POST-SAN DIEGO 2024
Novità dal Meeting della Società Americana di Ematologia

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Bologna
Palazzo Re Enzo
13-15 Febbraio 2025

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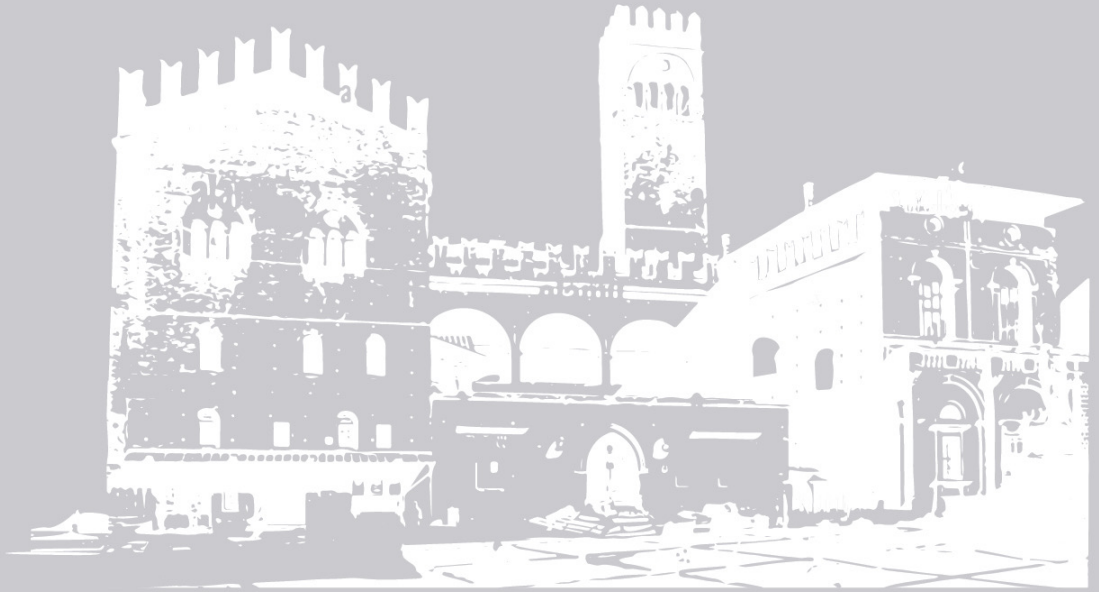

Cinzia Pellegrini

Linfomi di derivazione T linfocitaria

IRCCS, Azienda Ospedaliero-Universitaria di Bologna
Bologna, Italy

Disclosures of Name Surname

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Roche							x
Gilead							x
Takeda						x	
Janssen-Cilag						x	
Abbvie							x

Relapsed/Refractory Peripheral T-cell lymphomas

① Building on CD30 directed therapy

- *Renau J. C. et al. a*bs #4438 Final Results of a Phase II Study of **Brentuximab Vedotin and Lenalidomide** in Relapsed and Refractory T-Cell Lymphomas---**trial chiuso per scarso accrual**
  poster session

- *Wang X.* Et al. abs #4447 The Short-Term Efficacy and Safety of **Brentuximab Vedotin** Chemotherapy Combined with **Chidamide** in the Treatment of CD30-Positive Peripheral T-Cell Lymphoma
  poster session

Relapsed/Refractory Peripheral T-cell lymphomas

② PI3K inhibitors

- *Lyer S. P.* et al. abs #4449 Phase II Clinical Study Exploring the Safety and Efficacy of the Oral PI3Kd Inhibitor, **Linperlisib**, in Relapsed Refractory T Cell Lymphoma; poster session.
- *Neha Mehta-Shah et al.* abs #3061 **Duvelisib** in Patients with Relapsed/Refractory Peripheral T-Cell Lymphoma: Final Results from the Phase 2 PRIMO Trial; poster session.
- *Cwynarski K. et al.* abs #3074 A Multicenter, Open-Label, Phase 3, Randomized Controlled Trial of **Duvelisib** Versus Investigator's Choice of **Gemcitabine** or **Bendamustine** in Patients with Relapsed/Refractory Nodal T Cell Lymphoma with T Follicular Helper Phenotype; poster
- *Hayder S. et al.* abs #3065 Phase I Study of **Duvelisib** in Combination with **Oral Azacitidine** (BMS-986345) in Mature T Cell Lymphoma; poster session.

Relapsed/Refractory Peripheral T-cell lymphomas

③ Combination with JAK/STAT Inhibition

- Moskowitz A. et al. abs #464 Dual targeted therapy with **Ruxolitinib** plus **Duvelisib** for T-cell lymphoma oral presentation

④ Immunomodulatory drugs

- Gordon M.J. Et. Abs # **Romidepsine**, **Azacitidina**, **Dexamethasone** and **Lenalidomide** (RAdR) for relapsed/refractory T-cell lymphoma oral presentation

Relapsed/Refractory Peripheral T-cell lymphomas

⑤ New drugs

- *Zain J. et al*. abs # Results from the first phase I clinical study of **DR-01**, a non fucosylated anti-CD94 targeting antibody in patients with relapsed/refractory citotoxic lymphomas: dose esclalation and optimization oral presentation

- Horwitz S. et al. abs# 467 Initial results of phase I first in human study of **Cemsidomide** (CFT7455), a novel monoDAC degrader, in patients with non Hodgkin's lymphoma ----oral presentation

Prognostic biomarker and model

- *Neha Mehta-Shah, et al. abs # 4342* Prediction of Clinical Response By Phased Variants in Circulating Tumor DNA (ctDNA) in the **VALENTINE-PTCL01** Trial of Patients with Relapsed or Refractory (R/R) Peripheral T-Cell Lymphoma (PTCL); poster presentation.

- *Min J. K. et al.* **,** *abs* #465 Development of a Novel Prognostic Score for Relapsed/Refractory Mature T-Cell and NK-Cell Lymphomas (**PIRT**): Results from a Global Peripheral T-Cell Lymphoma (**PETAL**) Consortium; oral presentation. WEBsite for PIRT Score Calculator

- *Dylan T. Jochum, et al. abs #456* An **LImpp Study**: Genomic Characterization of Novel PTCL- Biological Subtypes Reveal Distinctive Therapeutic Vulnerabilities; oral presentation.

- *Takeshi S. a*bs #454 Integrating Genomic & Transcriptomic Features for Noninvasive Detection, Characterization, and Monitoring of T-Cell Lymphomas; poster presentation

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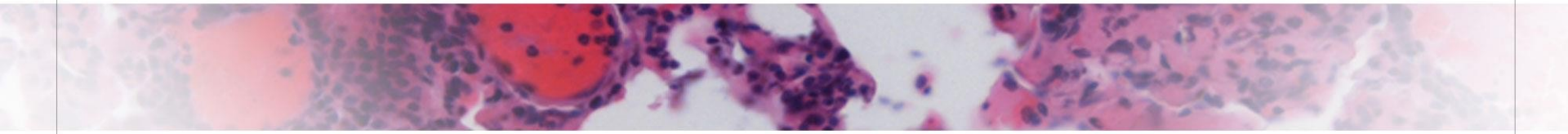


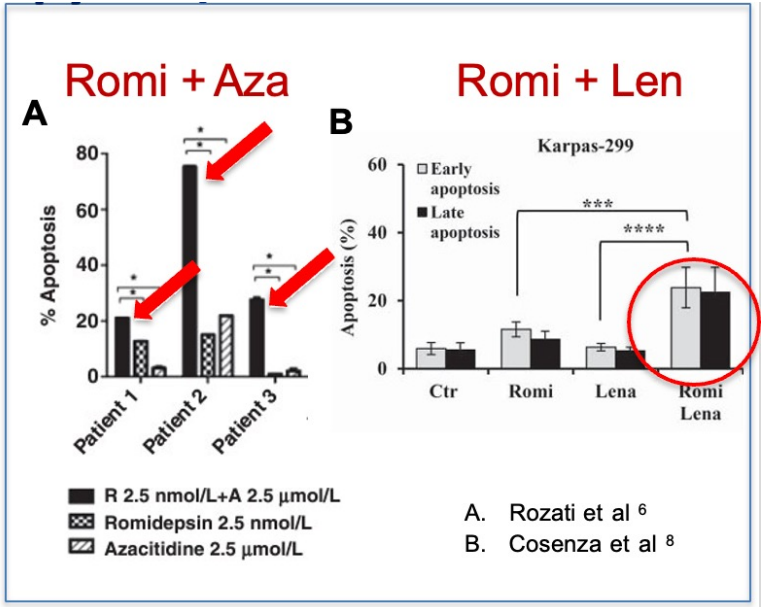
Romidepsin, azacitidine, dexamethasone, and lenalidomide (RAdR) for relapsed/refractory T-cell lymphoma

Max J. Gordon[1], Milos D. Miljkovic[1,2], Samuel Ng[1], Rahul Lakhotia[1], Christopher Melani[1], Kevin Conlon[1], James D. Phelan[1], Bonita Bryant[1], Laura Yee[3], Stefania Pittaluga[4], Elaine S. Jaffe[4], Louis M. Staudt[1], Wyndham H. Wilson[1], Mark Roschewski[1]

1 – Lymphoid Malignancies Branch, Center for Cancer Research, National Cancer Institute, Bethesda, MD, USA
2 – Cartesian therapeutics, Gaithersburg, MD, USA
3 – Biostatistics, Center for Cancer Research, National Cancer Institute, Bethesda, MD, USA
4 - Laboratory of Pathology, Center for Cancer Research, National Cancer Institute, Bethesda, MD, USA

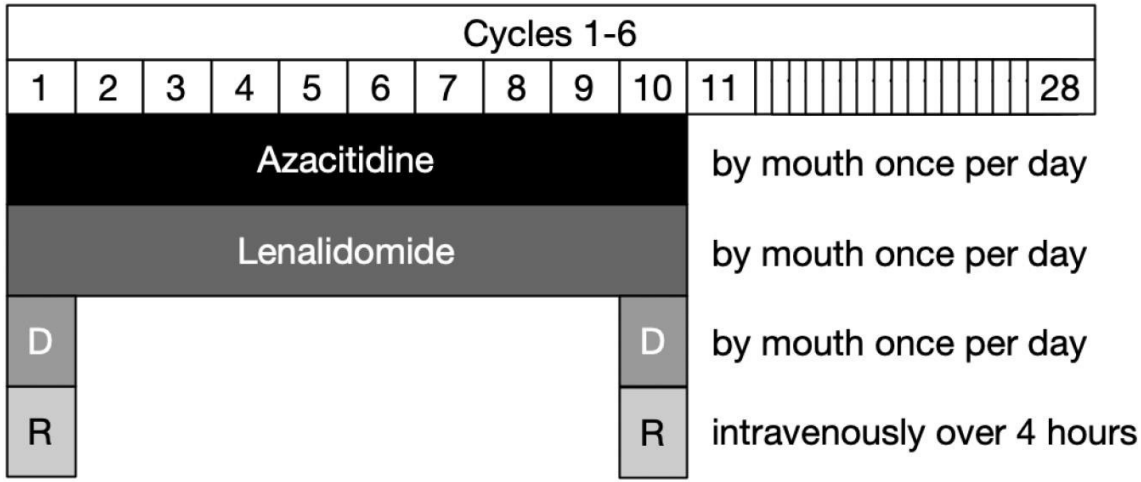
Multi-agent targeted therapy in R/R TCL

- Chemotherapy is ineffective in R/R TCL [1]
- ORR with **romidepsin**, **azacitidine & lenalidomide** is ~30% [2-5]
- Preclinical studies show **synergy** with romidepsin combinations [6-8]
- ORR with doublets is ~60% (> in TFH) [9, 10]
- **Hypothesis:** Time-limited RAdR would induce durable remissions in R/R TCL



1. *J Clin Oncol* 2013, **31**(16):1970-1976.
2. *N Engl J Med* 2012, **366**(1):95-96.
3. *J Clin Oncol* 2012, **30**(6):631-636.
4. *The Lancet Haematology* 2024, **11**(6):e406-e414.
5. *Blood* 2011, **117**(22):5827-5834.
6. *Clin Cancer Res* 2016, **22**(8):2020-2031.
7. *Br J Haematol* 2015, **171**(2):215-226.
8. *Cancer Biol Ther* 2016, **17**(10):1094-1106.
9. *Blood* 2021, **137**(16):2161-2170.
10. *Blood Adv* 2023, **7**(19):5771-5779.

RAdR treatment schedule



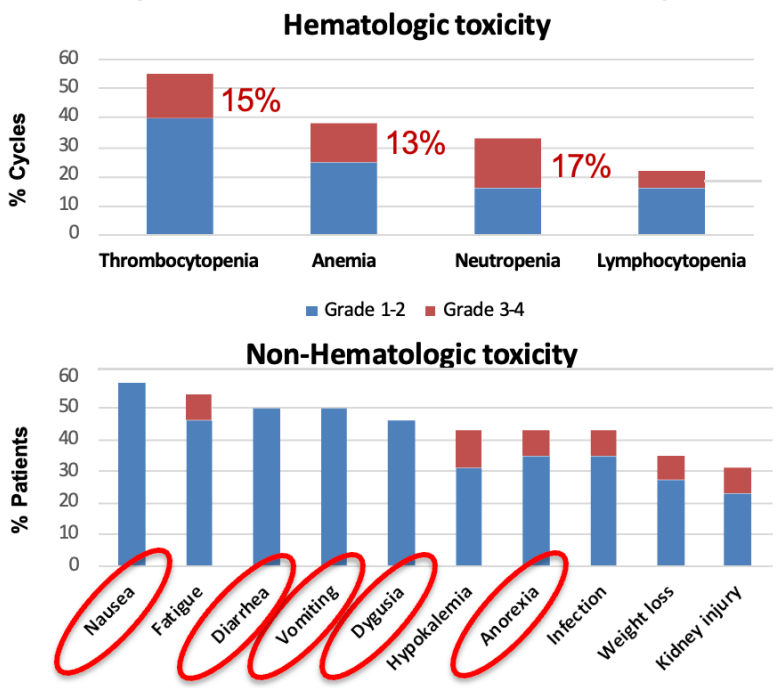
- **Romidepsin** 12 mg/m^2 IV
- **Azacitidine** (CC-486) 300 mg PO
- **Dexamethasone** 40 mg PO
- **Lenalidomide:** 5 mg, 10 mg, 15 mg, 20 mg (DL 1-4)

Baseline patient characteristics (N=26)

Age	Median (range)	61 (28-80)
Gender	Female	8 (31%)
	Male	18 (69%)
Race/ethnicity	Black	11 (42%)
	White	8 (31%)
	Hispanic	3 (12%)
	Asian	4 (15%)
Diagnosis	PTCL, NOS	8 (31%)
	AITL	5 (19%)
	ALCL ALK-	2 (8%)
	ENKTL	1 (4%)
	ATLL	4 (15%)
	MF	6 (23%)
Prior lines	Median (range)	2 (1-8)

PTCL (N=15)

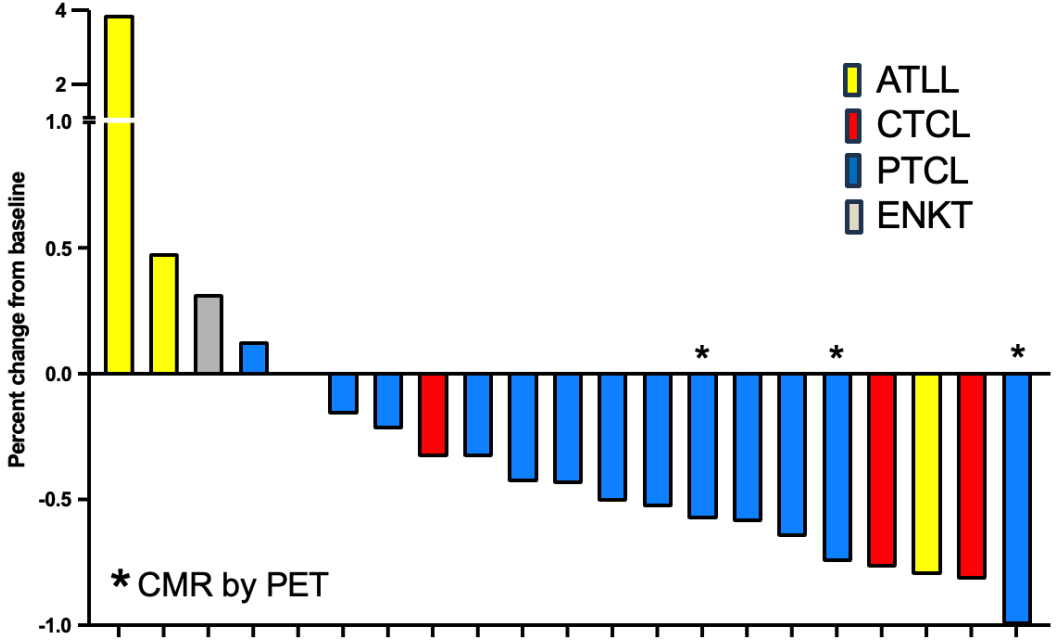
Hematologic and GI toxicity is common



Maximum tolerated dose

- **Dose limiting toxicity**
  - Gr4 thrombocytopenia (DL1)
  - Gr3 abdominal pain (DL2)
- **Maximum tolerated dose**
  - Lenalidomide 20 mg (DL4)
- **Dose reductions**
  - 29% of patients (N=7); Len 15%, Aza 9%, Romi 2%
- **34% of cycles were delayed**
  - Cycles 21 →28 days
- **25% discontinued due to toxicity**
  - Thrombocytopenia (N=4), abdominal pain (N=1), anxiety (N=1)

Response evaluable patients (N=21)

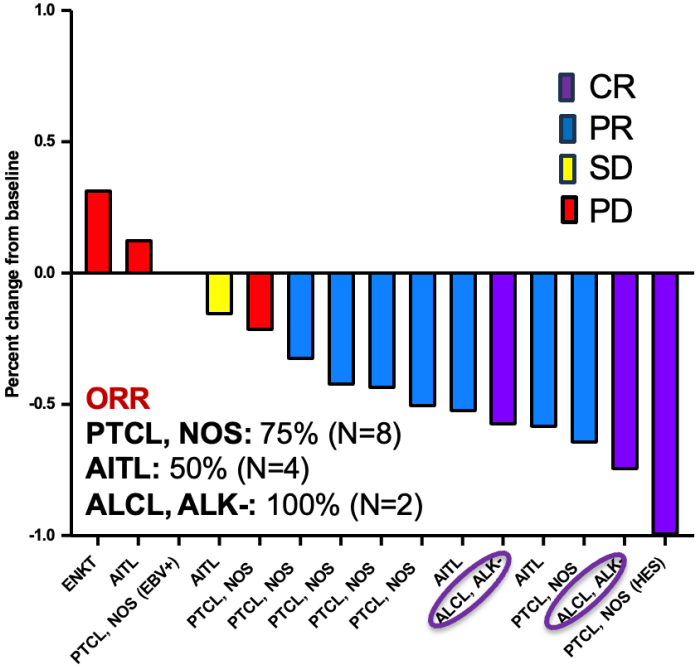


Best overall response

- **CR:** 14% (N=3)
- **PR:** 52% (N=11)
- **SD:** 10% (N=2)
- **PD:** 24% (N=5)

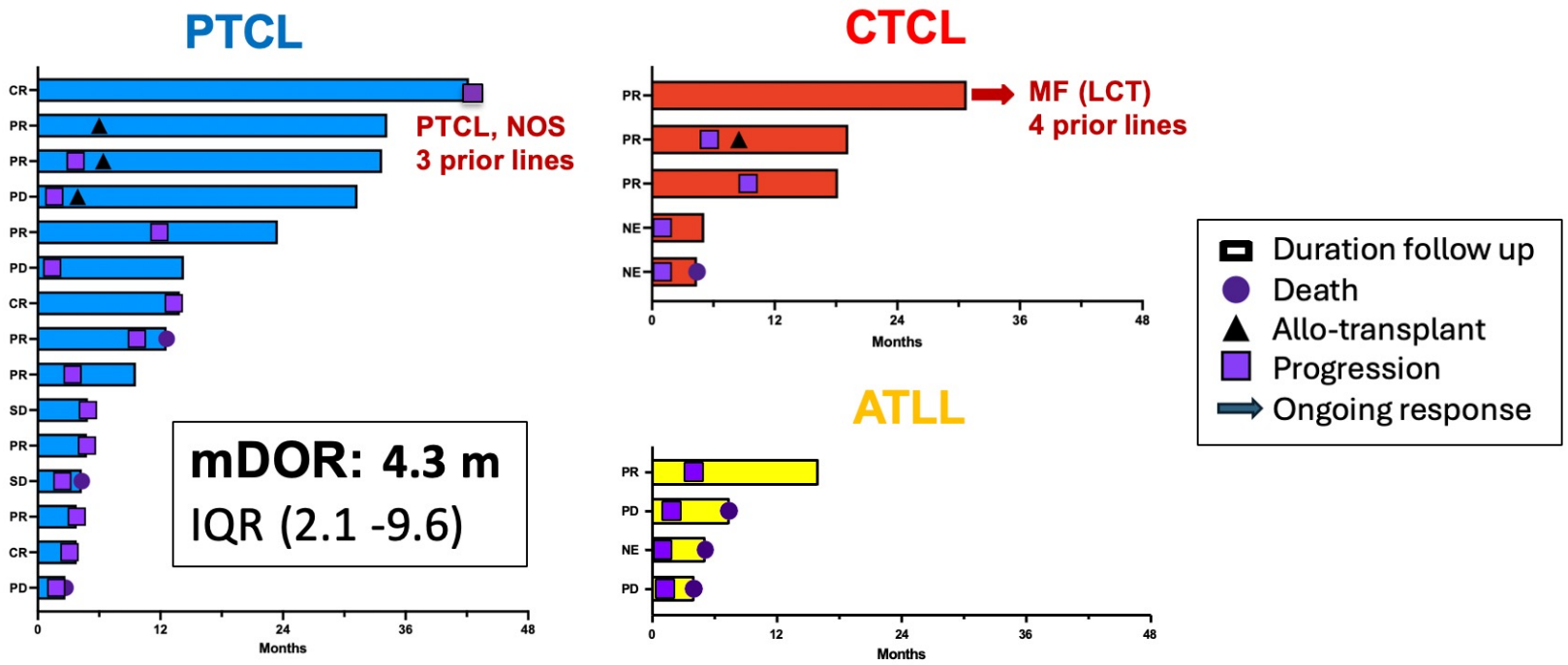
Response assessed by RECIL 2017

RAdR is active across PTCL subtypes

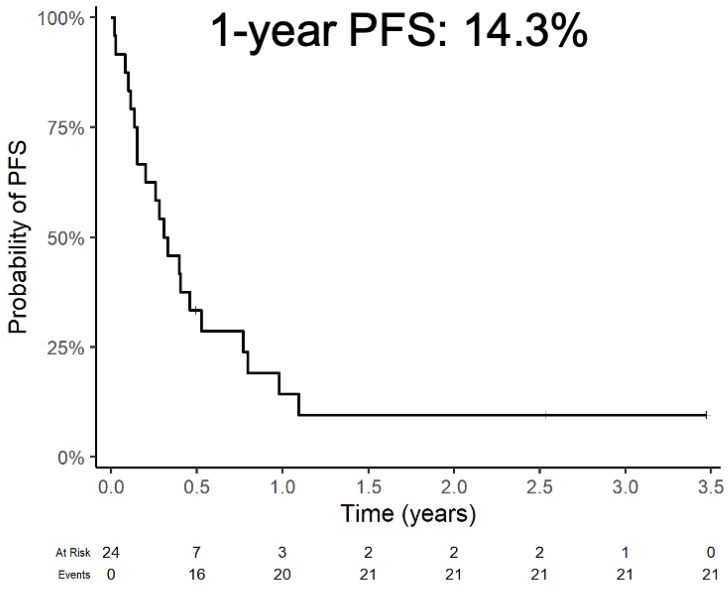


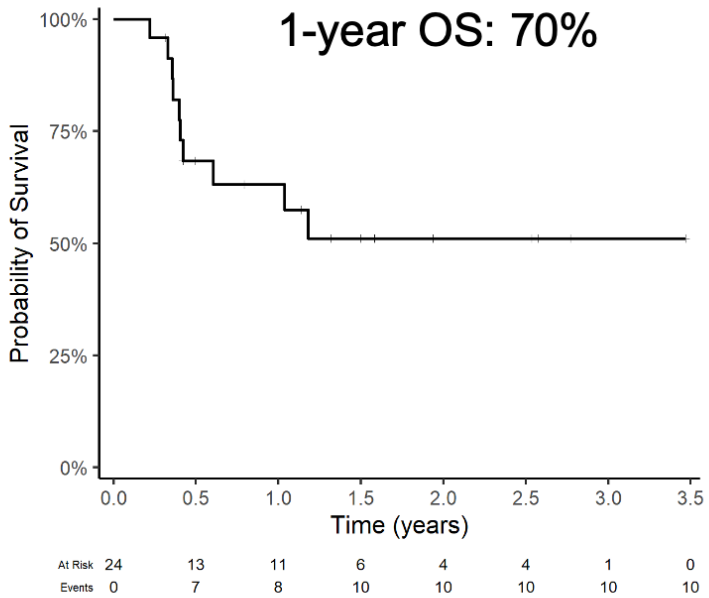
CR: 20% (N=3)
PR: 47% (N=7)

Rare durable remissions



Progression free and overall survival





Conclusions

- **Multi-agent targeted therapy** can be delivered in a time limited manner in R/R TCL
- RAdR is active in most TCL subtypes, but **durable remissions are rare** with time limited therapy
- **Preclinically validated rational therapies** are needed in TCL
- This is challenging in a **rare and heterogeneous disease**

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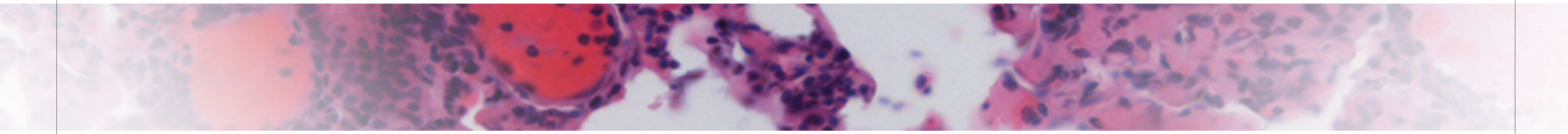


Results from the First Phase 1 Clinical Study of DR-01, a Non-Fucosylated Anti-CD94 Targeting Antibody in Patients with Relapsed/Refractory Cytotoxic Lymphomas: Dose Escalation and Optimization

Jasmine Zain, MD[1], Swaminathan P Iyer, MD[2*], Enrica Marchi, MD, PhD[3], Mitul Gandhi, MD[4], Youn H. Kim, MD[5], Michael S. Khodadoust, MD, PhD[6], Jonathan E. Brammer[7], Christina Poh, MD[8], Pierluigi Porcu[9], Kimberley Dilley, MD, MPH[10*], Matthias Will, MD[10], Andrea Kantor[10*], Cathrine Leonowens, PhD[10*], Nenad Tomasevic, PhD[10*], H. Miles Prince, MD, MBBS[11] and Steven Horwitz, MD[12]

[1]City of Hope, Duarte, CA; [2]University of Texas MD Anderson Cancer Center, Houston, TX; [3]University of Virgina Comprehensive Cancer Center, Charlottesville, VA; [4]Next Oncology, Fairfax, VA; [5]Stanford Cancer Center, Stanford, CA; [6]Stanford Cancer Center, Palo Alto, CA; [7]The Ohio State University Comprehensive Cancer Center, Columbus, OH; [8]Fred Hutchinson Cancer Center, Seattle, WA; [9]Jefferson Health, Philadelphia, PA; [10]Dren Bio, Inc, Foster City, CA; [11]Epworth HealthCare and University of Melbourne, Melbourne, VIC, Australia; [12]Memorial Sloan Kettering Cancer Center, New York, NY

Cytotoxic lymphomas are rare and have a high unmet need

Cytotoxic Lymphoma Histologies

- ENKTL, nasal type
- EATL
- MEITL
- HSTCL
- SPTCL
- PCγδTCL
- ET-CTCL
- ANKL
- HVLPD
- PTCL-NOS*
- Cutaneous PTCL-NOS*

*Some cases are cytotoxic

ANKL: aggressive NK leukemia; EATL: enteropathy-associated TCL; ENKTL: extranodal NK/TCL; ET-CTCL: epidermotropic cytotoxic TCL; HSTCL: hepatosplenic TCL; HVLPD: Hydroa vacciniforme-like lymphoproliferative disorder; MEITL: monomorphic epitheliotropic intestinal TCL; PCγδTCL: primary cutaneous γδ TCL; PTCL-NOS: peripheral TCL, not otherwise specified; SPTCL: subcutaneous panniculitis-like TCL; TCL: T-cell lymphoma

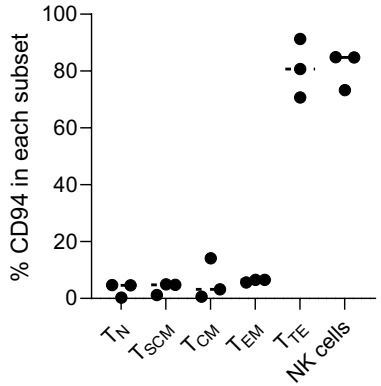
- Cytotoxic lymphomas (CTLs) are a group of rare lymphoma subtypes characterized by **cytotoxic cells expressing CD94**
- CTLs account for **25-40%** of mature NK/T-cell lymphomas (or 3-6% of NHL)[1]
- **No standard of care** has been established for patients with CTL and few CTL patients are represented in randomized studies
- **Outcomes** in CTL patients **are poor** with mOS < 1 year in newly diagnosed HSTCL, EATL and ENKTL patients[2], and only mOS of ~3 months in R/R ENKTL[3]
- Therefore, there is a high unmet need for patients with CTLs and **safe and effective therapies are needed**

[1]Leukemia and Lymphoma Society 2024; [2]Vose et al. *JCO* 2008; [3]Bellei M et al. *Haematologica* 2018

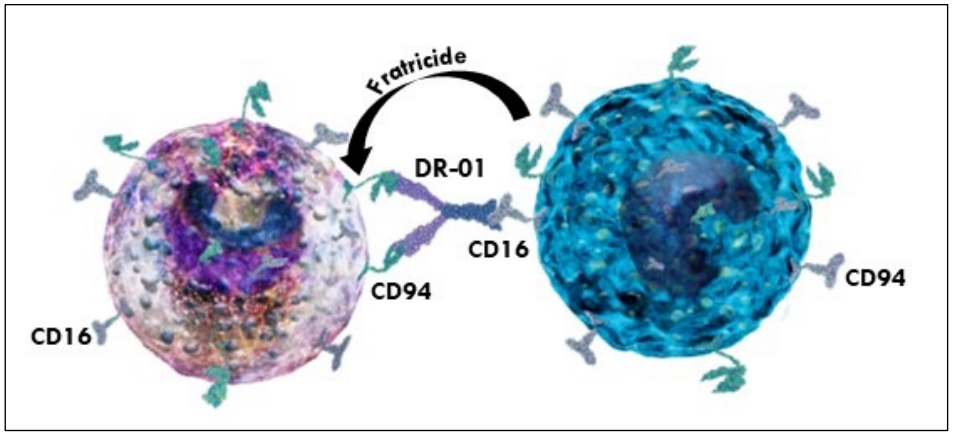
DR-01 is Novel Targeted Antibody against CD94

- **DR-01** is a non-fucosylated human **IgG antibody against CD94** that is selectively **expressed** on a subset of terminally differentiated as well as **malignant cytotoxic T cells and NK cells**
- As a result, DR-01 engages Fc-gamma receptors, such as CD16a and triggers antibody-dependent cellular cytotoxicity (**ADCC**), by effector cells or fratricide, resulting in rapid target cell depletion

CD94 expression on CD8 T cell subsets in healthy donor PBMCs



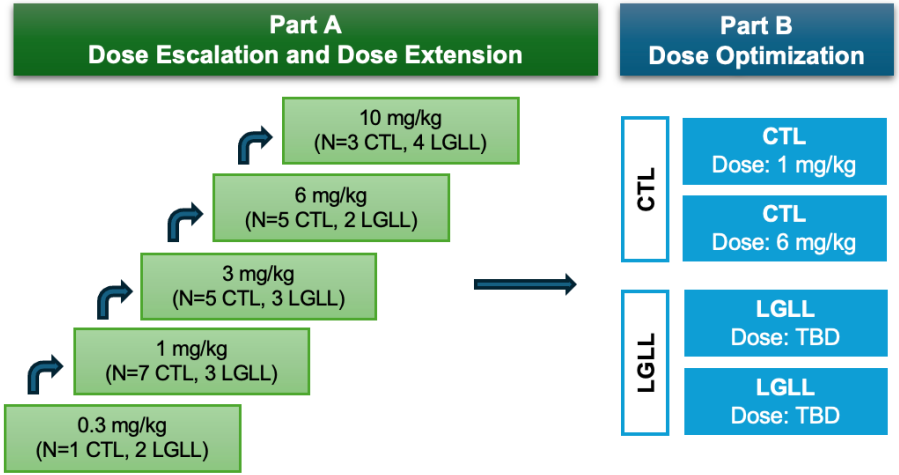
N = Naïve
SCM = Stem cell memory
CM = Central memory
EM = Effector memory
TE = Terminal effector
NK = Natural Killer



Target Cell Effector Cell

First-in-Human Phase 1/2 Study for DR-01 - Study Schema

Patient Eligibility
- R/R CTL and LGLL
- Adequate organ function
- Part A:
  - CTL: ≥2 prior lines of therapy, ECOG PS 0-1
  - LGLL: ≥1 prior line of therapy, ECOG PS 0-2
- Part B CTL: ≥1 prior line of therapy



Dosing: Induction regimen for C1 (28 days) followed by maintenance dose once every 28 days
- Primary induction: 1st dose over D1-2, D15
- Secondary induction: 1st dose over D1-2, D8, D15
- Tertiary induction: 1st dose D1-5, D15

Study Objectives
- Primary: Evaluate the safety and tolerability of DR-01, determine the optimized dose/regimen for DR-01
- Secondary: ORR, DoR, PK profile of DR-01, immunogenicity of DR-01

Baseline Demographics – Safety Population

- 54 patients (40 CTL and 14 LGLL) were safety evaluable (≥1 dose of DR-01) as of 23 October 2024

	0.3 mg/kg (N=3)	1 mg/kg (N=22)	3 mg/kg (N=8)	6 mg/kg (N=14)	10 mg/kg (N=7)	Total (N=54)
Median age (range)	64 (53-75)	55 (19-76)	60 (46-71)	48 (26-81)	59 (23-86)	57 (19-86)
Male, n (%)	3 (100)	18 (82)	5 (62.5)	5 (36)	4 (57)	35 (65)
ECOG PS, n (%)						
0-1	3 (100)	22 (100)	8 (100)	14 (100)	5 (72)*	52 (96)*
2	0	0	0	0	1 (14)	1 (2)
Histology						
LGLL	2 (66.7)	3 (13.6)	3 (37.5)	2 (14.3)	4 (57.1)	14 (25.9)
CTL	1 (33.3)	19 (86.4)	5 (62.5)	12 (85.7)	3 (42.9)	40 (74.1)

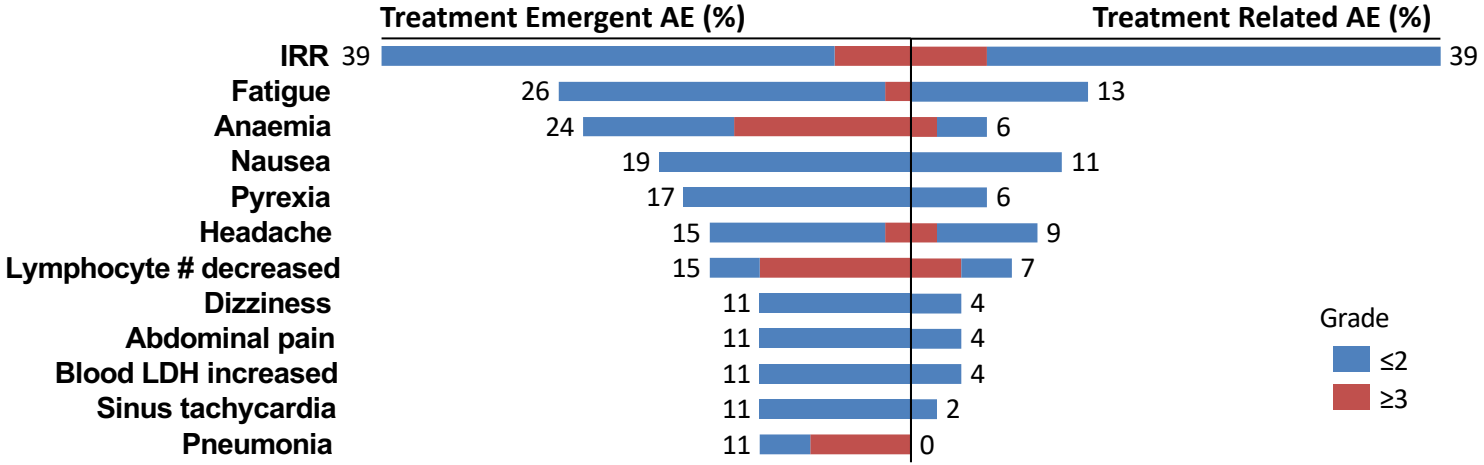
*ECOG PS of 1 for 1 LGLL pt entered after data cut-off

Baseline Characteristics for CTL Patients on Dose Escalation (Part A)

	0.3 mg/kg (N=1)	1 mg/kg (N=7)	3 mg/kg (N=5)	6 mg/kg (N=5)	10 mg/kg (N=3)	Total (N=21)
CTL Histology, n (%)						
PCγδTCL	0	2 (28.6)	0	2 (40)	2 (66.7)	6 (28.6)
ET-CTCL	1 (100)	0	1 (20)	0	0	2 (9.5)
HSTCL	0	0	0	0	1 (33.3)	1 (4.8)
SPTCL	0	1 (14.3)	0	0	0	1 (4.8)
ENKTL	0	1 (14.3)	1 (20)	0	0	2 (9.5)
MEITL	0	0	1 (20)	1 (20)	0	2 (9.5)
PTCL-NOS & Other*	0	3 (42.9)	2 (40)	2 (40)	0	7 (33.3)
Median Prior lines of therapy (range)	8 (8-8)	5 (2-14)	5 (2-7)	3 (2-6)	4 (2-9)	4 (2-14)
Reason for Discontinuation from Last Therapy, n (%)						
Lack of Response	1 (100)	4 (57.1)	1 (20)	2 (40)	2 (66.7)	10 (47.6)
Intolerance	0	0	1 (20)	2 (40)	0	3 (14.3)
Prior autologous or allogeneic HSCT, n(%)	0	1 (14.3)	3 (60)	0	0	4 (19)

*Other includes malignant cells expressing CD8 or CD56 and at least 1 cytotoxic marker (TIA-1, granzyme B, perforin)

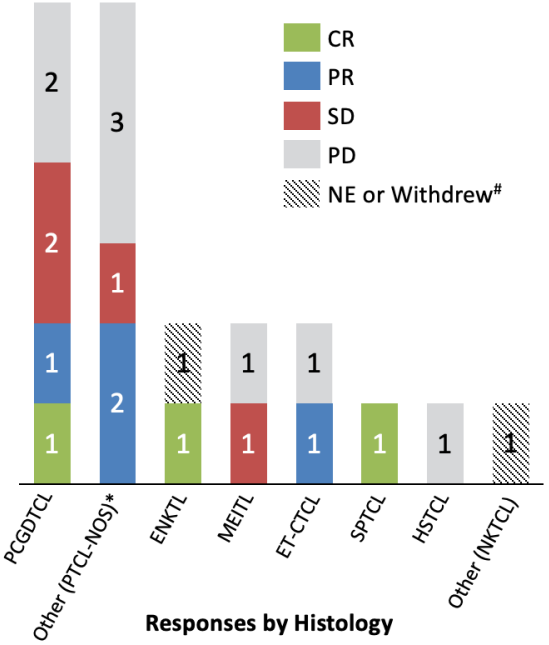
Most Common Adverse Events in Safety Evaluable Patients (TEAE > 10%)



- **No DLTs were reported** during dose escalation and the MTD was not reached
- **Infusion-related reactions** (IRR) were the most common TEAE
  - Majority of IRR events **were Grade 1-2** and all events were **manageable** with mitigation strategies including standard pre-medications and splitting the initial dose
- Only 2/54 (4%) AEs of **viral reactivation** (Gr 1 CMV, Gr 1 HSV) were noted and continued on study. Other acquired viral infections (e.g. COVID-19) resolved as expected

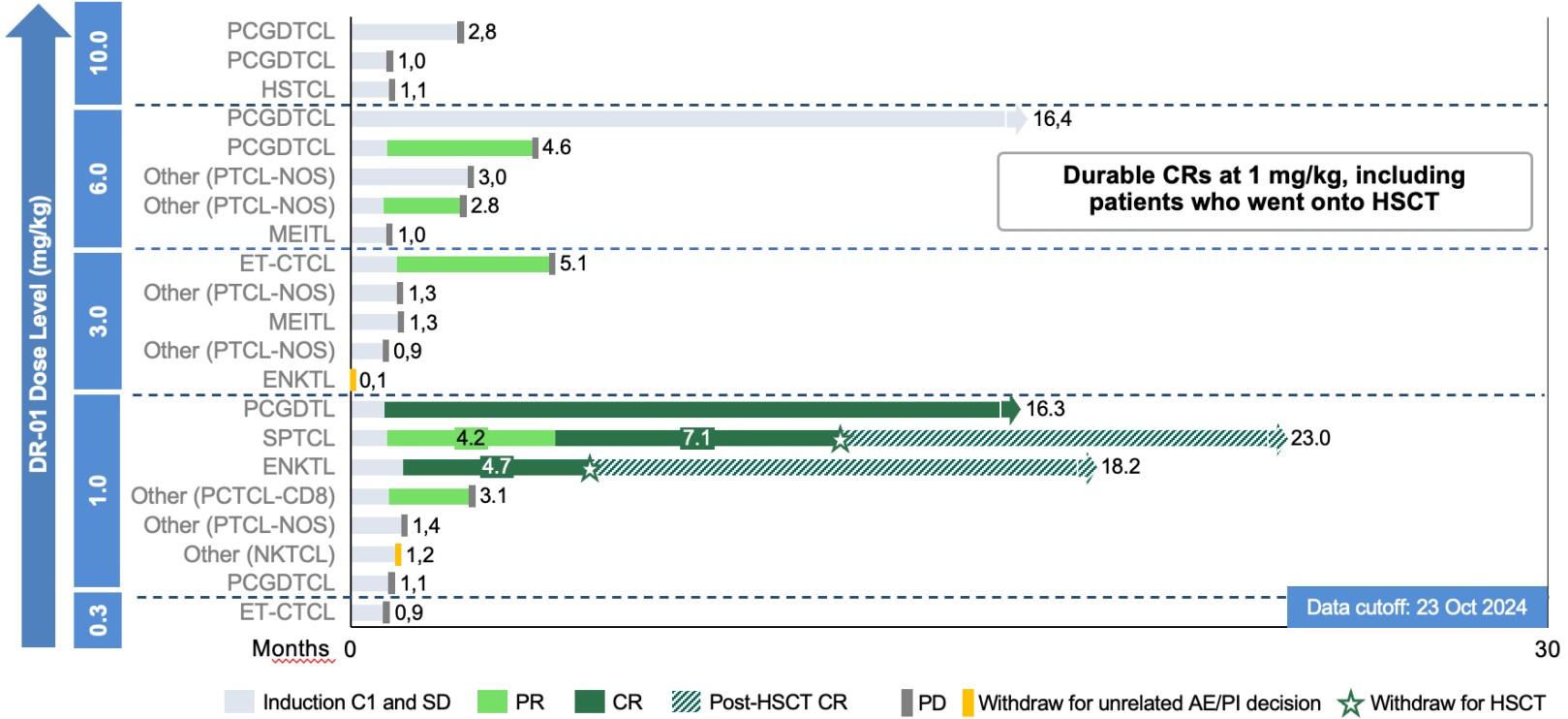
Promising Response Rate, including CRs, in CTL Patients During Dose Escalation in Majority of Histologies

	Dose Level (mg/kg)					
	0.3 (N=1)	1 (N=6)	3 (N=4)	6 (N=5)	10 (N=3)	Total (N=19)#
ORR, n (%)	0	4 (67)	1 (25)	2 (40)	0	7 (37)
CR	0	3 (50)	0	0	0	3 (16)
PR	0	1 (17)	1 (25)	2 (40)	0	4 (21)
SD	0	0	1 (25)	2 (40)	1 (33)	4 (21)
PD	1 (100)	2 (33)	2 (50)	1 (20)	2 (67)	8 (42)



One unrelated AE withdrawal and one PI withdrawal without assessment
*Includes cutaneous subtypes

Duration of DR-01 Treatment and Responses of CTL Patients on Dose Escalation



Conclusions

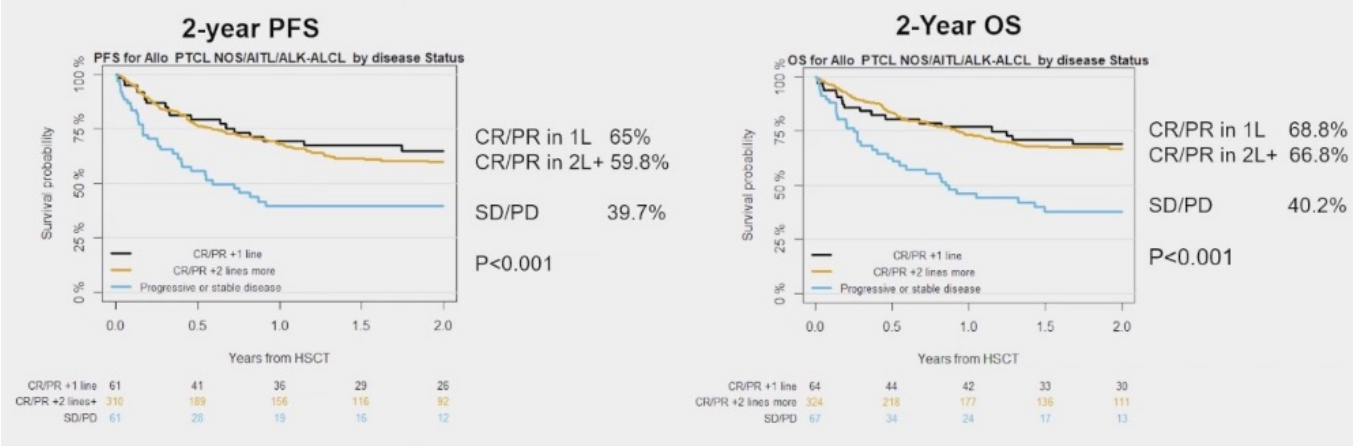
- DR-01 is a non-fucosylated human **IgG1 antibody targeting CD94**, a marker specifically expressed on cytotoxic T and NK cell lymphomas
- **54 R/R CTL and LGLL patients** have enrolled across dose levels ranging from 0.3 – 10 mg/kg, with 21 CTL patients treated in Part A dose escalation
- **No DLTs were observed** during dose escalation and no MTD was reached
- **IRR was the most common treatment-related AE**, typically occurred only after the first dose which was manageable with standard mitigation strategies
- Responses were seen across multiple CTL histologies including **durable CRs at 1 mg/kg**
- Preliminary clinical data demonstrate that DR-01 is safe and tolerable and has a favorable benefit/risk profile in a high unmet need population
- **Expansion cohort in CTLs continues to enroll** and dose escalation for LGLL is ongoing with responses observed

Outcomes of allo-SCT for major entities up-front and in R/R

1292 patients
Median age 55 years (19-78)
Conditioning:
- RIC 57%,
- MAC 43%

Number of therapy lines prior to allo-SCT
- One lines 14%
- Two lines 33%
- ≥Three lines 52%

Status at allo-SCT
- CR1/PR1 17% (n=64)
- CR2/PR2 64% (n=324)
- SD/PD 13% (n=67)



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SSD LINFOMI E SDR LINFOPROLIFERATIVE CRONICHE

Prof. Pier Luigi Zinzani