

# 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

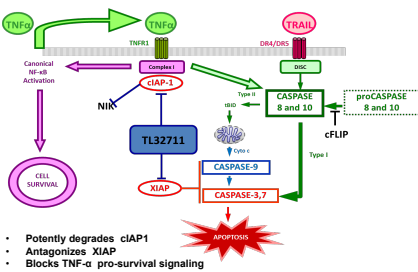
R.K. Amaravadi<sup>1</sup>, R.J. Schilder<sup>2</sup>, G.K. Dy<sup>3</sup>, W.W. Ma<sup>3</sup>, G.J. Fetterly<sup>3</sup>, D.E. Weng<sup>4</sup>, M.A. Graham<sup>4</sup>, J.M. Burns<sup>4</sup>, S.K. Chunduru<sup>4</sup>, S.M. Condon<sup>4</sup>, M.A. McKinlay<sup>4</sup>, A. A. Adjei<sup>3</sup>

<sup>1</sup>Abramson Cancer Center University of Pennsylvania, Philadelphia PA, <sup>2</sup>Fox Chase Cancer Center, Philadelphia PA, <sup>3</sup>Roswell Park Cancer Institute, Buffalo NY, <sup>4</sup>TetraLogic 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- $\kappa$ 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**



- Potently degrades cIAP1
- Antagonizes XIAP
- Blocks TNF- $\alpha$  pro-survival signaling

## 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  $\leq 2$ ; 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

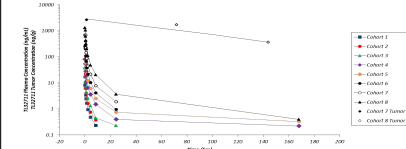
- Phase 1, multi-centered, open-label, dose-escalation 3+3 design, with dose expansion at recommended Phase 2 dose
- Dose levels escalated by 100%. If CTCAE v.4 drug-related AE Grade $\geq 2$  or >1 change above baseline, subsequent cohorts escalated by 50% or 33%
- TL32711 administered as a 30min IV 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 (+CID2, 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) | Anal               | 1 | 4%  |
| Gender, n (%)                  |                  | Appendiceal        | 1 | 4%  |
| Male                           | 16 (62.5%)       | Colon              | 5 | 21% |
| Female                         | 9 (37.5%)        | Gastric            | 2 | 8%  |
| ECOG Performance Status, n (%) |                  | Head & Neck        | 3 | 12% |
| 0                              | 13 (54%)         | Hodgkin's Lymphoma | 2 | 8%  |
| 1                              | 11 (46%)         | Melanoma           | 3 | 13% |
| 2                              | 0 (0%)           | Ovarian            | 2 | 8%  |
|                                |                  | Pancreatic         | 2 | 8%  |
|                                |                  | Sarcoma            | 2 | 8%  |
|                                |                  | SCLC               | 1 | 4%  |

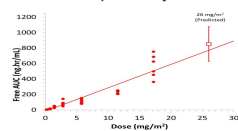
## Pharmacokinetics

**FIGURE 2 TL32711 Pharmacokinetics in Plasma and Tumor Tissue**



| Dose (mg/m <sup>2</sup> )      | Plasma                 |                        |                        |                        |                        |                        | Tumor                  |                        |
|--------------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|
|                                | 0.18 mg/m <sup>2</sup> | 0.36 mg/m <sup>2</sup> | 0.72 mg/m <sup>2</sup> | 1.44 mg/m <sup>2</sup> | 2.88 mg/m <sup>2</sup> | 5.76 mg/m <sup>2</sup> | 11.5 mg/m <sup>2</sup> | 17.2 mg/m <sup>2</sup> |
| Cmax (ng/ml)                   | 9.9                    | 22.4                   | 41.3                   | 86.1                   | 258.2                  | 292.5                  | 664.5                  | 1338                   |
| AUC <sub>0-24h</sub> (ng·h/ml) | 10.5                   | 20.0                   | 37.7                   | 119.6                  | 254.3                  | 328.9                  | 669.9                  | 1097                   |
| AUC <sub>0-12h</sub> (ng·h/ml) | 1.9                    | 2.5                    | 3.5                    | 6.7                    | 7.1                    | 6.3                    | 6.1                    | 34.6                   |

**FIGURE 3 Dose Proportionality of TL32711 in Plasma**

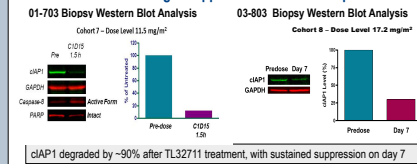


## Dose Escalation Status

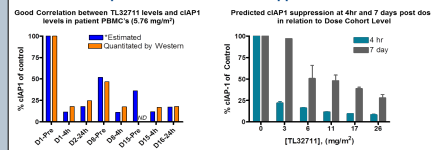
| Cohort No. | Dose (mg/m <sup>2</sup> ) | % Increase from Prior Dose | # Patients | # Grade 1 events (%) | # Grade 2 events (%) | # Grade 3/4 events (%) |
|------------|---------------------------|----------------------------|------------|----------------------|----------------------|------------------------|
| 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

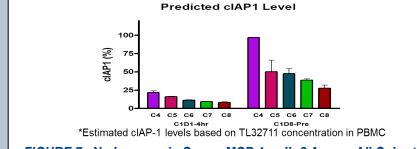
**FIGURE 4 cIAP1 Target Suppression in Tumor Biopsies**



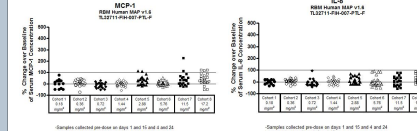
**FIGURE 5 Rapid and Sustained cIAP1 Suppression in PBMCs**



**FIGURE 6 Dose-Related Decrease in cIAP1 Levels in PBMCs**



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



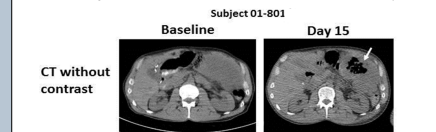
## Safety Summary

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

| 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/m<sup>2</sup>)
  - 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/m<sup>2</sup>)
  - Patient with rapidly progressive disease prior to study
  - Stable Disease by RECIST criteria after 2 cycles of TL32711
  - Progressed after 3<sup>rd</sup> cycle with increasing cutaneous lesions
- CRC Patient 01-801 (Dose cohort 17.2 mg/m<sup>2</sup>)
  - 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 1<sup>st</sup> 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, 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