ASCO 2020 Abstract #3030

Ongoing, First-in-human, Phase 1 Dose Escalation Study of the Investigational CD47-blocker TTI-622 in Patients with Advanced Relapsed or Refractory Lymphoma

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BACKGROUND

CD47 is an immune checkpoint that binds signal regulatory protein alpha (SIRPα) and delivers a "do not eat" signal to suppress macrophage phagocytosis (Figure 1). Tumor cells, including B- and T-cell lymphomas, frequently over-express CD47 to escape immune surveillance. TTI-622 is a fusion protein consisting of the CD47-binding domain of human SIRPα linked to the Fc region of human IgG4. It is designed to enhance phagocytosis and anti-tumor activity by preventing CD47 from delivering its inhibitory signal. Importantly, preclinical data indicate TTI-622 does not bind to human red blood cells (RBCs) (Figure 2).

Figure 1. CD47 Pathway in Cancer and TTI-622 Structure

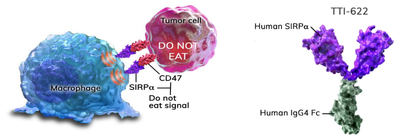
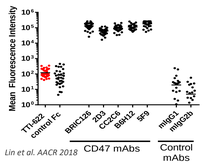


Figure 2. Binding of TTI-622 or CD47 mAb on RBCs

Unlike anti-CD47 antibodies, TTI-622 binds minimally to human RBCs.



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Binding of TTI-622 or anti-CD47 monoclonal antibodies (mAbs) to fresh human RBCs at saturating concentrations is shown. Data were analyzed by flow cytometry and the graph represents mean fluorescence intensity for 43 human donors.

Study Design

Phase 1a of a multicenter, Phase 1 study of a CD47 blocker, TTI-622 (NCT03530683) in patients with relapsed/refractory (R/R) lymphoma to characterize:

- safety, maximum tolerated dose (MTD) and Phase 1b starting dose,
- pharmacokinetics,
- pharmacodynamics, and
- preliminary antitumor activity.

Eligible patients were adults with R/R lymphoma who had previously progressed on at least 2 prior standard anticancer therapies or for whom no other approved therapy exists.

Dose Escalation was based on a modified 3+3 scheme escalating weekly doses through preplanned dose levels (0.05 - 8 mg/kg). The dose limiting toxicity (DLT) period was 3 weeks. During the first 2 weeks, patients received a lower 'run in' dose followed by the higher planned dose at week 3. For example, a low dose of 0.05 mg/kg was received in Weeks 1 and 2 followed by 0.1 mg/kg in Week 3. Thereafter, dosing continued at the higher dose (0.1 mg/kg in this example) administered once per week.

PK and PD assessments included serial PK sampling in Weeks 1, 6, and 12 with pre-infusion trough samples obtained before all other doses. Samples for PD assessments were obtained in Weeks 1, 2, 6, 7, 12, and 13.

Response assessments were performed by the investigator per Lugano criteria at screening, the end of every 2 cycles up to Cycle 6, every 3 cycles up to Cycle 24, then every 6 cycles, and finally at the end of treatment. Each cycle was 28 days.

RESULTS

Patients

- Presented in this poster are data (data cut-off: April 24, 2020) from 19 R/R lymphoma patients enrolled to Cohorts 1-5, including patients with DLBCL (n=10), Hodgkin lymphoma (n=5), peripheral T cell lymphoma (n=2), and mantle cell and follicular lymphoma (n=1 each). Data for the most recent patients enrolled in Cohort 6 (see Figure 3) are not included in this poster.
- Median age is 62 (range, 24–86) including 11 males and 8 females.
- Disease stage in all patients is either III (n=3), IV (n=15), or not specified (n=1).
- All patients received prior systemic therapy; 6 patients received prior cellular therapy: 3 CAR-T and 4 HSCT (Table 1).

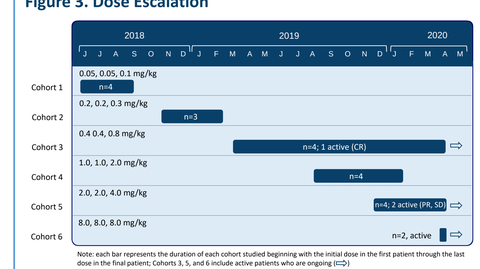
Table 1. Demographic and Baseline Disease Characteristics

Baseline Characteristics	Total n=19
Median Age, years (min-max)	62 (24-86)
Male, n (%)	11 (58)
ECOG PS 0-1, n (%)	19 (100)
Primary Diagnosis, n (%)	
Diffuse Large B Cell Lymphoma	10 (53)
Hodgkin Lymphoma	5 (26)
Peripheral T Cell Lymphoma	2 (11)
Mantle Cell Lymphoma	1 (05)
Follicular Lymphoma	1 (05)
Overall Stage at Study Entry, n (%)	
III	3 (16)
IV	15 (79)
NS	1 (05)
Prior Therapy, n (%)	
Systemic	19 (100)
HSCT	4 (21)
CAR-T	3 (16)
Median Lines of Prior Treatment, (min-max)	
Systemic	3 (1-9)

Dose Escalation

- At the time of data cut-off, 5 dose levels have been tested and determined safe; data from these first 5 cohorts are included in this poster.
- Cohorts 1-5 were tested by administering 2 initial lower doses followed by a 3rd higher dose as described in Figure 3 below. Weekly dosing then continued with the higher dose.
- Starting with Cohort 6, all doses are now administered at a flat dose without the lower initial weekly doses.
- Of the 21 patients enrolled to date, 5 continue to receive treatment in Cohorts 3, 5, and 6 (see Figure 3).

Figure 3. Dose Escalation



Note: each bar represents the duration of each cohort studied beginning with the initial dose in the first patient through the last dose in the final patient; Cohorts 3, 5, and 6 include active patients who are ongoing (⇨)
Results for 19 patients in Cohorts 1-5 included in this poster

Dose Exposure

- Treatment exposure through Cohort 5 to date:
  - Median cumulative dose received: 285 mg/kg (range, 6-5301).
  - Median number of doses received: 6 (range, 2-46).

Related Adverse Events

- Majority of AEs in Cohorts 1-5 have been Grade 1-2 (Table 2).
- No related Grade ≥3 anemia or thrombocytopenia observed to date.
- Related Grade ≥3 adverse events have been limited to neutropenia occurring in 2 patients; 1 event each of Grade 3 and 4 intensity, each resolving within 1 and 4 days, respectively.
- There have been no related SAEs or DLTs to date.
- Dosing actions required due to related adverse events have included interruptions in 2 patients due to:
  - Pruritus/rash.
  - Neutropenia (resolved within 4 days).

Table 2. Adverse Events Occurring in ≥ 2 Patients

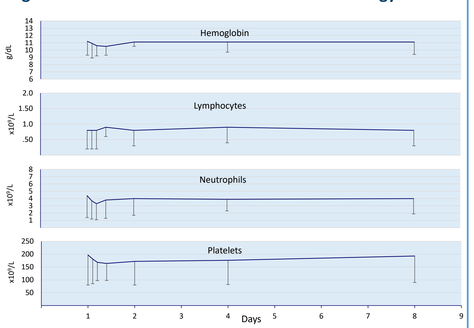
Adverse Events n (%)	Related Gr 1-2	Related Gr 3-4	All Gr 1-2	All Gr 3-4	Total n=19
Constipation			6 (32)		6 (32)
Nausea	2 (11)		4 (21)		6 (32)
Abdominal pain	2 (11)		1 (5)		3 (16)
Back pain	1 (5)		2 (11)		3 (16)
Fatigue	2 (11)		1 (5)		3 (16)
Insomnia			3 (16)		3 (16)
Leukocytosis	1 (5)		2 (11)		3 (16)
Pain			3 (16)		3 (16)
Pruritus	2 (11)		1 (5)		3 (16)
Thrombocytopenia	1 (5)		2 (11)	1 (5)	3 (16)
Creatinine increased			2 (11)		2 (11)
Dyspnea	1 (5)			1 (5)	2 (11)
Dysuria			2 (11)		2 (11)
Fall			2 (11)		2 (11)
Headache	1 (5)		1 (5)		2 (11)
Hypotension			2 (11)	1 (5)	2 (11)
Neutropenia		2 (11)			2 (11)
Night sweats			2 (11)		2 (11)

Additional related adverse events occurring in 1 patient each included ALP increased, anemia, LDH increased and rash; all Gr 1-2 intensity

Week 1 Laboratory Results: Hematology

- Moderate platelet decrease occurred immediately following dosing but recovered quickly to baseline levels.
- Similar transient decreases followed by prompt recovery are noted with hemoglobin and other parameters (Figure 4).

Figure 4. Week 1 Median and Minimum Hematology Profiles

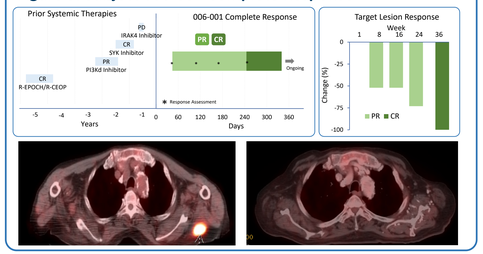


Note: hematology profiles include Cohorts 1-5, all patients combined

Efficacy: Objective Responses in 2 Subjects

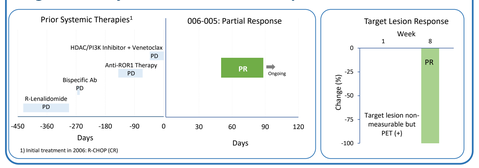
- Subject 006-001: 78 y/o male, non-GCB DLBCL, 0.8 mg/kg.
  - 4 Prior lines of therapy: R-EPOCH/R-CEOP, PI3Kd inhibitor, Syk inhibitor, and IRAK4 inhibitor (Figure 5).
  - Achieved PR Weeks 8, 16, 24; CR Week 36 by PET/CT.

Figure 5. Subject 006-001 Complete Response



- Subject 006-005: 81 y/o female, GCB DLBCL, 4.0 mg/kg.
  - 5 Prior lines of therapy: R-CHOP, R-lenalidomide, Bispecific Ab, anti ROR1 therapy, HDAC/PI3K inhibitor + venetoclax.
  - PR Week 8 with decrease of cavitary lymph node to non-measurable by PET/CT but with residual PET avidity (Figure 6).

Figure 6. Subject 006-005 Partial Response



Pharmacokinetics

- Dose-dependent increased exposure following single and repeat infusions (Figure 7).
- Following a single infusion, preliminary data suggests greater than dose proportional increase in exposure at a dose level of ≥ 1mg/kg.
- Following repeat infusions, exposure appears to be dose proportional (0.1 to 0.8 mg/kg) and T1/2 is approximately 4-5 days (Tables 3 and 4).

Figure 7. TTI-622 Mean Concentration Profiles Following IV Infusion

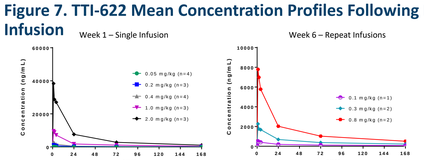


Table 3. Week 1 Mean PK Parameters

TTI-622 Week 1 – Mean PK Parameters				
Dose Cohort	Dose (mg/kg)	Cmax (ng/mL) Mean ± SD	AUC0-168 (ng*h/mL) Mean ± SD	Thalf (hrs) Mean ± SD
1	0.05	108 ± 21 (n=4)	320 ± 74 (n=4)^	ND
2	0.2	1095 ± 250 (n=3)	29759 ± 9954 (n=3)	64 ± 36 (n=3)
3	0.4	2690 ± 727 (n=4)	66729 ± 15109 (n=4)	73 ± 8 (n=4)
4	1	9808 ± 2983 (n=3)	251342 ± 163162 (n=3)	65 ± 21 (n=3)
5	2	38376 ± 20893 (n=3)	945736 ± 436257 (n=3)	58 ± 2 (n=2)

^AUCt (dosing to last measurable concentration) presented
ND =not determined, samples in terminal phase were BLQ

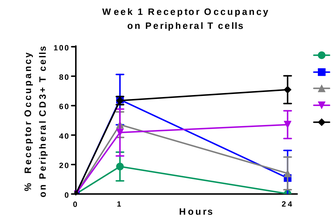
Table 4. Week 6 Mean PK Parameters

TTI-622 Week 6 – Mean PK Parameters				
Dose Cohort	Dose (mg/kg)	Cmax (ng/mL) Mean ± SD	AUC0-168 (ng*h/mL) Mean ± SD	Thalf (hrs) Mean ± SD
1	0.1	508 (n=1)	24279 (n=1)	128 (n=1)
2	0.3	2265 ± 357 (n=2)	82487 ± 27107 (n=2)	90 ± 7 (n=2)
3	0.8	7793 ± 2596 (n=2)	254807 ± 60343 (n=2)	87 ± 0.5 (n=2)

Translational Assessments

- Receptor occupancy (RO) of CD47 on peripheral T cells was determined using a flow cytometry-based competitive binding assay.
- RO at end of infusion was consistently above 60% at 2 mg/kg.
- RO at 24 hrs post dose was more sustained at higher dose. levels (1 mg/kg and 2 mg/kg) compared to lower dose levels (Figure 8).

Figure 8. Receptor Occupancy



Negative RO values due to changing CD47 levels are reported as 0
Mean +/- SD of each cohort is shown

CONCLUSIONS

- TTI-622 administered weekly IV is well tolerated at doses up to 4 mg/kg. Related anemia or thrombocytopenia of Grade ≥3 intensity have not been observed.
- Preliminary data indicate dose-dependent increases in PK exposure.
- End of infusion RO at 2 mg/kg was above 60%; sustained RO at 24 hrs was observed at dose levels of 1 mg/kg and above.
- Objective responses in 2 DLBCL patients occurred within 8 weeks and include both a PR and a CR, both ongoing through Days 90 and 340, respectively.
- Further dose escalation is ongoing.

Disclosures: KP has consulting/advisory relationships with Celgene, Genentech, BeiGene, Juno Therapeutics, Pharmacyclics, AstraZeneca; speakers' bureau relationship with Genentech, Celgene, Pharmacyclics/Janssen; and institutional research funding from Kite/Gilead, AstraZeneca, Pharmacyclics, Celgene, MEI Pharma, Curis, Takeda, Xencor, BMS, Trillium, Roche/Genentech, Aptevo Therapeutics, Fate Therapeutics, Sunesis Pharmaceuticals; BD has consulting/advisory board relationships with Abbvie, Astra Zeneca, Celgene, TG Therapeutics, Morphosys, Symbio, Epizyme, Parexel, Karyopharm, Janssen, Pharmacyclics, Reddy; and institutional research funding from Trillium, Roche-Genentech, Celgene, Abbvie, TG Therapeutics, AstraZeneca, Epizyme, Kite/Gilead, Portola; JZ has a steering committee relationship with Takeda; institutional research funding from Celgene, BMS; and consulting relationships with Prothena, Caelum, Intellia; AL has institutional research funding from BMS, Trillium, Genentech, Janssen; advisory/honoraria relationships with Boehringer Ingelheim, Genmab; and receives royalties from Serametrix; ES receives institutional research funding from Karyopharm; TC, GL, YS are employees of Trillium; GvK, MM, SI, and RR have no disclosures.

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Acknowledgments: This study was funded by Trillium Therapeutics Inc.; the authors would like to thank all patients and their families, and all investigators for their valuable contributions to this study.

Table 1: Demographic & Baseline Disease Characteristics

- Cohorts 1-5 were tested in 19 patients with relapsed or refractory lymphoma .
- The most common tumor types were DLBCL (n=10) and HL (n=5).
- The median age was 62 (range, 24–86); 11 males and 8 females were included.
- Disease stage was predominantly Stage IV (n=15).
- All patients had received prior systemic therapy; 6 had received prior cellular therapy including 3 CAR-T and 4 HSCT.

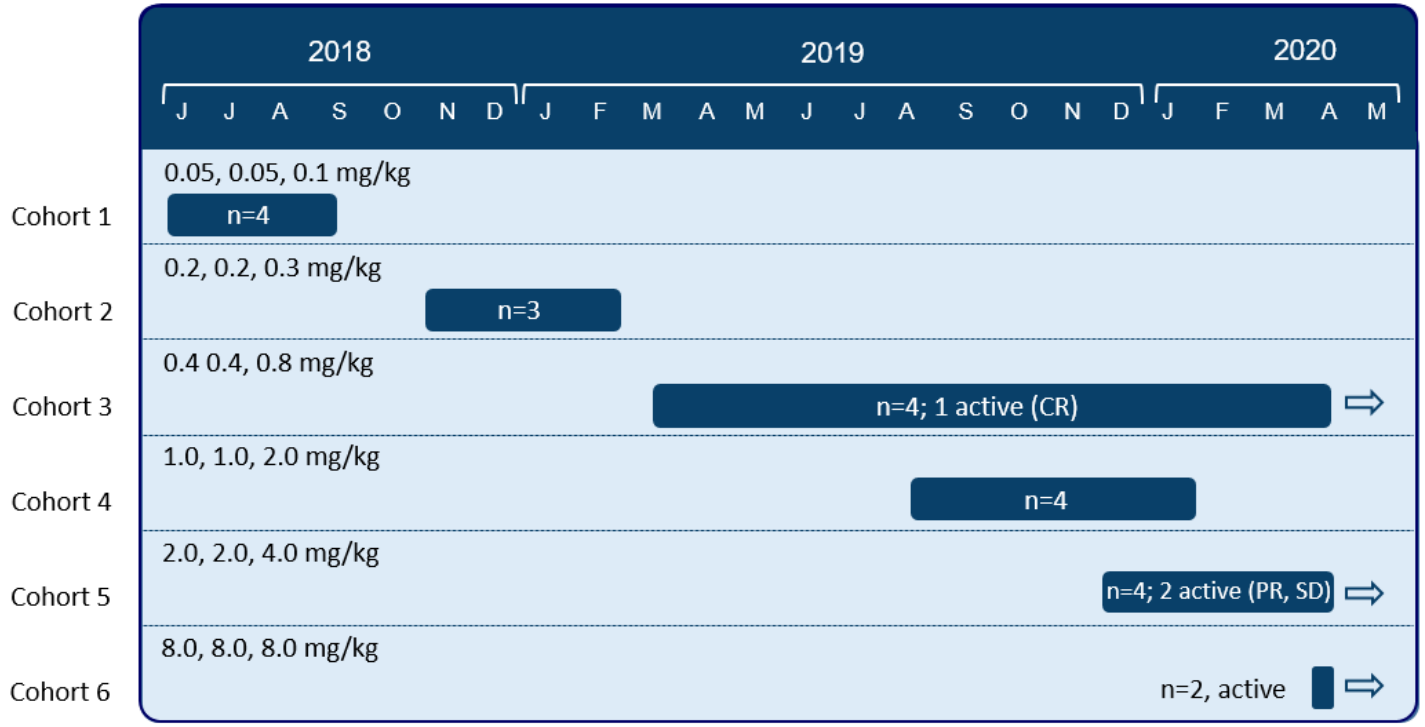
Poster Table 1

Baseline Characteristics	Total n=19
Median Age, years (min-max)	62 (24-86)
Male, n (%)	11 (58)
ECOG PS 0-1, n (%)	19 (100)
Primary Diagnosis, n (%)	
Diffuse Large B Cell Lymphoma	10 (53)
Hodgkin Lymphoma	5 (26)
Peripheral T Cell Lymphoma	2 (11)
Mantle Cell Lymphoma	1 (05)
Follicular Lymphoma	1 (05)
Overall Stage at Study Entry, n (%)	
III	3 (16)
IV	15 (79)
NS	1 (05)
Prior Therapy, n (%)	
Systemic	19 (100)
HSCT	4 (21)
CAR-T	3 (16)
Median Lines of Prior Treatment, (min-max)	
Systemic	3 (1-9)

Figure 3: Study Status

- Cohorts 1 through 5 have completed testing of doses ranging 0.05-4.0 mg/kg in 19 patients
- Cohorts 3, 5 and 6 continue to accrue safety information in 5 active patients
- Starting with Cohort 6, patients now receive flat TTI-622 dosing without the initial lower doses in Weeks 1 and 2

Poster Figure 3



Note: each bar represents the duration of each cohort studied beginning with the initial dose in the first patient through the last dose in the final patient; Cohorts 3, 5, and 6 include active patients who are ongoing (⇨)
Results for 19 patients in Cohorts 1-5 included in this poster

Table 2: All & Related Adverse Events in ≥ 2 Patients

- The majority of adverse events in Cohorts 1-5 have been Grade 1-2
- No related Grade ≥3 anemia or thrombocytopenia observed to date
- Related Grade ≥3 adverse events have been limited to neutropenia occurring in 2 patients; 1 event each of Grade 3 and 4 intensity, each resolving within 1 and 4 days, respectively
- There have been no related SAEs or DLTs to date

Poster Table 2

Adverse Events n (%)	Related		All		Total n=19
	Gr 1-2	Gr 3-4	Gr 1-2	Gr 3-4	
Constipation			6 (32)		6 (32)
Nausea	2 (11)		4 (21)		6 (32)
Abdominal pain	2 (11)		1 (5)		3 (16)
Back pain	1 (5)		2 (11)		3 (16)
Fatigue	2 (11)		1 (5)		3 (16)
Insomnia			3 (16)		3 (16)
Leukocytosis	1 (5)		2 (11)		3 (16)
Pain			3 (16)		3 (16)
Pruritus	2 (11)		1 (5)		3 (16)
Thrombocytopenia	1 (5)		2 (11)	1 (5)	3 (16)
Creatinine increased			2 (11)		2 (11)
Dyspnea	1 (5)			1 (5)	2 (11)
Dysuria			2 (11)		2 (11)
Fall			2 (11)		2 (11)
Headache	1 (5)		1 (5)		2 (11)
Hypotension			2 (11)	1 (5)	2 (11)
Neutropenia		2 (11)			2 (11)
Night sweats			2 (11)		2 (11)

Additional related adverse events occurring in 1 patient each included ALP increased, anemia, LDH increased and rash; all Gr 1-2 intensity

Figure 4: Week 1 Hematology Profiles
(Median and Minimum values)

- To date in Cohorts 1-5, moderate and manageable platelet decreases have occurred immediately following dosing and have recovered quickly to baseline levels
- Similar transient decreases followed by prompt recovery have been observed with hemoglobin and other parameters

Poster Figure 4

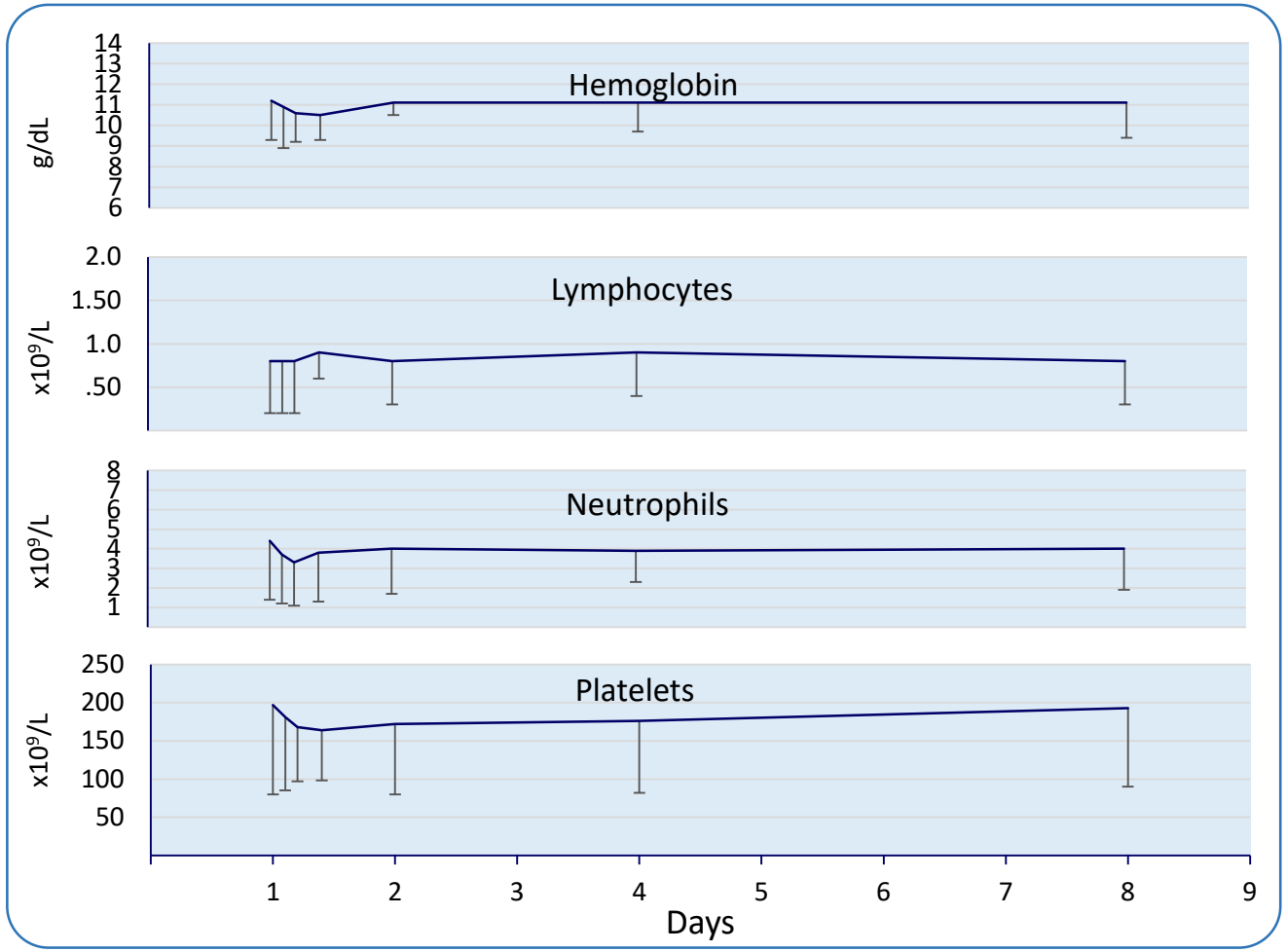


Figure 5: Subject 006-001 Complete Response

- 78 y/o male with non-GCB DLBCL
- Prior Lines of therapy:
  - *R-EPOCH/R-CEOP,*
  - *PI3Kd inhibitor,*
  - *Syk inhibitor,*
  - *IRAK4 inhibitor*
- Dose 0.8 mg/kg
- Achieved PR Weeks 8, 16, 24
- Achieved CR Week 36 by PET/CT
- Response ongoing for ~ 1 year

Poster Figure 5

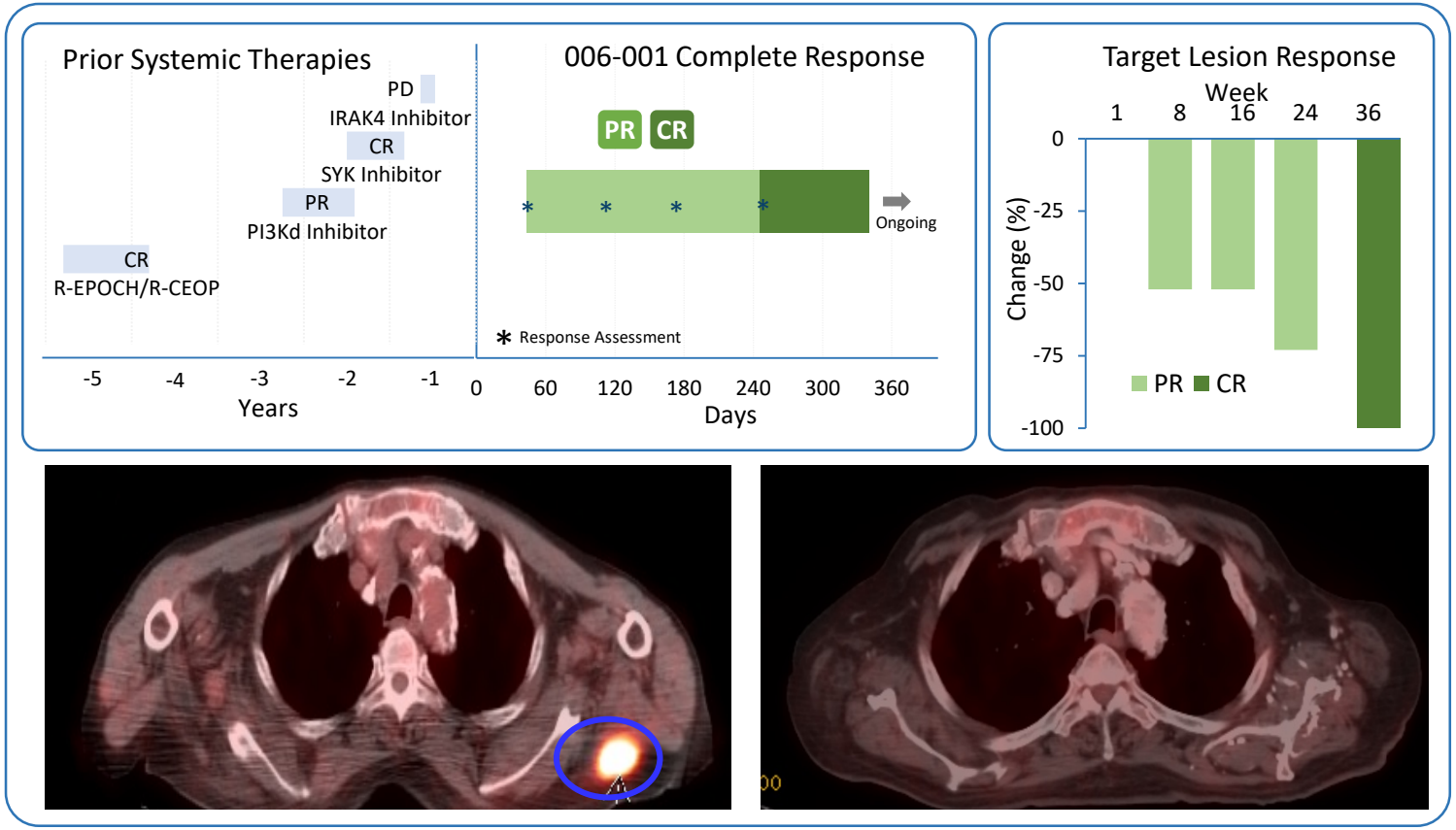


Figure 6: Subject 006-005 Partial Response

- 81 y/o female with GCB DLBCL
- No response to recent prior lines of therapy:
  - *R-CHOP (2006)*
  - *R-Lenalidomide*
  - *Bispecific Antibody*
  - *Anti-ROR1 Therapy*
  - *HDAC/PI3K Inhibitor + venetoclax*
- Dose 4.0 mg/kg
- Achieved PR Week 8
- Response ongoing for ~ 4 months

Poster Figure 6

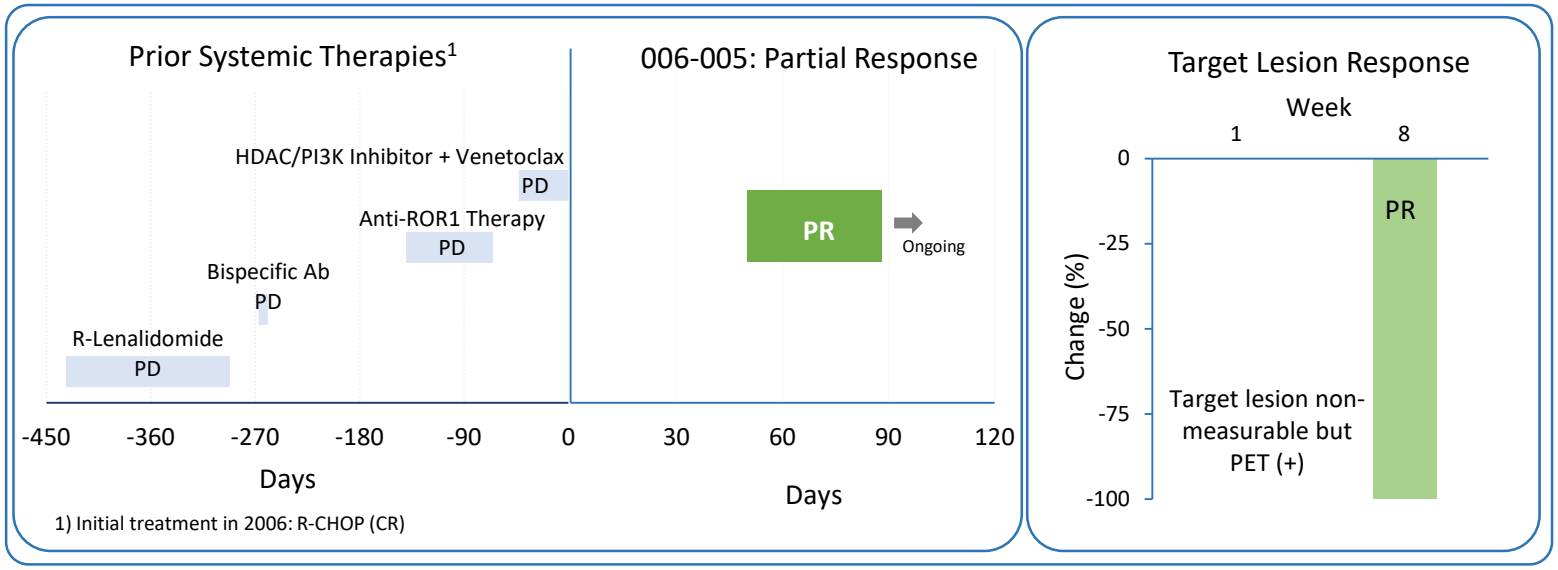
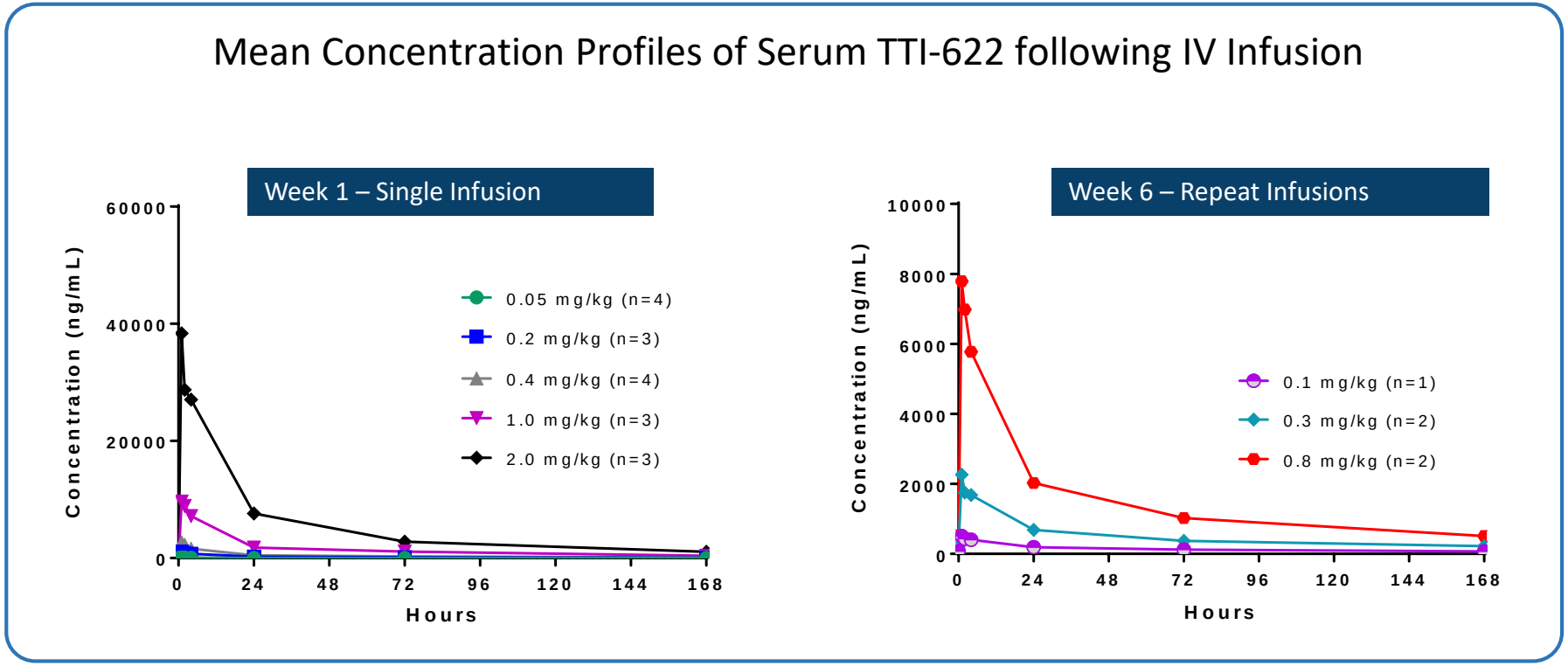


Figure 7: Dose Dependent Serum Concentration Profiles

Dose-dependent increases in TTI-622 serum concentrations following single and repeated infusions

Poster Figure 7



Tables 3 & 4: Week 1 and 6 Mean PK Parameters

- Following a single infusion, preliminary data suggests greater than dose proportional increase in exposure at dose levels ≥ 1 mg/kg.
- Following repeat infusions of 0.1 - 0.8 mg/kg, exposure appears to be dose proportional and T1/2 is approximately 4-5 days.

Tables 3 & 4: Week 1 and Week 6 Mean PK Parameters

		TTI-622 Mean PK Parameters			
Week	Dose Cohort (n)	Dose (mg/kg)	Cmax (ng/mL) Mean ± SD	AUC0-168 (ng*h/mL) Mean ± SD	Thalf (hrs) Mean ± SD
Week 1	1 (n=4)	0.05	108 ± 21	320 ± 74^	ND
	2 (n=3)	0.2	1,095 ± 250	29,759 ± 9,954	64 ± 36
	3 (n=4)	0.4	2,690 ± 727	66,729 ± 15,109	73 ± 8
	4 (n=3)	1	9,808 ± 2983	251,342 ± 16,3162	65 ± 21
	5 (n=3)	2	38,376 ± 2,0893	945,736 ± 43,6257	58 ± 2 (n=2)
Week 6	1 (n=1)	0.1	508	24279	128
	2 (n=2)	0.3	2,265 ± 357	82,487 ± 27107	90 ± 7
	3 (n=2)	0.8	7,793 ± 2,596	254,807 ± 60,343	87 ± 0.5

^AUCt (dosing to last measurable concentration) presented.
ND =not determined, samples in terminal phase were BLQ.

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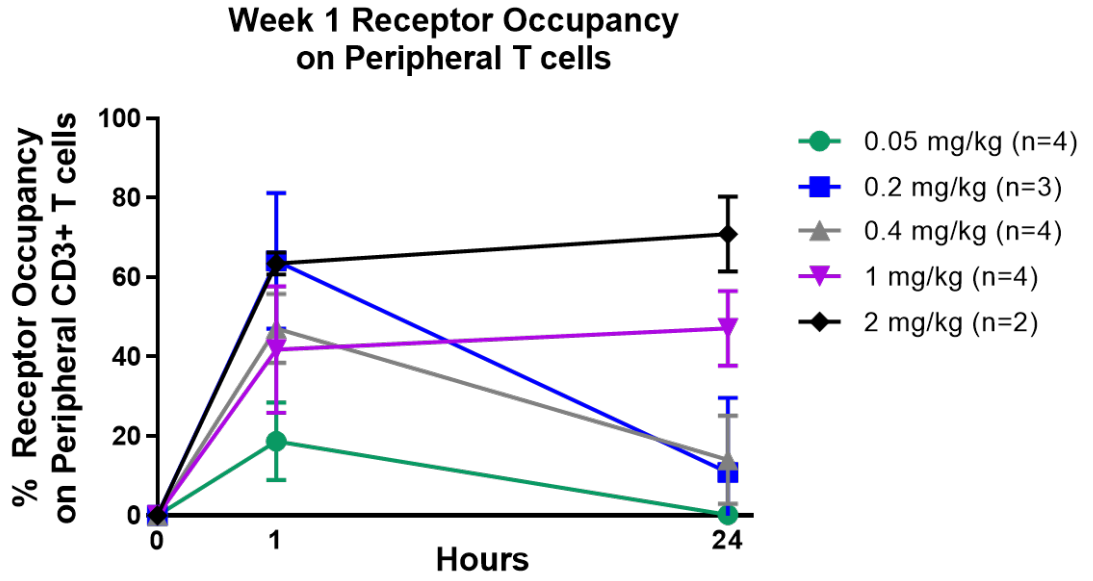
Figure 8: CD47 Receptor Occupancy on Peripheral T Cells

- Receptor Occupancy (RO) of CD47 on peripheral T cells was determined using a flow cytometry-based competitive binding assay.
- RO at end of infusion was consistently above 60% at 2 mg/kg.
- RO at 24 hrs post dose was more sustained at higher dose. levels (1 mg/kg and 2 mg/kg) compared to lower dose levels (Figure 8).

Poster Figure 8



- Negative RO values due to changing CD47 levels are reported as 0.
- Mean +/- SD of each cohort is shown