

Phase 1 Study of the Smac Mimetic TL32711 in Adult Subjects with Advanced Solid Tumors & Lymphoma to Evaluate Safety, Pharmacokinetics, Pharmacodynamics and Anti-tumor Activity

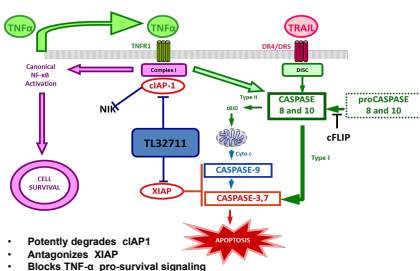
R.K. Amaravadi¹, R.J. Schilder², G.K. Dy³, W.W. Ma³, G.J. Fetterly³, D.E. Weng⁴, M.A. Graham⁴, J.M. Burns⁴, S.K. Chunduru⁴, S.M. Condon⁴, M.A. McKinlay⁴, A. A. Adjei³

¹Abramson Cancer Center University of Pennsylvania, Philadelphia PA, ²Fox Chase Cancer Center, Philadelphia PA, ³Roswell Park Cancer Institute, Buffalo NY, ⁴TetraLogic Pharmaceuticals, Malvern PA

Introduction

TL32711 is a small molecule Smac mimetic that potently and specifically antagonizes inhibitor of apoptosis proteins (IAPs), resulting in caspase-dependent apoptosis and inactivation of NF- κ B signaling. In preclinical studies, single agent tumor regression was observed for multiple tumor types and potent anti-tumor activity was observed when TL32711 was combined with specific chemotherapies and death receptor ligands. This first-in-human study assesses the safety, pharmacokinetic (PK), and pharmacodynamic (PD) profile and anti-tumor activity of intravenous administration of single agent TL32711.

FIGURE 1 TL32711 Mechanism of Action



Study Objectives

Primary Objectives:

- To determine the maximum tolerated dose and characterize the safety and tolerability of TL32711 when administered as a 30 minute intravenous (IV) infusion once weekly for 3 consecutive weeks followed by one week off (Cycle) repeated every 4 weeks as tolerated in patients with refractory solid tumors or lymphoma

Secondary Objectives:

- To assess the pharmacokinetics, pharmacodynamic effects and anti-tumor activity of TL32711

Eligibility

Inclusion Criteria:

- Confirmed advanced metastatic or unresectable malignancy that is refractory to currently available standard therapies
- ECOG performance status of ≤ 2 ; life expectancy > 3 mo
- Adequate renal, hepatic and bone marrow function

Exclusion Criteria:

- Received standard or investigational anti-cancer therapy within 4 weeks prior to first dose of TL32711
- Symptomatic or uncontrolled brain metastases requiring current treatment
- Clinically significant auto-immune, cardiac or pulmonary disease

Trial Design

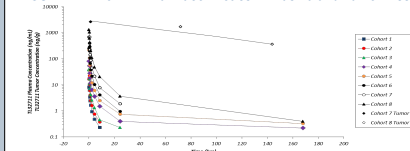
- Phase 1, multi-centered, open-label, dose-escalation 3+3 design, with dose expansion at recommended Phase 2 dose
- Dose levels escalated by 100%. If CTCAE v.4 drug-related AE Grade ≥ 2 or >1 change above baseline, subsequent cohorts escalated by 50% or 33%
- TL32711 administered as a 30min IV infusion once weekly for 3 consecutive weeks followed by one week off (Cycle) repeated every 4 weeks IV until progression/ toxicity/ voluntary withdrawal.
- Weekly study assessments (+C1D2, C1D16) until treatment discontinued
 - PK/PD markers (IAPs, apoptosis activation) - pre-dose and 4 and 24 hours post dose on Day 1 and 15, and pre-dose and 4 hours post-dose on Day 8 dose
 - Restaging was done at the end of Cycle 2

Patient Characteristics

Patients Treated (Cohorts 1-8)	24	Cancer Type	n	%
Median Age, yrs (range)	56.5 (31-80 yrs)	Anaplastic	1	4%
Gender, n (%)		Colon	5	21%
Male	15 (62.5%)	Gastric	2	8%
Female	9 (37.5%)	Head & Neck	3	12%
ECOG Performance Status, n (%)		Hodgkin's Lymphoma	2	8%
0	11 (46%)	Melanoma	3	13%
1	13 (54%)	Ovarian	2	8%
2	0 (0%)	Pancreatic	2	8%
		Sarcoma	2	8%
		SCLC	1	4%

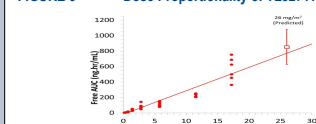
Pharmacokinetics

FIGURE 2 TL32711 Pharmacokinetics in Plasma and Tumor Tissue



	0.18 mg/m ²	0.36 mg/m ²	0.72 mg/m ²	1.44 mg/m ²	2.88 mg/m ²	5.76 mg/m ²	11.5 mg/m ²	17.2 mg/m ²	17.2 mg/m ²
Cmax (ng/mL)	9.9	22.4	41.3	86.1	258.2	292.5	664.5	1338	2000
AUC ₀₋₂₄ (ng·h/mL)	10.5	20.0	37.3	119.6	264.3	328.9	699.3	1097	2042
t _{1/2} (h)	1.9	2.5	3.5	6.7	7.2	6.3	6.1	14.6	19.0

FIGURE 3 Dose Proportionality of TL32711 in Plasma



Dose Escalation Status

Cohort No.	Dose (mg/m ²)	% Increase from Prior Dose	# Patients	# Grade 1 events (%)	# Grade 2 events (%)	# Grade 3/4 events (%)
1	0.18		3	3/3 (100%)	None	None
2	0.36	100%	3	1/3 (33%)	None	None
3	0.72	100%	3	2/3 (67%)	None	None
4	1.44	100%	3	1/3 (33%)	1/3 (33%)	None
5	2.88	100%	3	1/3 (33%)	None	None
6	5.76	100%	3	None	None	None
7	11.5	100%	3	1/3 (33%)	1/3 (33%)	None
8	17.2	50%	3	3/3 (100%)	None	None
9	26	50%	Pending	Pending	Pending	Pending

Pharmacodynamics

FIGURE 4 cIAP1 Target Suppression in Tumor Biopsies

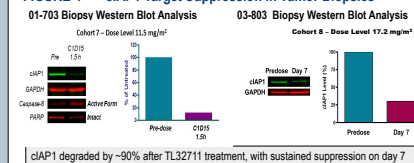


FIGURE 5 Rapid and Sustained cIAP1 Suppression in PBMCs

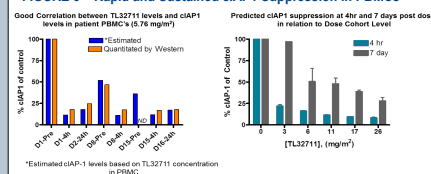


FIGURE 6 Dose-Related Decrease in cIAP1 Levels in PBMCs

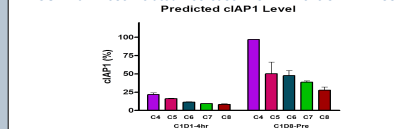
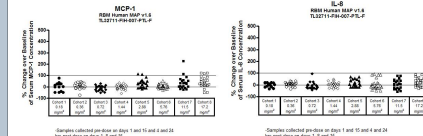


FIGURE 7 No Increase in Serum MCP-1 or IL-8 Across All Cohorts



Safety Summary

- No Grade 3 or Grade 4 Adverse Events attributed to study drug
- Most Common Drug -Related Adverse Events with incidence ≥ 2

Adverse Event	Number of Grade 1 or 2 Events (%)
Nausea	5 (14%)
Fever	4 (11%)
Rash	3 (8%)
Lymphocytopenia	2 (6%)

Anti-Tumor Activity

- CRC Patient 01-202 (Dose cohort 0.36 mg/m²)**
 - Patient with relapsed progressive disease after 7 prior regimens
 - CT scan: 3 of 5 metastatic lesions decreased after 2 cycles of TL32711 – Stable Disease by RECIST criteria
 - Patient received 6 cycles (24 weeks) of TL32711 before disease progression
- Melanoma Patient 01-703 (Dose cohort 11.5 mg/m²)**
 - Patient with rapidly progressive disease prior to study
 - Stable Disease by RECIST criteria after 2 cycles of TL32711
 - Progressed after 3rd cycle with increasing cutaneous lesions
- CRC Patient 01-801 (Dose cohort 17.2 mg/m²)**
 - Patient with progressive disease after multiple prior therapies
 - Patient's CEA decreased (150 to 90) and developed a 4-5cm photopenic lesion in a hepatic metastasis after 1 cycle of TL32711. Patient had marked clinical improvement of early satiety and pain during 1st 2 cycles.
 - Patient progressed with development of a new liver lesion after 2 cycles



Conclusions

- TL32711 is well tolerated in patients with solid tumors and lymphoma with no dose-limiting toxicities and the MTD has not been reached
- TL32711 displays dose proportional pharmacokinetics, moderate to low inter-patient variability in C_{max} and AUC, and a long terminal half-life in plasma (35 hrs) with high uptake and retention in tumor tissues (half-life 49 hrs)
- TL32711 causes rapid (within 4 hours) and sustained (for 7 days) suppression of cIAP1 that is dose-dependent as measured in both PBMCs and tumor biopsies
- TL32711 causes dose-related activated serum caspase-3/7 and cleaved cytokeratin-18 levels (data not shown)
- Evidence of anti-tumor activity observed
- Patient accrual to this study continues
- A TL32711 Phase 1b/2a five-arm combination clinical trial with docetaxel, gemcitabine, irinotecan, carboplatin/paclitaxel and liposomal doxorubicin is ongoing