Linperlisib in PTCL

Dr.Swami iyer

Disclosures

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
CRISPR	✓					✓	
MERCK	✓						
SEAGEN/PFIZER	✓					✓	
YINGLI	✓					✓	
ACROTECH	✓					✓	
INNATE	✓						
TRILLIUM	✓						
ASTRA ZENECA	✓						
ONO	✓						
LEGEND	✓						
SALARIUS			✓				
SECURA BIO						✓	

The Road Taken

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Three-pronged approach to a cure in Cancer- "Reaching out to one and all"

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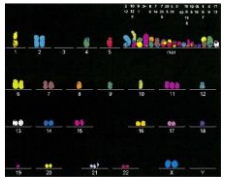
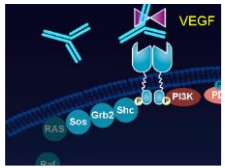
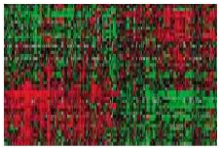
- Lymphoma is a Genomic disease



- Current cancer therapies are based on sophisticated molecular approaches- SMI and MoAb, Immunotherapies and cellular therapies



- Each patient's tumor is unique



2022 Classification of Peripheral T-cell Lymphoma (PTCL)- WHO do we follow?

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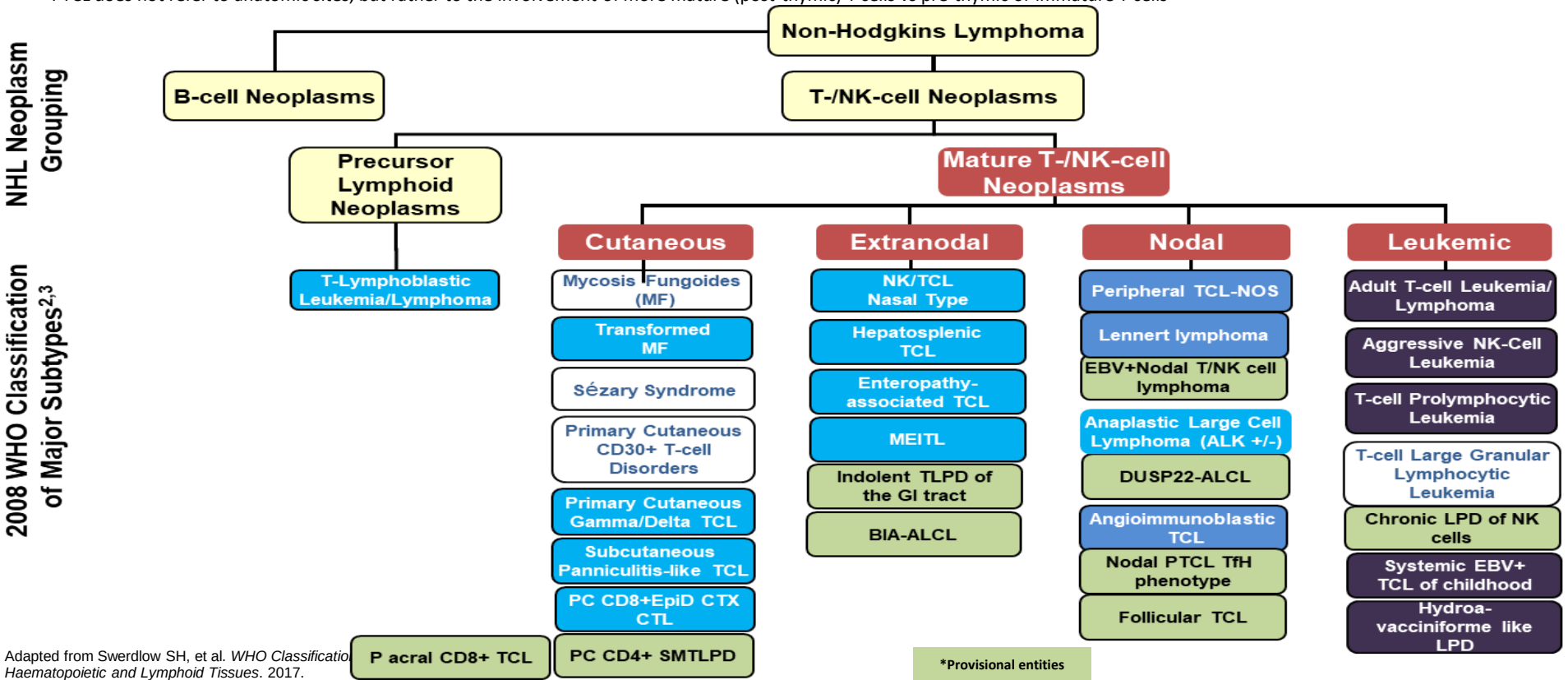
PTCL is a heterogeneous group of aggressive mature T-/NK-cell lymphomas

PTCL does not refer to anatomic sites, but rather to the involvement of more mature (post-thymic) T cells vs pre-thymic or immature T cells[1]



Adapted from Swerdlow SH, et al. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. 2017.

Progression Free Survival: Relapsed/Refractory PTCL

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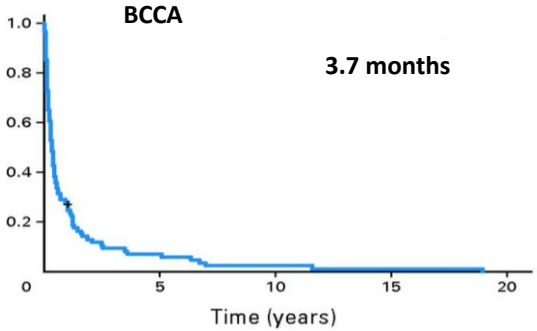

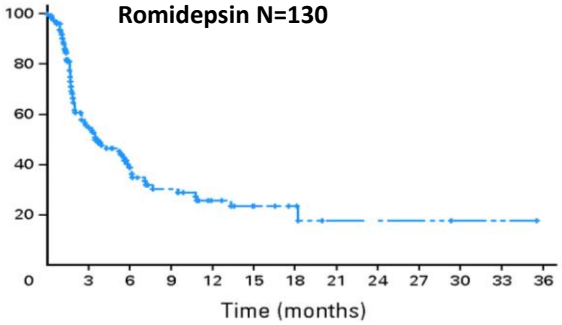

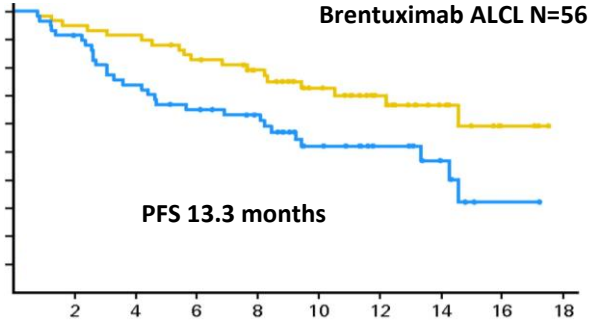

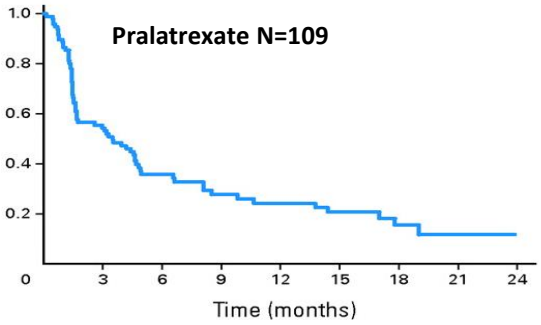

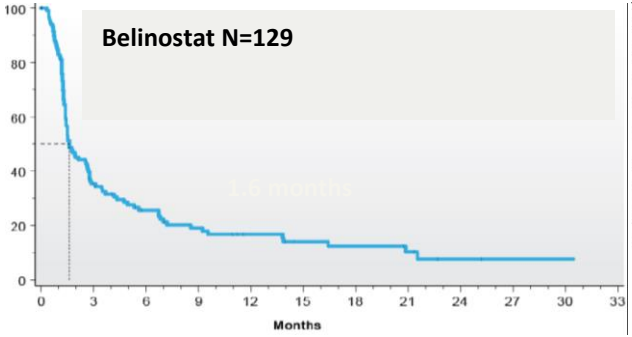

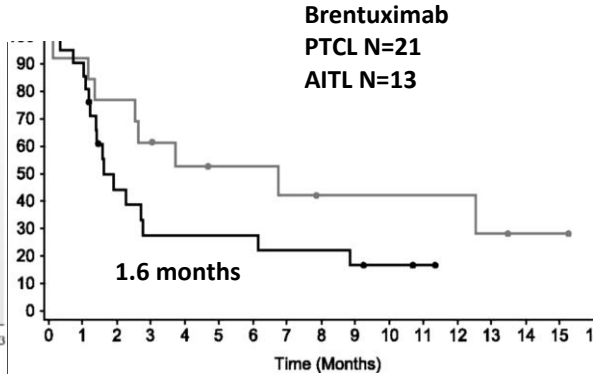

Mak V et al. JCO 2013;31:1970-1976, O'Connor OA, et al. *J Clin Oncol*. 2011;29:1182-1189,Coiffier B, et al. *J Clin Oncol*. 2012;30 :631-636, O'Connor OA et al ASCO 2013, Pro B, et al. J Clin Oncol. 2012;30:2190-2196, Horwitz S M et al. Blood 2014;123:3095-3100

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

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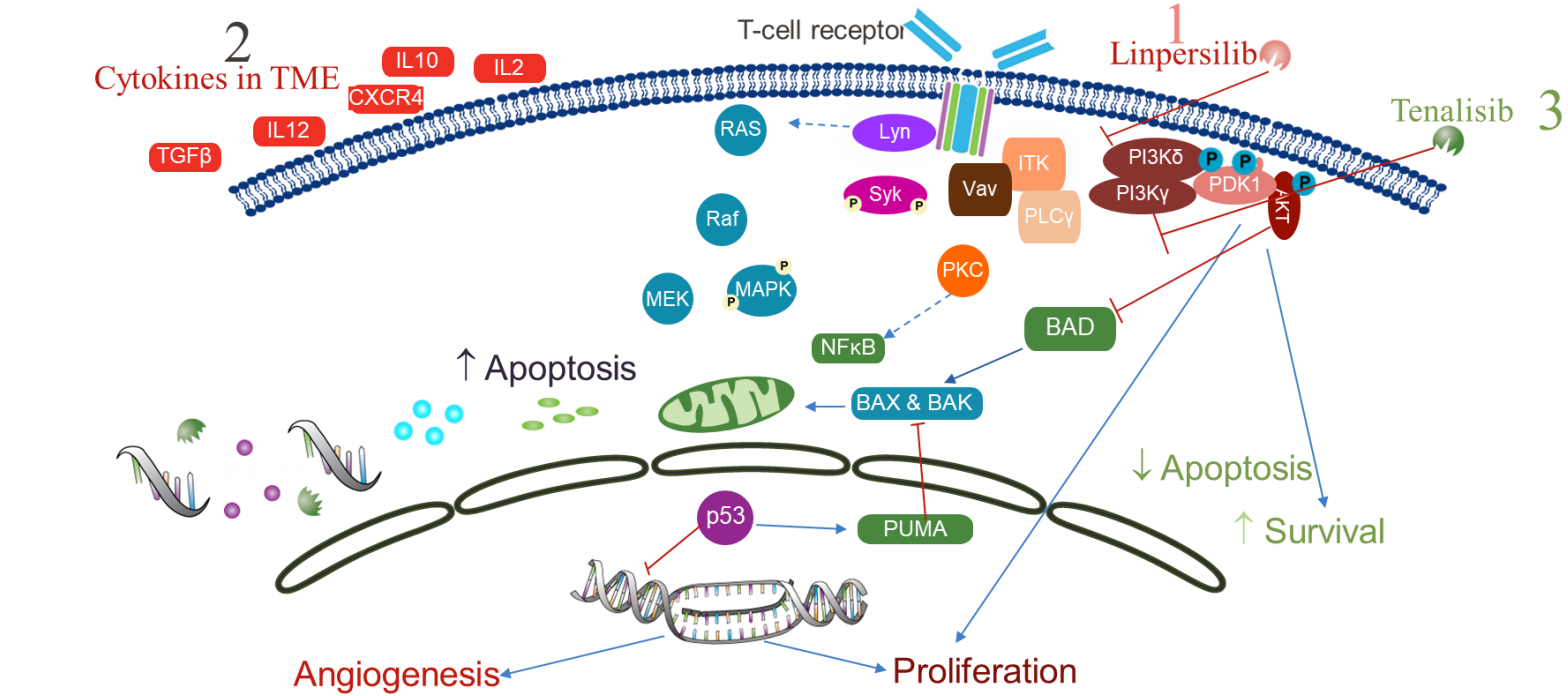
1. Cell autonomous: blocking mitogenic and survival signaling
2. Tumor Microenvironment (TME): Blocking mitogenic and survival signaling induced by cytokines and chemokines
3. Combined inhibition of PI3K-γ/δ, and downstream Bcl2 family of proteins to enhance the responses.



Jumaa et al. *Ann Rev Immunol.* 2005;23:415-445. Kharas et al. *J Clin Invest.* 2008;118:3038-3050. Decker et al. *Ann Hematol.* 2008; epub.

Background

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The approved standard therapies for r/r PTCL are limited with a median PFS of only 3-4 months

PI3Kδ inhibitors have demonstrated clinical activity in T-cell and B-cell lymphomas

Linperlisib is an oral PI3Kδ-selective inhibitor, shown to be efficacious with a favorable safety profile in phase 1 and 2 clinical trials in r/r Follicular Lymphoma (FL) and PTCL*

Linperlisib received marketing approval in China in 2022 for r/r FL patients with 2 or more prior systemic therapies^

^ *Intare® (linperlisib) Package Insert*

**Jiang et al. JHematolOnc (2021)*
Wang et al. ClinCancRes (2023)
Jin et al., ASH Abstract 4228 (2022)

Pharmacokinetics for Linperlisib

Increased kidney and lower GI excretion

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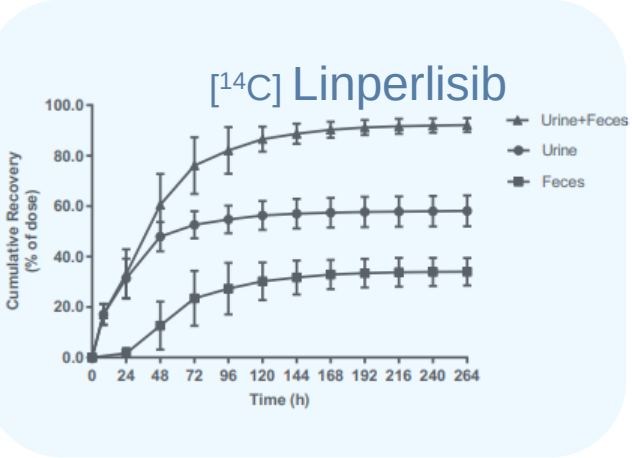

Cumulative radioactive recovery from urine and faeces after a single oral administration of [14C]YY-20394 to 6 healthy subjects (%, mean ± SD)

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

- Renal excretion is the predominant elimination route of [^{14}C] 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

Source Data: Yu et al. (2022) Xenobiotica 52:3, 254-264;
FDA-Approved Drugs: https://www.accessdata.fda.gov/scripts/cder/daf/

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

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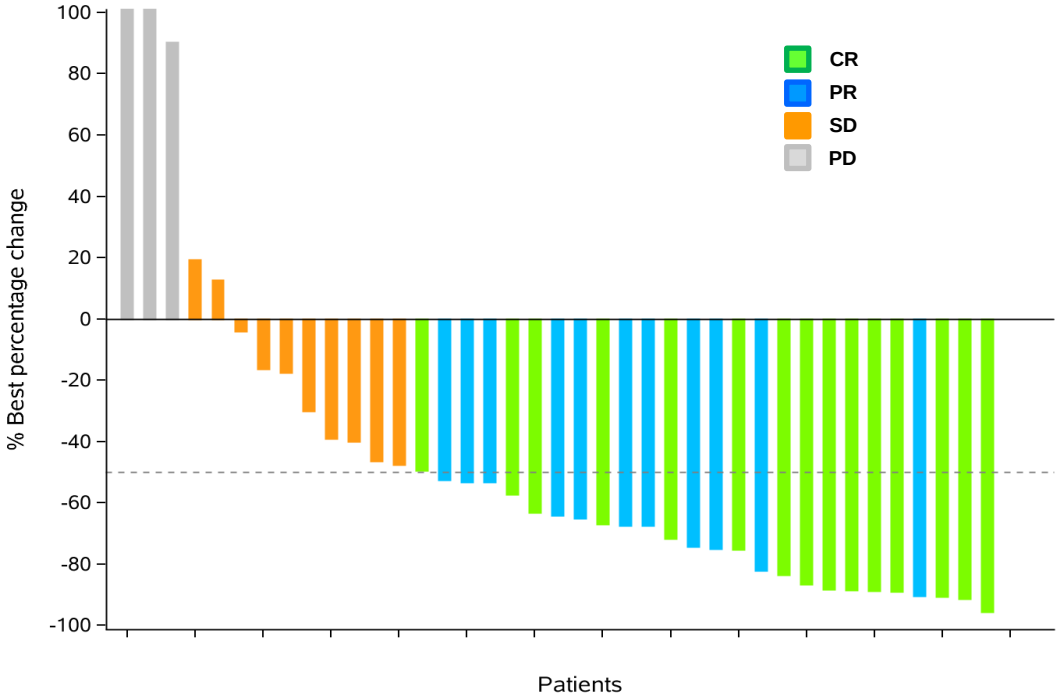


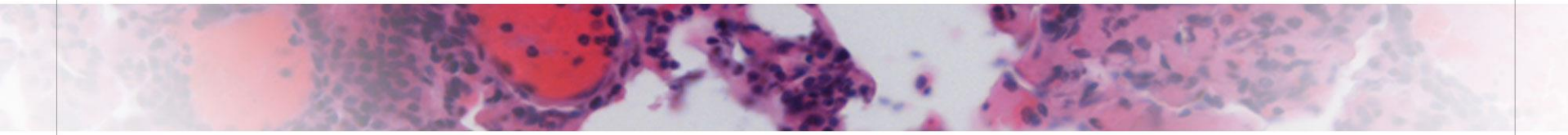
- **n=43 patients**
- **40 pts evaluable for efficacy**

- **ORR 61%**
  - CR 32% (15 pt)
  - PR 29% (11 pt)
  - SD 25% (10 pt)
  - PD 10% (5 pt)
  - DCR of 84%

- **Responses in all PTCL subtypes**
  - AITL (75%, 16pt)
  - PTCL-NOS (44%,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

American Society of Hematology
Helping hematologists conquer blood diseases worldwide



A multicenter Phase 2 Trial of Linperlisib in Relapsed or Refractory Peripheral T/NK Cell Lymphomas

Yuqin Song, MD*, Zengjun Li, MD, Huijing Wu, MD, Jie Jin, MD, Hui Zhou,MD, Keshu Zhou, MD, Liling Zhang, MD, Zhigang Peng, MD, Zhiye Zhang,MD, Hong Cen, MD, Youchao Jia, MD, Yuerong Shuang, MD, Zhiming Li, MD, Haiyan Yang, MD, Liqun Zou, MD, Zhifeng Li, MD, Zhihui Zhang, MD, Junmin Li, MD, Junning Cao, MD, Lugui Qiu, MD, Shaojie Wu, MD, Tiejun Gong, MD, Xiaohong Xu, MD, Zhen Wang, MD and Jun Zhu, MD*

*Lymphoma Department, Peking University Cancer Hospital & Institute, Beijing, China

(Clinicaltrials.gov NCT04705090)

Study Design

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- Single-arm, open-label Phase 2 trial of Linperlisib monotherapy in patients with r/r PTCL;
- 25 clinical sites in China participated in the clinical trial;
- May 2021-October 2022, Data cutoff April 24, 2023.

Linperlisib 80 mg PO once daily

N=98

- **Primary endpoint**
  - ORR, based on Lugano 2014 criteria assessed by IRC
- **Secondary endpoints**
  - DoR, PFS, OS, DCR, TTR, Safety

Key Inclusion Criteria

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- Adult patient ≥18 years of age, male or female;
- Pathologically confirmed with PTCL, including but not limited to: PTCL-NOS, AITL, ALK positive or negative ALCL, NKTCL, HSTCL, EATL, et al;
- Received and failed at least one line of systemic therapy for PTCL, or deemed intolerable to systemic therapy for PTCL;
- For r/r ALCL, prior therapies including anti-CD30 monoclonal antibody(BV) was required; extranodal NK/T was to have been adequately treated with asparaginase-based regimen;
- ECOG 0~1;
- At least one measurable target lesion (2014 Lugano criteria);
- Adequate organ functions.

Key Exclusion Criteria

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- **Cutaneous T-cell lymphomas**;
- Progressed after PI3Kδ inhibitors (except for due to intolerance);
- Receiving steroids therapy continuously for more than 14 days with dosage higher than 20 mg/day (prednisone equivalent) during 4 weeks before enrollment;
- Central Nervous System (CNS) involvement;
- Complicating hemophagocytic syndrome;
- Autologous hematopoietic stem cell transplantation performed within 90 days prior to initial administration of the investigational agent.

Demographic and Baseline Characteristics

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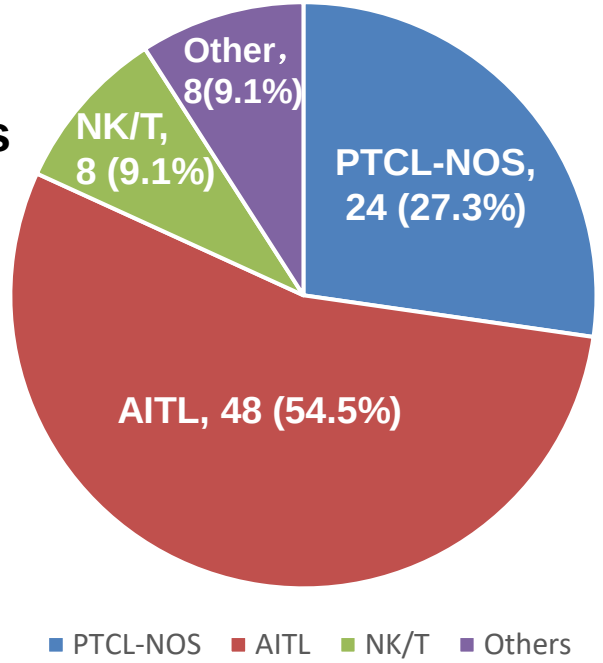
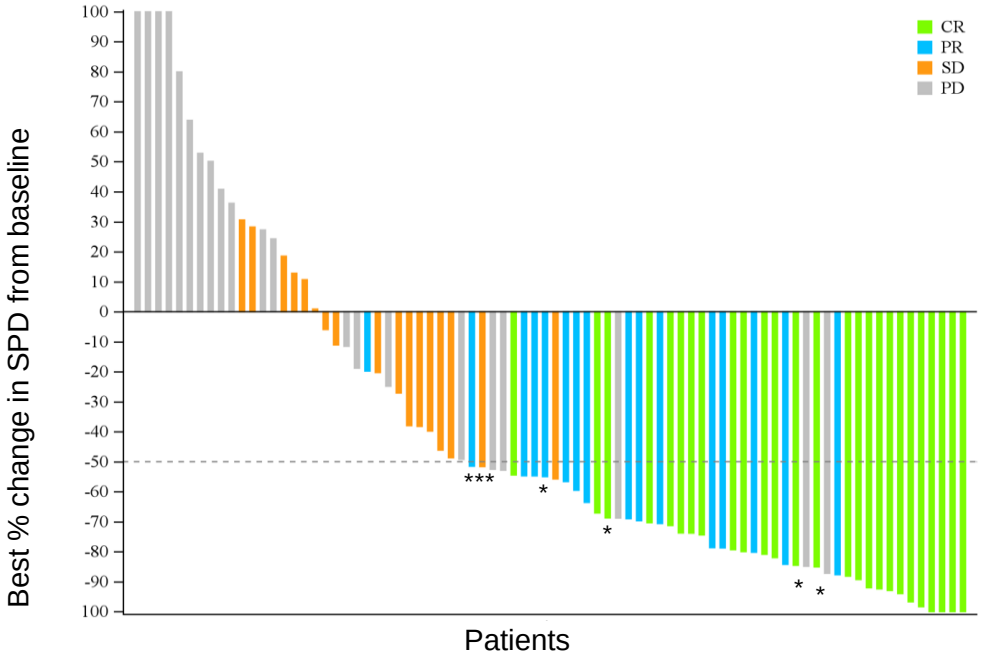
- Median age：57 (25~82) years
- Male 63.6%, female 36.4%
- ECOG 0~1：100%
- Lugano 2014 stage III：33% (29 pts)
- Lugano 2014 stage IV：56% (49 pts)
- A median of 2 lines of prior systemic therapies
- 73% patients refractory to prior treatment
- Safety Analysis Set (SAS) = 98 pts
- Full Analysis Set (FAS) for efficacy = 88 pts
  - 10 pts in Safety Set were confirmed as misdiagnosed PTCL

PTCL subtypes



*Other, includes ALCL, MEITL, or unclassified PTCL

Efficacy: Response Rates



Response	n(%)
ORR, n(%)	42(48)
95% CI	(37, 59)
CR	**26(30)**
PR	16(18)
SD	18(21)
PD	21(24)
NE	7(8)
DCR, n(%)	60(68)
95% CI	(57, 78)

- FAS, n=88 patients
  - ✓ The study met the primary endpoint
  - ✓ CR 30%, PR 18%
- A disease control rate of 69% observed

* Five PD patients had new lesions appearing, even though target lesions met the response criteria

Efficacy: Duration of Response

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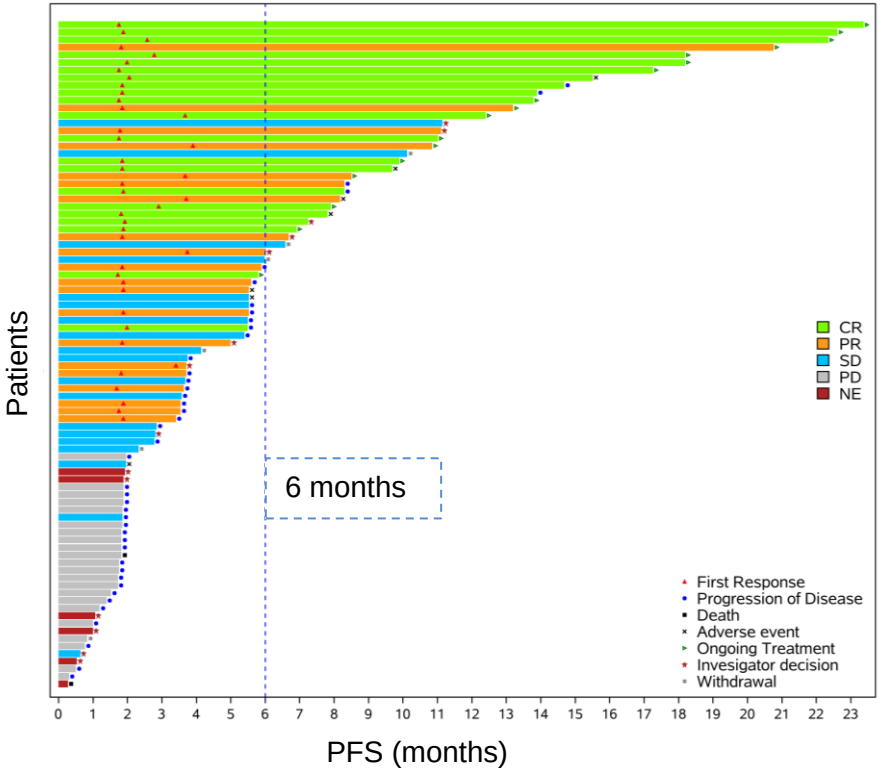

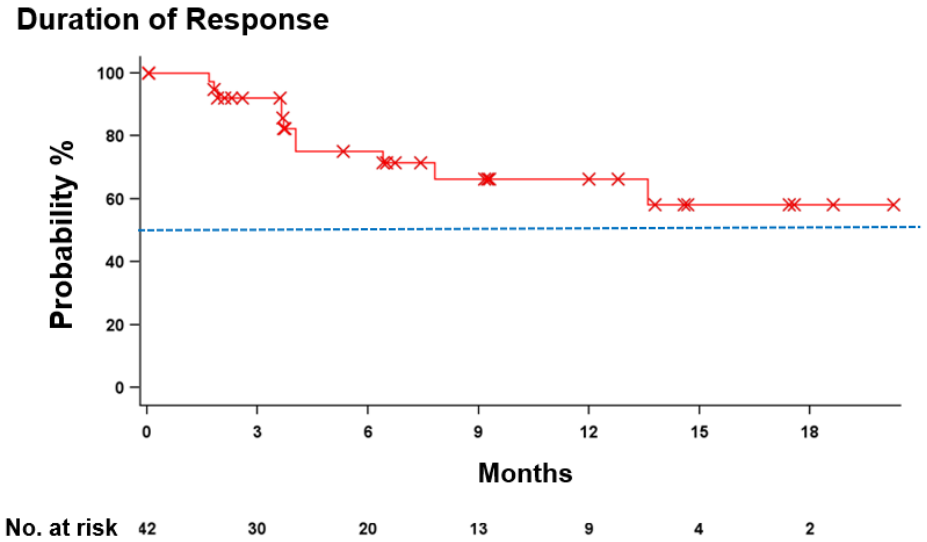

- Median TTR was 1.9 months (range: 1.7, 3.8) (1st assessment)
- 6-month Duration of Response: 75%
- Median Duration of Response has not been reached (95%CI:7.8, NR)

Efficacy: PTCL subtypes

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	AITL n=48	PTCL-NOS n=24	NK/T n=8	Other* n=8	Total n=88
Best Response， n (%)					
CR	23(48)	2(8)	0(0)	1(13)	26(30)
PR	8(17)	5(21)	2(25)	1(13)	16(18)
SD	8(17)	7(29)	3(38)	0(0)	18(21)
PD	6(13)	9(38)	2(25)	4(50)	21(24)
NE	3(6)	1(4)	1(13)	2(25)	7(8)
ORR, n(%)	31(65)	7(29)	2(25)	2(25)	42(48)
95% CI	(50, 78)	(13, 51)	(3, 65)	(3, 65)	(37, 59)
DCR, n(%)	39(81)	14(58)	5(63)	2(25)	60(68)
95% CI	(67, 91)	(37, 78)	(25, 92)	(3, 65)	(57, 78)

*Other, includes ALCL, MEITL, or unclassified PTCL

Efficacy: PFS and OS

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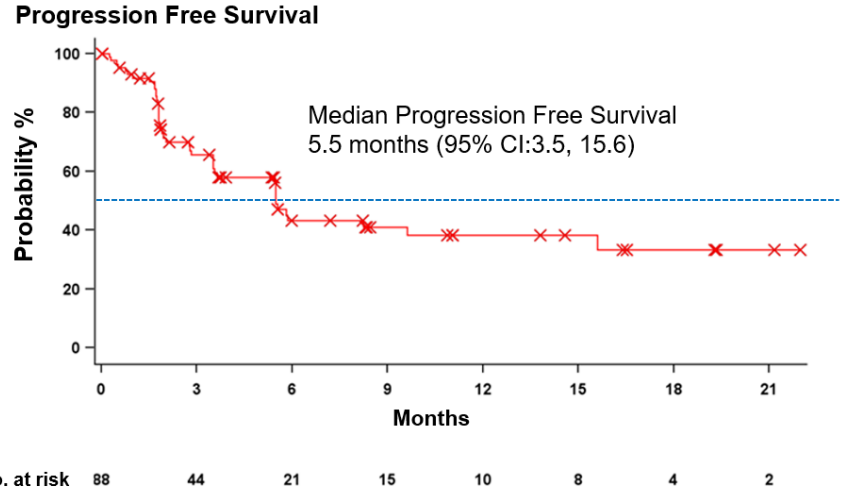
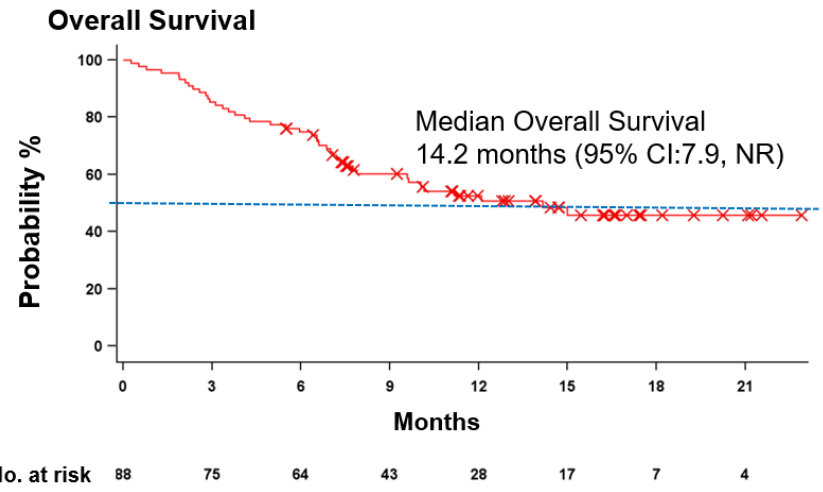
- The median follow-up time was 14.8 months
- mPFS: 5.5 months (95%CI: 3.5, 15.6)
- 6-month OS rate: 75% (95% CI: 64.51%, 82.74%)
- Median OS:14.2 months (95%CI: 7.9, NR)
- As of April 24, 2023, 16 pts continued with linperlisib treatment





Safety

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Any Grade TRAEs, Preferred Term	(≥10%) n (%)
Neutropenia	58 (59)
Leukopenia	46 (47)
Thrombocytopenia	31 (32)
Anemia	24 (24)
Elevated ALT	23 (23)
Elevated AST	20 (20)
Pneumonia	20 (20)
Lymphocytopenia	17 (17)
Hypertriglyceridemia	15 (15)
Fever	15 (15)
Diarrhea	14 (14)
Elevated lipase	13 (13)
Hyperuricemia	13 (13)
Rash	13 (13)
Hypercholesterolemia	12 (12)
Hyponatremia	11 (11)
Elevated lactate dehydrogenase	10 (10)
Elevated creatinine	10 (10)

SAS = 98 patients

≥Grade 3 TRAE, Preferred Term	(≥5%) n (%)
Neutropenia	31 (32)
Pneumonia	14 (14)
Leukopenia	10 (10)
Anemia	6 (6)
Thrombocytopenia	5 (5)
Upper respiratory tract infection	5 (5)
Lymphocytopenia	5 (5)

- TRAEs were observed in 94 pts (95.9%)
- The most frequent ≥Grade 3 TRAE were **neutropenia, pneumonia and leukopenia;**
- ***Immune-related ≥Grade 3 TRAEs as elevated ALT,AST, diarrhea, colitis, rash were observed at <5%;***
- The most frequent drug-related SAE was pneumonia (11%);
- Twenty-two pts (22.4%) had dose reductions, and 9 pts (9.2%) discontinued from the study due to AEs.

Conclusions

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- **Efficacy**
  - In this r/r PTCL Phase 2 study, linperlisib led to 48% ORR (30% CR)
    - The primary endpoint was reached
    - Responses were observed across PTCL subtypes
  - Linperlisib monotherapy showed promising durable responses with 6-month DoR 75%, and the median duration of response has not been reached

- **Safety**
  - Linperlisib showed a relative well-tolerated safety profile
  - The safety profile was consistent with previously reported data in other linperlisib clinical studies

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

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- A Phase2 study (NCT05274997) opened in August 2022
  - First trial to evaluate linperlisib-treated patients in the U.S. and E.U.
  - Stage 1, interim analysis for safety (including CTCL)
  - Stage 2, study completion N=45 pts
- r/r T-cell lymphomas with ≥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 cohort-pilot
- Dose schedules for 28-day cycles
  - 80 mg QD (RP2D) to progression
  - 80 mg QD for 4 cycles or until response, followed by 40 mg QD
- Primary endpoint is Overall Response Rate
- Principal Investigators: Dr. Ranjit Nair, Dr.Pierluigi Zinzani, Dr. Swami Iyer
- Study is closed

Case Presentation

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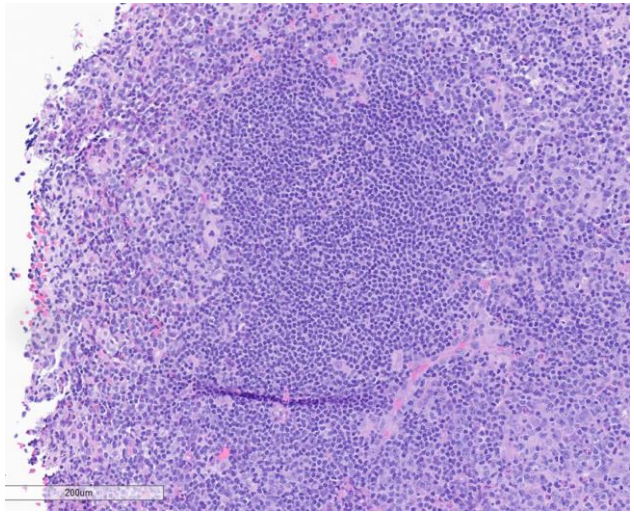
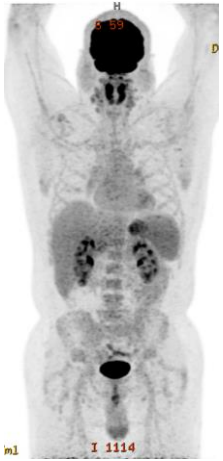


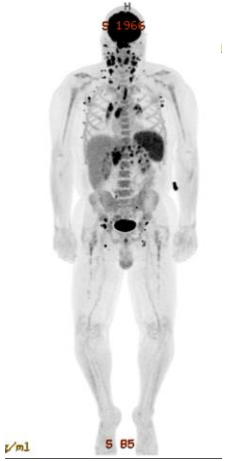
AITL

Feb 2022



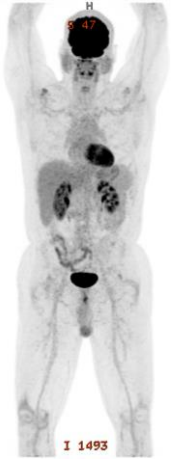
Baseline: b/l tonsils

Aug 2022



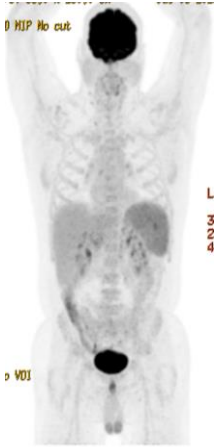
After CHP-BVx6

Nov 2022



After Linperlisib x2

Jun 2023



After Linperlisib x9

Linperlisib Clinical Development in Asia, US and Europe

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Parameters	YY-20394-04 PTCL Phase 1b China	YY-20394-010 PTCL Phase 2 China	YY-20394-012 PTCL Phase 2 US & EU	YY-20394-012 CTCL Phase 2 US & EU
Number of Patients	43	98	35	10
Age	58 y	57 y	67 y	61.5 y
Asian	43	98	1	-
Non-Asian	-	-	34	10
ECOG status 0-1	95%	100%	100%	100%
Median prior systemic therapies (range)	2 (1,5)	2	2 (1,8)	5 (2,10)
Relapsed	16%[a]	67%	63%	80%
Refractory	84%[b]	73%	74%	90%
Relapsed and Refractory	n.d.	40%	37%	70%
PTCL-NOS	17	24	18	9 MF, 1 SS
AITL	16	48	13	-
Other	10	16	4	-

[a]Relapsed to last line of therapies. [b]Refractory to last lines of therapies.
MF = Mycosis Fungoides; SS = Sezary Syndrome; n.d. = not determined.

PI3K inhibitors in PTCL

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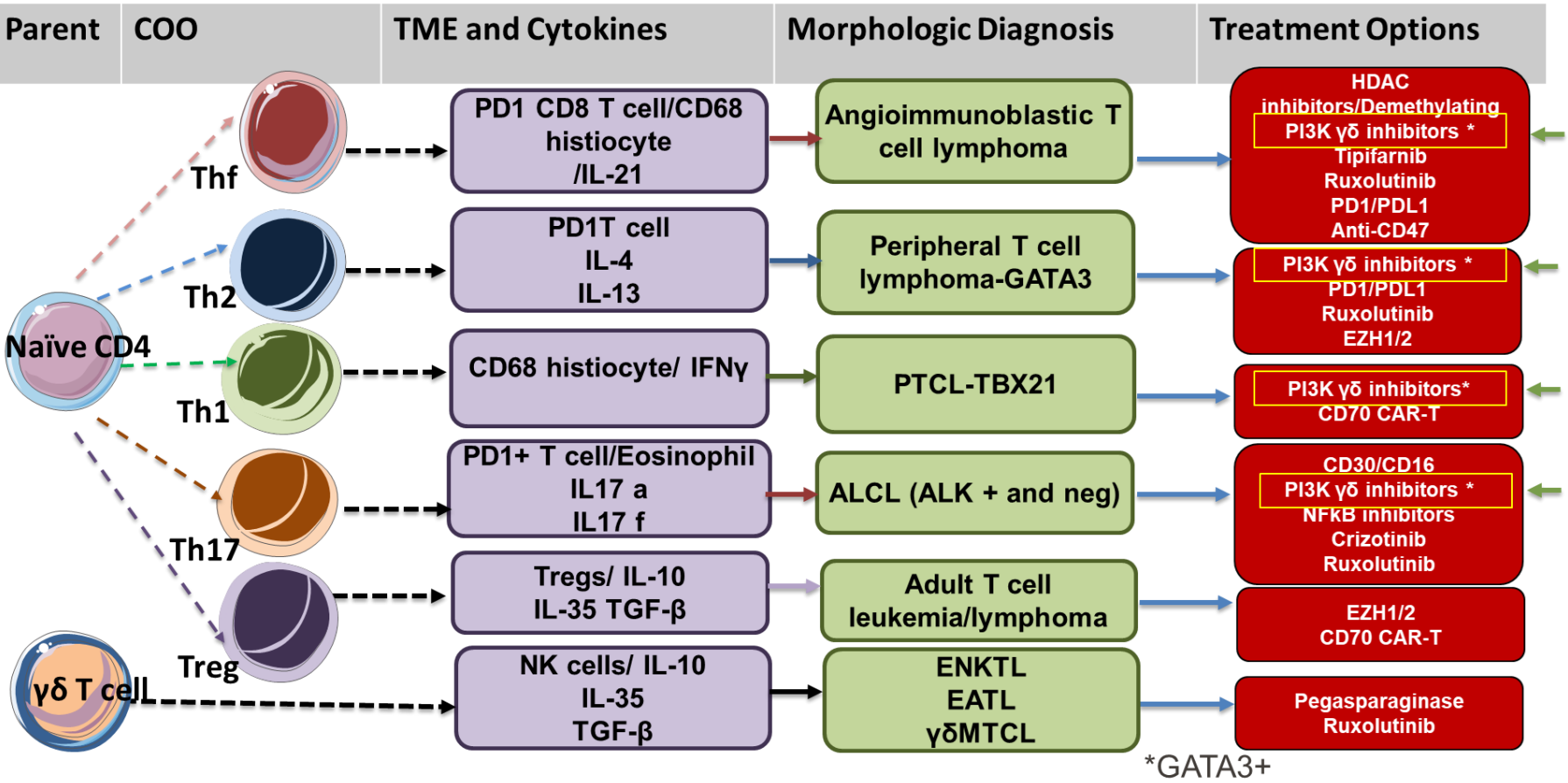
PI3K Inhibitor	# pts	ORR	CR	Reference
Duvelisib	35	50%	19%*	Horwitz et al.
Tenalisib	35	45.7%	26%	Huen et al.
Linperlisib	48	48%	30%	Song et. al

*CR=34% in PRIMO study (n=101)

PI3K Inhibitor	Neutropenia	Diarrhea /Colitis	Elevated Liver Enzymes	Infections (e.g., Pneumonitis)	Rash	Hyperglycemia	Hypertension	Other Side Effects
Duvelisib	↑↑	↑↑	↑↑	↑↑	↑			
Parsaclisib	↑	↑	↑↑		↑↑			Dermatological reactions (↑)
Tenalisib	↑↑		↑		↑			Thrombocytopenia (↑↑)
Linperlisib	↑			↑				
Copanlisib	↑↑		↑	↑		↑↑	↑↑	Hepatotoxicity (↑)

Horwitz S.M., et al. Blood. 2018; Huen A, et al. Cancers (Basel). 2020;Song Y, et al. ASH 2023

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

Targetable pathways evaluated at MDACC

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Upfront studies:

Completed trials

- Newly Dx-ECHELON 2- CHP-BV vs. CHOP in CD30+ T-NHL. (Iyer S) **ECHELON-2-** - 23 patients-
- Newly Dx-CHEP-BV- SCT and BV maintenance, best accrual (Iyer S)- 24/42 patients- CR~90%. Manuscript in Preparation
- CHOP-Pralatrexate- 22/60 patients- CR~90%

Ongoing/starting trials: CD30 negative TCL

- CHP-BV in non ALCL with 1-10% CD30 expression
- PI3K inhibitor+ and CHOP

CAR-T:

- CTX-130- Allo-CD70
- Auto-CD4 CAR-T
- Auto-CD5- short CAR-T

R/R Combination therapy:

- R/R Tenalisib/Romi- (National PI)-COMPLETED- manuscript in revision
- Romidepsin + Pembrolizumab in R/R TCL. (IIT)-COMPLETED- Dr.Agbedia
- Phase 1-2, Tolinapant with Oral Decitabine/Cedazuridine vs. Oral Decitabine/Cedazuridine in R/R PTCL (PI: Dr.Malpica)
- Proposal for JAK/STAT inh + HDAC inh (in process, IIT, PI: Malpica).

R/R Single-agent:

- CD-47 blocker “do not eat me” (TTI-622) single-agent in R/R lymphomas.
- JACKPOT8 study (AZD4205) in R/R PTCL. (PI: Malpica)
- Alliance grant- Linpersilib in R/R PTCL (PI: Nair)
- Lacutumab (anti-KIR3DL2).
- EBV Lymphomas (Nanatinostat and Valgancyclovir) (PI: Nair)
- Pacritinib in R/R TCL. (in process, IIT, PI: Malpica- collaboration with Univ of Michigan)
- Ono-4685 anti-PD1xCD3 BiTE
- CD94 mAb in NK and cytotoxic T cell lymphomas (collaboration with Leukemia)
- STAT degraders (PI: Huen)

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MOON SHOTS

T/NK-Cell Malignancy Moon Shots

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ADOPTIVE CELL THERAPY
APOLLO
B-CELL LYMPHOMA
BREAST CANCER
CANCER GENOMICS LABORATORY
CANCER PREVENTION AND CONTROL
CLL
COLORECTAL CANCER
ECLIPSE
GLIOBLASTOMA
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
PROTEOMICS
TRACTION
TRANSLATIONAL RESEARCH ACCELERATOR

Summary: PTCL

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- **The Problem:** T cell lymphomas are heterogenous, difficult to diagnose and poor outcomes.
- **Solution: Needs** multidisciplinary platform for TCL and develop a collaborative program that can address the various aspects of biology, pathology and better guidelines for clinical care.
- **Aims:** Advance knowledge of biology, find opportunities for integrated diagnostics and cutting edge therapeutics.
- **Deliverables :** Oversight in data architecture and governance, interdepartmental and interdisciplinary collaborations, education and training of in state of the art technologies
- **Strengths:** Unique presentations in large numbers for a rare lymphoma, outstanding multidisciplinary team members passionate about improving outcomes

T Cell Lymphoma Group

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Lymphoma:
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- Dr.Felipe Samaniego
- Dr.Nathan Fowler
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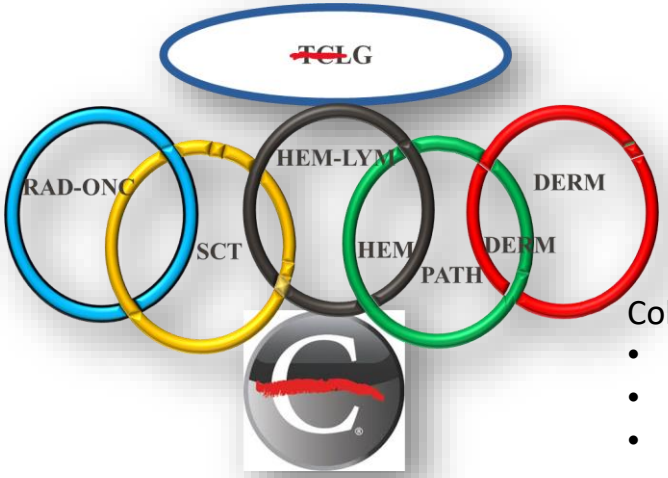

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- Section Rare Lymphoma
- Dept. Lymphoma/Myeloma
- Div. Medicine

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PTCL Informatics- PATH forward
Thank you

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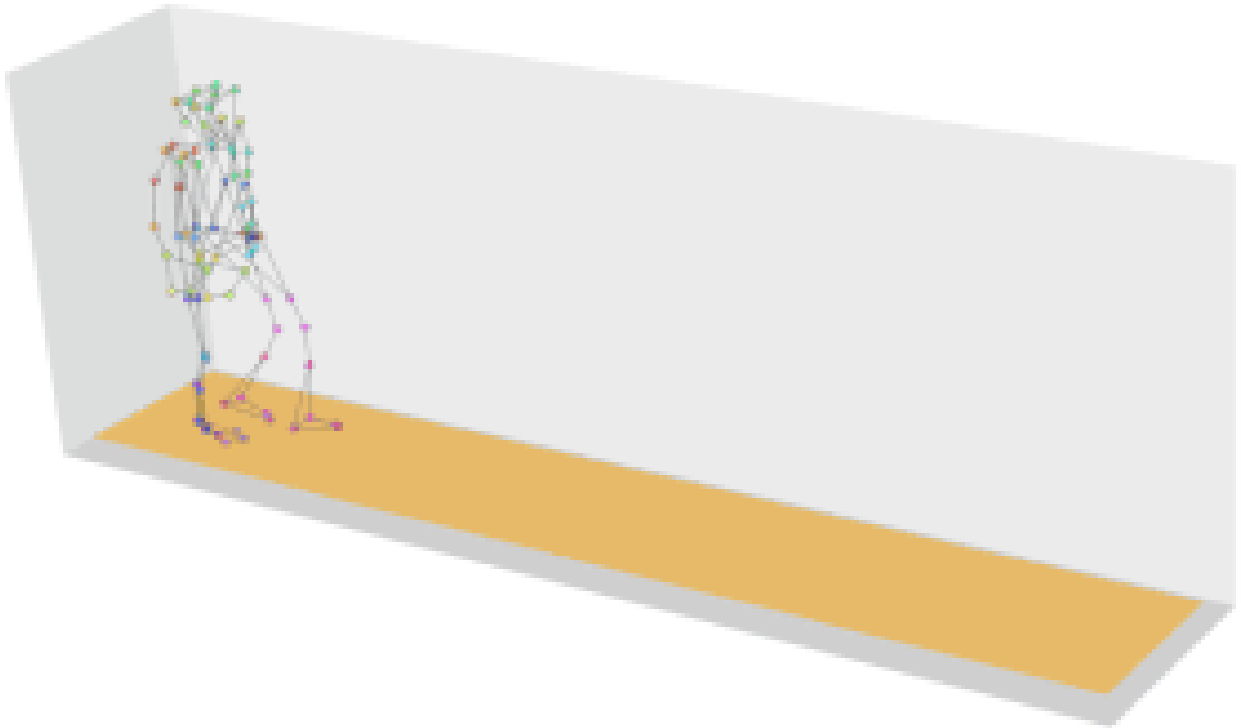

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Thank you

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