WP 2 – skills, Exercise 1

Choose the right trial (Study Protocol A,B or C) for the patient

Case report: 1 ID: K-V, YOB: 1975

Diagnosis and treatment:
- dg. 3/2020 Rectosigmoid tumor, Histology: well-differentiated adenocarcinoma, KRAS wt, NRAS wt, BRAF wt, dMMR/MSI-H. TNM: T4a N0 M0 , Stage IIB
- 3/20 surgery: sigmoideostomy
- 4-7/2020 complete neoadjuvant chemoradiotherapy (Chemo: Capecitabine + Oxaliplatine)
- 9/2020 surgery: open resection of rectosigmoid, histology: ypT4 ypN0, M0, TRG =3, Mandard
- 11/2020 metastases in liver and peritoneal cavity, bowel obstruction
- 1/2021 surgery: palliative left-sided hemicolectomy, transversostomy, histology: invasive mucinous carcinoma, G1, dMMR/MSI-H
- 2/2021 1st line study treatment for metastatic disease – screening, ECOG PS:1

Medical history:
2/2021 - hydronephrosis l.sin. of unknown etiology, SP left JJ stent insertion 2/2021,
2/2021 – baseline conditions: fatigue G1, anemia G1, hypomagnesemia G1, cancer pain G2

Concomitant medication:
Tamsulosin 0.4mg TBL 0-0-1; Novalgin 500mg TBL PRN ; Itoprid 5mg TBL 1-1-1 ; Tezeo 40 mg TBL 1-0-0; Tezeo 40 mg 1-0-0

Study Protocol A

An open-label, multi-center, phase II study evaluating the efficacy and safety of „NIS“ and “Tislelizumab” combinations with standard of care (SOC) anti-cancer therapy for the second line treatment of metastatic colorectal cancer (mCRC)

Main inclusion criteria:
1. Histologically or cytologically confirmed metastatic colorectal adenocarcinoma that is not amenable to potentially curative surgery and progressed on or within 6 months after the last dose of one prior line of systemic anti-cancer therapy administered for metastatic disease.
2. Presence of at least one measurable lesion assessed by CT and/or MRI according to RECIST
3. Eastern Cooperative Oncology Group (ECOG) Performance Status 0 or 1.
4. Adequate organ function as defined by the following laboratory values (assessed by central laboratory for eligibility except where indicated):
   - Absolute neutrophil count $\geq 1.5 \times 10^9$/L
   - Platelets count $\geq 100 \times 10^9$/L
   - Hemoglobin ≥ 9 g/dL
   - Calculated creatinine clearance ≥ 60 mL/min (e.g. by using Cockcroft-Gault equation)
   - Albumin ≥ 3 g/dL
   - PT/INR and PTT ≤ 1.5 x ULN.
   - Total bilirubin ≤ 1.5 X ULN
   - AST, ALT ≤ 3.0 x ULN (≤ 5 x ULN in presence of liver metastasis)
5. Participant must have recovered from treatment related toxicities of prior anticancer therapies to grade ≤ 1 (CTCAE v5.0) at the time of screening, except alopecia.

Main exclusion criteria:
Participants meeting any of the following criteria are not eligible for inclusion in this study:

1. Prior administration of anti-cancer immunotherapy (e.g. anti-PD-1, anti-PD-L1, anti-CTLA-4 antibody) or TGF-β targeted therapies.
2. Microsatellite instability-high (**MSI-H**)/mismatch repair-deficient (**dMMR**) and/or **BRAFV600 mutation positive** colorectal cancer (tests performed by local laboratory and per local guidelines).
3. Presence of symptomatic CNS metastases, or CNS metastases that requires directed therapy (such as local radiotherapy or surgery), or increasing doses of corticosteroids 2 weeks prior to study entry
4. Participant has not recovered from a major surgery performed prior to start of study treatment or has had a major surgery within 4 weeks prior to start of study treatment.
5. Radiation therapy ≤ 4 weeks or brain-radiotherapy ≤ 4 weeks prior to start of study treatment (palliative radiotherapy to bone lesions allowed ≥ 2 weeks prior to start of study treatment).
6. Impaired cardiac function or clinically significant cardio-vascular disease.
7. Use of hematopoietic growth factors or transfusion support ≤ 2 weeks prior to start of study treatment.
8. Participant has conditions that are considered to have a high risk of clinically significant gastrointestinal tract bleeding or any other condition associated with or history of significant bleeding.
9. Serious non-healing wounds.
10. Stroke or transient ischemic attack, or other ischemic event, or thromboembolic event (e.g., deep venous thrombosis, pulmonary embolism) within 3 months before start of study treatment.
11. Concurrent malignancy other than the disease under investigation with exception of malignancy that was treated curatively and has not recurred within 2 years prior to the date of screening.

Study Protocol B
A Phase 3 Randomized Clinical Trial of Nivolumab alone, Nivolumab in Combination with Ipilimumab, or Investigator's Choice Chemotherapy in Participants with Microsatellite Instability High (MSI-H) or Mismatch Repair Deficient (dMMR) Metastatic Colorectal Cancer

Main Inclusion Criteria:
1) Histologically confirmed recurrent or metastatic CRC
2) no prior treatment history with chemotherapy and/or targeted agents not amenable to surgery
3) Known tumor MSI-H or dMMR status per local standard of practice.
4) All participants must have measurable disease by CT or MRI per RECIST 1.1 criteria
5) Participants with lesions in a previously irradiated field as the sole site of measurable disease will be permitted to enroll provided the lesion(s) have demonstrated clear progression and can be measured accurately.

6) ECOG Performance Status ≤ 1

Main Exclusion Criteria:
1) Active brain metastases or leptomeningeal metastases.
2) Ascites that cannot be controlled with medical therapy alone.
3) Participants with an active, known or suspected autoimmune disease. Participants with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
4) History of interstitial lung disease or pneumonitis.
5) Known history of positive test for HIV or known AIDS.
6) Participants with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of randomization. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.
7) Prior malignancy active within the previous 2 years.

8) Prior major surgery, open biopsy or significant traumatic injury within 28 days prior to randomization.
9) Clinically significant cardiovascular disease, including but not limited to congenital long QT syndrome. Pre-existing hypertension should be adequately controlled.
10) Non-healing wound, ulcer, or bone fracture.
11) Persistence of toxicities related to first-line chemotherapy grade > 1 (CTCAE v5.0) (except alopecia, fatigue or peripheral sensory neuropathy which can be Grade 2)
12) Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody

Study Protocol C

A Study Of Nivolumab In Combination With Trametinib With Or Without Ipilimumab In Participants With Previously Treated Metastatic Colorectal Cancer.

Main Inclusion Criteria:

1) Histologically or cytologically confirmed previously treated metastatic colorectal cancer with adenocarcinoma histology and in Stage IV
2) Microsatellite status should be performed per local standard of practice, IHC and/or PCR.
3) KRAS and NRAS (extended RAS) and BRAF mutation status should be verified based on available local testing results as part of medical history prior to study treatment.
Participants with colorectal cancers that are RAS wild-type or mutant may be enrolled.
4) Prior lines of therapies:
    a) Participants with 2L mCRC in must have progressed or been intolerant to one prior line of chemotherapy in the metastatic disease setting, which must include at least a fluoropyrimindine and oxaliplatin- or irinotecan-containing regimens.
    c) Participants with 3L mCRC in Part 1 and 3L+ mCRC in Part 2 must have progressed or been intolerant to 2 prior lines or at least 2 prior lines (no more than 4 prior lines) of therapy, respectively, in the metastatic disease setting, which must include at least a fluoropyrimindine and oxaliplatin- and irinotecan-containing regimens.
5) Participants must have measurable disease per RECIST 1.1
6) ECOG Performance Status of 0-1 at screening and on C1D1.

Main Exclusion Criteria:

1) Participants with BRAF V600 mutant colorectal cancer are NOT eligible for this study.
2) Active brain metastases or leptomeningeal metastases.
3) Any serious or uncontrolled medical disorder that, in the opinion of the investigator, may increase the risk associated with study participation or study drug administration, impair the ability of the participant to receive protocol therapy, or interfere with the interpretation of study results.
4) Prior malignancy active within the previous 3 years except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the prostate, cervix, or breast.
5) Participants with an active, known or suspected autoimmune disease. Participants with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
6) Participants with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration.
7) Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation.
8) All toxicities attributed to prior anti-cancer therapy other than alopecia and fatigue must have resolved to Grade 1 (NCI CTCAE or baseline before administration of

study drug.
9) Received chemotherapy and other approved SOC within 14 days prior to first dose
10) Prior major surgery within 28 days prior to first dose. Any surgery-related AE(s) must have resolved at least 14 days prior to first dose.
11) Received radiation therapy with curative intent within 28 days prior to first dose. Prior focal palliative radiotherapy must have been completed at least 14 days prior to first dose.
12) Prior treatment with any MEK inhibitor
13) History of interstitial lung disease or pneumonitis.
14) Inability to take oral medication or significant nausea and vomiting, malabsorption, external biliary shunt, significant bowel resection that would preclude adequate absorption of oral medication.