(Ktrans) and the initial area under gadolinium concentration (IAUGC) were evaluated 24 hours before and 2 hours after dosing in 25 patients (DLs: 80–275) by dynamic contrast enhanced magnetic resonance imaging (DCE-MRI).
Results: Overall, 42 patients (PS 0/1: 18/24; M/F: 33/9) with a median age of 61 years (range 23 to 76) received a total of 101 cycles (range 1 to 7). Prior treatment lines ranged from 1 to 7 (median 3). No DLT occurred and MTD has not yet been reached. Related toxicities were grade 1 chills in 18 patients (53%) over 34 cycles (42%). Nine patients (26%) had grade 2 toxicities. Cmax and AUC increased with dose ($p = 0.0006$ and $p = 0.001$, respectively). Levels of sR2 peaked higher than those of sR1 (7.9 v 3.6 ng/mL; p<.0001). Changes in sRs however did not differ across DLs ($p = 0.49$ for sR1 and $p = 0.43$ for sR2), suggesting a plateau in shedding kinetics. By DCE-MRI, median values pre- and post-first cycle were 0.15 and 0.09 min-1 for Ktrans and 10.4 and 7.2 mM/L/sec for IAUGC, respectively ($p = 0.02$ for both). Twenty patients (80%) showed dose-unrelated reductions in tumour vascularity. In these patients, Ktrans significantly decreased from 0.19 to 0.07 min-1 ($p < 0.0001$), with a median change of −62% (range −24 to −91), whereas IAUGC declined from 14.6 to 5.4 mM/L/sec ($p < 0.0001$), with a median reduction of −54% (range −3 to −97). These decreases correlated inversely with high baseline values of Ktrans ($r = -0.91$, $p < 0.0001$) and IAUGC ($r = -0.51$, $p = 0.02$). Additional dose escalations are ongoing.
Conclusion: NGR-hTNF can be safely escalated at doses higher than MTD and induces low shedding of receptors and early antivascular effects.

1206 ORAL

Smaller, Faster Phase III Trials − New Approach for Assessing Targeted Agents?

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Background: Traditional clinical trial designs strive to definitively establish the superiority of an experimental treatment, which results in risk adverse criteria and large sample sizes. Increasingly, common cancers are recognized to consist of small subsets with a specific aberration for targeted therapy, making large trials infeasible. We performed simulations studies to compare the performance of different trial design strategies to determine over a 15 year research horizon.
Methods: We simulated a series of two-treatment superiority trials over 15 years using different trial design parameters. Trial parameters examined included: number of positive trials to establish superiority (1 versus 2), α-level (from 0.025 to 0.50), and number of trials over 15 years (thus trial sample size, SS). Different disease scenarios (median survivals), accrual rates, and distributions of treatment effect were studied. Metrics used included: gain in survival rate (Hazard Ratio, HR, year 15 versus year 0) and risk of an overall effect of harm ($HR > 1$).
Results: For all scenarios, overall gains were greater using the criterion of 1 positive trial (versus 2) and as α increased from 0.025 to 0.50. Gains increased substantially as α increased from 0.025 to 0.20, but plateaued for values beyond 0.20. Important gains in survival were achieved with SSs smaller than required under traditional criteria. Reducing the SS and increasing α increased the mean gain but also the likelihood of having a poorer survival rate at year 15, but the chance was <7% in all scenarios with α lower or equal to 0.20. Results were consistent under different assumed distributions for treatment effect. The greatest gains were achieved in disease scenarios with smallest expected median survival.
Below is an example of results: median survival 1 year, accrual rate 100/year, historical scenario (mean HR 0.95).

Decision criterion		Optimal strategy		Performance	
No. of positive trials	0.025	No. of trials	SS	Mean HR (at 15 year)	Risk of HR > 1
1	0.025	7	114	0.59	0.5%
1	0.05	8	88	0.55	1%
1	0.10	10	50	0.50	3%
1	0.20	10	50	0.42	3%
2	0.025	5	200	0.69	<0.1%
2	0.05	7	114	0.65	<0.1%
2	0.10	8	88	0.60	0.5%
2	0.20	9	66	0.53	1%

Conclusions: A traditional trial design strategy yields smaller expected gains over a 15 year horizon compared to strategies using larger α and smaller SSs. As patient populations become more specific (and thus smaller), the current risk adverse trial design strategy may slow long term progress and deserves reexamination.

Poster Presentations (Mon, 26 Sep, 14:00−16:30)
Drug Development

1207 POSTER

Phase I Dose-Finding Study for Pazopanib (P) and Paclitaxel (T) in Combination in the First-line Setting in Patients (pts) With Advanced Solid Tumours

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Background: This open-label Phase I study (VEG111109, NCT00866528, sponsored by GSK) investigated the safety and pharmacokinetics (PK), of P, an oral multikinase angiogenesis inhibitor, in combination with T in pts with advanced solid tumours. A secondary objective was to describe clinical activity. Results from the dose-escalation phase of the study are reported; 6 additional pts are currently being enrolled in an expansion cohort at the recommended Phase II dose.
Material and Methods: A 3+3 design was used for dose-escalation. T (3h infusion q3W x6 cycle) started at 135 mg/m^2 due to an anticipated PK interaction with P (once daily po from Cycle 1, Day 2 [C1D2]). PK samples were obtained C1D1 (T alone) and C2D1 (T+P) from pre-dose to 24h post-dose to determine area-under-curve (AUC) and max concentration (Cmax).
Results: The dose-escalation phase of the study enrolled 24 pts (median age 58 years [31−80], 13M/11F, ECOG PS 0−1) with previously untreated advanced solid tumours (14 metastatic melanoma/10 advanced NSCLC); 22 pts received T+P (median cycles 5; P up to 274 days). The most frequent AEs were: hypertension (95%), alopecia (86%), fatigue (73%), nausea (64%), diarrhea (55%), hair color change (50%), and myalgia (50%); 94% AEs were G1/2, 5% G3, and 1% G4. DLTs were seen in 3 pts; 1 pt in Cohort 1 resulting from a possible drug-drug interaction with a concurrent medication and 2 pts in Cohort 2, thereby exceeding the MTD. No DLTs were observed in Cohort 3 or 4; however 2/6 subjects in Cohort 4 had reduced dose T in C2 due to C1 neutropenia. Cohort 3 was a better tolerated dose level than Cohort 4. Median T AUC increased in the presence of P by approximately 25−30% at each dose level tested.

T mg/m^2/ P mg	N	T PK, median ratio C2:C1		No. of subj by worst	DLT
		AUC(0-inf)	Cmax	Grade AE G3/G4	
135/800	6	1.23, n = 5	1.25, n = 5	2/2	1 G4 ALT
175/800	4	1.30, n = 2	1.14, n = 3	3/1	1 G3 rash 1 G3 ALT+G2 rash
150/800	6	1.33, n = 6	1.31, n = 6	4/0	
175/400	6	1.28, n = 4	1.23, n = 4	2/1	

T+P was active at each dose level; of the 20 pts evaluable for response, 10 (4 NSCLC, 6 melanoma) had confirmed PRs and 6 (3 NSCLC, 3 melanoma) had SD $\geqslant$12 weeks.
Conclusions: The 150 mg/m^2 T/800 mg P dose level was selected as the recommended Phase II dose. Due to PK interaction, T exposure at this dose level is approximately equal to exposure after 200 mg/m^2 T alone. T+P demonstrated promising anti-tumour activity in both NSCLC and melanoma.