Scions of Ifosfamide

Ifosfamide- A DNA-alkylating agent

Ifosfamide (N,3-(bis(2-chloroethyl)-tetradydro-2H-1,3,2-oxazaphosphorin-2-amine 2-oxide, Ifex or Holoxan, IFO) is a widely used and effective DNA-alkylating agent (Zhang, Tian, and Zhou 2006). Ifosfamide, however, is actually a prodrug (figure 1- blue box) that is metabolized in the liver (by hepatic cytochrome P450 (CYP)-catalyzed 4-hydroxylation) to produce the active DNA-alkylating agent of ifosforamide mustard conjugate. The metabolism of ifosfamide produces a number of other active molecules. Acrolein (figure 1 orange box) is one of the most significant byproduct because it is a toxic compound with little anti-tumor effect and actually generates many of the toxicities seen with ifosfamide. In addition to the negative effects of some byproducts, ifosfamide can become inactivated by *N*-dechloroethylation (figure 1 red box), which produces *N*dechloroethylated metabolites and another toxic compound: chloroacetaldehyde (CAA).

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Ifosfamide- A DNA-alkylating agent (cont.)

While it is certainly useful that the metabolism of the ifosfamide prodrug leads to an effective DNA-alkylating agent, the problem is that same process generates both CAA and acrolein. CAA is associated with both neurotoxicity and nephrotoxicity and acrolein is linked to urotoxicity. In order to minimize these negative side-effects and create a therapeutic window for ifosfamide, it is often administered with various aldehyde dehydrogenases (ALDHs) and by conjugation with glutathione (GSH) *via* GSH *S*-transferases (GSTs). Despite the efforts to mitigate the adverse events, ifosfamide is essentially an effective non-specific DNA-alkylating agent with a severe dose limiting toxicity of myelosupression and a neurotoxicity that can induce a coma or death (Fleming 1997: 4).

Despite the toxic side effects, ifosfamide is used in the treatment of a wide range of cancers, where the Mayo clinic notes the following uses (see side bar). The breadth of tumors that ifosfamide is used to treat is impressive and speaks to the effectiveness of the compound despite its clear toxicities. Ziopharm and Threshold are both attempting to capitalize on this by developing a molecule that includes the active metabolite of ifosforamide mustard but eliminates the need to metabolize the prodrug. This would keep the DNA-alkylating effect without the production of the toxic metabolites of acrolein and chloroacetaldehyde (CAA).

Ziopharm and Threshold are both attempting to capitalize on this by developing a molecule that includes the active metabolite of ifosforamide mustard but eliminates the need to metabolize the prodrug.

Uses of Ifosfamide (from the Mayo):

- Acute lymphocytic leukemia.
- Cancer of the bladder.
- Cancer of the bone (including Ewing's sarcoma).
- Cancer of the breast.
- Cancer of the cervix.
- Cancer of the endometrium.
- Cancers of the head and neck.
- Cancer of the lungs.
- Cancer of the ovaries.
- Lymphomas.
- Neuroblastoma.
- Thymoma and other cancer of the thymus.
- Tumors in the ovaries.
- Wilms' tumor.

Palifosfamide- I'll Take Some Lysine with my Mustard

Palifosfamide is ifosforamide mustard that has been stabilized by the addition of L-lysine (Struck et al, AACR 2006). The idea is that the stabilization of the ifosforamide mustard would lead to similar anti-cancer effects without the generation of toxic side effects. This was supported in early pre-clinical work that looked the effect of palifosfamide on rabbit kidney proximal tubule cells. These cells are known to die when exposed to acrolein or chloroacetaldehyde (CAA) but they survive exposure to palifosfamide (Taub et al, BMT 2006). In addition, the pre-clinical work and early studies confirmed palifosfamide's anti-cancer effect (Gale et al, ASCO 2006). Finally, palifosfamide should have fewer patient-to-patient differences in response as compare to ifosfamide (Jones et al 2012). This happens because ifosfamide can only affect a tumor after its metabolized and patient-to-patient differences in metabolism affects the amount of ifosforamide mustard generate per similar dose of ifosfamide. Palifosfamide avoids this problem as it is already the active agent.

The anti-cancer activity of palifosfamide becomes quite clear when looking at the phase II results in soft tissue sarcoma (Verschraegen et al, ASCO 2010). The PICASSO trial was a randomized, open label, multi-center study that examined the effect of palifosfamide plus doxorubicin compared to doxorubicin alone. The trial divided the STS patients into three subtypes: leiomyosarcoma, synovial sarcoma, and others.[1] The primary endpoint was progression free survival (PFS) as measured every six weeks. The hazard ratio for PFS was 0.47 in favor of palifosfamide (statistically significant with a p-value of 0.019). The median PFS for the doxorubicin group was 4.4 months (17.6 weeks) and for the palifosfamide/doxorubicin combo median PFS was 7.8 months (31.2 weeks). Looking at the PFS in weeks is interesting in combination with the fact that PFS was evaluated every 6 weeks. So with the control arm just about half of the patients progressed before the third review and half after. In contrast, the treatment arm had slightly less than half progressing before the fifth evaluation and slight more than half after the fifth evaluation. Finally, the study showed an overall survival benefit with a hazard ratio of 0.78 (see slide 36). The OS benefit was not statistically significant, which is likely related to the trial not being powered for OS and the crossover trial design.

Palifosfamide- I'll Take Some Lysine with my Mustard (cont)

It was also important to note that the safety between the two arms was similar. In particular, there were no cases of encephalopathy, hemorrhagic cystitis, or Fanconi's syndrome. The main adverse events were neutropenia and elevated creatinine levels, which were similar between the arms. In general, then, the phase II results are consistent with the hypothesis that palifosfamide would be able to generate similar efficacy with significantly fewer adverse side effects (as compared to ifosfamide). With these results, the company is running a phase III trial (PICASSO 3), which is expected to read out PFS data in 4Q2012. The phase III trial has a similar dosing scheduled and inclusion/exclusion criterion.

Ifosfamide also has shown activity in small cell lung cancer (SCLC). In fact, Loehrer et al (1995) showed that the addition of ifosfamide to cisplatin and etoposide generated a statistically significant survival advantage (compared to cisplatin and etoposide alone). This is one of the only contemporary phase III trials in this space to find an OS advantage (see slide 20 for failed trials). Given this, it is not surprising that palifosfamide has seen some activity in SCLC. In an early phase I trial, palifosfamide plus doxorubicin generated 1 partial response at out of the 2 patients that had SCLC (see slide 14 for results). A larger phase Ib trial examined the effect of palifosfamide added to a carboplatin and etoposide regime (Harb et al, AACR-NCI-EORTC 2011). At the time of the presentation, they had treated 4 SLCL patients and they had 2 partial responses, 1 stable disease, and 1 progressive disease. A later update of that trial had one additional SCLC patient who had a stable disease response (see slide 17 for results). The company has decided to initiate an adaptive phase III trial (MATISSE) with a single pre-planned analysis at 125 events that could lead to a decrease in sample size, an increase in the sample size, or no change.

TH-302- Whatever You Can Do, Can I Do Better?

Palifosfamide is not the only drug that uses ifosforamide mustard as its base. Threshold has developed TH-302 but rather than stabilize it with lysine they created another prodrug that only metabolizes in hypoxic regions of the body. This is important in that many solid tumors develop oxygen starved regions that are difficult to target with conventional agents. TH-302 is an inactive prodrug that activates in the hypoxic regions of a tumor (see figure 2), which releases the ifosforamide mustard directly in and around the tumor. Keep in mind that ifosforamide mustard is a non-specific DNA-alkylating agent and as such will kill any dividing cell. The added advantage of TH-302 over palifosfamide is that ifosforamide mustard is only released in tumors, which should limit the effect on non-tumor cells.

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TH-302- Whatever You Can Do, Can I Do Better? (cont)

While only pre-clinical data, it is interested to look at the cancer killing ability at various levels of hypoxia. Figure 3 shows the IC_{50} of TH-302 under conditions of hypoxia (blue box) and normal conditions (orange box). Perhaps the most important point to take from the figure is that the IC_{50} decreased for each cell line between the hypoxic and normal conditions, which provides evidence that the prodrug is actually releasing its toxic payload when expected. In fact, figure 4 additionally shows a strong correlation between tumor inhibition and hypoxia.

TH-302 has been tested in a number of tumors but the two lead indications are soft tissue sarcoma and pancreatic cancer. Just like Ziopharm, Threshold has a phase III trial ongoing in STS based from solid early trial results. The TH-CR-403 trial was a single arm trial of TH-302 and doxorubicin that treated 89 patients with advance STS. The trial reported an overall rate of response of 36% with an additional 48% with stable disease. The trial (Chawa et al, CTOS 2011) had a median PFS of 6.7 months and a median OS of 17.5 months. Obviously since this was a single arm study, there is no control or hazard ration but these are certainly higher than the historical control (3.5 month PFS and 9.5 month OS historic control but one should keep in mind all of the normal caveats about drawing conclusions from historic controls). In addition, these results are certainly on par with those of palifosfamide but there are always problems comparing across trials.

Threshold has moved onto a pivotal phase III trial in local advance non-resectable or metastatic STS under and SPA with a primary endpoint of overall survival (progression free survival is available at an interim look). The target enrollment is 450 patients in a global, open label study. Unlike Ziopharm, there are fewer restrictions on the type of STS that are allowed into the trial (trial accepts synovial sarcoma, high grade fibrosarcoma, undifferentiated sarcoma; sarcoma not otherwise specified (NOS), liposarcoma, leiomyosarcoma (excluding GIST), angiosarcoma (excluding Kaposi's sarcoma), malignant peripheral nerve sheath tumor, pleomorphic rhabdomyosarcoma, myxofibrosarcoma, epithelioid sarcoma, and undifferentiated pleomorphic sarcoma/malignant fibrous histiocytoma (MFH) (including pleomorphic, giant cell, myxoid and inflammatory forms). The study started in September 2011 and the company expects to provide an update on the PFS interim analysis in the first half of 2013.

Threshold has also tested TH-302 in combination with gemcitabine for the treatment of pancreatic cancer (locally advanced or metastatic pancreatic ductal adenocarcinoma confirmed by histology or cytology). The TH-CR-404 trial was a randomized, open label trial and compared gemcitabine to gemcitabine plus 240 mg/m2 of TH-302 to gemcitabine plus 340 mg/m2 of TH-302. The trial showed (Hart el al, AACR Pancreatic Cancer 2012 also see Borad et al 2012) a statistically significant difference between the gemcitabine arm compared to the gemcitabine and TH-302 combo (they grouped both dosing schedules in the analysis). When splitting out the TH-302 dosing schedules both showed a statistically significant PFS effect (240 mg/m2 had a median PFS of 5.5 months and the 340 mg/m2 had a median PFS of 6 months) and there is a hint at a dose response but not large enough to be statistically significant. The effect was also only statistically significant in the metastatic disease sub-set (240 mg/m2 and 340 mg/m2 combined) but did show a trend in the locally advanced group (the 340 mg/m2).

Perhaps the biggest question deals with the imbalance in patient characteristics. Figure 5 has the basic characteristics and it looks like the gemcitabine alone treatment group had more ECOG 1 patients compared to the TH-302 combinations. That being said the TH-302 groups had higher CA 19-9 markers and the TH-302 340 mg/m2 group had more lung metastases. When looking at the forest plot (figure 6), however, it seems like the effect of TH-302 is strongest in the ECOG 1 patients. This would imply that more ECOG 1 patients in the TH-302 arms may have made the results stronger, although there are clearly not nearly enough patients to make any strong claim. Ultimately, however, one could argue that the trial had a signal of efficacy with some questions marks but a signal strong enough to move the drug forward.

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Scions of Ifosfamide and the STS Battle Royale

While both palifosfamide and TH-302 have signals in multiple cancers both are targeting STS as the lead indication. So the question is how will these drugs stack up in STS? While it is always problematic to compare efficacy across trials, figure 7 summarizes the current treatments (in addition to palifosfamide and TH-302). What seems immediately clear is that both drugs have some of the best ORR as well as OS rates. In addition, both compounds appear to have a better safety profile than ifosfamide and many of the other treatments. Pazonpanib is also highlighted in the figure as it recently was approved for the treatment of STS and both palifosfamide and TH-302 seem much more efficacious. Of course, it should be noted that pazonpanib was approved for second-line as opposed to the first-line of palifosfamide and TH-302. As such, the patients in the pazonpanib trial were likely sicker and more difficult to treat. Regardless, the results as of now seem to indicate that both palifosfamide and TH-302 would be strong players in the STS treatment regimen.

At this point, palifosfamide has a couple of advantages over TH-302. First, it is further along than TH-302 and should get to market first. While TH-302 is likely only 6-12 months behind palifosfamide in the clinic, it still remains a potential hurdle (if a relatively small one). Second, and perhaps more importantly, the phase III palifosfamide trial is more likely to be successful. This is not to say TH-302 will fail or that the drug is not an active compound. The key is that Threshold failed to take advantage of a couple options to enrich the phase III population. Remember that STS is a very diverse set of diseases with overlapping and non-overlapping pathologies. As such, it is exceptionally unlikely that any drug would work across all histologies. Ziopharm, in their phase II trial, tried to narrow down the histologies that they believed palifosfamide would be most effective. This means then that it is less likely that the distribution of histologies in the phase III trial will dramatically affect the results (because they exclude those that might be a problem). In contrast, Threshold was much more open in their earlier trials and this is also the case in the phase III as to the types of STS that are included.

One might argue that since the phase II trials for TH-302 were as open as the current phase III, then the results should be similar. If the distribution of histologies are the same, then yes. One could also argue yes if the effectiveness of TH-302 did not differ across the histologies in the earlier trials. Looking at Chawa et al, (2011), however, there are clear differences in the ORR. For instance, leiomyosarcoma had an ORR of 46% compared to liposarcoma with an ORR of 22% and within the trial 31% of the patients had leiomyosarcoma compared to 20% of the patients with liposarcoma. If the trial had reversed the percentage of patients with those histologies, then the ORR would drop by 13% to 33.1%. In addition, the trial saw a high ORR (41%) in unclassified/MFH, so that could also decrease in another trial as the distribution of unclassified might change. Again, the point here is not that TH-302 is an inactive compound but that by including such a large number of histologies, Threshold is inevitably including poor responders and potentially diluting their results.

Finally, Threshold had another opportunity to increase the odds of the phase III success but did not. The pre-clinical results were quite clear that the drug was activated in hypoxic conditions (see figure 3), so why not screen the patients for hypoxic tumors? In other words, it is unlikely that all STS have identical amounts of hypoxia, so the company could screen the patients to measure the amount of hypoxia and include only those with higher levels. This would certainly enrich the trial population to those that would be the best responder (like Endocyte, who screen for cancers that exhibit the folate receptor). Perhaps it is not feasible but Dehdashti et al (2008) have shown the ability of ^{60}Cu-Labeled Diacetyl-Bis(N^4-Methylthiosemicarbazone) to identify hypoxia in cervical cancer with a PET scan. Again, this is not to say that the trial will fail but to note some missed opportunities to enrich the phase III population with patients who will be the most likely responders.

If the TH-302 phase III trial does not have clear results, I would not immediately bet the farm against TH-302. While one would obviously have to look at the phase III trial results, there is a strong possibility that poor results might be more a function of poor trial design than an inactive compound. Of course, even with the caveats I expect the phase III trial to produce positive results or at worst mixed (effect in some histoligies but not others).

Conclusions

Ifosfamide has spawned to active compounds in palifosfamide and TH-302. Both have shown impressive anti-cancer effects in early trials and are set to unveil phase III results in the next 6-12 months. While it is likely that both will ultimately be approved, palifosfamide has a slightly better chance given the design of the phase III trial. That being said, the ability of TH-302 to preferentially activate in hypoxic areas of the tumor makes it more selective and possible the more active and less toxic of the two. Ultimately these remaining questions will be better addressed once the phase III trials are completed and we see results from those larger trials.

Appendix: Figures

Figure 1: Metabolism of IFO prodrug (Zhang, Tian, and Zhou 2006:59)

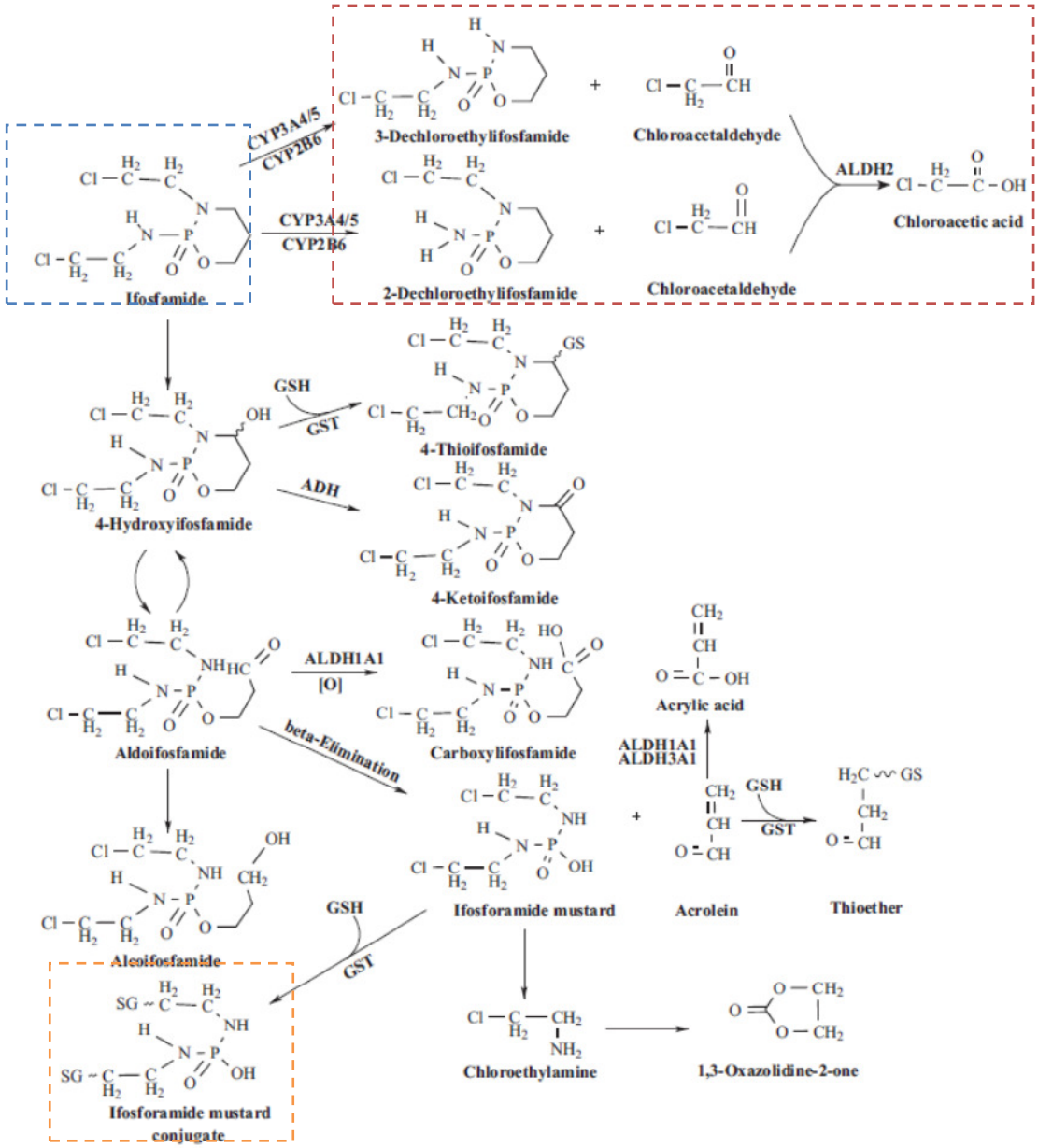

Fig. (3). Metabolism of ifosfamide. The metabolism of ifosfamide is similar to that of CPA, but there are some differences in the formation of metabolites as ifosfamide differs structurally from CPA in the position of one chloroethyl group. As a prodrug, ifosfamide is activated *via* 4-hydroxylation to form 4-hydroxyifosfamide which is inactivated to form 4-ketoifosfamide by alcohol dehydrogenase (ADH) and 4-thioifosfamide with conjugation of reduced glutathione. The tautomer of 4-hydroyifosfamide, aldoifosfamide, can be converted to carboxyifosfamide by ALDH1A1 and alcoifosfamide by aldo-keto reductase (AKR1). Alternatively, aldoifosfamide can decompose to generate cytotoxic ifosforamide mustard with concurrent formation of acrolein by spontaneous β-elimination. Notably, cyclophosphamide is almost completely converted to its active 4-hydroxy-metabolite in humans, whereas 25-60% of ifosfamide is metabolized to chloroacetaldehyde through 2- and 3-dechloroethylation.

Figure 2: TH-302 Prodrug Activation (from Hart 2012)

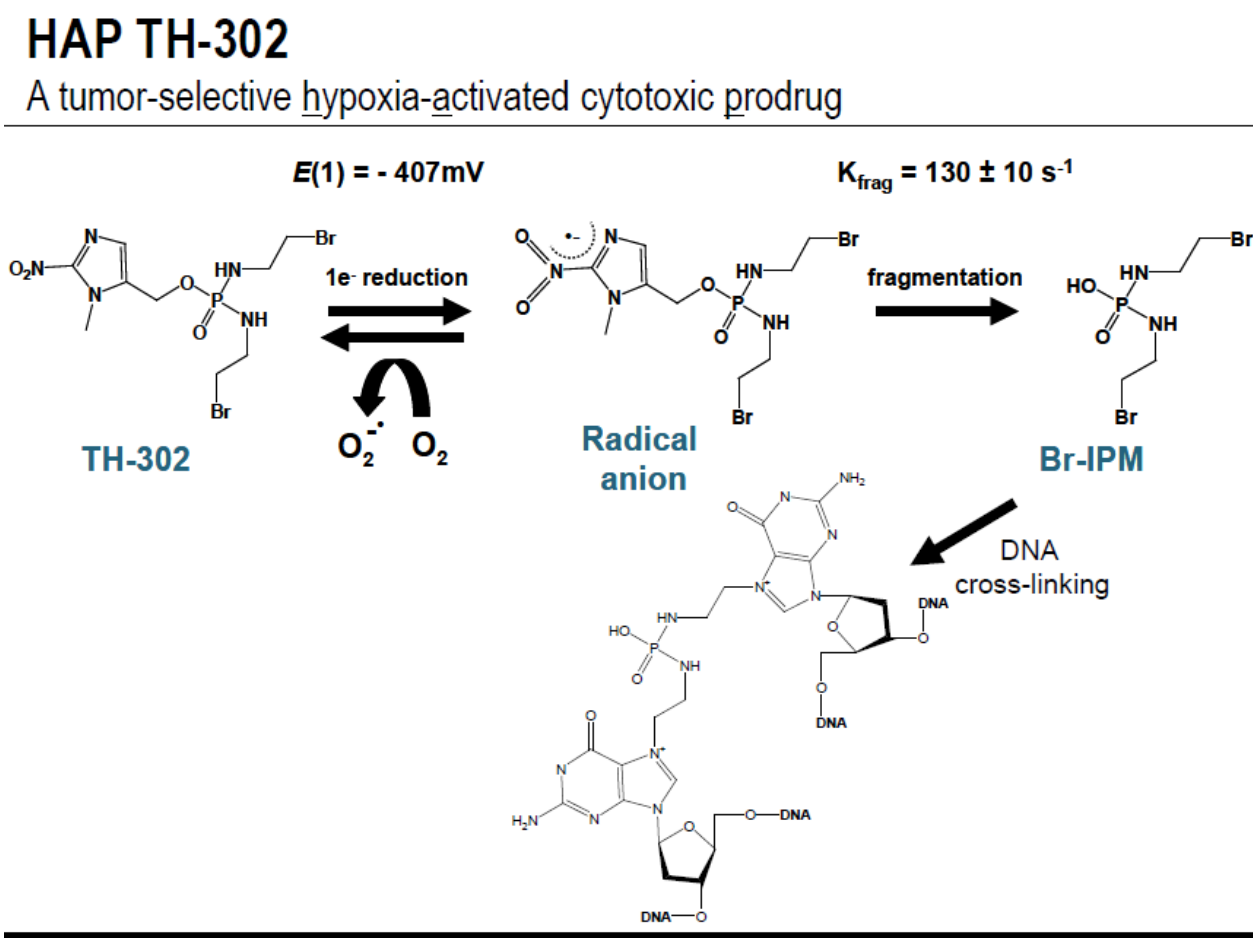

Figure 3: Comparative Effectiveness of TH-302 in Hypoxic and Normoxic Conditions (from Hart 2012)

Cell line	Cell type	IC_{50} (μmol/L; N_2)	IC_{50} (μmol/L; air)	HCR
H460	Lung	0.1 ± 0.03	55 ± 6	550
H82	Lung	0.3 ± 0.05	40 ± 8	130
Caki-1	Renal	0.4 ± 0.05	56 ± 20	140
ACHN	Renal	0.5 ± 0.3	65 ± 3	130
SK-MEL-5	Melanoma	0.7 ± 0.3	420 ± 120	600
DU145	Prostate	0.7 ± 0.3	170 ± 20	240
HCT116	Colon	0.8 ± 0.2	200 ± 62	250
RPMI-8226	Myeloma	1 ± 0.4	280 ± 27	280
A375	Melanoma	1.1 ± 0.2	190 ± 23	170
PC3	Prostate	1.5 ± 0.4	280 ± 8	190
786-O	Renal	1.7 ± 0.5	200 ± 45	120
MIA PaCa-2	Pancreatic	2.1 ± 0.7	210 ± 49	100
HT1080	Fibrosarcoma	2.4 ± 0.1	>300	>130
SK-MEL-2	Melanoma	5.6 ± 1	730 ± 80	130
MALME-3M	Melanoma	6.3 ± 0.1	330 ± 55	50
KHOS/NP	Osteosarcoma	6.4 ± 2.7	360	60
Calu-6	Lung	6.7 ± 1.6	710 ± 100	110
SiHa	Cervical	6.8 ± 2.2	770 ± 140	110
HT29	Colon	7.8 ± 2.4	>300	>40
BxPC-3	Pancreatic	7.9 ± 0.9	430 ± 85	50
LNCaP	Prostate	8.8 ± 2.3	520 ± 25	60
T47D	Breast	11 ± 4.1	560 ± 57	50
PLC/PRF/5	Hepatoma	11 ± 1	>300	>30
SU.86.86	Pancreatic	11 ± 2.8	470 ± 95	40
SK-BR-3	Breast	12 ± 1.2	360 ± 16	30
Panc-1	Pancreatic	16 ± 4.5	540	30
A549	Lung	20 ± 8.5	610	30
MDA-MB-231	Breast	42 ± 5.7	900 ± 82	20
IGROV-1	Ovary	52 ± 8.5	600 ± 75	12
Hs766T	Pancreatic	60 ± 7.5	1,400	23
SK-MEL-28	Melanoma	60 ± 5.5	>1,000	>16
U87-MG	Glioblastoma-astrocytoma	90 ± 4.5	~1,000	11

Figure 4: The Relationship between Hypoxia and Tumor Inhibition (from Hart 2012)

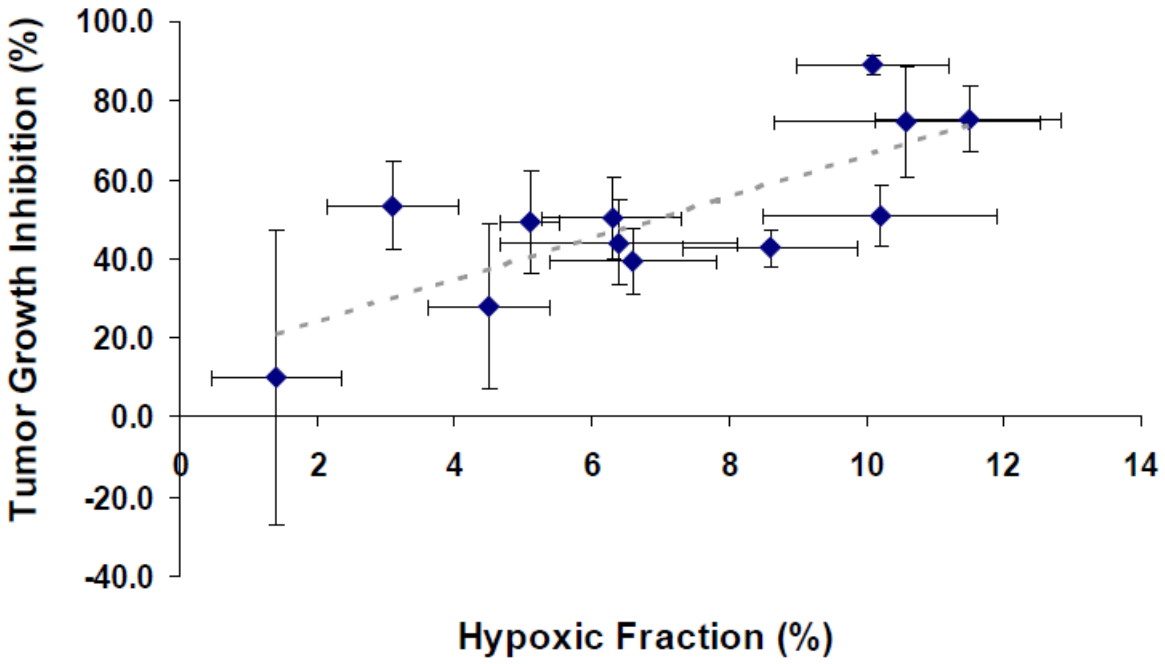

Figure 5: Baseline Characteristics (from Borad et al 2012)

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Study TH-CR-404

Baseline Performance Status and Disease Characteristics

	Gemcitabine (N=69)	Gemcitabine + TH-302 (240 mg/m²) (N=71)	Gemcitabine + TH-302 (340 mg/m²) (N=74)
Screening ECOG			
0	**20 (30%)**	**31 (45%)**	**28 (39%)**
1	**47 (70%)**	**38 (55%)**	**43 (61%)**
Site of primary pancreatic tumor involves Head N (%)	**41 (59%)**	**40 (56%)**	**44 (59%)**
Baseline CA19-9[1]	**(N=53)**	**(N=53)**	**(N=58)**
Median	**1291**	**2575**	**2391**
IQR	**427 – 4337**	**266 – 26751**	**204 – 13775**
Metastatic Sites			
Liver N (%)	**46 (67%)**	**45 (63%)**	**42 (57%)**
Lung[2] N (%)	**10 (14%)**	**11 (15%)**	**15 (20%)**

[1] Elevated CA19-9 at baseline (>35 U/mL); upper limit of quantification = 42,500 U/mL
[2] Five patients had metastases detected only in the lungs

Figure 6: TH-302 Pancreatic Cancer Forest Plot (from Borad et al 2012)

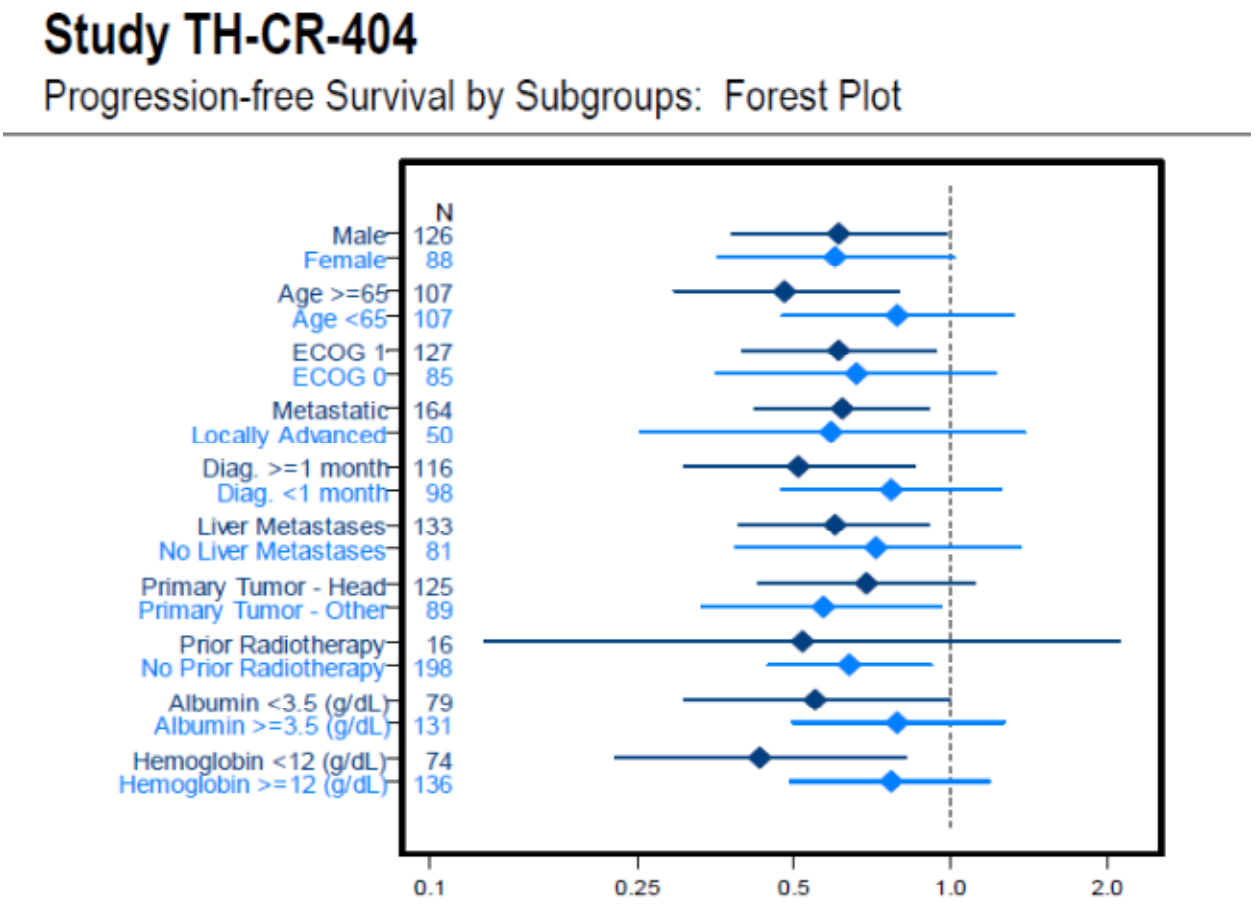

Figure 7: The STS Landscape (source: Morgan and Cranmer 2011)

Treatment	ORR	OS (median unless noted)	Cardiotoxicity	Hemorrhagic cystitis	Nephro- and neuro-toxicity
Anthracyclines					
Doxorubicin	9%-30%	8 - 12 months	Yes	No	No
Pegylated liposomal doxorubicin	0%-12%	11.4 months	No	No	No
Anthraquinone	1%-8%		No	No	No
Ifosfamide	5%-25%	6.5-12 months	No	Yes	Yes
High dose Ifosfamide	16%-42%	13-18.5 months	No	Yes	Yes
Palifosfamide	9%	30% 2-year survival	No	No	No
Anthracyclines and Ifosfamide Combo					
Doxorubicin and Ifosfamide	28%-34%	12.75 months	Yes	Yes	Yes
Palifosfamide and doxorubicin	23%	40% 2-year survival	No	No	No
Th-302 and doxorubicin	36%	17.5 months	No	No	Yes
Taxanes and Gemcitabine					
Docetaxel	0%	Not reported	No	No	Yes
Paclitaxel	7%	Not reported	Not reported	Not reported	Not reported
Gemcitabine	6%-18%	6 -13.9 months	No	No	Yes
Gemcitabine combined with decetaxel	16%-27%	6.2-17.9 months	No	No	Yes
Trabectedin	4%-17%	9.2-13.9 months	No	No	No
Targeted Therapies					
Imatinib	0%-4.5%	Not reported	Not reported	Not reported	Not reported
Sunitinib	2%-3%	Not reported	Not reported	Not reported	Not reported
Sorafenib	4.90%	14.3 months	Not reported	Not reported	Not reported
Pazonpanib	6.3%-7.6%	7-12 months	Not reported	Not reported	Not reported
Bevacizumab (and combined with doxorubicin)	12%-40%	Not reported	Yes	Not reported	Not reported
R1507	13%	Not reported	Not reported	Not reported	Not reported
Rexin-G	0%	1.2-7.8 months	No	No	No

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