A background image showing a microscopic view of cells, likely lymphocytes, with a light blue and white color scheme. The cells are out of focus, creating a soft, ethereal effect.

Linperlisib Phase 1b study in Peripheral T Cell Lymphoma

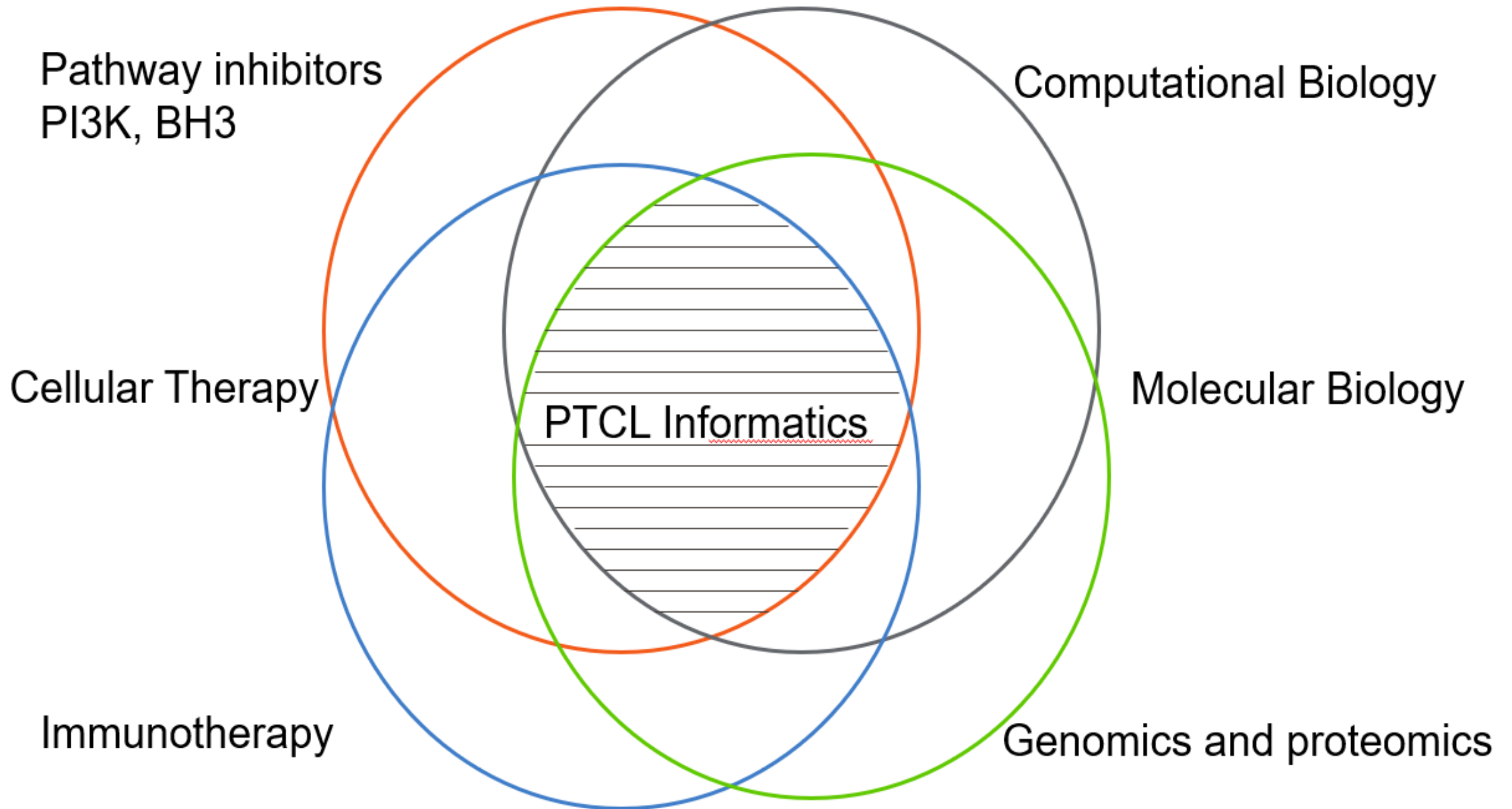
2018...2022 T-Cell Lymphomas: Finally vision and mission!

**Dr. Swami Iyer,
MDAnderson Cancer Center,
Houston, TX, USA**

Acknowledgement

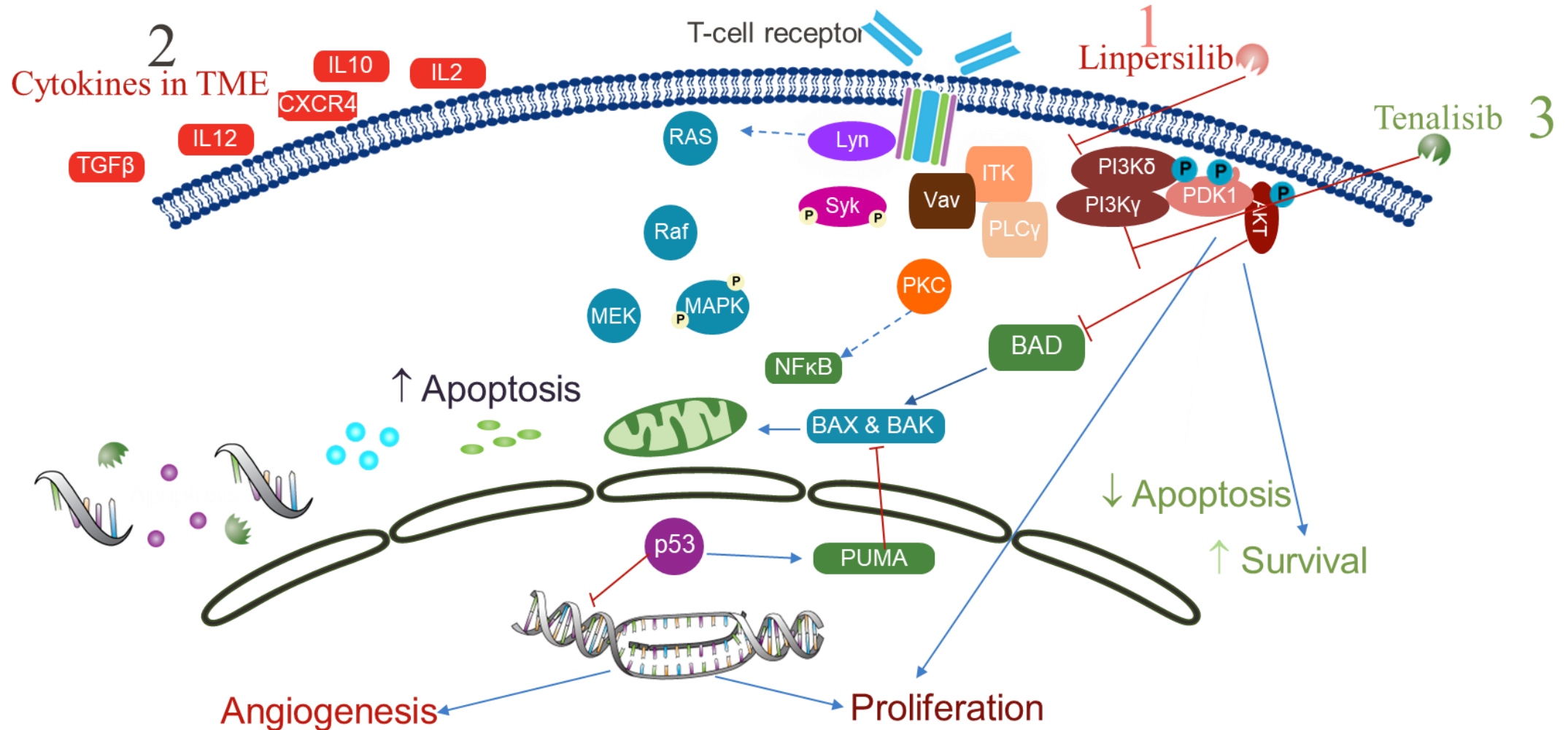
Many thanks to the patients and their families, and to the dedicated clinicians and staff supporting these patients

Overall Impact of T/NK-cell Malignancy Moon Shot



Three different mechanisms to enhance PI3K- δ and δ/γ inhibition in TCL

1. Cell autonomous: blocking mitogenic and survival signaling
2. Tumor Microenvironment (TME): Blocking mitogenic and survival signaling induced by cytokines and chemokines
3. Combined inhibition of PI3K- γ/δ , and downstream Bcl2 family of proteins to enhance the responses.

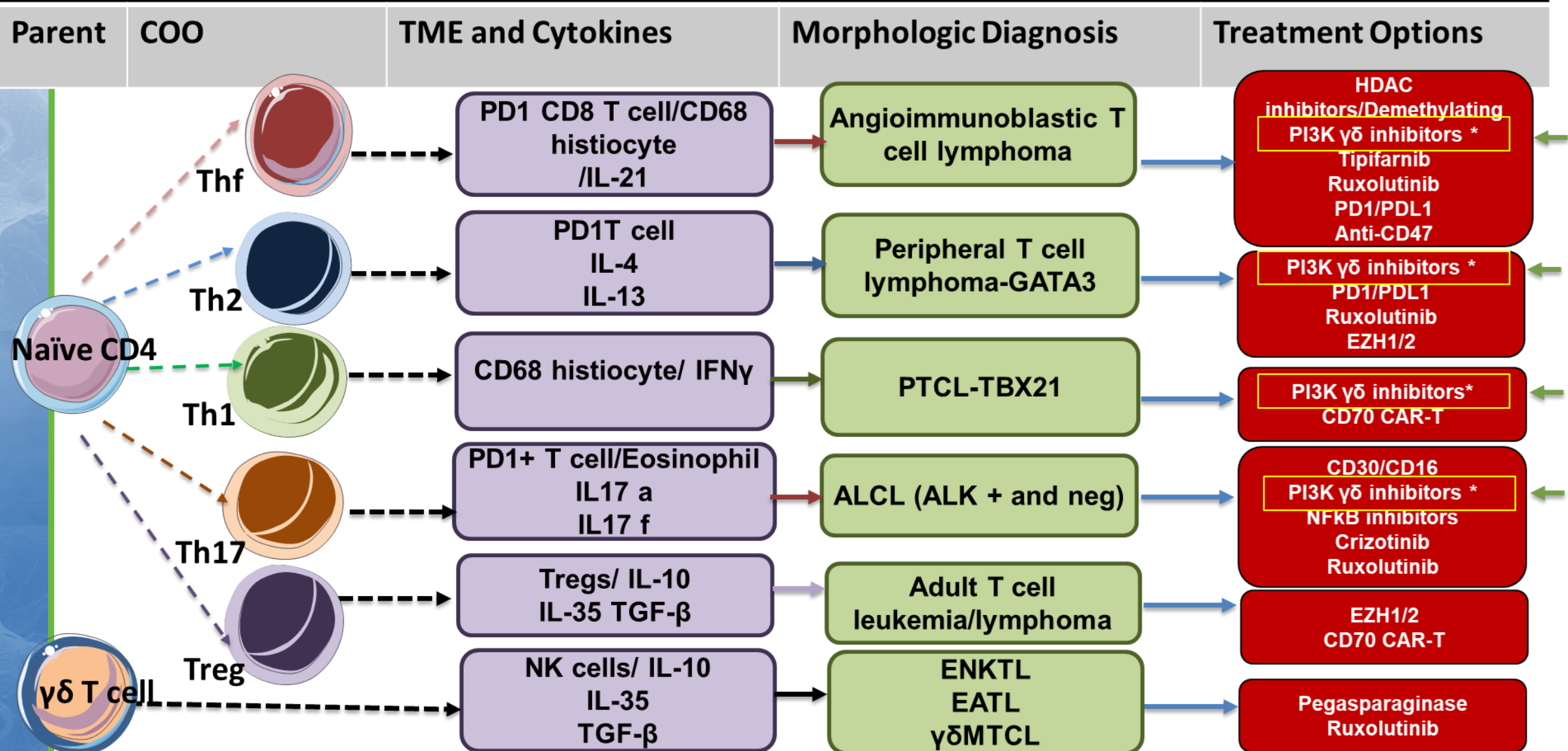


PI3K dependent pathway inhibition- clinical studies in TCL

Cell of origin for PTCL-NOS		
	PTCL-GATA3	PTCL-TBX21
Frequency	33%	49%
Gene expression	GATA3 and its target genes	TBX21 and its target genes
Phenotype	Th2 (IL4, IL5, IL13)	Th1 (IFN γ)
Cell Signaling	MYC and PI3K-mTOR	NF- κ B
Median OS	< 1 year	> 2 years

- PI3K/AKT/mTOR pathways are hyperactivated in many T-cell lymphomas
- The p110 δ and p110 γ , isoforms of PI3K promote mitogenic activity, survival signaling, and tumor associated macrophages (TAMs)
- GATA3+ TCL, a poor risk subset show significant enhancement of PI3K-associated pathway gene expression
- The two classes of PI3K inhibitors δ and δ/γ shown encouraging activity in r/r TCL as single agents and in combinations.

Rationale for PI3K pathway inhibition based on Cell of origin (COO) and Tumor microenvironment (TME)



Modified from Marchi, E. and O'Connor, O.A. 2020 CA A Cancer J Clin, 70: 47-70. Vega F, EXABS-TCL-052.2020

*GATA3+

A changing landscape for the PI3K drug class

PI3Ki are acknowledged to be highly efficacious in lymphomas and CLL, but are constrained by cumulative immune-mediated adverse events on extensive treatment

Withdrawal from market

Difficulty in running confirmatory studies - [Zydelig (idelalisib), Copiktra (duvelisib)]
Patient deaths drug-associated exceeding clinical benefit – (umbralisib, UNITY trial)

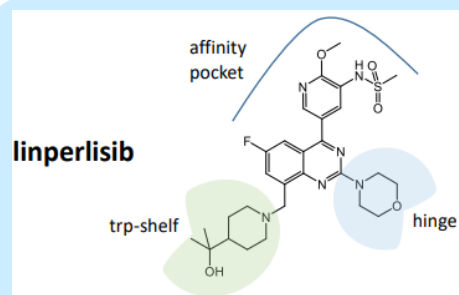
ODAC 2022 recommendations

Re-visit Dose schedules
Proof of optimal dose are being challenged (ie. Cautions about overdosing)

Decisions by pharma not to go forward

parsaclisib

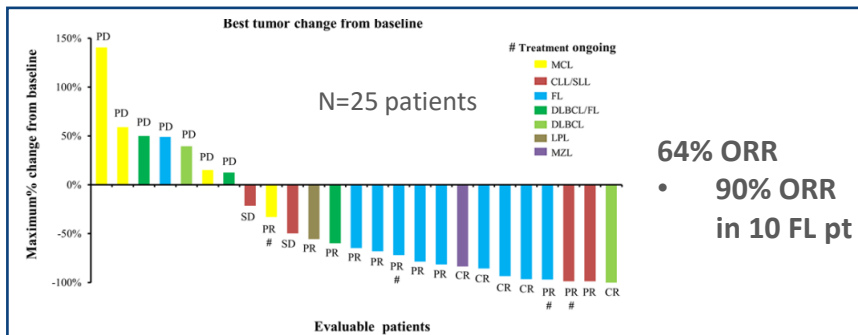
Linperlisib is an oral *Next Generation* PI3K δ that is safe and efficacious



Compound	PI3K δ IC50 (nM)	α/δ	β/δ	γ/δ
Linperlisib	4.6	252	30	1125
Idelalisib	4.5	227	40	13
Duvelisib*	2.5	640	34	11
Umbralisib*	22.23	>10000	>50	>48
Parsaclisib*	1	>10000	>10000	>10000
Zandelisib*	5	>1000	>65	>500

Linperlisib is an oral, potent, and selective Next Generation PI3K δ drug
SPONSOR, Yingli, 280BIO

Indolent Lymphoma (Phase1)



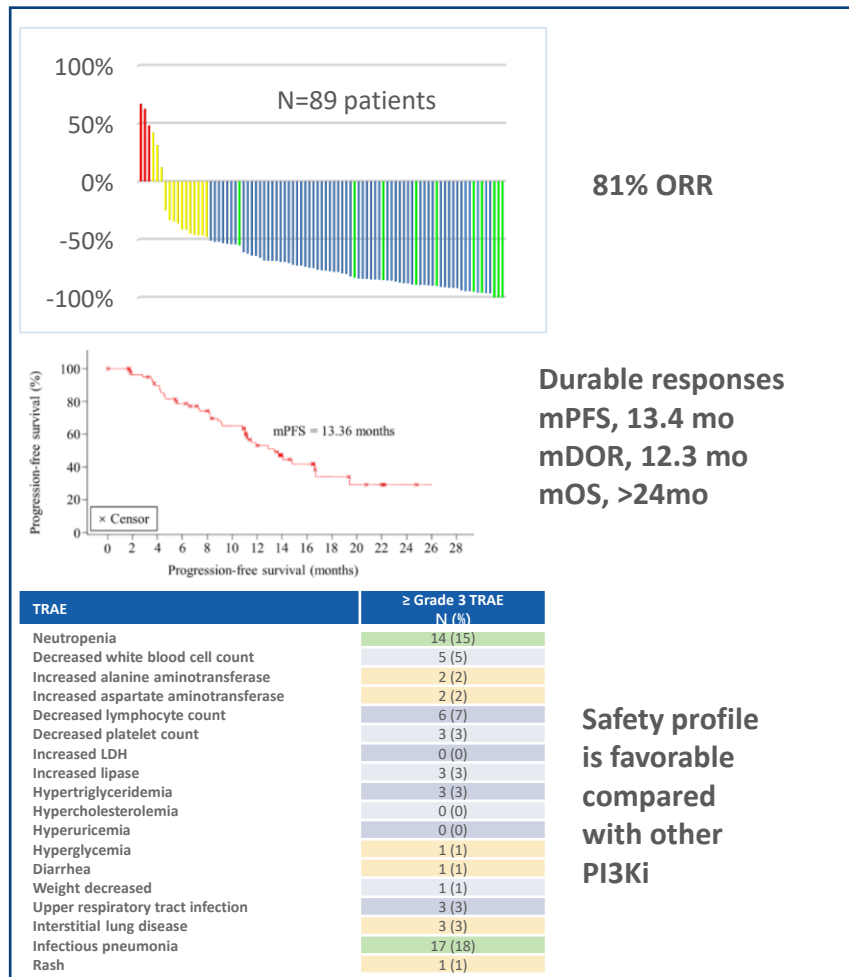
	Drug-related \geq Gr3 AEs (\geq 5% of patients)
neutropenia	44.0%
pneumonia	16.0%
hyperuricemia	12.0%
lymphocytomia	8.0%
leukopenia	8.0%
pneumonitis	8.0%

Very low transaminase elevations, diarrhea, colitis, skin rash

RP2D established as 80mg QD

Jiang et al. J Hematol Oncol (2021)14:130

Follicular Lymphoma (Phase2 registration)



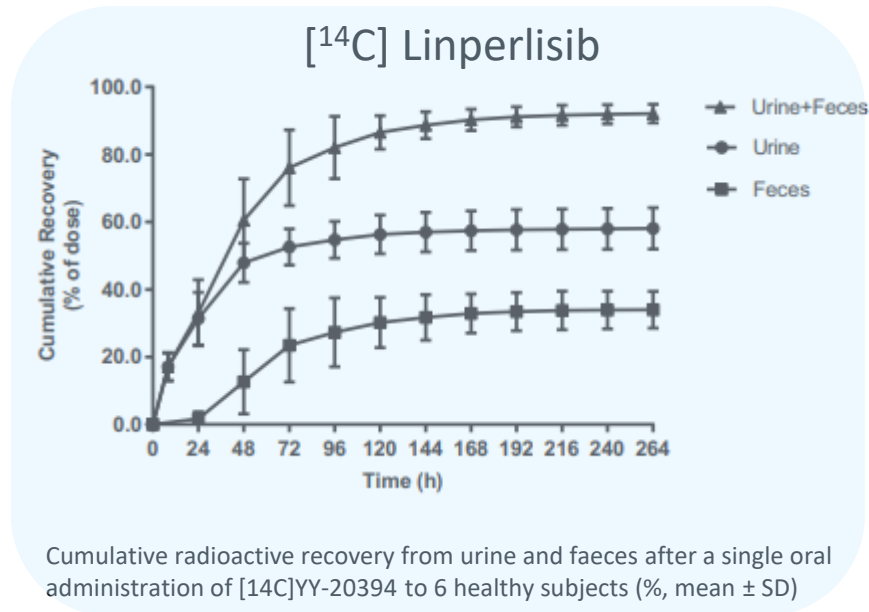
EHA 2021 EP792

Linperlisib development in China and U.S.

2020	Breakthrough Designation	<ul style="list-style-type: none">Linperlisib (YY-20394) received NMPA Breakthrough Designation for Follicular Lymphoma in China; Sponsor, Yingli Pharmaceuticals, Shanghai, China
	High ORR	<ul style="list-style-type: none">Dose escalation Phase1 in lymphomas completedLinperlisib is well-tolerated with a high overall response rate
	8 Ph 1 and Ph 2	<ul style="list-style-type: none">B cell malignancies, lymphomas, solid tumor clinical studies at RP2D
2021	Accelerated Approval application	<ul style="list-style-type: none">r/r FL registration study for NDA accelerated approval submitted> 400 patients treated
	T cell lymphoma	<ul style="list-style-type: none">FDA approval of Orphan Drug Designation for linperlisib in T cell lymphomar/r PTCL Phase 2 Registration study [2nd indication] launched
	China Partnership	<ul style="list-style-type: none">Strategic partnership with Hengrui Medicine jointly developing and commercializing linperlisib [Greater China region]
2022	US/EU Ph 2 trial	<ul style="list-style-type: none">US/EU Phase 2 study in r/r T-Cell Lymphomas launched in 2022
	China Ph 2 trials	<ul style="list-style-type: none">Ph2 studies of linperlisib in combination with SHR1459 (BTK) , camrelizumab, thymic cancers

Pharmacokinetics for Linperlisib

Increased kidney and lower GI excretion



PI3K DRUG	Dose	% in Urine	% in Feces
Linperlisib	80 mg, po	58	34
Idelalisib	25 mg, po	14	78
Duvelisib	150 mg, po	14	79
Copanlisib	12 mg, iv	22	64
Umbralisib	800 mg, po	3	81

Source Data: Linperlisib [published by Yu et al. (2022) Xenobiotica 52:3, 254-264; also for FDA-Approved Drugs: <https://www.accessdata.fda.gov/scripts/cder/daf/>

- Renal excretion is the predominant elimination route of [¹⁴C] linperlisib in a healthy subject tracing and metabolism study
- Fecal excretion is the predominant elimination route for the other marketed PI3K inhibitors (idelalisib, duvelisib, copanlisib and umbralisib)
- A higher urinary excretion rate of YY-20394 may lead to lower incidence of diarrhea and colitis and other AEs

Linperlisib PTCL Phase 1b study investigators

**A Phase 1b Study of Linperlisib (YY-20394) in the Treatment of Patients with Relapsed and/or Refractory
Peripheral T-Cell Lymphoma**

Jie Jin ¹, Hong Cen ², Keshu Zhou ³, Xiaohong Xu ⁴, Fei Li ⁵, Tao Wu ⁶, Haiyan Yang ⁷, Zhen Wang ⁸, Zhiming Li ⁹, Hanying Bao ¹¹, Zusheng Xu ¹¹, Lugui Qiu ^{10*}

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¹⁰Lymphoma Center, Institute of Hematology and Blood Diseases Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College (PUMC), Tianjin, China

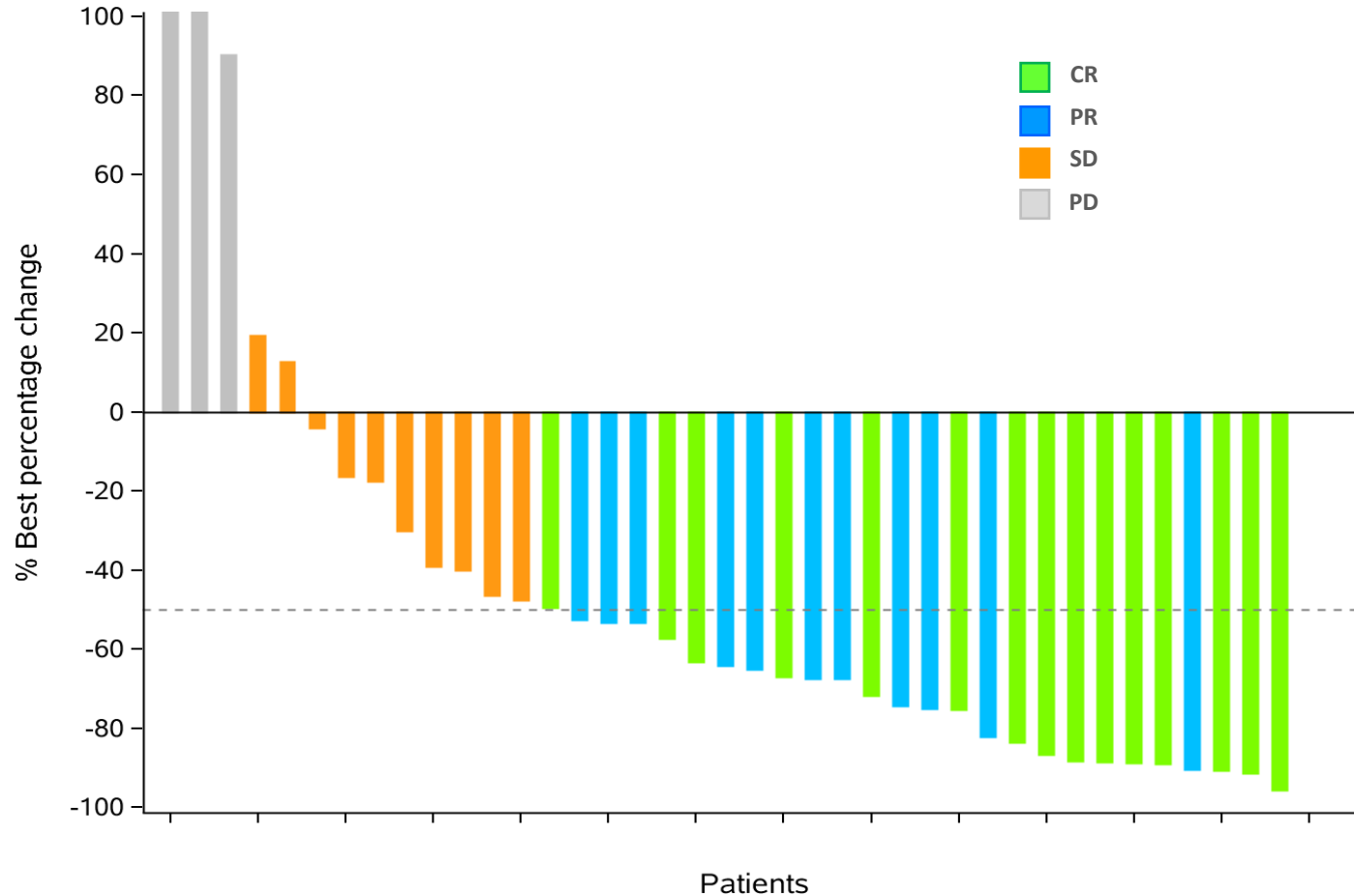
¹¹Shanghai Yingli Pharmaceutical Co., Ltd., Shanghai, China

Demographics and Baseline Characteristics in r/r PTCL single arm clinical trial

- Phase1b of 43 pts with r/r PTCL conducted at 10 clinical sites in China
- All patients received linperlisib at 80 mg QD for at least one dose (FAS)
- PTCL histology subtypes were PTCL-NOS (n=17), AITL (n=16), ALCL (n=6), NKTCL (n=3), and MEITL (n=1)
- Primary endpoint was Overall Response Rate
- Preliminary results from this study were previously reported at ASCO (2021) and ICML (2021)
- **Here is reported the completed study, with ≥ 1 year follow-up post LPI**

Age		
Years Median (min, max)		58 (18, 79)
Gender		
Male		27 (62.8%)
Female		16 (37.2%)
Race		
Chinese		43 (100%)
ECOG performance status, n (%)		
0		17 (39.58%)
1		24 (55.8%)
2		2 (4.7%)
Number of prior systemic therapies		
Median (min, max)		2 (1, 5)
Ann Arbor-Cotswolds Stage		
II		4 (9.3%)
III		18 (41.9%)
IV		21 (48.8%)
Prior lines of therapy, n (%)		
1		18 (41.9%)
2		12 (27.9%)
3		7 (16.3%)
4		4 (9.3%)
5		2 (4.7%)
Refractory to last regimen		
n (%)		36 (83.7%)

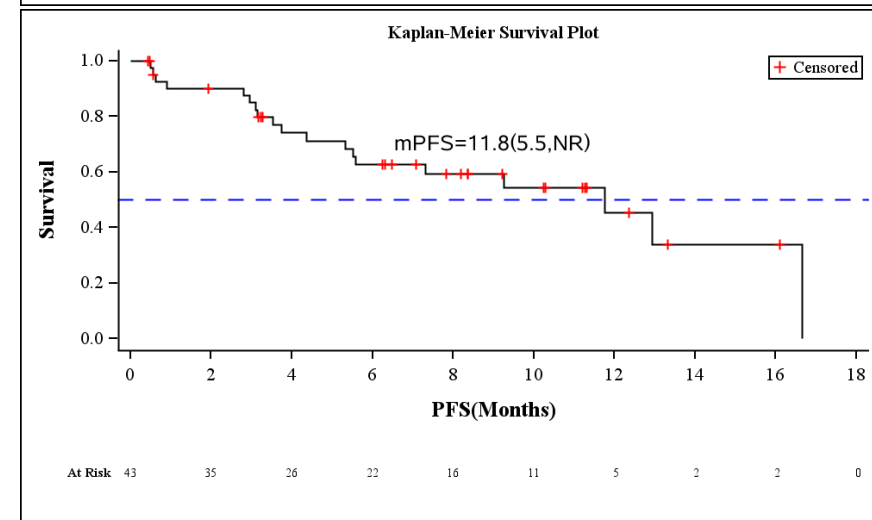
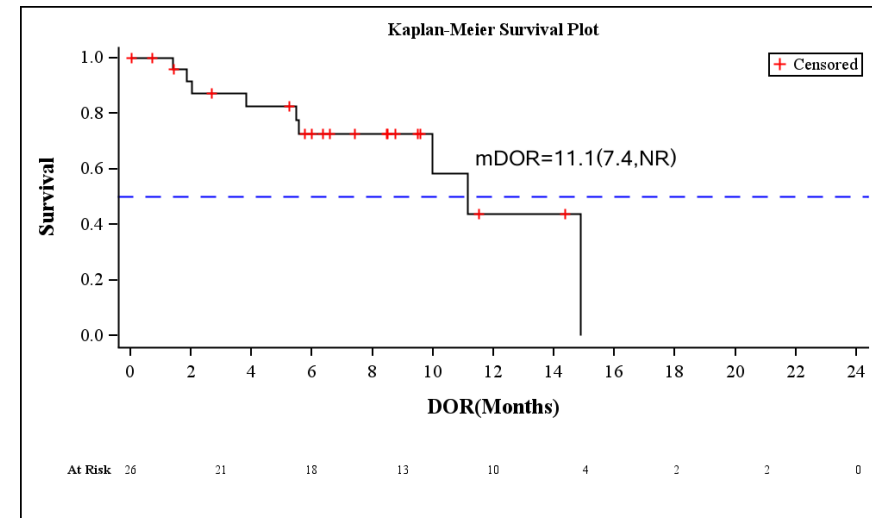
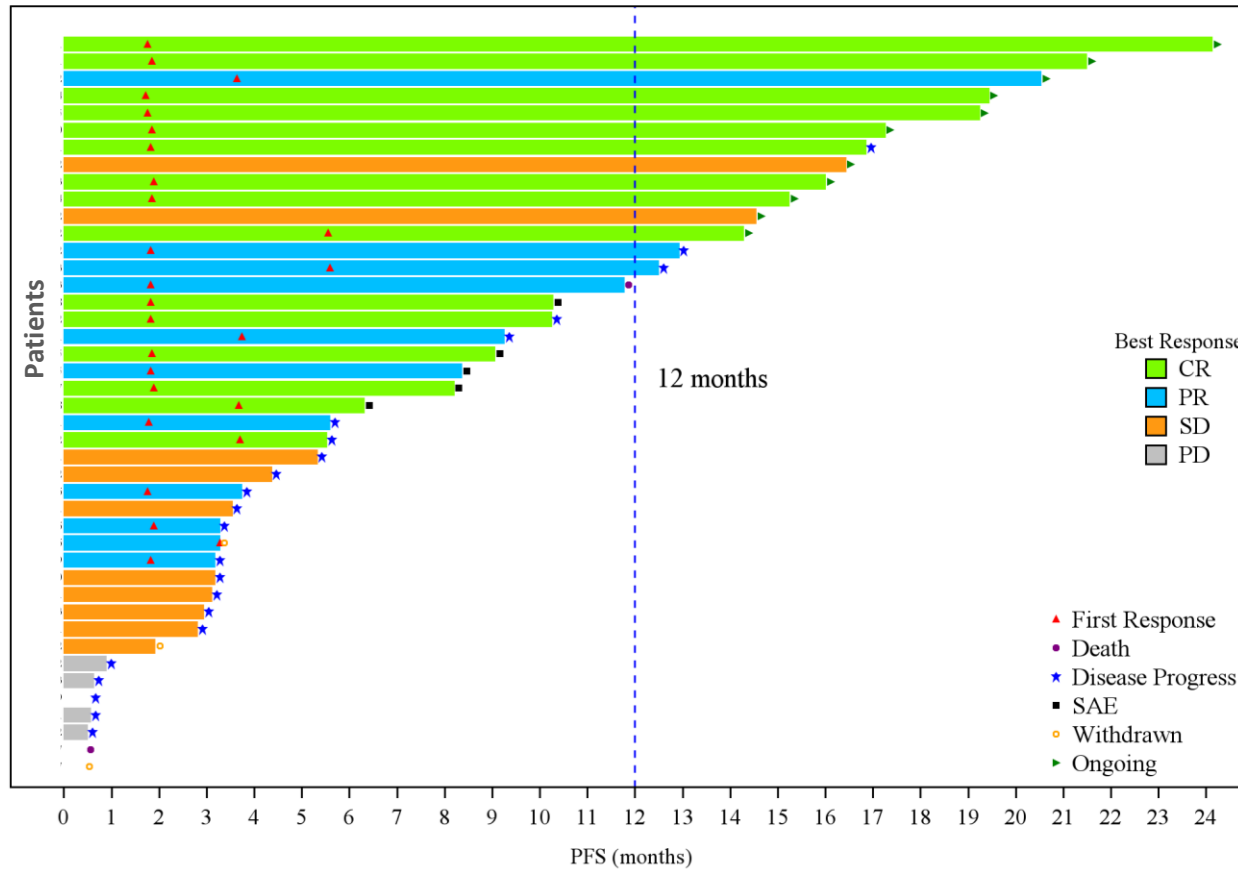
Linperlisib treatment leads to high Complete Response and Partial Response rates across PTCL subtypes



- n=43 patients
- 40 pts evaluable for efficacy
- **ORR 61%**
 - CR 38% (15 pt)
 - PR 28% (11 pt)
 - SD 25% (10 pt)
 - PD 10% (5 pt)
 - DCR of 84%
- **Responses in all PTCL subtypes**
 - AITL (81%, 16pt)
 - PTCL-NOS (41%, 17pt)
 - ALK-neg ALCL (2/5 pt)
 - NKT (2/3 pt)
 - ALK-pos ALCL (1/1 pt)
 - MEITL (1/1 pt)

Tumor response was assessed by IWG 2007 criteria with CT performed every 2 cycles. YY-20394-004 datacut May 31, 2022

Durable responses with linperlisib treatment in r/r PTCL



- 1 year of follow-up after the last patient has enrolled
- Median TTR 1.9 months (95%CI, 1.7,5.6 mo)

TEAE and TRAE in linperlisib-treated r/r PTCL patients

		YY-20394-004 (N=43)	
		N (%)	N events [#]
TEAE	Any TEAE*	39(90.7)	615
	Any TEAE ≥Grade 3	23(53.5)	44
	Any Serious TEAE	16(37.2)	18
	Any TEAE leading to dose reduction	3(7.0)	3
	Any TEAE leading to dose interruption	17(39.5)	54
	Any TEAE leading to dose withdrawal	7(16.3)	8
	Any TEAE leading to death	2(4.7)	2
TRAE	Any TRAE*	39(90.7)	459
	Any TRAE ≥Grade 3	21(48.8)	38
	Any Serious TRAE	11(25.6)	12
	Any TRAE leading to dose reduction	3(7.0)	3
	Any TRAE leading to dose interruption	14(32.6)	20
	Any TRAE leading to dose withdrawal	5(11.6)	6
	Any TRAE leading to death	0(0.00)	0

*Adverse events were code using MedDRA 25.0.

[#]In the event of multiple AEs being reported by the same pt, each pt is counted once for each intensity level/causality level. This means that the total number of pts for all levels of intensity/causality might be higher than the overall number of pts with at least one AE.

[^]Relatedness is assessed by the investigator; missing relatedness is imputed as 'Related'.

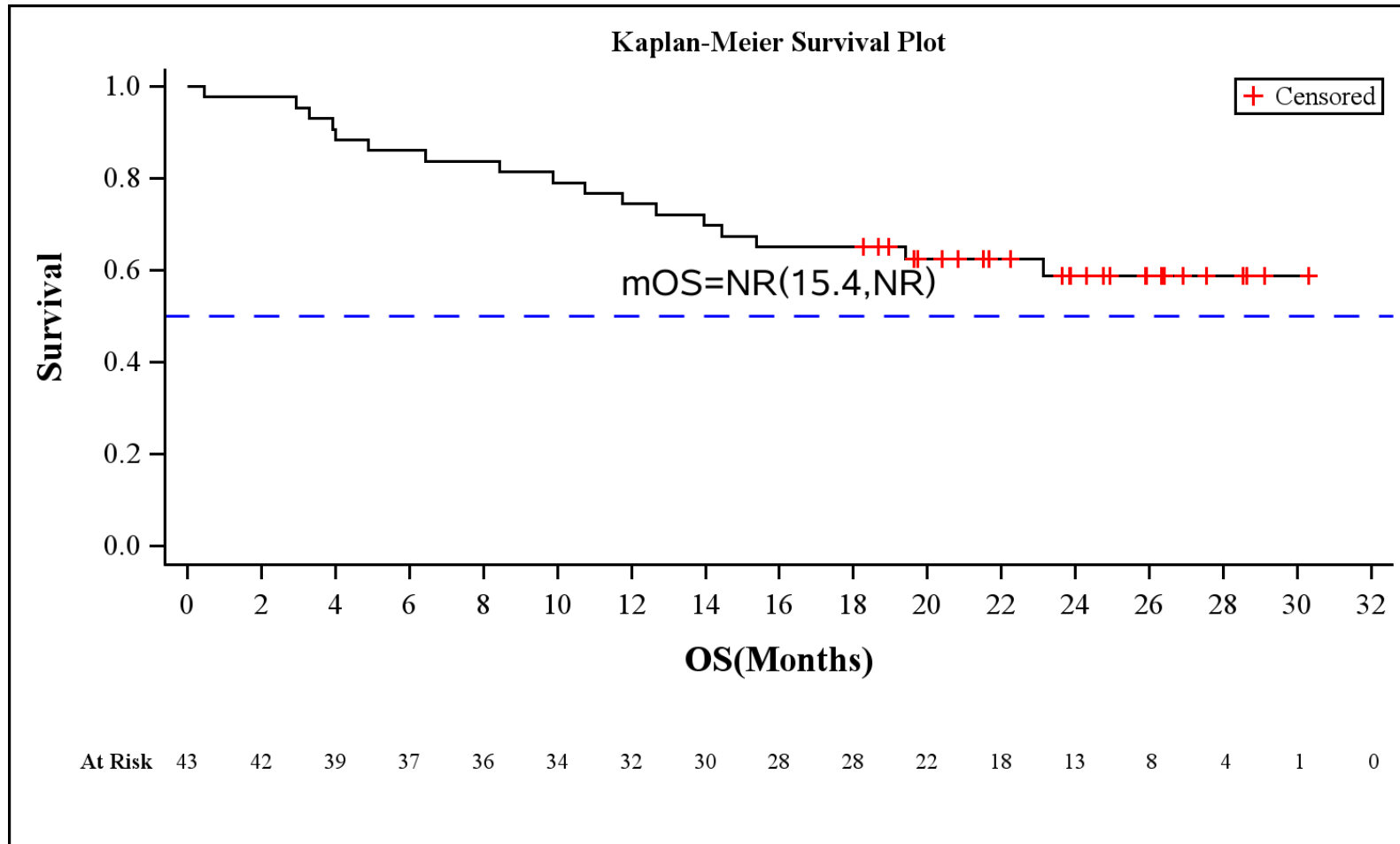
- 11 pts remain on study drug
- With the majority of AE events (48/54 events, 89%), patients recovered from AE and resumed treatment
- DOSE REDUCTIONS (3 pt)
 - pneumonia (N=1)
 - lipase increased (N=1)
 - neutrophils decreased (N=1)
- DISCONTINUATIONS
 - 3 pts withdrew consent
 - 21 pts discontinued due to progressive disease
 - 8 pts discontinued due to AEs
 - 3 of these pts discontinued due to pneumonia
- 2 deaths were attributed to multiple organ failure and decreased level of consciousness

Any Grade ($\geq 10\%$) and \geq Grade III drug-related AEs in r/r PTCL patients treated with linterlisib

Drug-related AEs category	Any Grade ($> 10\%$ incidence)	\geq Grade III
<i>Hematological</i>		
Neutropenia	28(65.1%)	9 (20.9%)
Leukopenia	18(41.9%)	2 (4.7%)
Anemia	11(25.6%)	0
Thrombocytopenia	7(16.3%)	1 (2.3%)
Lymphocytopenia	5(11.6%)	0
<i>Nonhematological</i>		
Hypertriglyceridemia	17(39.5%)	3 (7.0%)
Hypercholesterolemia	15(34.9%)	0
Elevated alanine aminotransferase	11(25.6%)	0
Elevated Aspartate aminotransferase	10(23.3%)	0
Pneumonia	10(23.3%)	5 (11.6%)
Gamma-glutamyltransferase increased	7(16.3%)	2 (4.7%)
Hyperamylasemia	7(16.3%)	1 (2.3%)
Blood alkaline phosphatase increased	6(14.0%)	1 (2.3%)
Lipase increased	5(11.6%)	1 (2.3%)
Hyperuricemia	5(11.6%)	0

- The most frequent \geq Grade 3 TRAE are decreased neutrophils (21%), infectious pneumonia (12%), hypertriglyceridemia (7%), decreased white blood cells (5%), and elevated gamma-glutamyltransferase (5%)
- Notably, ALT, AST, GI toxicities, and Rash are at very low levels
- The overall safety profile is consistent with the observed safety profile in 262 patients treated with 80mg YY-20394 daily dose
- Infectious pneumonia is observed with linterlisib, like in the other lymphoma clinical trials

Median Overall Survival Has Not Been Reached with liperlisib



Median Overall Survival, not reached (95%CI, 15.4-NR months)

11 patients remain on study drug

Open label single arm Phase2 Study Design in r/r T-Cell Lymphoma

- A Phase2 study (NCT05274997) opened in August 2022 with 97 pts to be enrolled
 - First trial to evaluate linterlisib-treated patients in the U.S. and E.U.
 - Stage 1, interim analysis for safety, efficacy after up to N=36 pts
 - Stage 2, study completion
- r/r T-cell lymphomas having ≥ 1 prior therapy
 - All PTCL subtypes enrolling, PTCL-NOS, AITL, ALCL, NKT, EATL, MEITL and CD30+ brentuximab-progressing or intolerant.
 - There is a Central Lab confirmation of diagnosis in this study
 - CTCL patients are enrolling
- Dose schedules for 28-day cycles
 - 80 mg QD (RP2D) to progression
 - 80 mg QD for 4 cycles or until response, followed by 60 mg QD
- Primary endpoint is Overall Response Rate
- Principal Investigator, Dr. Swami Iyer, MD Anderson Cancer Center, Houston, TX, USA
- We are recruiting additional clinical sites for this study

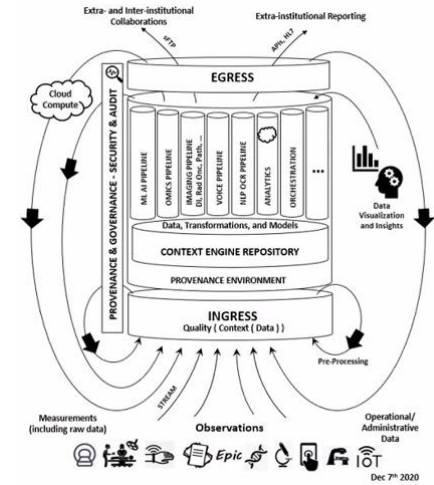
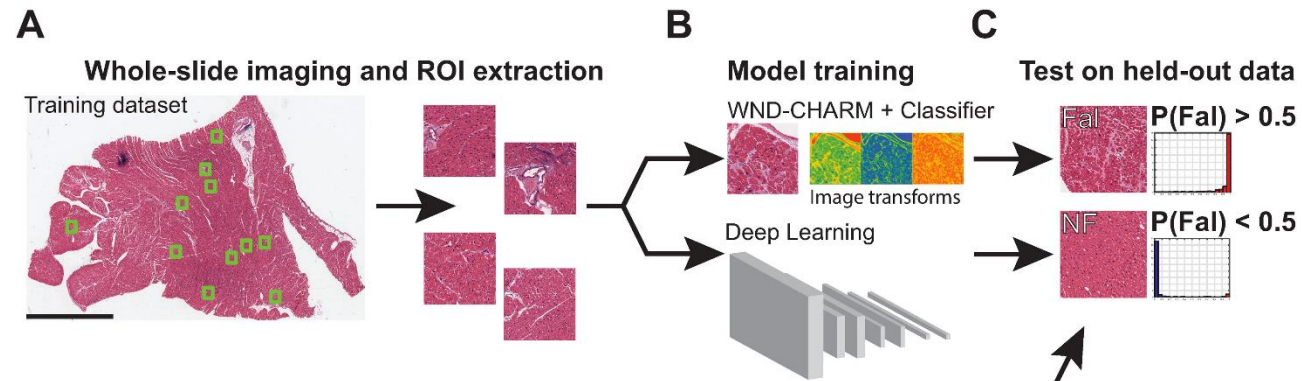
Integrating genomics and spatial transcriptomics

Data integration

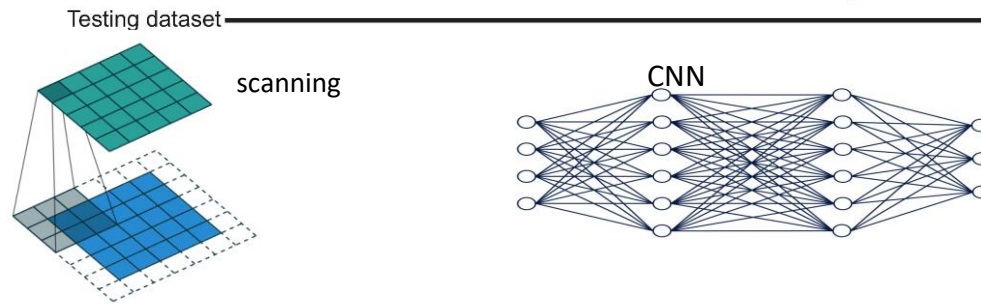


- Whole genome sequencing and RNAseq
- Digital pathology images through machine learning models
- Spatial features of genes and proteins through CODEX & DSP

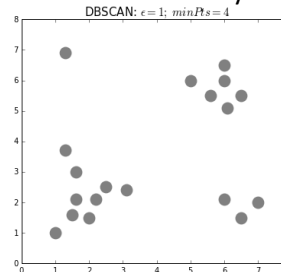
Team Data Science



Deep learning models depend on imaging features but not the cells themselves

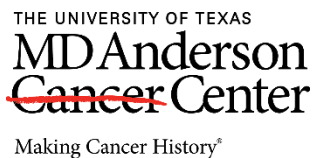


Point cluster analysis



Genomics+ Spatial Transcriptomics + Machine learning of images = Predictive pathway biomarkers

ADOPTIVE CELL THERAPY APOLLO B-CELL LYMPHOMA BREAST CANCER CANCER GENOMICS LABORATORY CANCER PREVENTION AND CONTROL
MULTIPLE MYELOMA HPV-RELATED CANCERS IMMUNOTHERAPY INSTITUTE FOR APPLIED CANCER SCIENCE LUNG CANCER MDS AND AML MELANOMA ORBIT OVARIAN CANCER PANCREATIC CANCER PROSTATE CANCER
CANCER GENOMICS LABORATORY
RECTAL CANCER ECLIPSE GLOBLASTOMA HIGH-RISK MULTIPLE MYELOMA HPV-RELATED CANCERS IMMUNOTHERAPY INSTITUTE FOR APPLIED CANCER SCIENCE
CANCER PANCREATIC CANCER PROSTATE CANCER PROTEOMICS TRACTION TRANSLATIONAL RESEARCH ACCELERATOR
CANCER PREVENTION AND CONTROL CLL COLORECTAL CANCER ECLIPSE GLOBLASTOMA HIGH-RISK MULTIPLE MYELOMA HPV-RELATED CANCERS IMMUNOTHERAPY
CANCER MDS AND AML MELANOMA ORBIT OVARIAN CANCER PANCREATIC CANCER PROSTATE CANCER PROTEOMICS TRACTION TRANSLATIONAL RESEARCH ACCELERATOR
LYMPHOMA BREAST CANCER CANCER GENOMICS LABORATORY CANCER PREVENTION AND CONTROL CLL COLORECTAL CANCER ECLIPSE GLOBLASTOMA HIGH-RISK MULTIPLE MYELOMA HPV-RELATED CANCERS
IMMUNOTHERAPY INSTITUTE FOR APPLIED CANCER SCIENCE LUNG CANCER MDS AND AML MELANOMA ORBIT OVARIAN CANCER PANCREATIC CANCER PROSTATE CANCER
ACCELERATOR ADOPTIVE CELL THERAPY APOLLO B-CELL LYMPHOMA BREAST CANCER CANCER GENOMICS LABORATORY CANCER PREVENTION AND CONTROL
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MOON SHOTS

T/NK-Cell Malignancy Moon Shot

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OVARIAN CANCER
PANCREATIC CANCER
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LUNG CANCER MDS AND AML MELANOMA ORBIT OVARIAN CANCER PANCREATIC CANCER PROSTATE CANCER PROTEOMICS TRACTION TRANSLATIONAL RESEARCH ACCELERATOR & TRACTION

Linperlisib in r/r PTCL

- Linperlisib is an exciting next generation PI3K δ inhibitor for treatment of lymphomas
- r/r PTCL patients evaluated to date are deriving clinical benefit
 - This Phase 1b study was completed on 43 r/r PTCL patients with a median of 2 prior therapies
 - ORR (61%) with responses across the major subtypes
 - OS benefit is promising (median not reached)
 - Safety profile supports the drug being well-tolerated
 - Linperlisib-treated patients have low levels of immune-mediated AEs
- Linperlisib is undergoing evaluation in a Chinese registration study in r/r PTCL
- A Phase 2 of linperlisib in r/r PTCL has launched in the U.S. and Italy



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 Dr. Tej Pandita

BCM/TCH

Dr. Debananda Pati

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Guiding Light



