CHARACTERISTICS OF TNBC SUPPORTING EVALUATION OF IMMUNE THERAPIES IN EARLY BREAST CANCER

- Heterogeneous group of cancers characterized by:
  - High-grade tumors
  - <1% of cells + for ER and PR receptors
  - Negative for HER2 amplification or overexpression
- TNBC is associated with higher percentages of pCR to neoadjuvant chemotherapy (NAC), and women with a pCR have a favorable prognosis
- Patients (pts) with residual TNBC following NAC have higher risk for recurrence than pts with other subtypes of BC with residual disease (1,2)
- Poor survival once metastatic disease develops
- Increased incidence and worse outcomes in women of African descent

BACKGROUND

- Therapeutic blockade of PD-L1 binding by atezolizumab has resulted in relevant anti-tumor efficacy in TNBC (1,2,3)
- The Phase III IMPASSION130 study in first-line metastatic TNBC reported the addition of atezolizumab to nab-paclitaxel prolonged PFS from 8.5 to 7.2 mos (HR=0.80; p=0.0025) in the overall population and from 5.0 to 7.5 mos (HR=0.62; p<0.001) in the PD-L1 positive cohort (HR=0.62). Median OS was improved from 17.6 to 21.3 mos (HR=0.84; p=0.08) overall and was improved from 15.5 to 25.0 mos in the PD-L1 positive cohort (HR=0.62) (4)
- Addition of pembrolizumab to neoadjuvant paclitaxel increased estimated pCR from 20% to 60% in TNBC
- Ongoing Phase III studies in metastatic TNBC:
  - Study of atezolizumab and paclitaxel vs. placebo and paclitaxel in patients with previously untreated locally advanced or metastatic triple negative breast cancer (TNBC) (IMPASSION131)
  - Study of pembrolizumab plus chemotherapy vs. placebo plus chemotherapy for previously untreated locally recurrent inoperable metastatic TNBC (KEYNOTE-355)
- Ongoing Phase III study of atezolizumab in early TNBC:
  - Study to investigate atezolizumab and chemotherapy compared with placebo and chemotherapy in the neoadjuvant setting in patients with early stage triple negative breast cancer (IMPASSION131)

ELIGIBILITY

- Diagnosis of invasive adenocarcinoma of the breast by core needle biopsy
- Primary tumor must be:
  - T2 or T3 if node negative
  - T1c-T2, or T3 if node positive
- Central testing must confirm:
  - HER2 negative by ASCO/CAP guidelines
  - ER and PR negative by ASCO/CAP guidelines
  - LVEF ≥55%
  - Serum TSH and AM cortisol WNL
- Standard exclusions for cardiac disease and for checkpoint inhibitor trials

STATIFICATION VARIABLES

- Size of Primary Tumor:
  - <1.1 - 3.0 cm
  - >3.0 cm
- Clinical Nodal Status:
  - Negative
  - Axillary imaging is negative OR
  - Axillary imaging is suspicious or abnormal but FNA/core biopsy not done
  - Positive
- FNA or core biopsy of node(s) positive OR
- Axillary imaging suspicious or abnormal but FNA/core biopsy not done
- AC/EC schedule:
  - q2wk
  - q3wk
- Region:
  - North America
  - Europe

RATIONAL FOR CARBOPLATIN AS COMPONENT OF CHEMOTHERAPY REGIMEN

- GEPARsITXO TNBC Cohort (1,2):
  - pCR breast and nodes increased from 36.9% to 53.2% (p=0.005) with addition of carboplatin to weekly anthracycline/taxane regimen
  - Carboplatin improved 3yr DFS (85.5% vs 76.1%, p=0.035)
- CALGB 40603 (3,4):
  - pCR breast and nodes increased from 41% to 54% (p=0.0029) with addition of q3wk carboplatin AUC 6 to weekly paclitaxel → AC
  - 3yr EFS was 76% with carboplatin and 71% (p=0.38) without
  - Paclitaxel delivery reduced by requirement to end therapy after 12 wks
- BrighTNEss (5):
  - pCR breast and nodes increased from 31% to 57% with addition of q3wk carboplatin AUC 6 to weekly paclitaxel → AC
  - Pre-specified analyses by stratification factors demonstrated no differences in pCR by germline BRCA status or schedule of anthracycline administration
  - EFS data not mature
  - Paclitaxel delivery improved by extending therapy to 16 wks if needed

RATIONAL FOR MAINTAINING PLACEBO CONTROL POST SURGERY

- Hypothesis is that cohort receiving atezolizumab will have higher pCR rate, and the increased activity will result in improved EFS
- Imbalance of non-protocol therapy following surgery would confound the integrity of trial for EFS, particularly administration of PD-1/PD-L1 inhibitors
- No evidence additional chemotherapy following Carb/ Taxol → AC will improve outcomes
- CREATE-X was conducted in pts who did not receive neoadjuvant carboplatin

BIOSPECIMEN COLLECTIONS IN SUPPORT OF CORRELATIVE STUDIES

- Plasmas for ctDNA also obtained at 2 yrs and relapsed Research Breast biopsy
- Carcinobin AUC of 5
  - Paclitaxel 80 mg/m² weekly x 12 doses
  - Doxorubicin 60 mg/m² IV or Epirubicin (E) 90 mg/m² IV
  - Cyclophosphamide (C) 600 mg/m² IV
  - Atezolizumab 1200 mg or placebo IV every 3 wks initiated with chemotherapy and administered for 1 year with break for surgery

STATISTICAL CONSIDERATIONS

- Sample size: 1,520 pts
- Co-primary endpoints:
  - pCR breast and lymph nodes (ypT0/Tis ypN0)
  - Event-free survival (EFS)
- Secondary endpoints:
  - pCR breast (ypT0/Tis)
  - pCR breast and lymph nodes (ypT0 ypN0)
  - Positive nodal status conversion rate
  - Overall survival
  - Recurrence-free interval
  - Distant disease-free survival
  - Brain metastases-free survival
  - Toxicity
  - Cardiac safety lead-in study

CARDIAC SAFETY LEAD-IN COMPONENT

- First 60 pts to begin AC/EC
  - Tropolin T collected prior to AC/EC in Cycle 1 at baseline
  - Tropolin T collected immediately after AC/EC administration prior to atezol/ placebo administration in Cycles 1 and 3
  - ECG obtained with each Tropolin T collection to allow administration of atezol/ placebo without waiting for troponin T result if no change from baseline
  - LVEF assessed prior to Cycle 3 of AC/EC
  - Cardiac evaluation if troponin T elevated or LVEF declines
  - All pts have post op and 18-month LVEF