spots than those obtained for C-857 under experimental conditions. This technique was used also to demonstrate the DNA adduct formation by C-1748 in human colon carcinoma HT-29 cells. The chromatographic pattern of DNA adducts detected resembled the ones observed in cell-free system. In conclusion, current studies along with interstrand DNA crosslinking demonstrated for a number of 4-substituted analogues suggest that also this new generation of 1-nitroacridines with lowered toxicity are able to bind covalently to DNA. This implies that DNA represents their major molecular target whose covalent modification induces a cascade of biological events eventually leading to apoptosis.

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Oral administration of clofarabine daily × 5 every 4 weeks in patients with advanced solid tumours in a phase I and pharmacokinetic study

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Background: Clofarabine, a next-generation purine nucleoside analogue, inhibits DNA polymerase α and ribonucleotide reductase and disrupts mitochondrial integrity resulting in release of cytochrome C and apoptosis-inducing factor. Several clinical trials examined the activity of an intravenous infusion (IV) of clofarabine in solid tumors and hematological malignancies. However, the oral administration of clofarabine is also possible and may offer advantage over the IV form. For example, superior curative activity was observed with daily oral compared to IV clofarabine administration in HT-29 and colon 36 xenograft models. Therefore, a phase I study to determine the safety and appropriate dose of oral clofarabine is warranted. **Methods:** Pts with advanced solid tumors that failed conventional therapy were treated with clofarabine administered orally for 5 consecutive days every 28 days. Cohorts of pts were dose-escalated according to a modified Fibonacci scheme to determine DLT and the MTD. **Results:** To date 11 pts (M/F: 4/7; median age=64) with advanced solid tumors (kidney n=4, colon n=2, adenoid cystic n=1, bladder n=1, cervical n=1, non-small cell lung n=1, and squamous cell skin n=1) have received 29 cycles (median 3; range 1–4) of oral clofarabine over 4 dose levels (1.0, 1.5, 2.25, and 3.5 mg/m^2). Best response to date: stable disease in 7 pts; progressive disease in 3 pts; and 1 pt pending response assessment. Cycle 1 drug-related grade 1–2 toxicities include: fatigue (n=6), nausea (n=4), abdominal cramping (n=2), anemia (n=2), stomatitis (n=2), leucopenia (n=1), thrombocytopenia (n=1), emesis (n=1), pruritis (n=1), diarrhea (n=1), and myalgias (n=1). One pt with cervical cancer treated at 2.25 mg/m^2 experienced grade 3 diarrhea on cycle 1 day 2, but subsequently was removed from study on day 19 due to obstruction from a large pelvic mass requiring an ileocolostomy. Maximal plasma clofarabine concentrations in the 1, 1.5 and 2.25 mg/m^2 cohorts averaged 5.3 (±1.6), 7.6 (±4.0) and 10.3 (±4.3) ng/mL, respectively. $AUC_{(0-24)}$ averaged 40.7 (±13.9), 59.6 (±16.1), and 87.8 (±27.4) ng*h/mL. Both C_{max} and $AUC_{(0-24)}$ increased with clofarabine dose. The accumulation ratio after 5 days was 1.4 (±0.33). Based on historical IV data, the oral bioavailability of clofarabine was estimated to be >70%. **Conclusion:** Oral clofarabine shows good bioavailability with characteristics of dose-dependent absorption. Accrual continues at 3.5 mg/m^2 to further define the MTD.

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HKH40A, potent agent agaist GI cancers, targets p53 or when that is mutated, Akt

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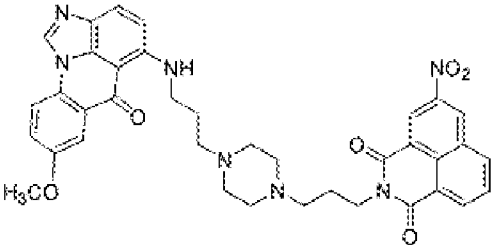
HKH40A is a synthetic agent with very potent but selective activity against gastro-intestinal cancers.

The compound binds to genomic DNA by intercalation of one of the aromatic residues, with the rest of the molecule residing in the minor groove. The operational hypothesis is that the complex "hijacks" critical proteins involved in DNA repair and transcription. Expression array studies have shown that the compound affects the expression of numerous genes in tumor cells, many of them associated with the cell cycle and apoptosis. HKH40A and its closely related des-methoxy analog WMC79 are very toxic to human colon cancer cell lines that express the wild type p53 tumor suppressor gene (LC_{50} = 25nM for RKO and HCT116 cells for HKH40A). Those cells are killed by a p53-dependant apoptotic cascade, initiated by a rapid upregulation of p53, which results in the activation of the FasL pathway, upregulation of the Bax/Bcl2 ratio and the resultant activation of the mitochondrial apoptosis pathway. All these biochemical changes result in activation of caspase 3 that in turn activates pro-apoptotic endonucleases. Upregulation of p53 is frequently a response to DNA damage, which in this case may be the consequence of HKH40A (and WMC79) being potent topoisomerase-1 poisons. However, experiments with topoisomerase-1 deficient cells showed that the enzyme is not the only target for the drugs. HKH40A is also a very potent agent against pancreatic and liver cancer cells (LC_{50} = 80 nM for ASPC-1 and 60 nM for Hep3B). The target for the drug in these tumors is not p53 since that is either mutated or not expressed. The compound arrests the growth of these cells at the G2-M checkpoint (upregulation of cyclin B1 and sustained phosphorylation of cdk1). All of these cell lines overexpress the phophorylated form of Akt, which is a pro-survival protein since it inhibits several key elements of apoptosis. HKH40A is a very potent inhibitor of phospho-Akt and the upstream PI3 kinase in pancreatic adenocarcinoma and hepatocellular carcinoma cells that we examined. The cell cycle effects are consistent with this finding. We conclude, that phospho-Akt is the molecular target for HKH40A in those cancers that express the protein (pancreas and liver). However, in wt p53 cancers the inhibition of topoisomerase 1 and the activation of the p53 cascade appear to be the principal targets for the drug. HKH40A is curative for orthotopic liver cancer in rats, with no evidence of toxicity. HKH40A is a prime agent for clinical development.



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Phase I and pharmacokinetic (PK) study of trabectedin (ET-743) administered as a 1-hour infusion weekly for 3 consecutive weeks every 4 weeks to patients with advanced cancer

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Trabectedin is a tetrahydroisoquinoline alkaloid isolated from *Ecteinascidia turbinata* covalently targets guanine in GC-rich region of DNA minor groove creating DNA bend towards the major groove; interferes transcription factors-DNA interaction; and causes DNA breaks by nucleotide excision repair. Thus cancer cells undergo apoptosis or cell cycle arrest. Trabectedin has been tested in phase I and II studies using different infusion schedules and doses and is well tolerated with preliminary activity in sarcoma, breast and ovarian cancer. To maximize the tolerability, efficacy, and overall therapeutic index of trabectedin, this study evaluated the feasibility, safety, and PK behavior of trabectedin as a 1-h infusion weekly ×3 every 4 weeks. The results of a previous study at our institution indicated a favorable toxicity profile and antitumor activity when the agent was administered over 3 hours weekly ×3 every 4 weeks. To date, 31 pts (median age 45, [23–75]; M:F 17:14; tumor types: sarcoma:ovarian:breast:melanoma 27:2:1:1; 105 Cycles was delivered with a median of 2 [1–14] over 6 dose levels (460 [6], 580 [3], 610 [6], 700 [8], 800 [6 lightly-pretreated (LP) & 1 heavily-pretreated (HP)], 920 mcg/m2 [1]). Dose-limiting toxicities (DLTs) during the first 2 cycles include: gr 4 ANC >5 d [1] at 460; gr 3 myalgia/fatigue [1] at 610; delay of Cycle 2 >2 wk for ANC<1,500, gr 3 neuropathy/fatigue, febrile neutropenia [1 each] at 700; gr 4 neutropenia, followed by rhabdomyolysis and death at 800 in a heavily-pretreated ovarian cancer pt with compromised bone marrow reserve due to repeated carboplatin exposure; treatment held for 2 weeks [1] at 920. Toxicities were mostly mild to moderate except: asymptomatic gr 3 transaminase elevation [22.5%], gr 3/4 CK [6%], gr 3/4 ANC [19%], gr 3 fatigue and myalgia [3%] and gr 3 vomiting [3%], which all occurred at doses ⩾700. PK evaluation up to 700 demonstrated linearity, similar to prior data of other dosing schedules, with $\tau_{1/2}$ 56.5±54.2 h and Vss 2463±1580 L. A confirmed PR was observed for 36 wk in a second-line metastatic uterine leiomyosarcoma; and SD in 4 leiomyosarcoma [24–28 wk], 2 liposarcoma [14, 56 wk] and 1 fibrosarcoma [16 wk] were observed. Clinical activity was seen in selected soft tissue sarcoma subtypes, which failed prior doxorubicin and/ifosphamide-based