cell proliferation was seen. Exploring the possibility of radiosensitization, results showed that treatment with 17-AAG indeed sensitized esophageal cancer cells towards gamma photon radiation in an at least addidative manner.
Conclusions: Hsp90 was specifically expressed in oesophageal cancer. Our data support the notion that Hsp90 inhibition may be a way to sensitize esophageal tumor cells toward radiotherapy, conceivably by downregulation of EGF receptor expression and inhibition of downstream proliferative and anti-apoptotic signaling pathways.

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Pharmakokinetic/phamacodynamic relationship in human xenograft models and PBMC's treated with the Hsp90 inhibitor NVP-AUY922

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NVP-AUY922 is a synthetic inhibitor of Heat Shock Protein 90 (Hsp90) ATPase activity. Hsp90 is a ubiquitously expressed molecular chaperone which plays an important role in the conformational maturation and activation of a large number of "client" proteins that have been implicated in oncogenesis. Hsp90 has attracted considerable interest as a therapeutic target for cancer treatment since Hsp90 ATPase inhibition induces the simultaneous degradation of multiple oncogenic proteins. Antitumor activity and tolerability of NVP-AUY922 was determined in preclinical cancer animal models. The pharmacokinetic profile of NVP-AUY922 in plasma and tumor tissues was evaluated at well tolerated, efficacious dose levels. We observed tumor specific compound retention and rapid tissue and plasma clearance. *Ex vivo* PK/PD analyses of tumor tissues upon acute dose or after termination of *in vivo* efficacy studies showed a time-dependent correlation between compound concentration and down-regulation of target proteins. In addition to the effect on targeted oncogenic proteins, other markers of activity were investigated.
Disruption of the Hsp90 chaperone hetero-complex, resulting in a loss of Heat Shock Factor-1 (HSF-1) repression and induction of Heat shock protein 70 (Hsp70) is considered to be one of the most robust biomarkers to detect inhibition of Hsp90 ATPase activity in clinical trials. In the current dose escalation study in patients with solid tumors, induction of Hsp70 is being evaluated for pharmacodynamic effect of AUY922 treatment in a surrogate tissue, peripheral blood monocytes (PBMC), at multiple time-points. In concordance with pre-clinical studies, there is a good correlation between NVP-AUY922 blood concentration and the effect on Hsp70 levels in PBMCs.

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BIIB021, a fully synthetic oral small molecule inhibitor of Hsp90, shows potent anti-tumor activity as a single agent and in combination with standard of care therapies in preclinical tumor models

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The heat shock protein 90 (Hsp90) is a molecular chaperone that functions in the maturation and stabilization of its so called client proteins. Hsp90, in complex with other co-chaperone proteins, catalyzes the conformational changes required for client protein function via its ATPase activity. Mutant and over-expressed oncoproteins that drive malignant progression are particularly dependent on Hsp90 chaperone activity. In tumor cells, inhibition of Hsp90 results in degradation of these proteins followed by cell death making Hsp90 a target of substantial interest for cancer therapy. BIIB021, formerly known as CNF2024, is a novel, fully synthetic oral inhibitor of Hsp90. BIIB021 binds competitively with geldanamycin in the ATP binding pocket of Hsp90. In cell-based assays with a variety of human cell lines, BIIB021 induced the degradation of HER-2 and other key client proteins including AKT, ERK, Raf-1, EGFR. BIIB021 upregulated the expression of the heat shock proteins including Hsp70 and Hsp27, in a similar manner to other Hsp90 inhibitors. Oral administration of BIIB021 led to the degradation of HER-2, the induction of apoptosis and the inhibition of tumor growth in several human tumor xenograft models. BIIB021 showed antitumor activity when administered on both daily and intermittent dosing schedules. Furthermore, the administration of BIIB021 in combination with a range of standard of care chemotherapies and molecularly targeted therapies enhanced the activity of either monotherapy alone. BIIB021 is a promising new Hsp90 inhibitor that is fully synthetic and designed to be given orally, thereby supporting flexible therapeutic dosing schedules. BIIB021 is currently undergoing Phase 1 and Phase 2 clinical trials in hematological and solid tumors.

Hormonal agents

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BMS-641988: A highly potent and rationally designed inhibitor of the androgen receptor (AR), with efficacy in castration resistant human prostate cancer xenograft models

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Background: 1st-line androgen ablation therapy (AAT) is a highly effective treatment for metastatic prostate cancer (PC), however, most patients will progress to a castration resistant form of the disease. Research suggests that reactivation of the AR pathways is a major factor leading to castration resistant PC, suggesting that new agents that act at the level of the AR should be effective in treating this disease.
Methods: Through AR co-crystal structures, we applied structure based drug design to create a new, highly potent inhibitor of the AR, BMS-641988 (988). The activity of 988 was examined in a series of *in vitro* reporter assays and *in vivo* PD and human PC xenograft models.
Results: 988 demonstrates increased potency compared to the clinically used anti-androgen bicalutamide (BC), in both binding affinity to AR and inhibition of AR mediated transactivation in cell based reporter assays.

Table 1

	BMS-641988	bicalutamide
Radioligand competitive binding assay in MDA-MB453 cells		
Ki (nM)	1.8±02	37±3
PSA driven reporter transactivation		
MDA-MB-453 (wtAR) IC50 (nM)	11±3	166±38
LNCaP (mutant AR) IC50 (nM)	110±62	680±376
CWR22rv1 (mutant AR) IC50 (nM)	322±130	3432±962

988 potently inhibits the AR dependent growth of the prostate and seminal vesicle in a mature and immature rat prostate weight model. In these models, 988, compared to BC, created a proteomics and prostate histological profile that better recapitulated that of surgical castration. 988 exhibited a greater average %-tumor growth inhibition compared to BC (D%TGI of >90 vs. <50) in the human PC xenograft model CWR-22LD1 (LD1), an androgen insensitive variant of the CWR22 line. 988 is efficacious in a LD1 model made refractory to treatment with BC. 988 is highly efficacious in the LuCaP 23.1 human PC xenograft model, a model derived a patient who failed AAT, inducing stasis at 3 mg/kg (po). Using the LD1 line, in a genome wide AR-positioning analysis of cells treated with either 988 or BC, and in a transcriptomic analysis of tumors from mice treated with 988, BC, or surgical castration, 988 promotes a gene expression profile distinct from BC and more similar to castration.
Conclusion: BMS-641988 shows potent activity in a variety of PC tumor lines and xenograft models derived from patients who failed AAT. Compared to BC, 988 generates a profile more indicative of full castration in rodents. Based on the promising preclinical activity of BMS-641988, it has been advanced into clinical development for the treatment of PC.