Initial Results of a Phase 1 First-in-Human Study of Cemsidomide (CFT7455), a Novel MonoDAC® Degrader, in Patients with Non-Hodgkin's Lymphoma

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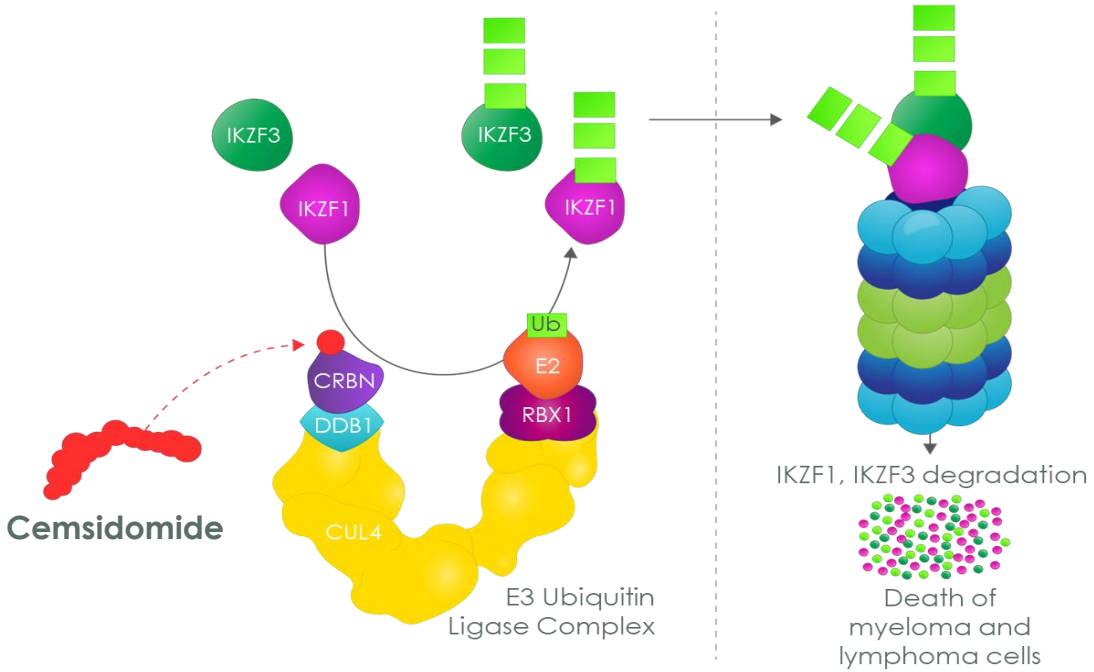
Cemsidomide (CFT7455) Background

- Cemsidomide is a novel, potent, cereblon-based IKZF1/3 MonoDAC® degrader with:
  - Catalytic activity enabling rapid and deep target degradation
  - High binding affinity to overcome resistance due to low cereblon levels
  - Pharmacologic profile to promote tumor residence time and sustained IKZF1/3 degradation

Mechanism of Action for Cemsidomide



- Cemsidomide binds to cereblon to facilitate the recruitment and ubiquitination of IKZF1 and IKZF3, leading to the proteasomal degradation of both proteins

IKZF1/3 Degradation Induces:

- NHL and multiple myeloma cell death
- Stimulation of the immune system
  - Activates fully differentiated T-cells, preventing T-cell exhaustion
  - Promotes secretion of key immune stimulating cytokines (e.g., IL-2)
- On-target neutropenia
  - Disrupts hematopoietic stem cell differentiation

IKZF 1/3, Ikaros zinc finger protein 1/3; NHL, non-Hodgkin lymphoma; 14/14, 14 days on/14 days off

Cemsidomide Multiple Myeloma Poster: Sunday 6 PM- 8 PM; Poster #3366

CFT7455-1101 Phase 1/2 Trial Study Design: Arm C, Cemsidomide in NHL

- Open-label, multicenter, phase 1/2 clinical trial with dose escalation and expansion phases (NCT04756726)*
- Dose escalation phase, beginning with a starting oral dose of 25 µg MWF 14 days on/14 days off, followed by a Bayesian logistic regression model until determination of the MTD and/or RP2D
  - Escalation cohorts enrolled 3-6 patients; once a dose was declared safe by SRC, additional patients were eligible to enroll at that dose
    - G-CSF and transfusions were not allowed in cycle 1 for dose escalation patients
    - Once a dose was declared safe, additional patients at each dose level were allowed G-CSF use at any timepoint

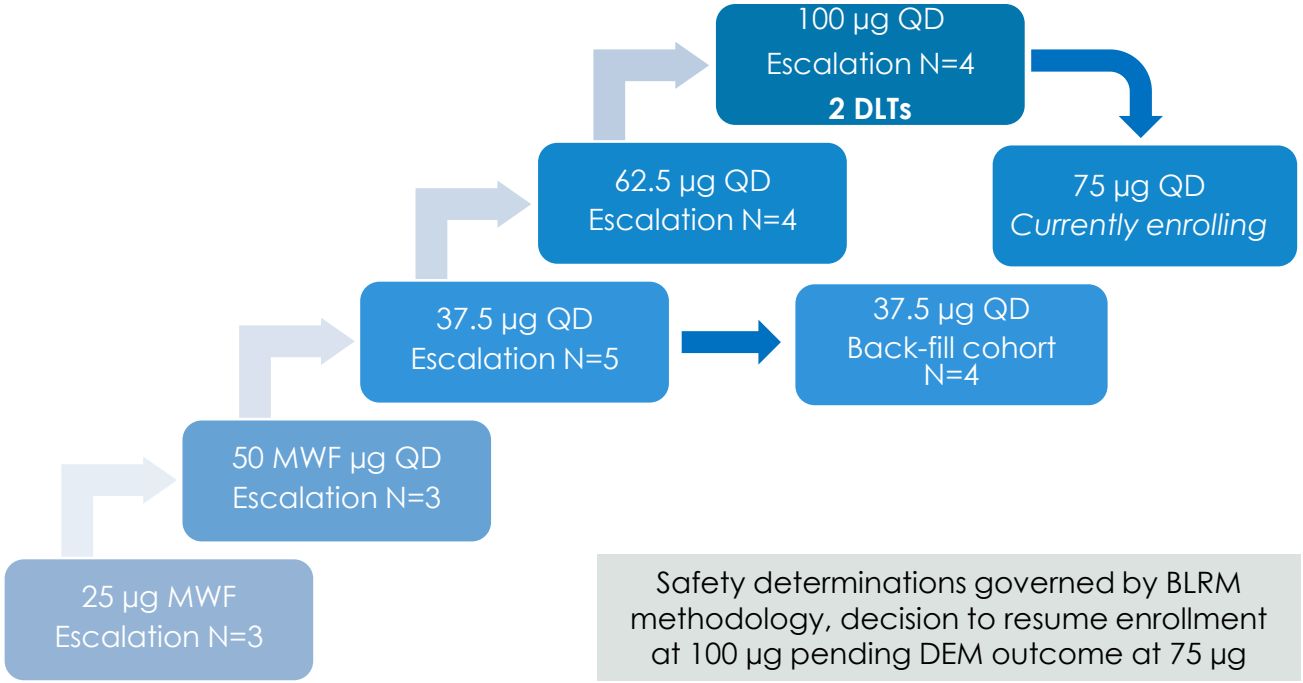
KEY INCLUSION CRITERIA

- Adults with NHL, R/R to prior therapy
  - For PTCL patients must have received at least 1 prior alkylator-based chemotherapy. For ALCL patients must have also received a CD-30 mAb
- Nonresponsive to or progressed within 60 days of prior therapy
- Creatinine clearance ≥40 mL/min
- ECOG ≤2

Phase 1 Study Endpoints

- **Primary: assess safety, tolerability and define the RP2D/MTD**
- **Secondary: assess PK, PD, and preliminary anti-tumor activity per Lugano**

Phase 1 Dose Escalation 14/14 Dosing Schedule*



Phase 2: Cohort Expansion

*CFT7455 administered as 14 days on/14 days off in a 28-day cycle; 3 patients at 75µg are excluded as dose escalation meeting has not occurred as of cut-off date
2 DLTs occurred at 100 µg due to grade 4 thrombocytopenia, both patients dose reduced to 62.5 µg.

ALCL, anaplastic large cell lymphoma; BLRM, Bayesian logistic regression model; ECOG, Eastern Cooperative Oncology Group; G-CSF, granulocyte colony stimulating factor; mAb, monoclonal antibody; MTD, maximum tolerated dose; MWF, Monday Wednesday Friday; NHL, non-Hodgkin lymphoma; PD, pharmacodynamics; PK, pharmacokinetics; PTCL, peripheral T-cell lymphoma; SRC, safety review committee; RD2D, recommended phase 2 dose; R/R, relapsed/refractory; 14/14, 14 days on/14 days off.

Data cutoff: 10/11/24

Baseline Characteristics and Disease History

Heavily Pretreated NHL Patient Population

Characteristics	Safety Population (N=23)
Age, median (range)	68 (28-85 years)
Male, n (%)	14 (61)
Years since initial diagnosis, median (range)	2 (0.4-21)
ECOG performance status, n (%)	
0	11 (48)
1	9 (39)
2	2 (9)
Missing	1 (4)
Black or African American, n (%)	6 (26)
White, n (%)	13 (57)
Other, n (%)	4 (17)
IPI at screening, n (%)	
1	2 (9)
2	6 (26)
3	7 (30)
4	3 (13)
Missing	5 (22)

Characteristics	Safety Population (N=23)
Median of prior therapies (range)	3 (1-14)
1	2 (9)
2	7 (30)
3	3 (13)
≥4	11 (48)
PTCL, n (%)	17 (74)
PTCL-NOS	5 (22)
AITL	4 (17)
ALCL	3 (13)
ATLL	5 (22)
B-cell Lymphoma, n (%)	6 (26)
DLBCL	4 (17)
MCL	1 (4)
MZL/MALT	1 (4)
Prior CAR-T Therapy, n (%)	4 (17)
Prior HCT, n (%)	4 (17)
Autologous	3 (13)
Allogenic	1(4)

AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large cell lymphoma; ATLL, adult T-cell lymphoma; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; HCT, hematopoietic cell transplantation; IPI, international prognostic index; MCL, mantle cell lymphoma, MZL/MALT, marginal zone lymphoma/mucosa-associated lymphoid tissue lymphoma; NHL, non-Hodgkin lymphoma; PTCL, peripheral T-cell lymphoma; PTCL-NOS, peripheral T-cell lymphoma not-otherwise specified.

Data cutoff: 10/11/24

Treatment Disposition
The Majority of Discontinuations Were Due to Progressive Disease

Patient Disposition, n (%)	Safety Population (N=23)
Ongoing	3 (13)
Discontinued	20 (87)
Progressive disease	14 (61)
Physician decision	3 (13)
Adverse event	2 (9)
Death	1 (4)*

- Treatment was ongoing for 3 patients (13%)
- The primary reason for discontinuation was progressive disease (14/20)

*The 1 death reported was considered unrelated to cemsidomide

Data cutoff: 10/11/24

Overview of AEs Across Dose Levels

Cemsidomide Monotherapy Was Well Tolerated With 2 DLTs Observed at 100 µg

Adverse Events, n (%)	25 µg MWF (N=3)	50 µg MWF (N=3)	37.5 µg QD (N=9)	62.5 µg QD (N=4)	100 µg QD (N=4)	Total (N=23)
TEAEs	3 (100)	2 (67)	9 (100)	4 (100)	4 (100)	22 (96)
TEAEs possibly related to cemsidomide	1 (33)	2 (67)	7 (78)	4 (100)	4 (100)	18 (78)
TESAEs	0	0	4 (44)	1 (25)	3 (75)	8 (35)
TESAEs possibly related to cemsidomide	0	0	4 (44)	1 (25)	3 (75)	8 (35)
Any grade ≥3 TEAEs	0	0	8 (89)	4 (100)	4 (100)	16 (70)
Any grade ≥3 TEAEs possibly related to cemsidomide	0	0	7 (78)	4 (100)	4 (100)	15 (65)
TEAEs leading to discontinuation	0	0	1 (11)	1 (25)	0	2 (9)
Dose limiting toxicities	0	0	0	0	2 (50)	2 (9)

- Discontinuation rates due to AEs were low
- 2 patients had a DLT at 100 µg QD due to grade 4 thrombocytopenia with one also having grade 3 febrile neutropenia
- 3 patients dose reduced in the 100 µg cohort to 62.5 µg: 2 DLT patients and 1 patient due to nausea and vomiting

AEs, adverse events; DLT, dose limiting toxicities; TEAEs, treatment emergent adverse events; TESAEs, treatment emergent serious adverse events.

Data cutoff: 10/11/24

Most Common TEAEs and AEs of Interest

Majority of Grade 3/4 TEAEs Were Hematologic With Limited Non-Hematologic TEAEs

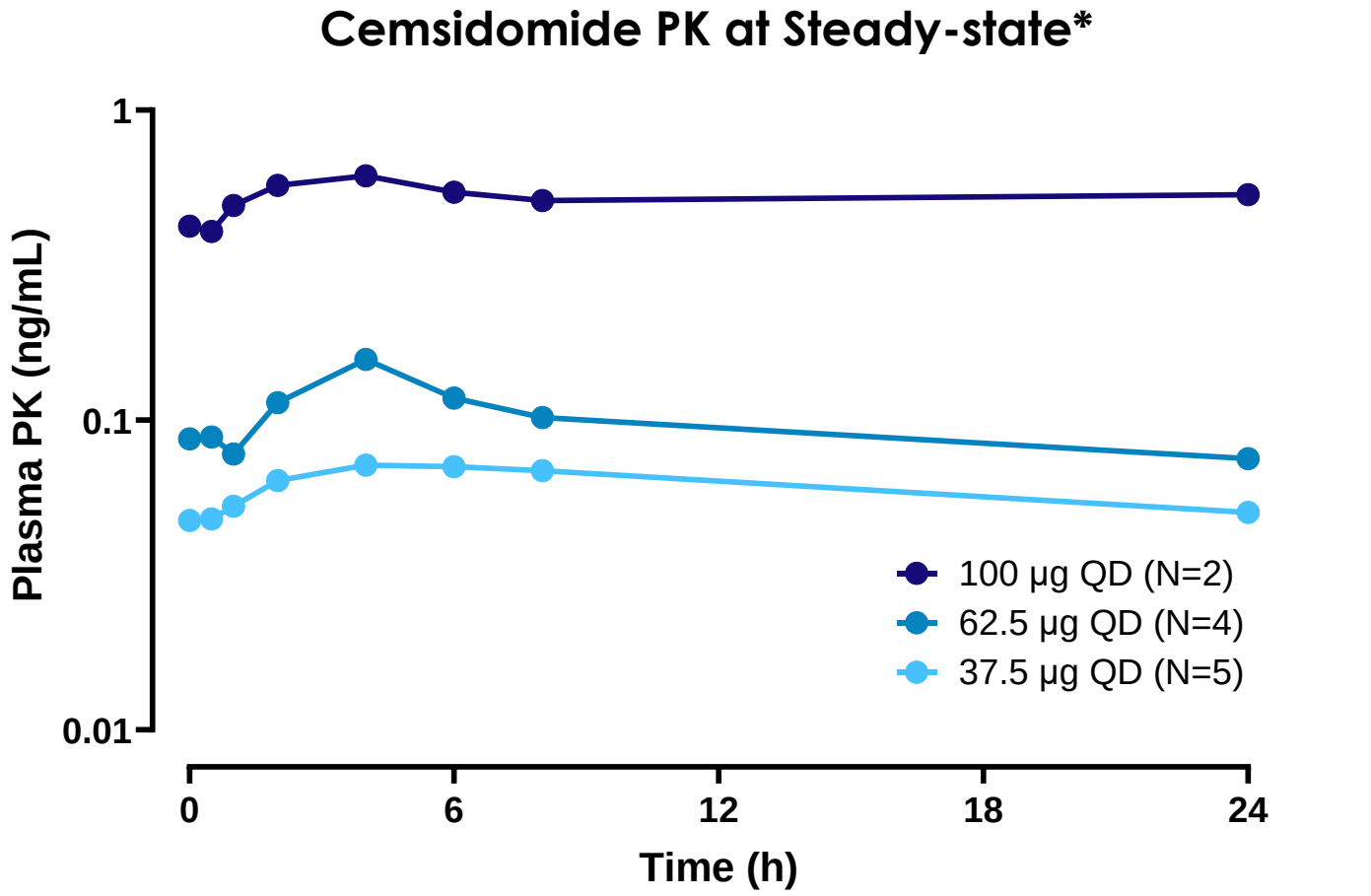
Common (>20% all grades) TEAEs and Events of Interest*, n (%)	All grade (N=23)	Grade 3 (N=23)	Grade 4 (N=23)
Infections	15 (65)	4 (17)	2 (9)
Upper respiratory tract infection	4 (17)	0	0
Sepsis	1 (4)	0	1 (4)
Bacteremia	1 (4)	0	1 (4)
Pneumonia	2 (9)	2 (9)	0
Neutropenia	11 (48)	4 (17)	7 (30)
Fatigue	11 (48)	1 (4)	0
Cough	7 (30)	0	0
Anemia	6 (26)	4 (17)	0
Peripheral edema	5 (22)	0	0
Febrile neutropenia*	4 (17)	4 (17)	0
Thrombocytopenia*	4 (17)	1 (4)	2 (9)
Maculopapular rash*	3 (13)	2 (9)	0

- 1 patient experienced a grade 5 AE (hip fracture resulting in transfer to hospice)
- G-CSF support was not allowed during cycle 1 for patients in dose escalation cohorts
- 11/23 (48%) of patients experienced grade 3/4 neutropenia, an anticipated on-target effect of IKZF1/3 degradation
  - Cases of neutropenia were manageable with treatment interruptions and G-CSF support after cycle 1
  - 9/23 (39%) of patients received G-CSF, with 3 of 9 patients receiving it in cycle 1

*AEs of interest due to class effect of IKZF 1/3 degraders
G-CSF, granulocyte colony-stimulating factor.
Data cutoff: 10/11/24

Cemsidomide Pharmacokinetics

PK Was Dose-Proportional With an ~2-day Half-life



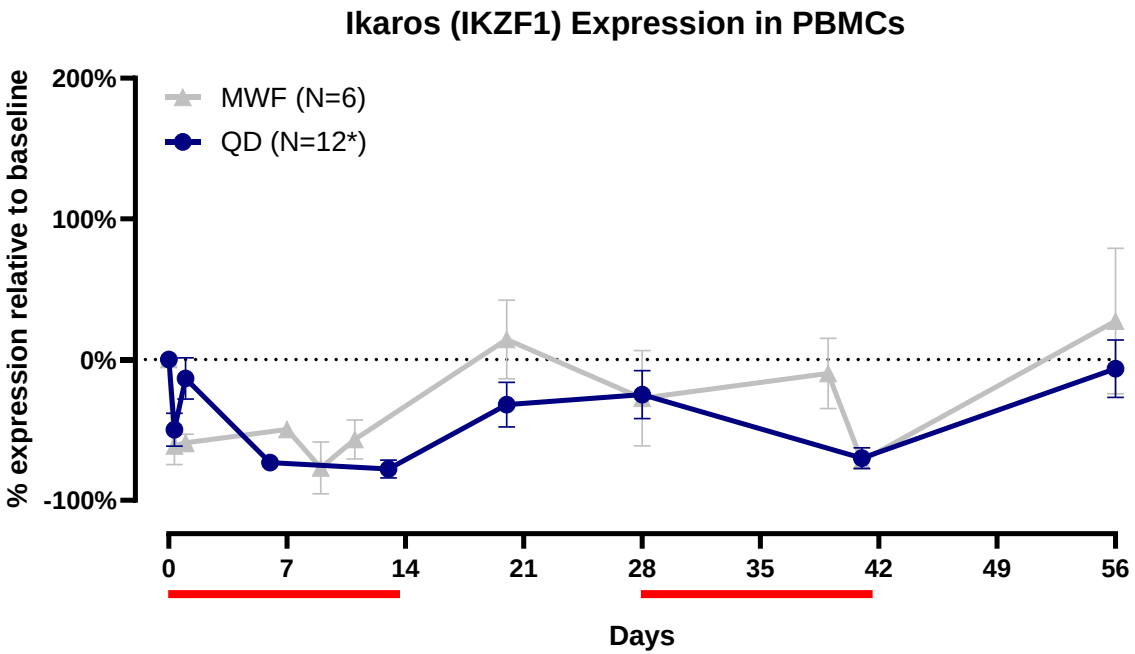
- Plasma exposure of cemsidomide monotherapy was dose-proportional
- The overall geometric mean half-life estimate is approximately 2 days

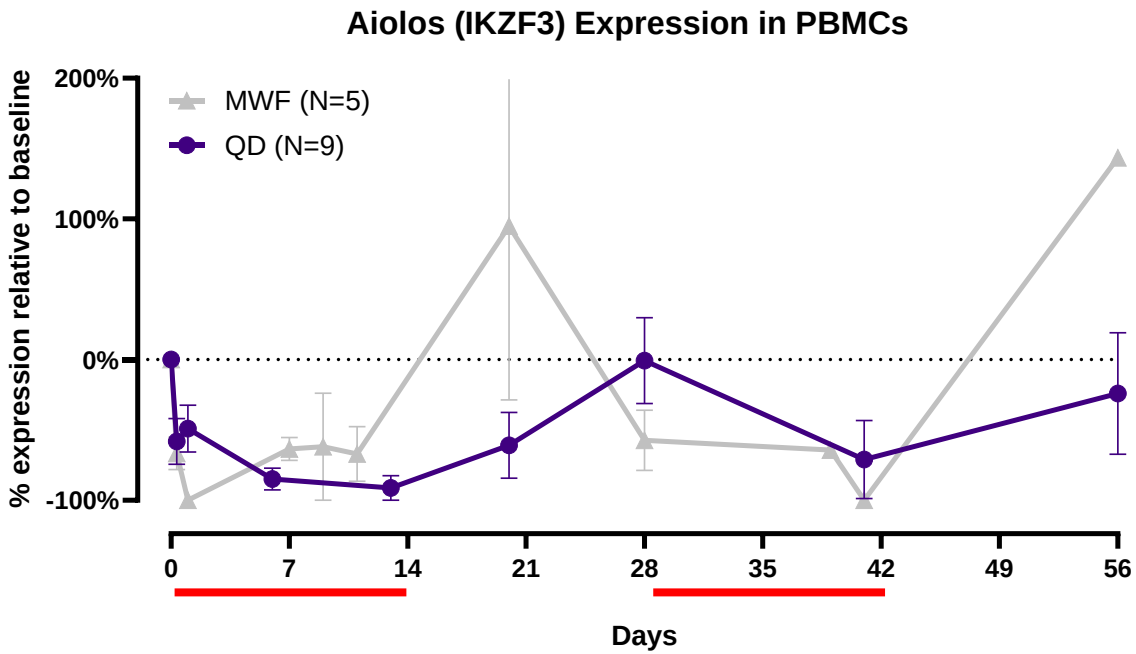
*Patients dosed MWF not included
PK, pharmacokinetics

Data cutoff: 10/11/24

Pharmacodynamics: IKZF1/3 Degradation

Rapid Degradation of IKZF1/3 Observed With Sufficient Neutrophil Recovery Time





- Cemsidomide induced at least 60% and 80% degradation of IKZF1 and IKZF3, respectively, when dosed daily and at least 40% and 60% degradation of IKZF1 and IKZF3, respectively, when dosed MWF
- IKZF1/3 rebound during off-treatment period enabled sufficient neutrophil recovery

*Data for a fourth patient dosed at 62.5 µg QD was censored from the analysis due abnormal values observed at all timepoints

IKZF 1/3, Ikaros zinc finger protein 1/3; MWF, Monday Wednesday Friday; PBMCs, peripheral blood mononuclear cells

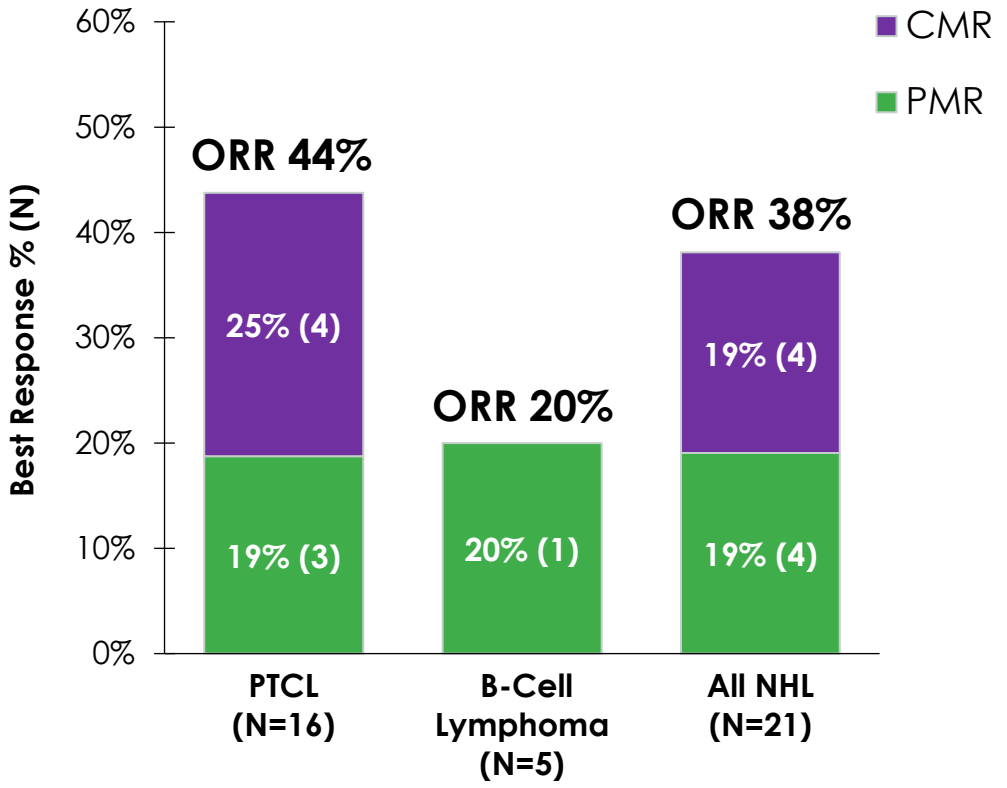
= The 14-day periods of cemsidomide dosing

Data cutoff: 10/11/24

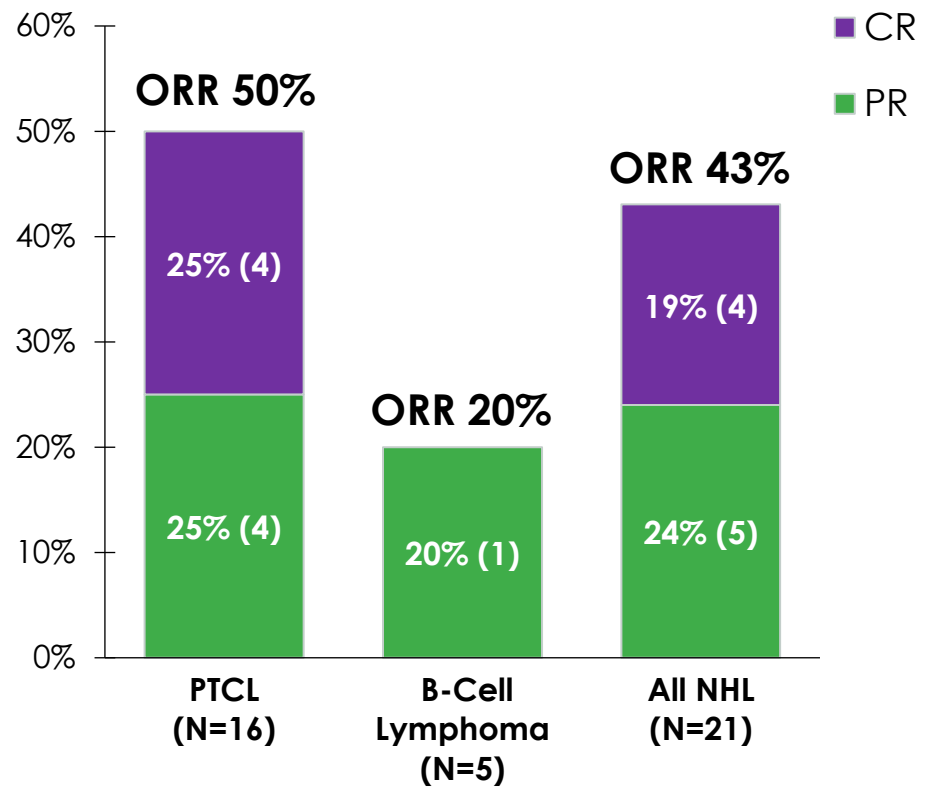
Best Response by NHL Subtype*

Response Rate of 38% Achieved in Heavily Pretreated NHL Patient Population

PET-CT–based Assessment



CT–based Assessment



- Cemsidomide monotherapy produced 44% and 50% ORRs in PTCL as assessed by PET-CT and CT, respectively, and several deep responses were assessed as indicated by a 25% CR rate

* Investigator assessed response; 2 patients were evaluated based on CT scan and were PD but not evaluable based on PET-CT, both patients are included as PMD for PET-CT based assessment; 2 additional patients came off study prior to follow up scans and were not considered efficacy evaluable.

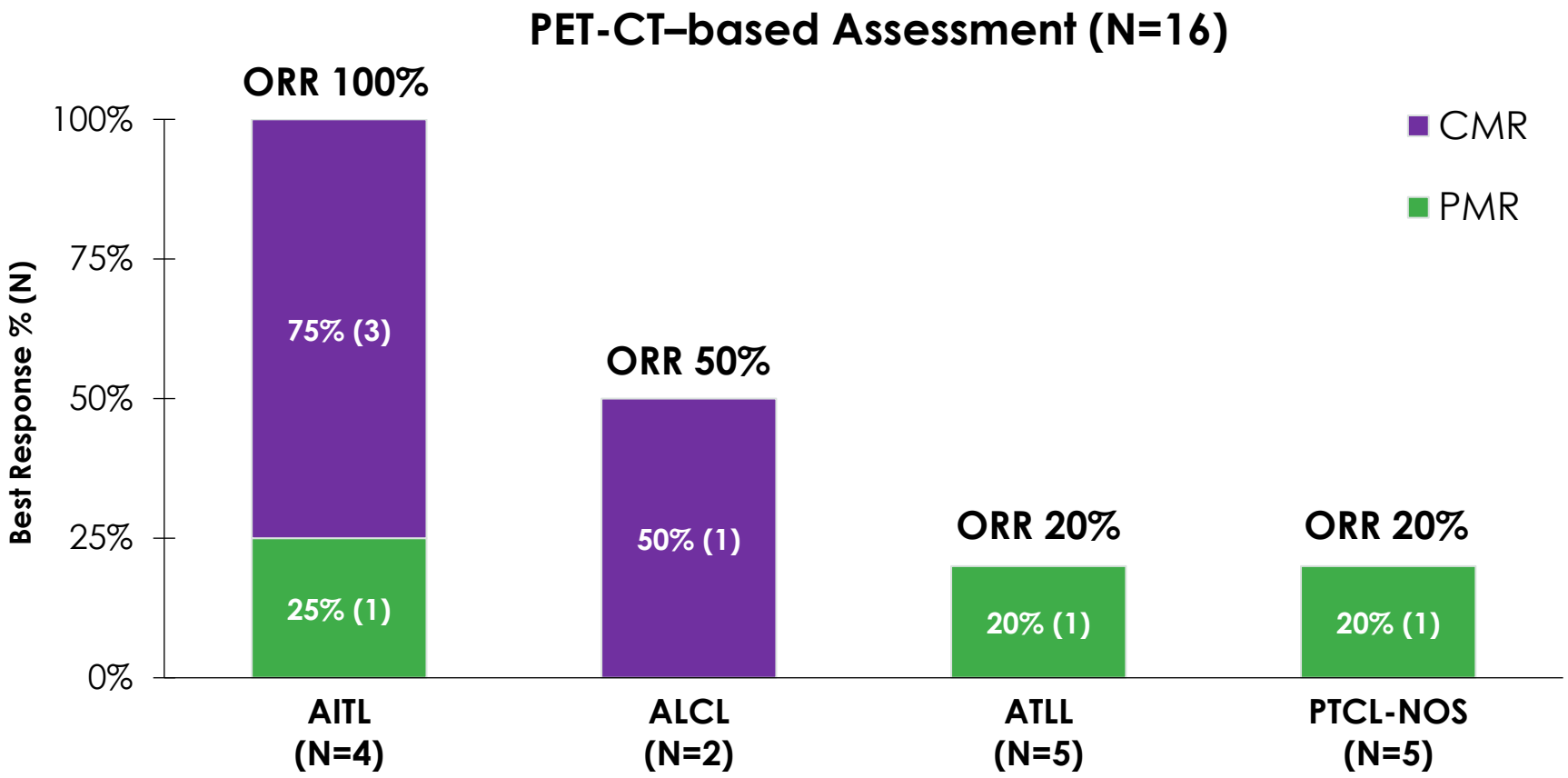
PET-CT–based response assessments: CMR = Complete Metabolic Response, PMR = Partial Metabolic Response, SD = Stable Disease, PMD = Progressive Metabolic Disease.
CT–based response assessments: CR = Complete Response, PR = Partial Response, SD = Stable Disease, PD = Progressive Disease.

NHL, non-Hodgkin lymphoma; ORR, overall response rate; PTCL, peripheral T-cell lymphoma.

Data cutoff: 10/11/24

Best Response by PTCL Subtype*

Response Rate of 44% Achieved in Difficult-to-treat PTCL Patient Population



- Cemsidomide monotherapy produced responses in all four PTCL subtypes evaluated
- All AITL patients (4/4) experienced a metabolic response

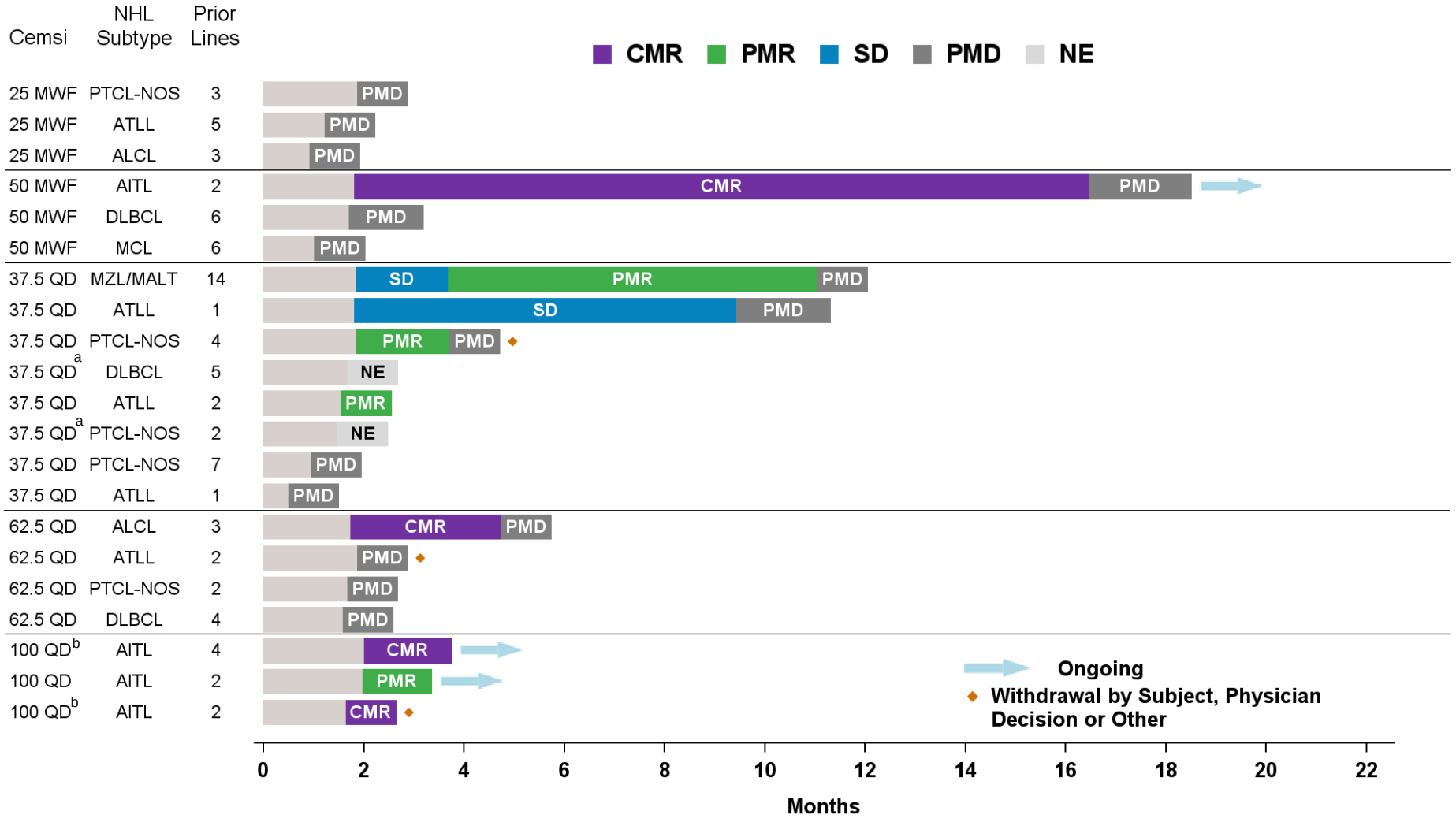
* Investigator assessed response; 2 patients were evaluated based on CT scan and were PD but not evaluable based on PET-CT, both patients are included as PMD for PET-CT based assessment; 2 additional patients came off study prior to follow up scans and were not considered efficacy evaluable.

AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large cell lymphoma; ATLL, adult T-cell lymphoma; CMR, complete metabolic response; ORR, overall response rate; PMR, partial metabolic response; PTCL, peripheral T-cell lymphoma; PTCL-NOS, peripheral T-cell lymphoma not-otherwise specified.

Data cutoff: 10/11/24

Swimmer Plot: Exposure Duration and Clinical Responses

Responses Were Observed Across a Broad Range of Doses



[a] Both patients were not evaluable based on PET-CT but were considered progressive disease due to CT scan.
[b] Both patients dose reduced to 62.5 ug following DLTs.

Data cutoff: 10/11/24

Patient Case Study – Background

- Age and Disease Type: 72 y/o woman with PTCL-TFH/AITL
- Past Medical History: gastroesophageal reflux disease, hypertension and irritable bowel syndrome
- Initial diagnosis: 2020
- Initial treatment: AZA-CHOP (on protocol) + HDT (BEAM) -ASCT 2020

ASCT, autologous stem cell transplant; GERD, gastro esophageal reflux disorder; HTN, hypertension; PTCL-TFH/AITL, Peripheral; T-cell lymphoma – T-follicular Helper/Angioimmunoblastic T-cell lymphoma; PMHX, past medical history; y/o, year old

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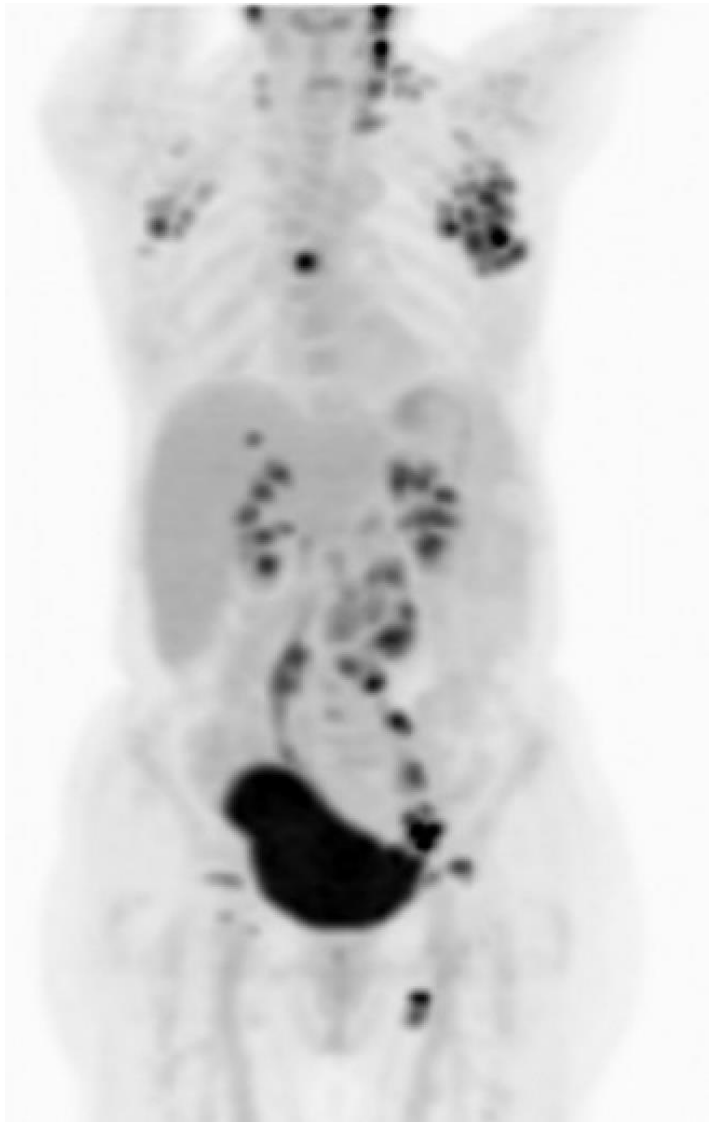
- Relapse: ~30 months later, 2023, PET diffuse LAN



ASCT, autologous stem cell transplant; GERD, gastro esophageal reflux disorder; HTN, hypertension; PET, positron emission tomography; PTCL-TFH/AITL, Peripheral; T-cell lymphoma – T-follicular Helper/Angioimmunoblastic T-cell lymphoma; PMHX, past medical history; y/o, year old

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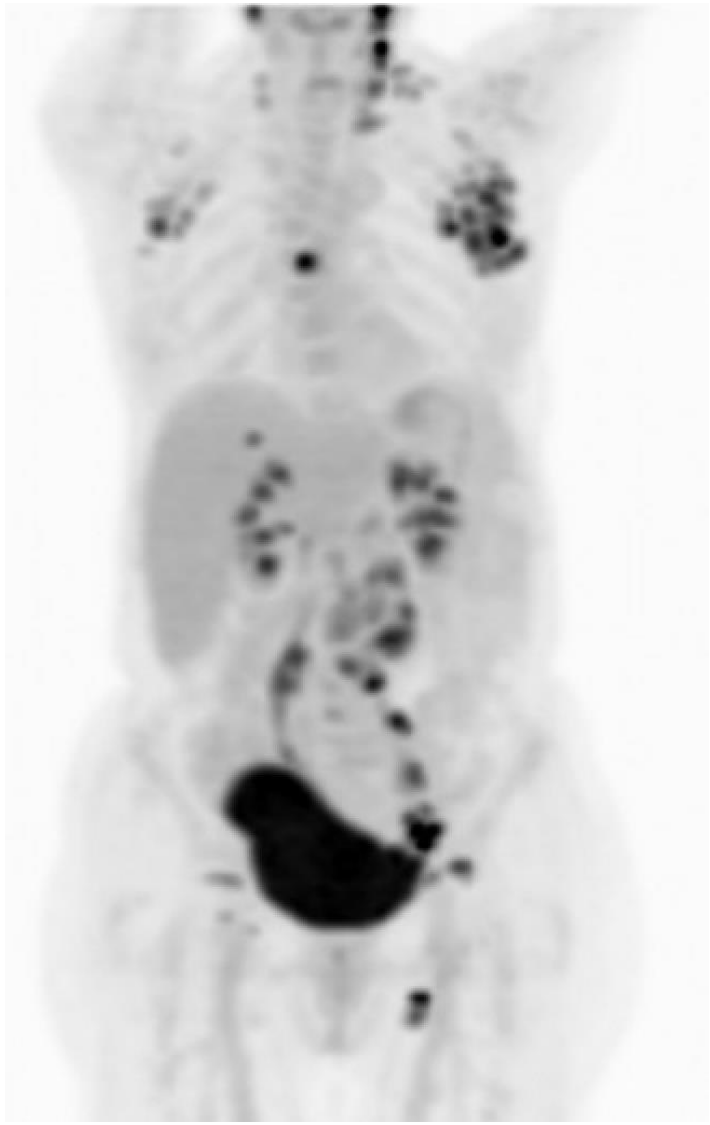
- Relapse: ~30 months later, 2023, PET diffuse LAN
- Biopsy: left inguinal lymph node
  - Abnormal T-cell Population: CD3, CD2, CD4, CD5, ICOS, PD1
  - Do not express: CD7 (lost), CD10, CD23, CD56, CXCL13
  - Pathological Finding: Increased disrupted FDC meshworks



Somatic alterations detected in this sample:

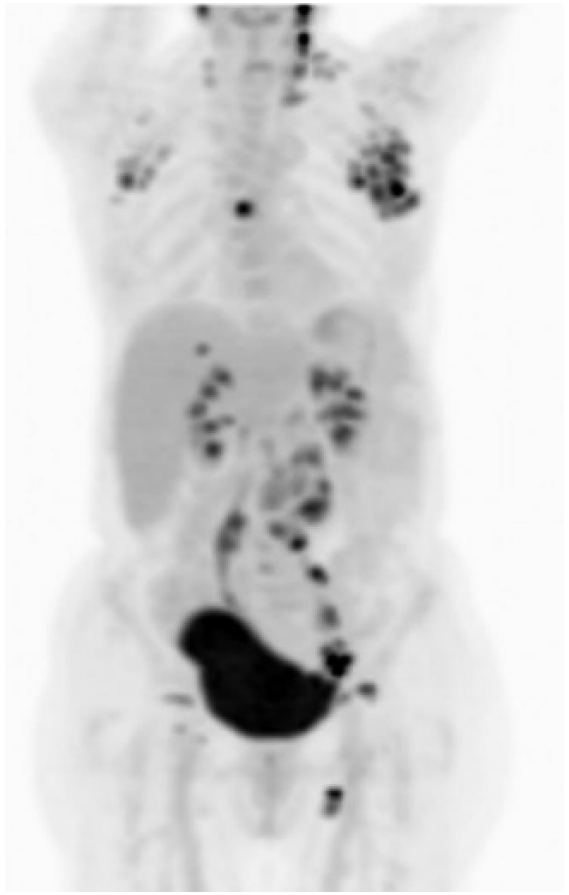
Gene/Chrom.	Type	Alteration	Location	Additional Information		
Mutations						
TET2	Frameshift Deletion	H990Lfs*17 *(c.2969del)*	exon 3	MAF: 32.4%		α
TET2	Splicing Mutation	X1319_splice *(c.3955-2A>G)*	exon 8	MAF: 40.6%		α
TNFRSF14	Frameshift Deletion	W7Gfs*14 *(c.19_22del)*	exon 1	MAF: 3.9%		
SOCS1	Frameshift Insertion	P83Afs*34 *(c.246dupG)*	exon 2	MAF: 2.6%		
IKZF3	Frameshift Deletion	E171Kfs*4 *(c.507_508del)*	exon 5	MAF: 15.7%		
SOCS1	Missense Mutation	S116R *(c.348C>G)*	exon 2	MAF: 2.0%		a

ASCT, autologous stem cell transplant; FDC, follicular dendritic cell; GERD, gastro esophageal reflux disorder; HTN, hypertension; PET, positron emission tomography; PTCL-TFH/AITL, Peripheral; T-cell lymphoma – T-follicular Helper/Angioimmunoblastic T-cell lymphoma; PMHX, past medical history; y/o, year old

Data cutoff: 10/11/24

Patient Case Study – On Treatment

- Age and Disease Type: 72 y/o woman with PTCL-TFH/AITL – now relapsed
- Treatment History: started oral cemsidomide 50 µg MWF 14 days on and 14 days off in 2023



Baseline

PTCL-TFH/AITL, Peripheral; T-cell lymphoma- T follicular Helper/ Angioimmunoblastic T-cell lymphoma; y/o, year old
Data cutoff: 10/11/24

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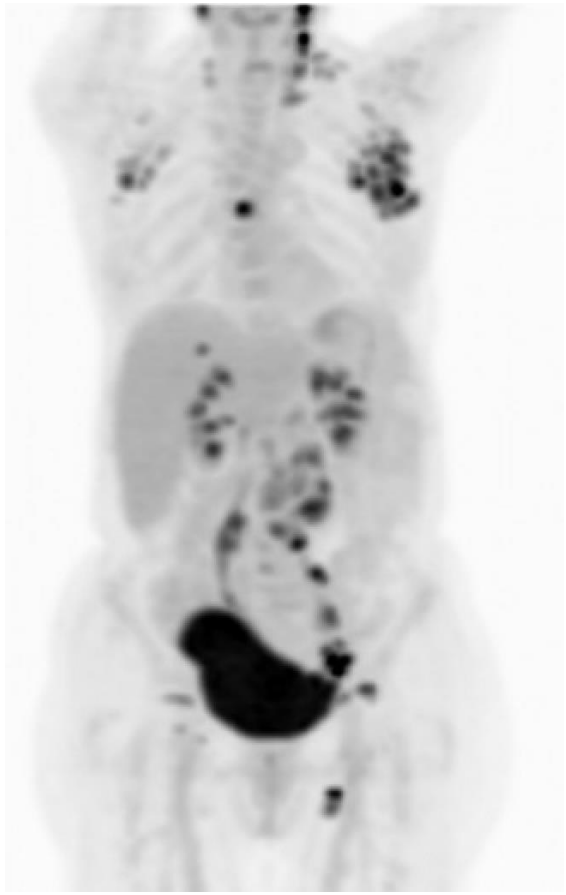
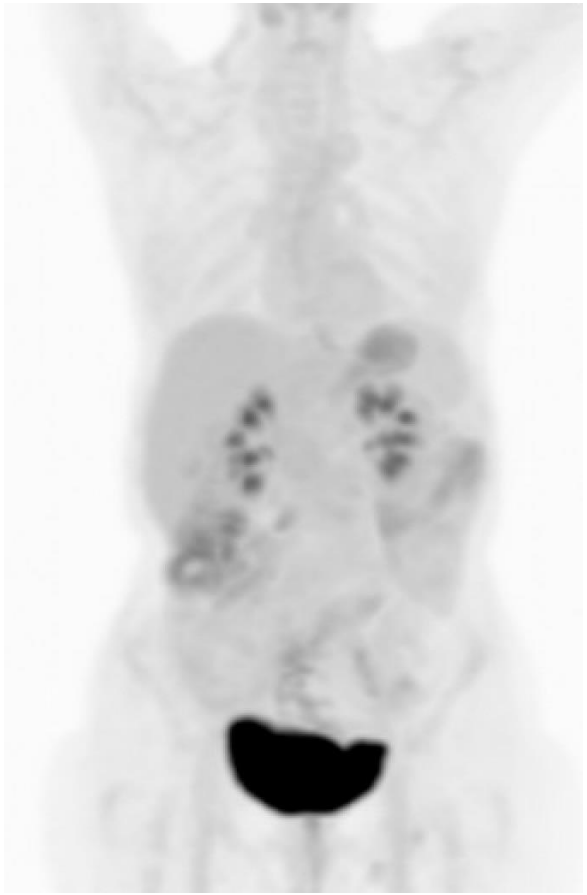


Baseline



Post Cycle 2

PTCL-TFH/AITL, Peripheral; T-cell lymphoma- T follicular Helper/ Angioimmunoblastic T-cell lymphoma; y/o, year old
Data cutoff: 10/11/24

Patient Case Study – On Treatment

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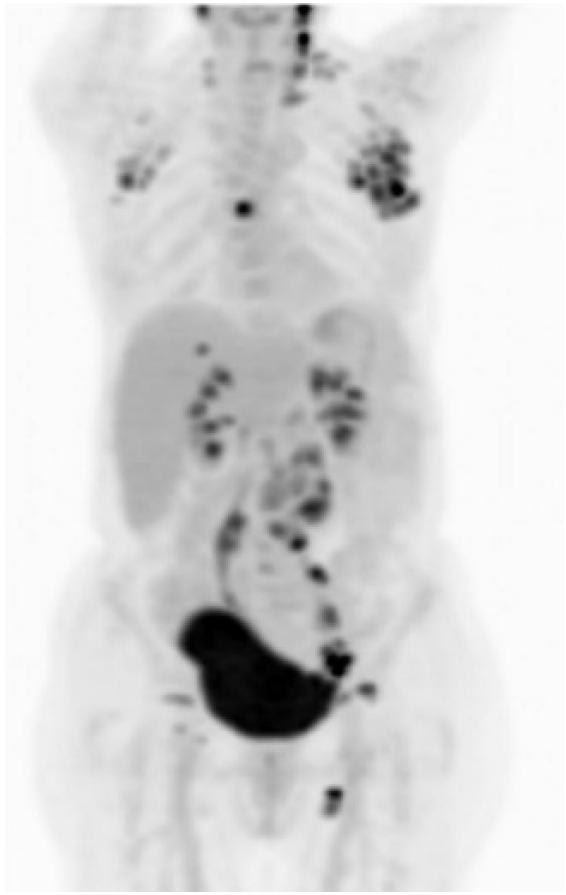
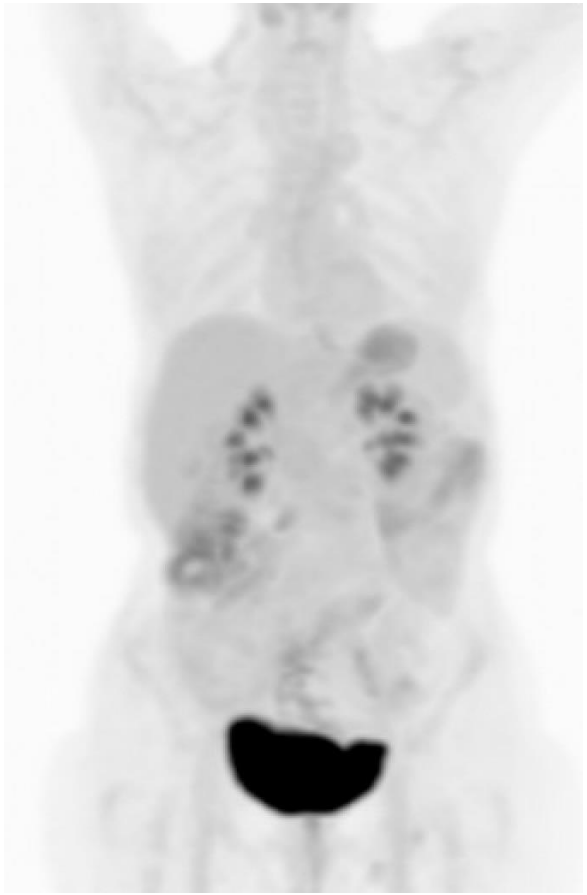
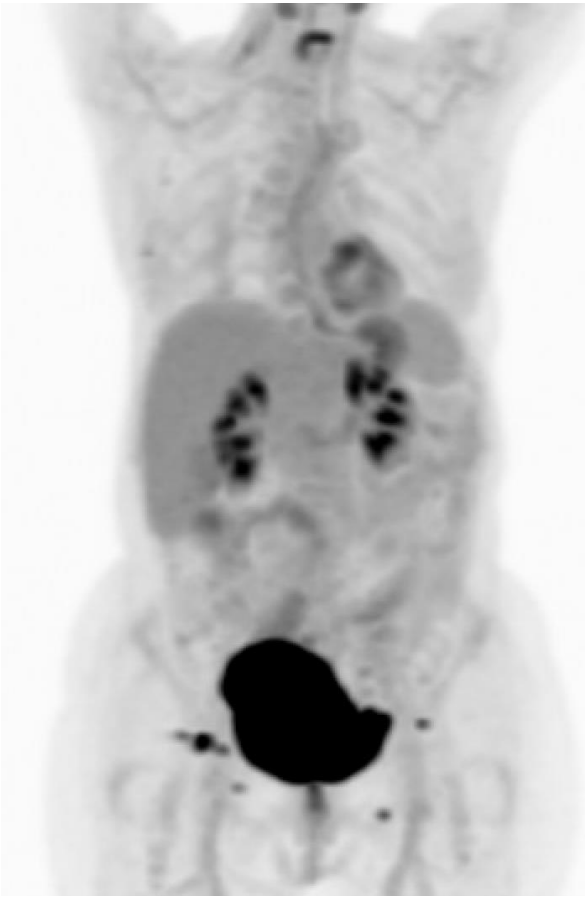


Baseline



Post Cycle 2

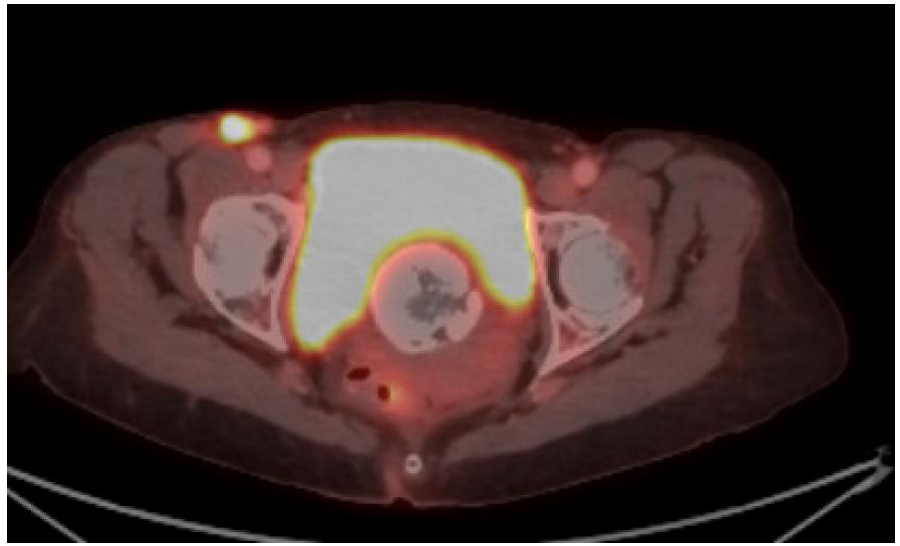


Post Cycle 16

PTCL-TFH/AITL, Peripheral; T-cell lymphoma- T follicular Helper/ Angioimmunoblastic T-cell lymphoma; y/o, year old
Data cutoff: 10/11/24

Patient Case Study – On Treatment

- Biopsy: right inguinal lymph node
- Diagnosis: right inguinal lymph node:
  - Partial involvement by previously diagnosed peripheral T-cell lymphoma with T-follicular helper (TFH) phenotype
- The immunophenotype of the abnormal T-cell population is similar to previous and in keeping with T-follicular Helper origin
- Abnormal T-cell population represents 7.6% of white blood count



Post Cycle 16

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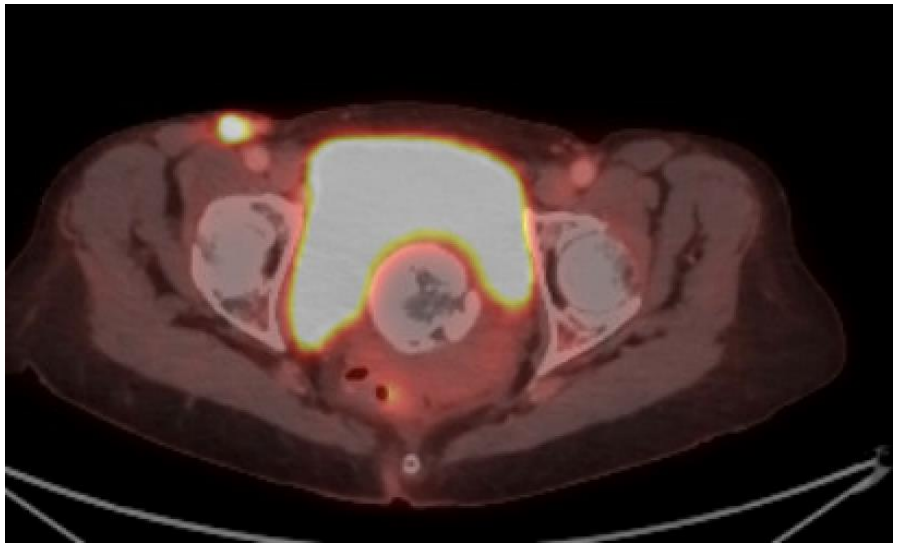
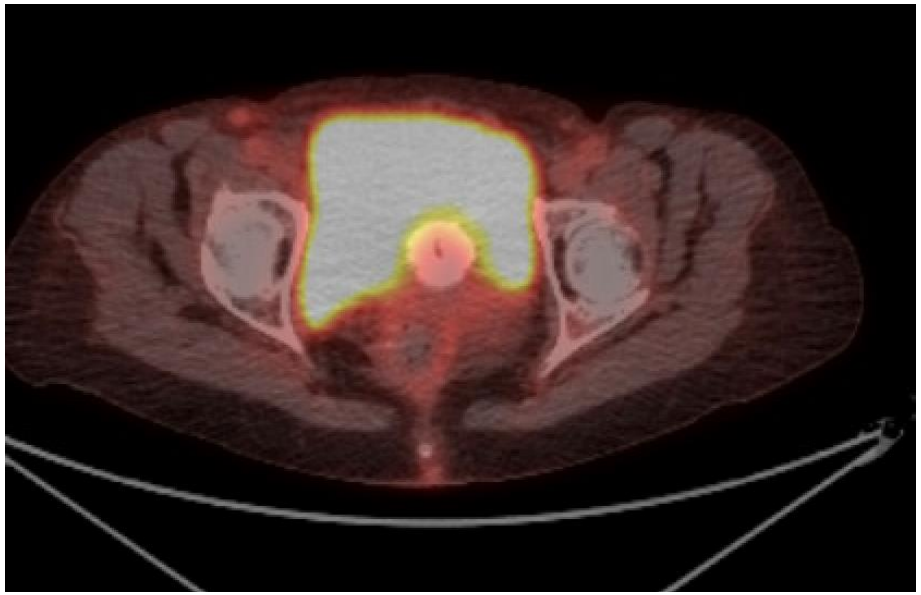


Post Cycle 16



Post Cycle 18

Data cutoff: 10/11/24

Conclusions

- Cemsidomide displays a differentiated PK profile with an approximately 2-day half life and induces rapid and potent degradation of IKZF1/3

- Cemsidomide was well tolerated with additional dose finding ongoing
  - 2 DLTs were observed at 100 µg (grade 4 thrombocytopenia) with enrollment currently ongoing at 75 µg
    - Per BLRM, maximum tolerated dose not yet exceeded
  - Grade 3/4 neutropenia cases were manageable with no cases resulting in discontinuation

- Cemsidomide as a single agent demonstrated compelling anti-lymphoma activity across a broad range of doses in the subset of patients enrolled with PTCL
  - Responses were observed at multiple dose levels tested, suggesting a wide therapeutic index
  - 44% ORR and 25% CR rates were observed in PTCL

- Cemsidomide is well suited for further development in earlier lines of treatment and in combination with other NHL agents

BLRM, Bayesian logistic regression model; CR, complete response; DLTs, dose limiting toxicities; IKZF 1/3, Ikaros zinc finger protein 1/3; NHL, non-Hodgkin lymphoma; ORR, overall response rate; PK, pharmacokinetics; PTCL, peripheral T-cell lymphoma

Data cutoff: 10/11/24

Acknowledgements

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- This study is sponsored by C4 Therapeutics, Inc.
- All authors contributed to and approved the presentation