TPS3650 Poster Session

Trials in progress: Alliance A022104/NRG-GI010—A randomized phase II/III trial testing the efficacy of triplet versus doublet chemotherapy regarding clinical complete response and disease-free survival in patients with locally advanced rectal cancer (LARC; the Janus Rectal Cancer trial).

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Background: A total neoadjuvant therapy (TNT) approach improves compliance with chemotherapy and increases rates of tumor response compared to neoadjuvant chemoradiation (CRT) alone in those with locally advanced rectal cancer. Recent data indicate that optimal sequencing of TNT involves consolidation (rather than induction) chemotherapy to improve complete response rates. The use of FOLFIRINOX has shown to improve response and outcomes compared to CRT and surgery alone. Data have also shown that patients with clinical complete response (cCR) after TNT may be managed with a watch and wait approach (WW) instead of preemptive total mesorectal resection (TME). However, the optimal consolidation chemotherapy regimen to improve cCR rates has not been established, and a randomized clinical trial has not robustly evaluated cCR as a primary endpoint. We designed this NCI-sponsored study of chemotherapy intensification to address this and to increase cCR rates, provide opportunity for organ preservation, and survival outcomes. **Methods:** In this multigroup randomized, seamless phase II/III trial (1:1), up to 760 patients with LARC, T4N0, any T with node positive disease (any T, N+) or T3N0 requiring abdominoperineal resection or coloanal anastomosis and distal margin within 12 cm of anal verge will be enrolled. Stratification factors include tumor stage (T4 vs T1-3), nodal stage (N+ vs N0) and distance from anal verge (0–4; 4–8; 8–12 cm). Patients will be randomized to receive neoadjuvant long-course chemoradiation (LCRT) followed by consolidation doublet (mFOLFOX6 or CAPOX (control arm)) or triplet chemotherapy (FOLFIRINOX (experimental arm)) for 3–4 months. LCRT in both arms involve 4500 cGy in 25 fractions over 5 weeks +900 cGy boost in 5 fractions with a fluoropyrimidine. Patients will undergo assessment 8–12 ($\pm$4) weeks post-TNT completion. The primary endpoint for the phase II portion will compare cCR between treatment arms. A total number of 312 patients (156 per arm) will provide statistical power of 90.5% to detect a 17% increase in cCR rate, at a one-sided alpha = 0.048. The primary endpoint for the phase III portion will compare disease-free survival (DFS) between arms. A total of 285 DFS events will provide 85% power to detect an effect size of hazard ratio 0.70 at a one-sided alpha of 0.025, requiring enrollment of 760 patients (380 per arm). Secondary objectives include overall survival, organ preservation time, time to distant metastasis, and adverse event rates. This study has accrued 587 patients as of January 2025, and is investigating exploratory correlatives (e.g., ctDNA). Support: U10CA180821, U10CA180882, U24 CA196171. https://acknowledgments.alliancefound.org. Clinicaltrials.gov ID: NCT05610163. Clinical trial information: NCT05610163. Research Sponsor: National Cancer Institute; U10CA180821; National Cancer Institute; U10CA180882; U.S. National Institutes of Health; U24CA196171; ECOG-ACRIN MEDICAL RESEARCH FOUNDATION; U10CA180820; National Cancer Institute; U10CA18086; National Cancer Institute; U10CA180888.