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Validation of a 12-gene colon cancer recurrence score (RS) in patients (pts) with stage II colon cancer (CC) from CALGB 9581.

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Background: The 12-gene RS (Genomic Health, Inc.) has been shown to predict risk of recurrence in stage II colon cancer (CC) pts in QUASAR. We conducted a validation study in tumor specimens from pts enrolled in CALGB 9581, which found no difference for edrecolomab (MoAb 17-1A) v. observation in 1672 pts with, on average, low risk stage II CC (14% 5-yr recurrence.)

Methods: Cohort sampling included all pts with available tissue and recurrence and random pts w/o recurrence (3:1 ratio). Gene expression was analyzed by RT-PCR using FFPE from primary tumor. Mismatch repair (MMR) protein status (D= Deficient; I= Intact) was assessed by IHC for MLH1 and MSH2. Primary aim: prognostic value of continuous RS alone and in presence of MMR and traditional clinical/pathologic prognostic variables. A weighted Cox proportional hazards model was used to test the association between RS and recurrence-free interval (RFI) based on a Wald-type test statistic constructed using a weighted partial likelihood estimate and robust variance estimate.

Results: Tumor was available for 1361/1672 (81%) pts. RT-PCR was successful in 690 (162 recurrences) of 736 pts (21% MMR-D, 35% > 70 yrs old, 47% < 12 nodes.) The continuous RS was significantly associated with RFI in univariate analysis (hazard ratio (HR)/ 25 units, 1.52; 95% CI, 1.09-2.12; p=0.01). MMR-D was also associated with RFI (HR, 0.62; 95%CI, 0.39-0.99; p=0.04); # nodes examined and lymphovascular invasion (LVI) were borderline significant (both p=0.06). In a pre-specified multivariate analysis w/ MMR, T-stage, nodes examined, grade, and LVI, RS was the only significant predictor of recurrence (HR/25 units=1.68, 95%CI 1.18-2.38; p=0.004). Recurrence risk at 5 yrs increased as RS increased and among subgroups defined by T-stage and MMR. In pts with T3, MMR-I tumors (n=488) pre-specified low (44% of pts RS < 29), intermediate (33%), and high (22% w/ RS > 39) RS groups had average 5-yr recurrence risks of 13%, 16%, and 21%, respectively.

Conclusions: In 9581, RS improves the ability to discriminate higher from lower recurrence risk stage II CC pts beyond known prognostic factors, particularly in T3, MMR-I pts where traditional factors like grade and LVI were not prognostic.