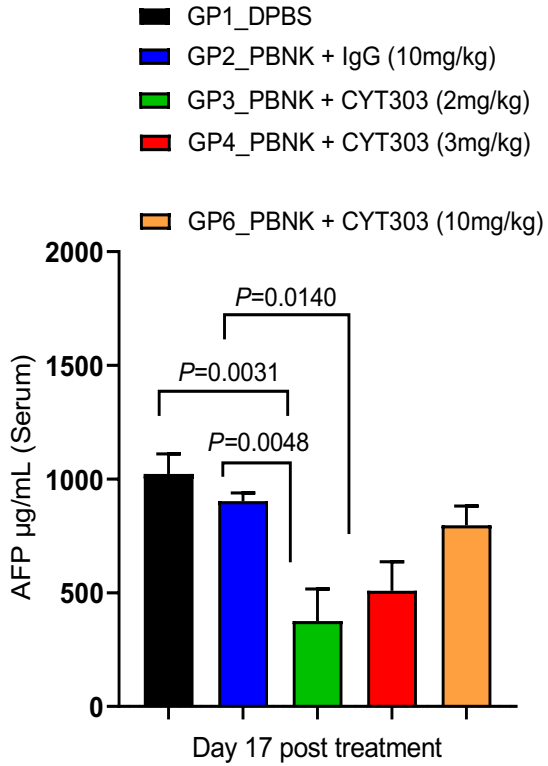
HCC Tumor growth Inhibition



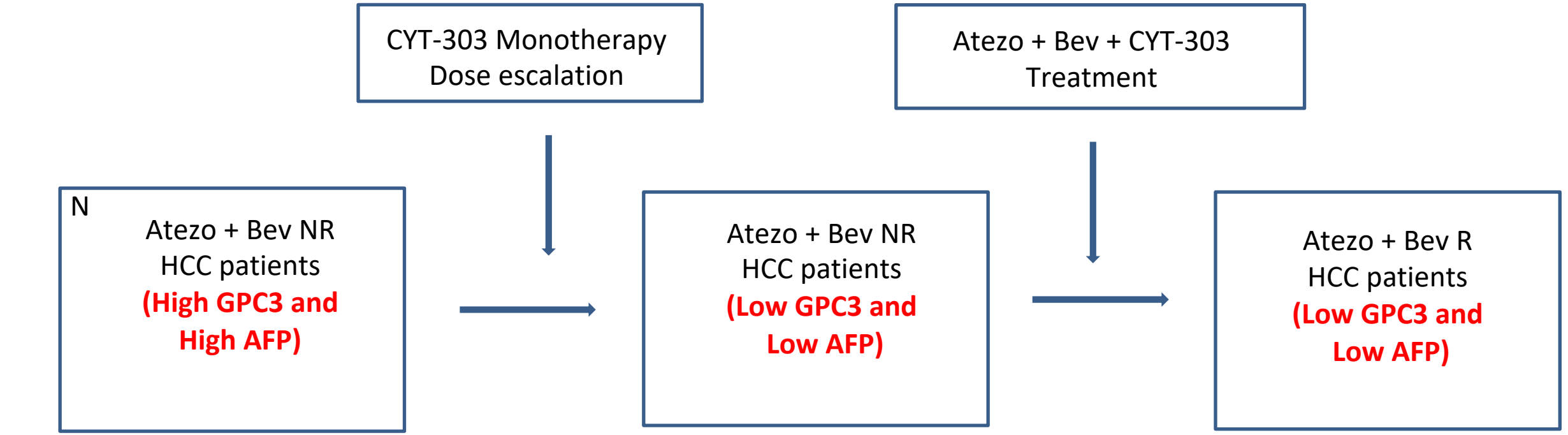
PBNK activation and expansion in tumor



Blood biomarker AFP reductions



HCC Biomarker Based CYT-303 Monotherapy Primes Responses to Atezo + Bev Checkpoint Combination Second Line Immunotherapy in Advanced HCC



NR = non responder

R = responder

CYT-303 Progress Towards IND

Milestones	CYT-303
In vitro data	✓
In vivo data	✓
Process Development	✓
GLP Batch	✓
Pharmacokinetics	✓
FDA pre-IND Meeting	✓
GLP Toxicology	✓
GMP Manufacturing	**2023**
IND Submission	**2023**

GLP: Good Laboratory Practices
IND: Investigational New Drug Application
GMP: Good Manufacturing Practices

- GPC3 Flex-NK™ Cell Engagers Showed to Redirect NK Cells to Kill HCC Tumors Cells *in vitro* (data presented at AACR 2022)
- The Combination of CYT-303 and iNKs Showed Greater Tumor Growth Inhibition Compared to iNKs Alone in HCC mouse model (data presented at AACR 2022)
- CYT-303 Demonstrated Dose Dependent Anti-Tumor Efficacy in Combination with donor derived PBNK or iNK Cells in HCC Tumor Models (data presented at ESMO 2022)
- CYT-303 PK Data in Non Human Primates Supported Weekly Administration in Patients (data presented at SITC 2022)
- No toxicity of CYT-303 at up to 20 times expected therapeutic dose in 4-week repeat dose cynomolgus monkey study (data presented at SITC 2022)

Acknowledgements and Thank You

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