First-in-Human Phase 1 Study of a Novel Claudin 6 (CLDN6) Targeted Antibody Drug Conjugate (ADC) TORL-1-23

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Introduction

- CLDN6 is a transmembrane protein of tight junctions important for cell-to-cell connectivity
  - Implicated in the initiation, progression, and metastasis of some cancers
  - Expressed at high levels in multiple cancers with little to no expression in normal tissues

Figure 1. CLDN6 Expression in Cancer

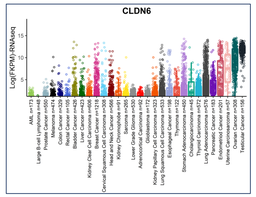


Figure 2. CLDN6 Expression in Normal Tissue

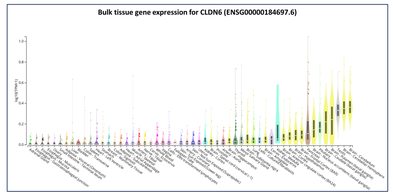
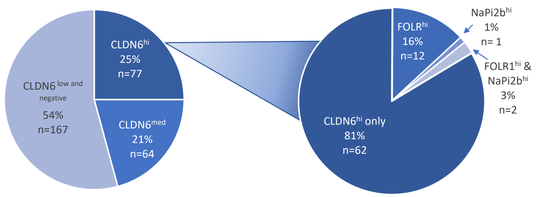


Figure 3. CLDN6 is a Unique Subset of Ovarian Cancer

Total Ovarian Patient Samples (n=308) **CLDN6^{hi} Patient Samples (n=77)**

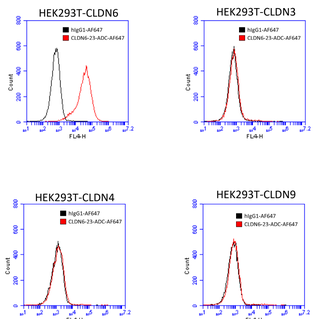


- The top 25% of CLDN6 expression (RNA based) was used as the cut off for high expression and within that population the number of patients that reached the 25% expression threshold for FOLR1a and NaPi2b was assessed and counted.

Pharmacology of TORL-1-23

- TORL-1-23 ADC is a fully humanized IgG1 (TORL-1-23-MAb) linked to MMAE through a cathepsin hydrolysable dipeptide VC linker (vc-MMAE)
- TORL-1-23 binds to CLDN6 with a high affinity and specificity with rapid ADC-CLND6 complex internalization and release of an MMAE payload which disrupts the microtubule network leading to cell cycle arrest and apoptosis. Fc effector function (eg, ADCC) contributes only ~10% to the mechanism of TORL-1-23.
- TORL-1-23 is in development for the treatment of CLDN6-positive cancers including ovarian and non-small cell lung cancer (NSCLC)

Figure 4. Specific Binding of TORL-1-23 to CLDN Family Members



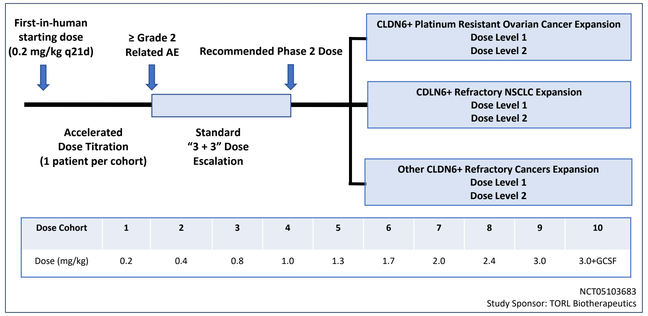
- Binding of TORL-1-23 (5µg/ml) in HEK293T cells artificially overexpressing CLDN3, CLDN4, CLDN6 or CLDN9 by flow cytometry.
- TORL-1-23 exhibited robust, selective binding to only CLDN6-overexpressing cells

Methods

TORL123-001 (TRIO-049) Study Objectives

- Characterize the safety, tolerability, and DLT and determine the MTD and RP2D for TORL-1-23
- Characterize the PK of TORL-1-23 and its breakdown products (MMAE and TORL-1-23 MAB)
- Assess the preliminary antitumor activity of TORL-1-23 in participants with advanced cancer
- Assess the immunogenicity of TORL-1-23

Figure 5. TORL123-001 (TRIO-049) Phase 1 Study Design



NCT05103683
Study Sponsor: TORL Biotherapeutics

Study Design

- Accelerated dose finding design in refractory tumors with expansion cohorts in CLDN6+ cancers
- TORL-1-23 given IV Q3W until disease progression, unacceptable toxicity, or study withdrawal
- Intra-patient dose escalation allowed

Key Study Eligibility

- Dose Finding: Advanced solid tumor unresponsive to standard therapies
- Dose Expansion: CLDN6+ cancers as determined by IHC
  - Platinum-resistant ovarian cancer, refractory NSCLC, other CLDN6+ refractory cancers
- Measurable disease, adequate organ function, ECOG performance status 0-1
- <Grade 2 toxicity from prior therapies at baseline

Dose Limiting Toxicity (DLT) Criteria

- Any death not clearly due to underlying disease or extraneous causes
- ≥Grade 4 hematologic toxicity, ≥Grade 3 febrile neutropenia, ≥Grade 3 thrombocytopenia with bleeding, ≥Grade 3 non-hematologic toxicity with exceptions for gastrointestinal events, changes in electrolytes, liver enzyme changes <14 days, or dose delays >14 days

Table 1. Demographics

Dose, mg/kg	0.2	0.4	0.8	1.0	1.3	1.7	2.0	2.4	3.0	3+GCSF	Total
N	1	1	1	3	3	5[a]	5[a]	6[a]	11[a]	6[a]	42
Age, years (range)	56 -	44 -	57 -	50 (30-69)	55 (48-70)	62 (52-66)	51 (27-65)	66 (59-74)	59 (26-78)	64 (53-74)	57 (26-78)
Gender, male/female	0/1	1/0	0/1	1/2	0/3	0/5	1/4	0/6	2/9	0/6	5/37
Cancer type, n											
Ovarian	1	0	1	2	3	4	4	4	8	3	30
Testicular	0	1	0	1	0	0	1	0	2	0	5
Endometrial	0	0	0	0	0	1	0	2	1	3	7
Median number of prior treatments (range)	6 -	3 -	3 -	5 (1-8)	4 (3-6)	5 (3-7)	6 (3-9)	4 (1-6)	3 (2-4)	3 (2-3)	4 (1-9)
CLDN6 Positive by IHC n/N	1/1	1/1	1/1	3/3	3/3	3/5	5/5	6/6	11/11	6/6	40/42

[a]Cohort expanded to further characterize and guide dose selection. Datacut 29SEP2023

Results

Table 2. Treatment Related Adverse Events Occurring in 10% of Patients or Greater

Preferred Term	Dose (mg/kg)	0.2 N=1	0.4 N=1	0.8 N=1	1.0 N=3	1.3 N=3	1.7 N=5	2.0 N=5	2.4 N=6	3.0 N=11	3.0 +GCSF N=6	Total N=42
Patients with any TRAE, n (%)		1 (100)	1 (100)	1 (100)	2 (66)	1 (33)	3 (60)	3 (60)	6 (100)	11 (100)	2 (40)	31 (74)
Alopecia	All Grades	1	-	-	-	-	-	1	4	7	1	14
	G1	1	-	-	-	-	-	1	2	2	1	7
	G2	-	-	-	-	-	-	-	2	5	-	7
Anemia	All Grades	-	-	-	1	-	1	-	3	8	1	14
	G1	-	-	-	-	-	1	-	2	4	1	8
	G2	-	-	-	-	-	-	-	-	3	-	3
	G3	-	-	-	1	-	-	-	1	1	-	3
Arthralgia	All Grades	-	-	-	-	-	-	-	-	6	-	6
	G1	-	-	-	-	-	-	-	-	3	-	3
	G2	-	-	-	-	-	-	-	-	2	-	2
	G3	-	-	-	-	-	-	-	-	1	-	1
Aspartate aminotransferase increased	All Grades	-	-	-	-	-	-	-	1	3	1	5
	G1	-	-	-	-	-	-	-	1	3	1	5
Constipation	All Grades	-	-	-	-	-	1	-	-	4	-	5
	G1	-	-	-	-	-	1	-	-	2	-	3
	G2	-	-	-	-	-	-	-	-	2	-	2
Decreased appetite	All Grades	-	-	-	-	-	1	-	2	2	1	6
	G1	-	-	-	-	-	-	-	2	1	1	4
	G2	-	-	-	-	-	1	-	-	1	-	2
Fatigue	All Grades	-	-	1	1	-	3	-	1	8	2	16
	G1	-	-	1	1	-	1	-	-	5	2	10
	G2	-	-	-	-	-	2	-	1	3	-	6
Nausea	All Grades	-	-	-	-	-	2	-	1	5	2	10
	G1	-	-	-	-	-	1	-	1	3	1	6
	G2	-	-	-	-	-	1	-	-	2	1	4
Neuropathy	All Grades	-	1	1	1	-	1	1	2	6	-	13
	G1	-	1	1	1	-	1	-	1	3	-	8
	G2	-	-	-	-	-	-	1	1	2	-	4
	G3	-	-	-	-	-	-	-	-	1	-	1
Neutropenia	All Grades	-	-	-	-	-	-	2	2	5	-	9
	G2	-	-	-	-	-	-	1	-	-	-	1
	G3	-	-	-	-	-	-	1	1	1	-	3
	G4	-	-	-	-	-	-	-	1	4	-	5
Pneumonia	All Grades	-	-	-	-	-	-	-	1	-	-	1
	G5	-	-	-	-	-	-	-	1	-	-	1
White blood cell count decreased	All Grades	-	-	-	-	-	-	-	2	7	-	9
	G1	-	-	-	-	-	-	-	2	2	-	4
	G2	-	-	-	-	-	-	-	-	4	-	4
	G4	-	-	-	-	-	-	-	-	1	-	1
Dose Limiting Toxicities (DLT)	All	0	0	0	0	0	0	0	0	3	0	3

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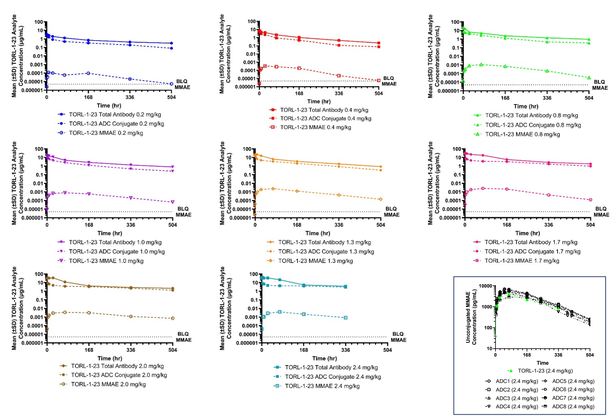
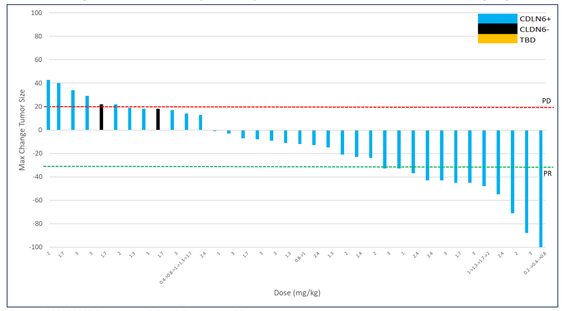
Figure 6. Average TORL-1-23 Concentrations by Dose: *ADC Conjugate, Total Mab, and MMAE Overlay for 0.2 to 2.4 mg/kg (3.0 mg/kg pending)*



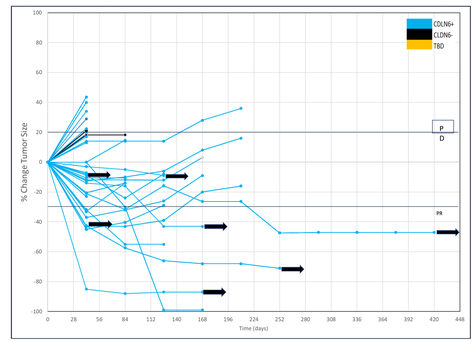
- Human PK characteristics of TORL-1-23 were compared to results from 8 other vc-MMAE ADCs (Li et al. *MAbs* 2020).

Figure 7. Tumor Response by RECIST 1.1 Dose Levels 0.2 to 3 mg/kg



Datacut 29SEP2023 Dose Levels 0.2 to 3.0 mg/kg (n=36)

Figure 8. Change in Tumor Size Over Time: Dose Levels 0.2 to 3 mg/kg



Datacut 29SEP2023 Dose Levels 0.2 to 3.0 mg/kg (n=36)

Conclusions

- **TORL-1-23 well tolerated from 0.2 to 2.4 mg/kg IV every 21 days**
  - No DLTs 0.2 to 2.4 mg/kg (MTD for other VC-MMAE ADCs)
  - 3.0 mg/kg IV every 21 days
    - G4 neutropenia observed without GCSF
    - No neutropenia with GCSF
- **Initial PK data indicate reduced exposure to free MMAE as compared to other MMAE-containing ADCs**
- **Encouraging antitumor activity observed in heavily pretreated population during dose finding below the MTD**
  - PRs in 11/36 (31%) in evaluable patients across dose levels
  - PRs in 9/27 (33%) with CLDN6+ platinum resistant/refractory ovarian cancer across dose levels
    - PRs in 6/12 (50%) patients across 2.4 mg/kg and 3.0 mg/kg doses (3 additional patients to be evaluated at 3.0 mg/kg)
    - Treatment duration at 2.4 mg/kg is 5 mos and duration at 3.0 mg/kg pending
  - 4.0 mg/kg with GCSF will be explored
- **Dose optimization evaluation to occur in expansion cohorts**

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