Immunotherapy for the Tail End of the GI Tract

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Colorectal Cancer: Biomarkers

• Outside of biomarker selected patients, immunotherapy for CRC has limited indication
• Outside of MSI and POLE ultramutated tumors, there are limited data to suggest utility for ICI therapy
• TMB-H, when accounting for MSI-H or hypermutated phenotype, suggest limited utility to ICI therapy
• PD-L1 testing should have no bearing on treatment decisions
Colorectal Cancer Rx: Biomarkers

**Diagnostic Workup**
- Disease stage confirmed: Surgically unresectable, metastatic, or stage IV
- Tissue-based biomarkers obtained: NGS (including TMB, MSI*, POLE/D1), KRAS/NRAS/BRAF, HER2 expression
- Immunotherapy-naive†
- Patient considered for available clinical trials

** MSI-H or dMMR?**

- **No**
  - **POLE or POLD1 mutation with ultramutated TMB‡**
    - **Yes**
      - Pembrolizumab
      - Nivolumab +/- ipilimumab
    - **No**
      - Refer to published guidelines for non-immuno-oncologic treatments

- **Yes**
  - Pembrolizumab (preferred)
  - Nivolumab + ipilimumab

* MSI: Microsatellite Instability
† Immunotherapy-naive: Indicates the patient has not previously received immunotherapy
‡ Ultramutated TMB: Indicates a high tumor mutational burden
Advanced CRC Treatment: MSI-H/dMMR

• For patients with untreated, advanced disease, pembrolizumab single agent is recommended, combination nivolumab/ipilimumab considered
  • KEYNOTE 177: pembrolizumab vs. SOC chemo +/- biologic
    • Median PFS 16.5 vs. 8.2 mos, OS trend toward experimental, high crossover (>60%). ORR 44% for pembrolizumab arm
  • Checkmate 142: nivolumab/ipilimumab first line setting
    • ORR 69%, median PFS not reached
    • Awaiting results of Checkmate 8HW confirmatory study
Advanced CRC Treatment: MSI-H/dMMR

• For patients with previously treated disease who have not received ICI, pembrolizumab monotherapy or nivolumab, with or without ipilimumab, are recommended
  • KEYNOTE 164: Median OS 31.4 months for patients with 2 or more lines of therapy
  • Checkmate 142: nivolumab monotherapy ORR 31% and OS at 12 months 73% led to approval post 5FU/oxaliplatin/irinotecan
  • Checkmate 142: nivo/ipi cohort, pretreated, ORR 55%, OS rates at 12 months 85%
• Dostarlimab is approved for previously treated, dMMR patients (GARNET)
• Optimal therapy duration unclear: 2 years vs. 1 year
Locoregional CRC: MSI-H/dMMR

• Pilot study dostarlimab in <20 patients with locally advanced rectal cancer
  • 100% complete clinical response rate
  • Clinical trial participation is preferred
  • Morbidity of traditional approach is acknowledged

• NICHE-2: neoadjuvant single dose ipi, two dose nivo
  • 95% path CR rate
  • No recurrence at just over year follow up
  • Longer follow up ongoing
CRC treatment: MSS/pMMR

• A number of studies have not shown clear benefit to ICI therapy
• Interesting conclusions regarding the role of liver metastases and extrahepatic disease in combinations of TKIs and ICI (rego/nivo, CAMILLA, COSMIC-021)
• Additional studies are reporting early data on studies controlling for the presence or absence of liver metastases (Agenus)
• These findings remain exploratory, trial participation is encouraged
CRC Treatment: MSS/pMMR

- This is the vast majority of our patients
- Regardless of PD-L1 expression, MSS and non-POLE tumors do not appear to respond significantly to ICI therapy
- ICI therapy should be reserved for clinical trial considerations
Squamous cell cancer of the anus (SCCA)

- Rare disease and high quality data sets are limited
- Pooled data for pembrolizumab monotherapy suggest ORR 14%, median PFS 3.0 mos for PD-L1 + patients
- Nivolumab monotherapy ORR 24%, higher PD-L1 expression correlated with response but very limited data
- Phase 2: Retifanlimab enrolled 94 patients with ORR 14%; responses independent of PD-L1, HIV; median DOR 9.5 mos
  - Approval deferred
- PD-L1 expression at present should not determine ICI therapy
SCCA: continuing efforts

- EA2176 assessing carboplatin/paclitaxel with and without nivolumab followed by maintenance nivolumab
- PODIUM-303: carboplatin/paclitaxel +/- retifanlimab
- Multiple studies assessing incorporation into early stage chemoRT treatments
- HIV status should not inform treatment restrictions or trial enrollment
SCCA: summary

• There are insufficient data to consider ICI use in front line
• For patients with chemotherapy-treated disease, nivolumab and pembrolizumab can be considered
• Treatment decisions at present should be made independent of PD-L1/HIV status.
• Trial participation is encouraged