CLINICAL IMPORTANCE OF INCLUDING NEW AND NON-TARGET LESION ASSESSMENT OF DISEASE PROGRESSION (PD) TO PREDICT OVERALL SURVIVAL (OS): IMPLICATIONS FOR RANDOMIZED PHASE II STUDY DESIGN.

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Background: Fridlyand (2011) retrospectively compared PFS vs. change in tumor burden as a primary endpoint in phase II non-small cell lung cancer (NSCLC) trials to inform phase III decision making and found the use of PFS was superior. Since the classic tumor burden model only uses measurements of target lesions, we investigated whether the model could be strengthened by incorporating new and non-target lesion progression. The ability to use a strong tumor burden model has the benefit of potentially earlier decision making and considerable timeline savings. **Methods:** We analyzed five phase III trials of combination chemotherapy ± targeted therapies with an OS primary endpoint: 1st, 2nd line NSCLC (ATTRACT-1, -2), 1st, 2nd line colorectal carcinoma (CONFIRM-1, -2), and 2nd line ovarian cancer (EPO906A2303). We applied Cox's proportional hazards model to OS using the covariates of baseline tumor burden, 1st tumor assessment percentage change from baseline, new lesions, and non-target PD. **Results:** See table. **Conclusions:** We show that predictive models for OS should consider new and non-target lesions for PD, as well as target lesion tumor burden, findings independently corroborated by Suzuki (2011). We propose a longitudinal rank-based randomized phase II design, ranking a patient's risk of death, differentially weighting PDs by type and time of PD, and percentage change in tumor burden. This may be more informative for phase II decision making for phase III trials based on OS, than PFS which only uses time of PD. Further studies with other tumor types and treatment modalities are warranted.

Study	Estimated hazard ratio (Wald test p-value)			
	Baseline tumor burden*	% change from baseline*	New lesion	Non-target lesion PD
ATTRACT-1	1.36 (p<0.001)	1.37 (p<0.001)	3.37 (p<0.001)	1.95 (p<0.001)
ATTRACT-2	1.21 (p<0.001)	1.49 (p<0.001)	3.91 (p<0.001)	1.19 (p=0.332)
EPO906A2303	1.09 (p=0.053)	1.12 (p=0.046)	2.20 (p<0.001)	1.67 (p<0.001)
CONFIRM-1	1.31 (p<0.001)	1.38 (p<0.001)	3.02 (p<0.001)	1.40 (p=0.087)
CONFIRM-2	1.41 (p<0. 001)	1.47 (p<0.001)	2.54 (p<0.001)	1.81 (p<0.001)

* Unit of measurement is one standard deviation.

BACKGROUND: UTILITY OF PHASE II MODELS AND ENDPOINTS FOR PREDICTING PHASE III OUTCOME BASED ON OVERALL SURVIVAL (OS)

- Baseline and % change from baseline tumor burden at weeks 6/8 as continuous variables predict OS well (NSCLC, MCRC and MBC) and may be useful in Phase II (Wang et al 2009, Bruno and Claret 2009)
- Lara et al (2008) propose use of the disease control rate (DCR=CR/PR/SD) at week 8 to predict OS in NSCLC
- Fridlyand et al (2011) show greater correct rate of 'Phase II go/no go' decisions with PFS than change in tumor burden
  - Optimal cutoff time at month 6 for both PFS and tumor burden assessments rather than weeks 6/8
  - PFS based on full analysis set (FAS); others use landmark analyses (exclude early deaths, early drop-outs, etc.) Phase III also based on FAS (all randomized patients)
  - NSCLC=non-small cell lung cancer; MCRC=metastatic colorectal cancer; NBC=metastatic breast cancer

KEY QUESTION AND METHODS

Key question:

- Can we strengthen Phase II endpoints related to OS prediction to improve success rate or decrease time to 'Phase III go' decision?
- Tumor burden model only considers target lesion changes
  - New lesion and PD in non-target lesions not considered
- Disease control rate endpoint does not consider type of PD, extent of PD and baseline tumor burden

Methods:

- We applied the Cox proportional hazards model to OS from 5 negative Phase III studies (covariates: baseline tumor burden and % change at week 6/8, new lesion PD and non-target PD) to investigate potential improvement to the tumor based model
- Baseline and post-baseline tumor burden data each standardized (mean 0, s.d. 1) to make these commensurate across the five studies

METHODS: 5 PHASE III TRIALS ANALYZED (DATA POOLED SINCE NO TREATMENT EFFECTS*) (1)

Study (week of tumor assessment)	Treatment	Indication	N analyzed/N randomized
ATTRACT-1 (week 6)	Carbo/taxol ± ASA404	1st line NSCLC	1078/1299
ATTRACT-2 (week 6)	Docetaxel ± ASA404	2nd line NSCLC	726/900
EPO 906 Study 2303 (week 8)	EPO906 vs. Doxil	2nd line OVCA	524/829
CONFIRM-1 (week 8)	FOLFOX4 ± PTK787	1st line MCRC	1071/1168
CONFIRM-2 (week 8)	FOLFOX4 ± PTK787	2nd line MCRC	776/855

OVCA=ovarian cancer; ASA404: Vascular disruptive agent; EPO906: microtubule stabilizing agent, PTK787: VEGF inhibitor

* Addition of investigational agent had no significant effect

METHODS : BASELINE TUMOR BURDEN AND % CHANGE FROM BASELINE (2)

Study	Baseline Tumor Burden (cm)		Percentage Change from Baseline (%) at weeks 6/8	
	Mean	Std	Mean	Std
ATTRACT-1	10.5	6.3	-16.1	23.6
ATTRACT-2	9.3	8.5	-1.5	23.7
EPO906 Study 2303	10.3	8.6	-3.5	36.8
CONFIRM-1	12.0	8.6	-22.3	26.2
CONFIRM-2	11.4	7.7	-8.2	27.0

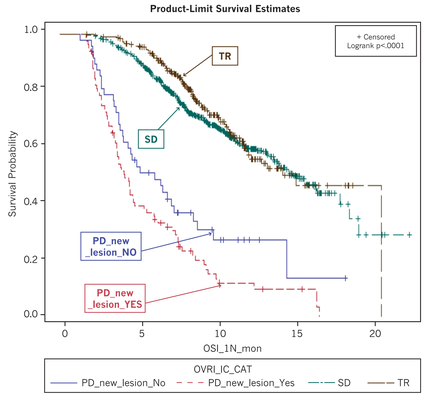
Std = standard deviation

RESULTS: COX MODEL EVALUATING THE IMPACT OF NEW LESION AND NON-TARGET PD AT WEEKS 6/8 ON OS

Study	Estimated hazard ratio (Wald test p-value)			
	Std baseline lesion size*	Std % change from baseline*	New lesion	Non-target lesion PD
ATTRACT-1 (n=1078) (1st line NSCLC)	1.365 (p<0.0001)	1.369 (p<0.0001)	3.367 (p<0.0001)	1.947 (p<0.0001)
ATTRACT-2 (n=726) (2nd line NSCLC)	1.211 (p<0.0001)	1.487 (p<0.0001)	3.907 (p<0.0001)	1.186 (p=0.3319)
EPO906 2303 (n=524) (2nd line OVCA)	1.092 (p=0.0519)	1.120 (p=0.0462)	2.202 (p<0.0001)	1.674 (p=0.0004)
CONFIRM-1 (n=1071) (1st line MCRC)	1.314 (p<0.0001)	1.385 (p<0.0001)	3.024 (p<0.0001)	1.401 (p=0.0867)
CONFIRM-2 (n=776) (2nd line MCRC)	1.412 (p<0.0001)	1.469 (p<0.0001)	2.538 (p<0.0001)	1.814 (p<0.0001)

* Standardized variable, the unit of measurement is one standard deviation. HR≥2, 1.5≤HR<2, HR<1.5

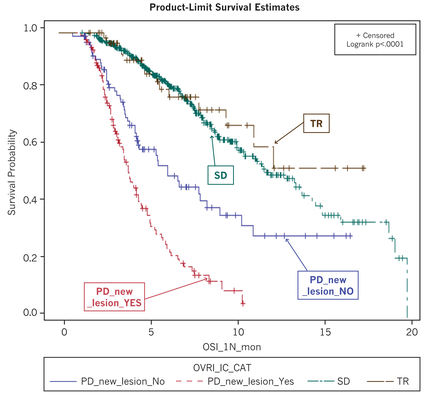
RESULTS: ADDING NEW LESION PD IMPROVES OS PREDICTION VS. DCR AT WEEK 6 FOR ATTRACT-1 (1ST LINE NSCLC)



	N	Death	Median Survival Time (month)	One Year Survival Rate
TR	248	77	15.3	0.60
SD	688	241	15.0	0.60
PD_new_lesion_No	47	33	6.1	0.27
PD_new_lesion_Yes	84	73	4.2	0.12

TR=Tumor Response (CR or PR at week 6)

RESULTS: ADDING NEW LESION PD IMPROVES OS PREDICTION VS. DCR AT WEEK 6 FOR ATTRACT-2 (2ND LINE NSCLC)



	N	Death	Median Survival Time (month)	One Year Survival Rate
TR	63	14	---	0.52
SD	450	141	12.7	0.50
PD_new_lesion_No	89	45	6.1	0.29
PD_new_lesion_Yes	117	82	3.9	0.05

TR=Tumor Response (CR/PR at week 6)

RESULTS: RELATIVE HAZARD BY TYPE AND EXTENT OF PD (ATTRACT-1 RELATIVE HAZARD TABLE)

Baseline tumor burden (cm)	Week 6 tumor burden (cm) (% change from baseline)	New lesion PD at week 6	Non-target lesion PD at week 6	Relative hazard
10.5 (mean)	8.8 (-16.1%)	No	No	1.00 (reference)
10.5 (mean)	12.6 (20%)	No	No	1.62
10.5 (mean)	**18.4 (75.1%)**	**No**	No	**3.37**
10.5 (mean)	8.8 (-16.1%)	No	Yes	1.95
10.5 (mean)	12.6 (20%)	No	Yes	3.15
10.5 (mean)	**8.8 (-16.1%)**	**Yes**	No	**3.37**
10.5 (mean)	12.6 (20%)	Yes	No	5.44
10.5 (mean)	8.8 (-16.1%)	Yes	Yes	6.56
10.5 (mean)	12.6 (20%)	Yes	Yes	10.60

SUMMARY OF FINDINGS AND INDEPENDENT CONFIRMATION

- Very consistent findings across 5 Phase III trials and 3 different solid tumor indications (NSCLC, ovarian, MCRC)
- Need target lesion data and information about both new lesions and non-target PD for OS prediction
- New lesions most significant predictor of OS (p<0.0001 in all 5 studies)
- Suzuki et al (2012) also found new lesions to be the most important predictor of OS as well as importance of non-target lesion PD in a randomized Phase III trial in 1st line MCRC patients (irinotecan vs. bolus or infusion 5-FU) (n=567)

PROPOSED RANDOMIZED PHASE II STUDY DESIGN INCORPORATING OUR FINDINGS

Design Requirement	Proposal
Type of early PD has differential risk on OS	Form 5 PD categories in descending order of risk on OS: Early death > new lesion + non-target PD > new lesion PD > non-target PD > no off-target PD
% change from baseline tumor burden important	For early death, rank in ascending order of OS; within each other category, rank in descending order of % change from baseline
Baseline tumor burden important	If ties occur, break ties by descending order of baseline tumor burden, use baseline as covariate in our analysis
Need to extend to ITT Population (Full analysis set)	Use midrank imputation (average of worst possible and best possible ranks) as per Hudgens and Satten (2002)
Greater ranks indicative of greater efficacy – use rank analysis of covariance model to compare treatment groups using statistical significance for Phase II decision making; can extend to longitudinal analysis	

FUTURE WORK: TO EVALUATE CORRECT PHASE II DECISION RATE FOR PROPOSED MODEL VS. DCR AND PFS

- We plan to simulate thousands of randomized Phase II studies from these Phase III trials
- Evaluate proposed design relative to DCR with early data cutoff (approximately 6-8 weeks after last patient randomized) and relative to PFS in same simulated study when PFS is mature (number of events reached)
- Compare rate of correct Phase II decisions (no go) for proposed method and DCR or PFS at the two cutoff times
- Determine distribution of difference in cutoff times
- Create "positive" Phase III trials by oversampling long-term survivors and repeat process (correct Phase II decision="go")

DISCUSSION: PROPOSED RANDOMIZED PHASE II DESIGN

- Pros: Incorporates type of PD, change of tumor burden (PD or shrinkage), baseline tumor burden and time of PD into analysis and uses full analysis set- more informed.
- Cons: More data preparation, more complex endpoint, less intuitive clinical interpretation than other randomized Phase II endpoints
- Caveats: Degree of improvement to Phase II decision making to be determined
- May not be applicable to other settings (e.g. immunotherapy)
- Further replication of results desirable including alternative modeling of tumor burden data (e.g. log ratio)

CONCLUSIONS

- Consistent findings across 5 Phase III trials with independent confirmation demonstrate that target lesion data and information about both new lesions and non-target PD are needed for optimal OS prediction
- These findings can be used to simulate randomized phase II designs and compare rate of correct phase II decisions (no go) of the proposed designs and DCR or PFS at early or mature timepoints
- May result in more informed Phase II decision making with more time and resource savings

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