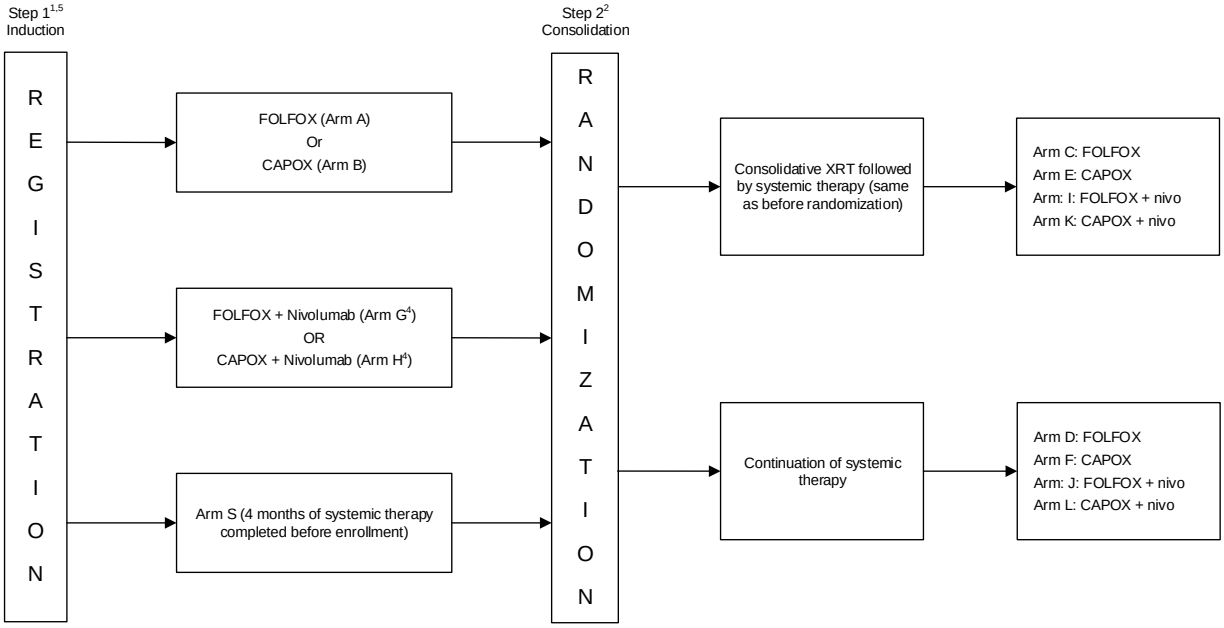
Schema

Stratification Factors:

- Number of Metastatic Sites: 1 vs >1 at the time of Step 1 Registration
- Choice of immunotherapy (IO) therapy and PD-L1 CPS Score
  - *Not choosing IO:*
    PD-L1 CPS<5 and not choosing IO at physician discretion vs. CPS ≥ 5 but not choosing IO due to contraindication
  - *Choosing IO Therapy:*
    PDL-1 CPS <5 and choosing IO at physician discretion vs. CPS ≥5 and choosing IO per recommendation
- Enrollment Status: Registering to study before vs. After induction systemic therapy



NOTE: *Consolidation Systemic Therapy as described above in Arms C-F and I-L can continue until disease progression or intolerable toxicities. Treatment will stop after two years if there is no evidence of disease)*

Accrual: Step 1 = 314, Step 2 = 204

FOLFOX Dosing:
Oxaliplatin 85mg/m^2 + Leucovorin 200mg/m^2 at the same time followed by 5-FU 400mg/m^2, followed by continuous infusion 5-FU IV over 46-48 hours for a total dose of 2400mg/m^2 on days 1 and 15 of each cycle.
**Cycle= 28 days. Total 4 cycles.*[6]

CAPOX Dosing:
Oxaliplatin 130mg/m^2 on day 1
Capecitabine 1000 mg/m2 BID on days 1-14.
**Cycle= 21 days. Total 6 cycles.*[6]

Nivolumab Dosing:
For Arms G, I & J: Nivolumab: 480 mg IV on Day 1 of each cycle
**Cycle = 28 days. Total 4 cycles*
For Arms H, K & L: Nivolumab: 360 mg IV on day 1 of each cycle
**Cycle = 21 days. Total 6 cycles*

1. Treatment physician will decide whether to place the patient on a FOLFOX or CAPOX based regimen (Arm A, B, G, or H).
2. Patients with progressive disease during Step 1 will not be randomized and will be removed from the study.
3. Patients are required to have at least a 1 week break between the last dose of Step 1 Induction chemotherapy and the first day of radiation to prevent increased toxicities.
4. Tumors with PDL1 CPS ≥5: nivolumab is mandatory, unless contraindications. Tumors with PDL1 CPS <5: nivolumab use at the discretion of a treating physician.
5. Patients that are registering to the protocol after receiving initial induction treatment (as described in section 5.1.1) will be assigned to Arm S on Step 1 and then will proceed directly to Step 2 randomization.
6. The total number of cycles is applicable to step 1 only. Doses are the same in step 1 and 2.