QUANTITATIVE ANALYSIS OF THE IMPACT OF DEEPNESS OF RESPONSE ON POST-PROGRESSION SURVIVAL TIME FOLLOWING FIRST-LINE TREATMENT IN PATIENTS WITH MCRC

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Background: The extent of tumor shrinkage in patients (pts) receiving chemotherapy with or without monoclonal antibodies is prognostic for progression-free survival (PFS) and overall survival (OS). The ‘Deepness of response (DpR)’ concept aims to relate tumor shrinkage to post-progression survival (PPS). If tumor shrinkage does take place, DpR is the percentage of tumor shrinkage observed at the nadir compared with baseline. DpR is 0 for no change and negative if the tumor load increases. Longest diameter (LD) based on RECIST or a calculated tumor volume (ASCO GI 2012 #635) can be used to quantify the tumor load. A joint model was presented (ASCO GI 2012 #580, ASCO 2012 #3603) which allows the prediction of PPS time for an individual patient based on DpR.

Methods: Based on the data from the randomized CRYSTAL and OPUS trials, four treatment regimens (FOLFIRI +/- cetuximab and FOLFOX4 +/- cetuximab) were studied. A joint model was used to quantify individual changes in tumor size over time and relate these changes to PFS and OS. Relationships between baseline tumor load and DpR and PPS were studied. A Spearman correlation was used to study the relationship between DpR and PPS for KRAS wild-type pts with progressive disease.

Results: Results are reported using LD-based measures for 841 pts with KRAS wild-type tumors and imaging data: 663 from the CRYSTAL study and 178 from the OPUS study. The 348 pts treated with FOLFIRI alone had a median DpR of 33.3% (interquartile range [IR]: 8.0%, 58.0%) while the 315 pts treated with FOLFIRI + cetuximab had a significantly higher median DpR of 50.9% (IR: 18.4%, 78.6%), p < 0.0001. The 96 pts treated with FOLFOX4 alone had a median DpR of 30.7% (IR: 4.0%, 55.9%) and the 82 pts treated with FOLFOX4 + cetuximab had a significantly higher median DpR of 57.9% (IR: 24.0%, 92.9%), p = 0.0008. Correlation between DpR and PPS for pts with documented disease progression was statistically significant in each of the two treatment groups and for both LD-based and volume-based measurements (p < 0.0001 for the CRYSTAL study and p < 0.005 for the OPUS study). The hazard ratios show a higher DpR to significantly favor a longer PPS time across the two studies and both treatment groups for both LD- and volume-based measurements.

Conclusion: Our results emphasize the value of DpR as a new efficacy outcome measure for clinical trials. Furthermore the addition of cetuximab to chemotherapy was shown to significantly increase DpR with the prolongation of PPS and thus OS.