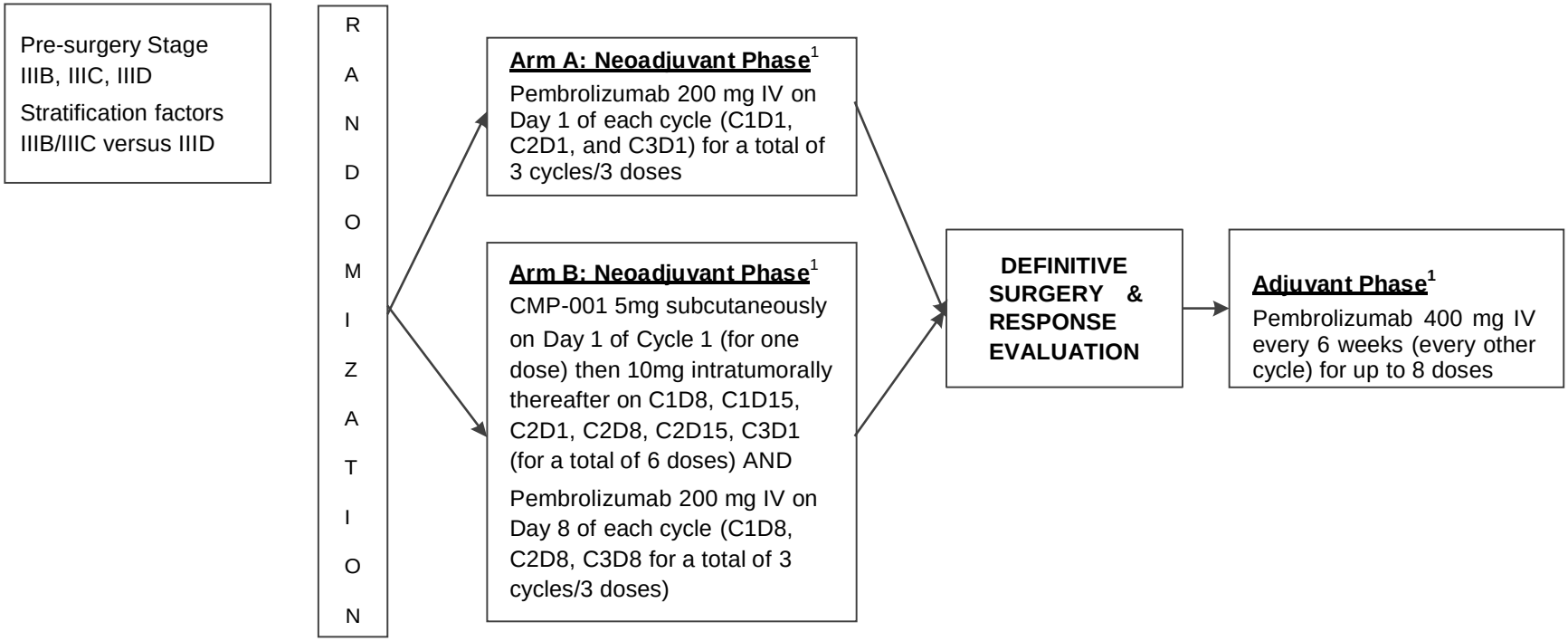
Schema



1. Neoadjuvant and Adjuvant cycle length: 1 cycle = 21 days

3. Selection of Patients

Each of the criteria in the checklist that follows must be met in order for a patient to be considered eligible for this study. Use the checklist to confirm a patient's eligibility. For each patient, this checklist must be photocopied, completed and maintained in the patient's chart.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28.

ECOG-ACRIN Patient No. _____

Patient's Initials (L, F, M) _

Physician Signature and Date _____

NOTE: CTEP Policy does not allow for the issuance of waivers to any protocol specified criteria (http://ctep.cancer.gov/protocolDevelopment/policies_deviations.htm). Therefore, all eligibility criteria listed in Section 0 must be met, without exception. The registration of individuals who do not meet all criteria listed in Section 0 can result in the participant being censored from the analysis of the study, and the citation of a major protocol violation during an audit. All questions regarding clarification of eligibility criteria must be directed to the Group's Executive Officer (EA.ExecOfficer@jimmy.harvard.edu) or the Group's Regulatory Officer (EA.RegOfficer@jimmy.harvard.edu).

NOTE: Institutions may use the eligibility checklist as source documentation if it has been reviewed, signed, and dated prior to registration/randomization by the treating physician.

3.1 Eligibility Criteria

_____3.1.1 Patient must be ≥ 18 years of age.

_____3.1.2 Patient must have an ECOG Performance Status of 0 or 1.

_____3.1.3 Patient must have a histologic diagnosis of melanoma belonging to the following AJCC 8th edition TNM stages:

- _____3.1.3.1 T0, Tx or T1-4; and
- _____3.1.3.2 N2b, N2c, N3b or N3c

——— 3.1.4 Patients may have a presentation with primary melanoma with concurrent regional nodal and/or in-transit metastasis; or patients may have a history of primary melanoma or unknown primary melanoma presenting with clinically detected regional nodal and/or in-transit recurrence; and may belong to any of the following groups:

- ——— 3.1.4.1 Primary cutaneous melanoma with clinically apparent regional lymph node metastases and/or in-transit metastases.
- ——— 3.1.4.2 Clinically detected recurrent melanoma at the proximal regional lymph node(s) basin.

_____ 3.1.4.3 Primary cutaneous melanoma with concurrent nodal disease involving a single regional nodal group.

_____ 3.1.4.4 Clinically detected nodal melanoma (if single site) arising from an unknown primary.

_____ 3.1.4.5 In-transit cutaneous metastases with or without regional lymph node involvement permitted if considered potentially surgically resectable at baseline.

NOTE: Patients with mucosal and/or uveal melanoma are not eligible for the study.

_____ 3.1.5 Patient must be candidate for definitive surgery and have met with the treating surgical oncologist prior to randomization.

_____ 3.1.6 Patient must not have received any live vaccine within 30 days prior to randomization. Live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine.

_____ 3.1.7 Patient must have the presence of injectable and measurable disease based on RECIST 1.1, documented by scans obtained within 4 weeks prior to randomization.

NOTE: Injectable disease is defined as an accessible lesion in the skin, subcutaneous tissue or lymph nodes (LN) close to the skin and palpable by physical examination or approachable with ultrasound guidance.

_____ 3.1.8 Patient must have adequate organ and marrow function as defined below, obtained within 4 weeks prior to randomization.

- Absolute neutrophil count (ANC) ≥1,500 /mcL

  ANC:_____ Date of Test:_____

- Hemoglobin ≥9 g/dL or ≥5.6 mmol/L

  Hgb_____Specify units (g/dL or mmo/L)

  Date of Test: _____

- _____Platelets ≥100,000 / mcL

  Platelet:_____Date of Test:_____

- Serum creatinine ≤1.5 X upper limit of normal (ULN) or measured or calculated creatinine clearance > 60mL/min (GFR can also be used in place of creatinine or CrCl for patients with creatinine levels > 1.5 X institutional ULN

  Serum creatinine_____Date of Test:_____

  or

  Creatinine clearance:_____Date of Test:_____

- Serum total bilirubin ≤ 1.5 X ULN; for total bilirubin level ≥ 1.5 X ULN but ≤ 3 X ULN, the direct bilirubin must be ≤ the ULN

  Total Bilirubin:_____Institutional ULN:_____

Direct Bilirubin:_____Institutional ULN:_____

Date of Test:_____

_____AST (SGOT) and ALT (SGPT) ≤ 2.5 X ULN

ALT:_____Institutional ULN:_____

Date of Test:_____

AST:_____Institutional ULN:_____

Date of Test:_____

_____International Normalized Ratio (INR) or Prothrombin Time (PT) ≤1.5 X ULN unless patient is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

INR:_____Institutional ULN:_____

Date of Test:_____

PT:_____Institutional ULN:_____

Date of Test:_____

_____ Activated Partial Thromboplastin Time (aPTT) ≤1.5 X ULN unless patient is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

aPTT:_____Institutional ULN:_____

Date of Test:_____

_____3.1.9 Women must not be pregnant or breast-feeding due to the potential harm to an unborn fetus and possible risk for adverse events in nursing infants with the treatment regimens being used.

All females of childbearing potential must have a blood test or urine study within 14 days prior to randomization to rule out pregnancy. A urine or serum pregnancy test must be repeated within 72 hours prior to receiving the first dose of pembrolizumab if the test done for eligibility/randomization is done outside of this 72 hour window. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

A female of childbearing potential is defined as any woman, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy; or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

Female of child bearing potential?_____(Yes or No)

Date of blood test or urine study: _____

3.1.10 Women of childbearing potential and sexually active males must not expect to conceive or father children by using accepted and effective method(s) of contraception or abstaining from sexual intercourse from time of randomization, while on study treatment, and continue for 26 weeks after the last dose of protocol treatment.

3.1.11 Patient must have the ability to understand and the willingness to sign a written informed consent document. Patients with impaired decision-making capacity (IDMC) who have a legally authorized representative (LAR) or caregiver and/or family member available will also be considered eligible

3.1.12 Patient must not have received prior systemic therapy for melanoma including systemic therapy with an anti-PD-1, anti-PD-L1, anti-CTLA-4, BRAF/MEK inhibitor combination and/or TLR-9 agonist.

3.1.13 Patient must not have a diagnosis of immunodeficiency or be receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to randomization, except as noted here.

- 3.1.13.1 Patients who are currently receiving steroids at a dose of prednisone ≤5mg daily (or equivalent) are permitted to enroll.
- 3.1.13.2 Patients who require topical, ophthalmologic and inhalational steroids are permitted to enroll.
- 3.1.13.3 Patients with hypothyroidism who are stable on hormone replacement are permitted to enroll.
- 3.1.13.4 Patients who require active immunosuppression with corticosteroids at a dose of prednisone >5mg daily (or equivalent) for any reason are ineligible.
- 3.1.13.5 Patients with adrenal insufficiency are ineligible.
- 3.1.13.6 Patients who have developed autoimmune disorders of Grade 4 while on prior immunotherapy are not permitted to enroll on this study. Patients who developed autoimmune disorders of Grade ≤ 3 may enroll if the disorder has resolved to Grade ≤1 and the patient has been off systemic corticosteroids at doses > 5mg for at least 2 weeks prior to randomization.

3.1.14 Human immunodeficiency virus (HIV)-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial.

3.1.15 For patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated.

3.1.16 Patients with a history of hepatitis C virus (HCV) infection must have been treated and cured. For patients with HCV infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load.

_____ 3.1.17 Patients with a history of brain metastases are not eligible for this study as they do not meet the eligibility staging criteria.

_____3.1.18 Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible for this trial.

_____3.1.19 Patients with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, should have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification. To be eligible for this trial, patients should be class 2B or better.

_____ 3.1.20 Patient must not have an allogeneic tissue/solid organ transplant.

_____3.1.21 Patient must not have a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.

_____ 3.1.22 Patient must not have severe hypersensitivity (≥Grade 3) to pembrolizumab and/or any of its excipients.

_____ 3.1.23 Patient must not have an active infection requiring systemic therapy.

_____ 3.1.24 Patient must not have a known psychiatric or substance abuse disorder that would interfere with the participant's ability to cooperate with the requirements of the study.