TH-302 MAINTENANCE FOLLOWING TH-302 PLUS DOXORUBICIN INDUCTION: THE RESULTS OF A PHASE 2 STUDY OF TH-302 IN COMBINATION WITH DOXORUBICIN IN SOFT TISSUE SARCOMA

CTOS 2012 Meeting

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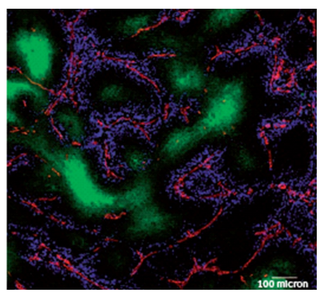
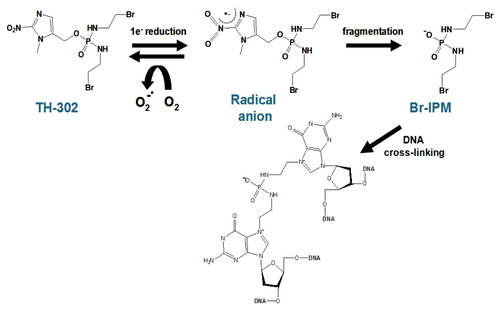
Introduction

Solid tumors' abnormal cell growth and insufficient blood vessel formation can lead to regions of hypoxia. These regions of hypoxia are known to be resistant to chemotherapy and radiation treatment. Traditional chemotherapies have poor tissue penetration and target the more rapidly cycling regions of tumors that are located in proximity to the tumor vessels. This is illustrated in a mouse mammary tumor (Minchinton and Tannock. Nature Reviews 006;6:583-92). Doxorubicin, labeled in blue, does not reach the regions of hypoxia, labeled in green.

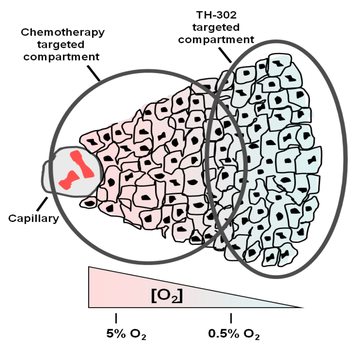




TH-302 is a nitroimidazole prodrug of the cytotoxin, bromo-isophosphoramide mustard (Br-IPM). Under normal oxygen conditions or normoxia, TH-302 is essentially inactive. In the presence of certain reductases and with hypoxic conditions, the nitroimidazole is reduced and Br-IPM is released to alkylate DNA, inducing intrastrand and interstrand crosslinks. The repair of TH-302-induced DNA damage is dependent on homologous recombination repair.

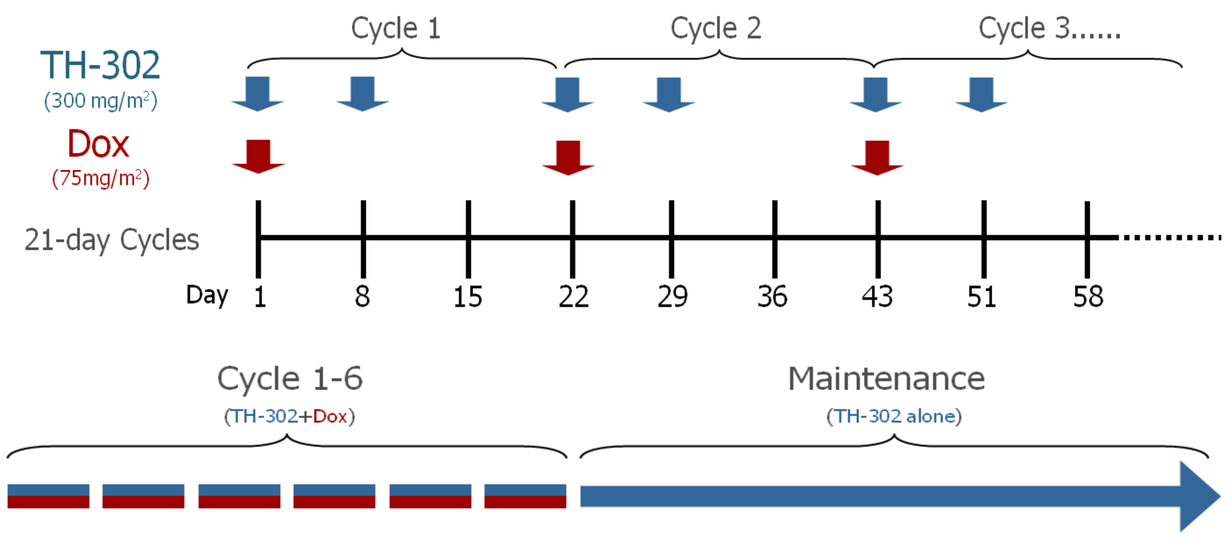
Combining doxorubicin with TH-302 may enable the complementary targeting of both the normoxic and hypoxic regions of soft tissue sarcoma (STS).

A Phase 1/2 study (NCT00742963) was conducted to Investigate TH-302 in combination with doxorubicin in STS. 48 of 91 (53%) patients who completed the initial 6 cycles of combination therapy without progression elected to continue on TH-302 maintenance monotherapy at induction dose.



Study Design: Induction and Maintenance

TH-302 was administered IV at MTD of 300 mg/m^2 over 30-60 min on Day 1 and Day 8 of 21 day cycle. Doxorubicin 75 mg/m^2 administered on Day 1 two hours after completion of TH-302 for a maximum of 6 cycles (450 mg/m^2 cumulative dose). RECIST 1.0 responses were evaluated after every even cycle. Pts with stable or responding disease and acceptable toxicity could receive TH-302 alone (maintenance) after 6 cycles of combination therapy until discontinuation for progression, toxicity or investigator decision.



Key Eligibility Criteria

- Pathologically confirmed diagnosis of soft tissue sarcoma with the following subtypes:
  - Synovial sarcoma, high grade fibrosarcoma, unclassified, undifferentiated sarcoma, liposarcoma, leiomyosarcoma (excluding GIST), angiosarcoma (excluding Kaposi's syndrome), pleomorphic sarcoma/malignant fibrous histiocytoma
- Locally advanced unresectable or metastatic disease and for whom treatment with single agent doxorubicin was considered appropriate
- No prior therapy with ifosfamide, cyclophosphamide, anthracycline or anthracenedione
- ECOG performance status 0 or 1
- Measurable disease by RECIST 1.0 (at least one target lesion)
- Adequate cardiac, hematologic, hepatic, and renal function

Demographics

- 91 patients initiated treatment between August 2009 and June 2011.
- 48 of 91 (53%) patients entered maintenance therapy.

Table 1: Baseline Demographics and Cancer History

Characteristic	All (N=91)			In Maintenance (N=48)	
Gender (N)	Female/Male	53/38		Female/Male	23/25
Age (years)	Median	57		Median	57
	Range	23-78		Range	28-78
ECOG (N/%)	0	45%		0	43%
	1	55%		1	57%
Prior adjuvant/neoadjuvant (%)	Yes	16%		Yes	21%
Histology (%)	Leiomyosarcoma	31%		Leiomyosarcoma	27%
	Unclassified/MFH	31%		Unclassified/MFH	35%
	Liposarcoma	21%		Liposarcoma	17%
	Angiosarcoma	3%		Angiosarcoma	6%
	Fibrosarcoma	3%		Fibrosarcoma	4%
	Synovial sarcoma	3%		Synovial sarcoma	4%
	Other subtype[a]	8%		Other subtype[b]	6%
Disease Status (%)	Locally Advanced Unresectable	18%		Locally Advanced Unresectable	12%
	Distant Metastases	82%		Distant Metastases	88%
Site of Metastatic Disease	Lung	69%		Lung	71%
	Liver	18%		Liver	21%

[a]Other: chondrosarcoma (4), chordoma, pleomorphic rhabdomyosarcoma, endometrial stromal cell sarcoma.
[b]Other: chondrosarcoma (3).

Study Drug Exposure

Table 2: Study Drug Exposure for Patients receiving Maintenance Therapy

Characteristic	Entire Study (N=48) All Cycles	In Maintenance (N=48) Cycle 7 and Later
Doxorubicin Cycles: Median (range)	6 (5-8)[a]	0 (0-2)[a]
TH-302 Cycles: Median (range)	10 (7-36)	4 (1-30)
TH-302 Average Dose Intensity over Doses	92.9%	94.2%

[a] One subject did not receive doxorubicin during cycle 6 and 1 subject received 2 additional cycles of doxorubicin while on maintenance (at cycle 13 and 14).

Safety

Hematologic toxicity is reported in **Table 3**. No grade 3 or 4 values were reported for platelets, WBC or ANC after maintenance The most frequent non-laboratory adverse events regardless of relationship to study drug are provided in **Table 4** (either ≥25% on induction or ≥10% on maintenance. Five subjects had a grade 3 TH-302 related AE on maintenance: urticaria and pruritus (2), anemia (1) and hypoalbuminemia (1) and hypokalemia (1).

Table 3: Hematologic Toxicity During Induction and During Maintenance for Patients receiving Maintenance (N=48)

	NCI CTC AE Grade	Induction N (%)	Maintenance N (%)
Platelets	Grade 0	9 (19%)	26 (54%)
	Grade 1	10 (21%)	19 (40%)
	Grade 2	13 (27%)	3 (6%)
	Grade 3	12 (25%)	0 (0%)
	Grade 4	4 (8%)	0 (0%)
ANC	Grade 0	19 (40%)	33 (69%)
	Grade 1	9 (19%)	8 (17%)
	Grade 2	5 (10%)	7 (15%)
	Grade 3	4 (8%)	0 (0%)
	Grade 4	11 (23%)	0 (0%)
Hemo-globin	Grade 0	0 (0%)	1 (2%)
	Grade 1	9 (19%)	30 (62%)
	Grade 2	24 (50%)	14 (29%)
	Grade 3	15 (31%)	2 (4%)
	Grade 4	0 (0%)	1 (2%)

Table 4: Non-Laboratory AEs During Induction and During Maintenance for Patients receiving Maintenance (N=48)

Adverse Event	Induction N (%)	Maintenance N (%)
Diarrhea	11 (23%)	10 (21%)
Rash	20 (42%)	10 (21%)
Pain in extremity	2 (4%)	8 (17%)
Fatigue	27 (56%)	8 (17%)
Constipation	18 (38%)	8 (17%)
Stomatitis	19 (40%)	7 (15%)
Pyrexia	11 (23%)	6 (12%)
Back pain	9 (19%)	6 (12%)
UTI	4 (8%)	5 (10%)
Vomiting	13 (27%)	4 (8%)
Nausea	31 (65%)	3 (6%)
Anorexia	18 (38%)	3 (6%)
Headache	12 (25%)	3 (6%)
Skin Hyperpigmentation	12 (25%)	3 (6%)
Alopecia	27 (56%)	1 (2%)

Efficacy

Response Rates:

- Overall response rate for 48 subjects receiving maintenance was 44% following induction and increased to 54% following maintenance (including both induction and maintenance).
- During the maintenance portion of the study 6 subjects had an upgrade in response category:
  - 5 SDs converting to PR
  - 1 PR converting to CR

Table 5: Best Response (Unconfirmed) to Overall Treatment

	All (N=91*)	Maintenance after Induction (N=48)	Maintenance (N=48)
Best Response			
Complete Response	2 (2%)	1 (2%)	2 (4%)
Partial Response	30 (34%)	20 (42%)	24 (50%)
Stable Disease	43 (48%)	27 (56%)	22 (46%)
Progressive Disease	14(16%)	0 (0%)	0 (0%)
Overall Response Rate (RR) (Partial Response + Complete Response)	32 (36%)	21 (44%)	26(54%)

* Two patients discontinued from treatment for reasons of subject decision (1) and PI decision (1) prior to initial tumor response assessment.

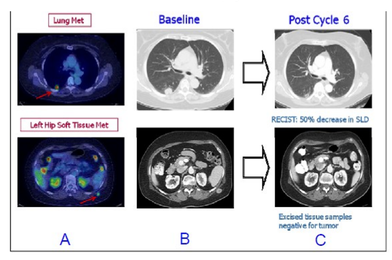
Example Case Reports:

Upgrade in Response in Maintenance

A 63F initiated treatment in March 2010. At baseline 7 target lesions were identified ranging in size from 1.1 to 7.9 cm with a baseline SLD of 198 mm. At the end of Cycle 6 the SLD had de-creased to 182 mm. Lesions continued to decrease and a PR after Cycle 21 with a SLD of 133 mm. The patient discontinued from study in Aug 2011 to take a break from treatment.

Post-maintenance resection

A 70F was diagnosed with high-grade MFH of lower extremity that was excised in Sept 2008. Following metastases to flank and lung, entered study in Oct 2009. Completed 6 cycles of TH-302 and doxorubicin and one cycle of maintenance. Involved regions were resected and both were negative for tumor cells. There has been no recurrence of STS as of Oct 2012.



Progression-free Survival:

- The median PFS on study was 6.7 months (95% CI: 6.2 to 7.8 months). **Figure 1A.**
- The median PFS after TH-302 maintenance was 3.7 months (95% CI: 2.5 to 5.5 months). **Figure1B**.

Figure 1A: Progression-free Survival on Study (N=91)

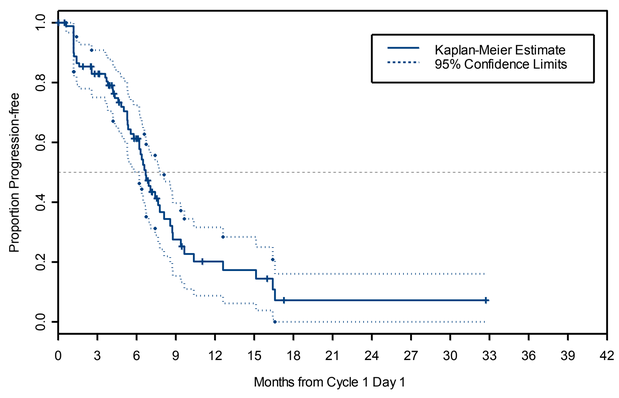
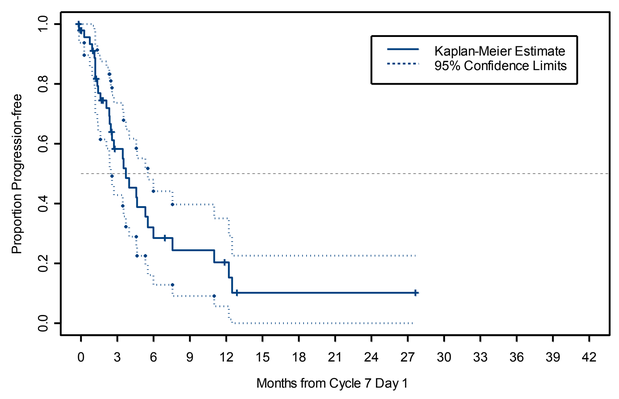


Figure 1B: Progression-free Survival after Initiating Maintenance (N=48)



Overall Survival:

- The median OS on-study was 21.5 months (95% CI: 16.0 to 27.6 months). **Figure 2A.** The 12-month OS was 73% (95% CI: 63% to 82%) and the 24-month OS was 44% (95% CI: 32% to 55%).
- The median OS after TH-302 maintenance was 18.0 months (95% CI: 16.2 to 27.8 months). **Figure 2B.**

Figure 2A: Overall Survival on Study (N=91)

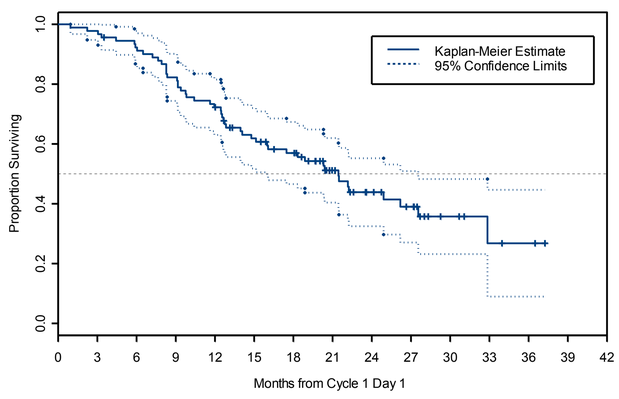
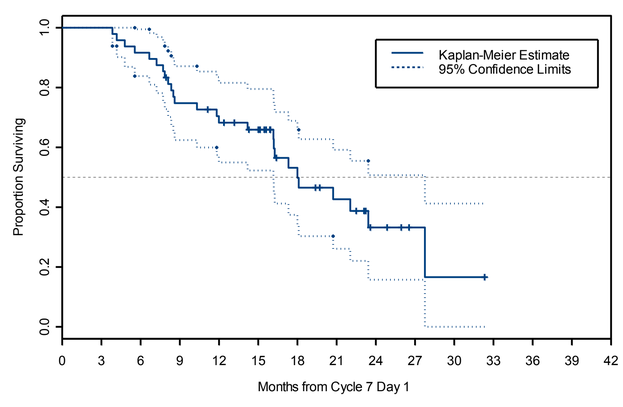


Figure 2B: Overall Survival after Initiating Maintenance (N=48)



Conclusions

TH-302 maintenance following induction of TH-302 combined with full dose doxorubicin in soft tissue sarcoma is tolerated with limited hematologic toxicity, manageable skin and mucosal toxicity, no additive renal, hepatic or cardiac adverse events and no cumulative toxicity. The PFS and upgrading of tumor responses indicate a potential additional contribution of TH-302 maintenance.

Further investigations are ongoing in a Phase 3 Study (NCT01440088).

We thank the patients, families and investigative site personnel for their participation.