ALLIANCE FOUNDATION TRIALS, LLC

PATINA

AFT-38: A Randomized, Open-Label, Phase 3 Trial to Evaluate the Efficacy and Safety of Palbociclib + Anti-HER2 Therapy + Endocrine Therapy Versus Anti-HER2 Therapy + Endocrine Therapy After Induction Treatment for Hormone Receptor Positive (HR+)/HER2-Positive Metastatic Breast Cancer

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TAP TO RETURN TO KIOSK MENU

rationale/ objective

study schema

treatment plan/ intervention

key eligibility criteria

follow up

- Cyclin D1 is downstream of HER2 and plays a critical role in HER2 transformation
- Cellular models of HER2-mediated transformation confirmed the importance of CCND1 and CDK4/6 activity for this process
- Data from in vivo mouse models showed that reducing Rb phosphorylation through CDK4 knockout or p16 overexpression is sufficient to block development of tumorigenesis
- Subsequent studies illustrated the relationship between elevation of cyclin D1 and HER2 amplification/overexpression in clinical specimens and refined the requirement of cyclin D1/CDK4 activity in HER2-driven breast cancer models
- HER2+ cell lines, such as MDA-MB-361 and BT474, are sensitive to palbociclib. Palbociclib has been shown to have synergistic anti-tumor activity when combined with trastuzumab
- Palbociclib is active in cell lines resistant to anti-HER2 therapy. Palbociclib potent cytostatic activity and induction of senescence reduced the number of vital cells at limiting dose of anti-HER2 therapy
- CDK4/6 activity drives resistance to HER2 targeted therapy and relieves feedback inhibition of the mTOR pathway and progression through the cell cycle. Inhibition of CDK4/6 suppresses phosphorylation of Rb and mTOR substrates when combined with HER2 inhibitors and sensitizes patient-derived xenografts to this therapy while delaying tumor recurrence
- The NA-PHER2 neoadjuvant phase II study evaluated the safety and efficacy of palbociclib given in combination with Trastuzumab, pertuzumab and fulvestrant in early stage HER2+ hormone receptor positive breast cancer. The treatment combination was well tolerated with diarrhea and neutropenia being the most common side effects. The pathologic complete response (pCR) rate was 30% and the clinical benefit rate 98% (n= 30 evaluable patients)

RATIONALE

Primary

- To demonstrate that the combination of palbociclib with anti-HER2 therapy plus endocrine therapy is superior to anti-HER2-based therapy plus endocrine therapy in prolonging PFS in participants with hormone receptor-positive, HER2+ metastatic breast cancer who have not received any prior treatment beyond induction treatment in this setting

Secondary

- To compare overall measures of tumor control (including PFS, OR, CBR, DOR) between the treatment arms
- To compare median overall survival and overall survival probabilities at 3-years and 5-years between the treatment groups
- To compare safety and tolerability between the treatment arms
- To compare the incidence of CNS metastasis between the treatment arms
- To compare patient reported time to symptom progression
- To compare patient reported breast cancer specific health related quality of life (HRQOL) and general health status

Translational Science

- To compare progression-free survival based upon investigator assessment of progression between patients in the two treatment arms in the subset of patients with tumors bearing a *PIK3CA* mutation

OBJECTIVE

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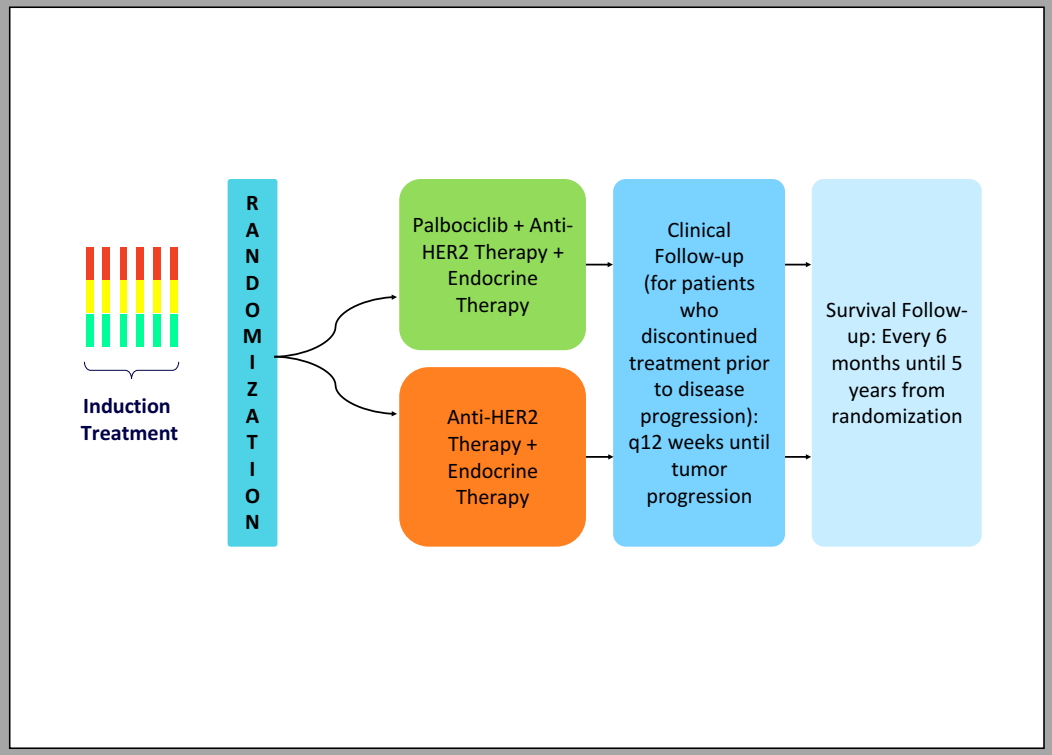
HER2+HR+Metastatic Breast Cancer (N=496)

- No prior treatment in the advanced setting beyond induction treatment
- Induction treatment: Anti-HER2based chemotherapy given prior to study randomization
- Screening procedures (before, during or after induction treatment):
  - Screening consent
  - Biopsy of metastatic disease strongly recommended (not mandatory)
  - Baseline clinic-pathologic characteristics

- Pre-study induction treatment includes standard first line treatment given for patients diagnosed with advanced HER2+ disease in the first line setting. Treatment options are either THP (taxane plus trastuzumab and pertuzumab) or trastuzumab given in combination with a taxane or vinorelbine. Patients must receive 6-8 cycles of induction treatment; 4-6 cycles is acceptable for those experiencing significant toxicity.
- Endocrine therapy options are either an aromatase inhibitor (AI) or fulvestrant. Premenopausal patients should receive ovarian suppression in combination with either AI or fulvestrant.
- Patients are eligible as long as they are without evidence of disease progression by local assessment after induction tx.



STUDY SCHEMA

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Protocol Specified Activities	Treatment Phase (cycle = 28 days)							Post-Treatment Continuation	
	Pre-Screening	Screening	Cycle 1 – Cycle 4				q12 wks until PD	End of treatment/ withdrawal	Follow-up (q6 mos)
Day			D1	D8	D15	D22*		Wthing 28 days after last dose	
(Window in days)	No limit	(-28 to -1)	±2			±2	±7		±14 days
Informed Consent, Inclusion/Exclusion Criteria	●	●							
Medical History, Complete physical exam, ECG		●							
Concomitant Medication, ECOG Performance Status, Blood chemistry		●	●				●		
Limited physical exam			●				●	●	
Vital signs, Adverse Events		●	●				●	●	
CBC and platelets*		●	●			●	●		
Pregnancy test**	●	●					●		
MUGA or echocardiogram***		●				●		●	
Tumor assessment, Bone-scan or PET scan		●	q 12weeks				●	●	
Archival FFPE tumor tissue	●								
Metastatic tumor research biopsy (optional)	●							●	
One 10 mL lavendar top (EDTA) tubes of blood****			●			●			
Two 10 mL Streck tubes of blood *****			●			●		●	
PRO assessments******			●			●	●	●	
IP (Palbociclib) Dispensing			●				●		
Trastuzumab/Pertuzumab infusions (every 3 wks)			●			●	● Every 3 wks		
Survival follow-up assessment (post disease progression)									●

Most assessments are done on D1 of Cycles 1-4 and then every 12 weeks, with the following exceptions:

*Arm A patients only come in for D22 CBCs and Platelets in 1st cycle only

**Pregnancy test is done at Screening, C4D1 and every 12 weeks until disease progression

***MUGA or ECHOs are done at Screening, C4D1, every 12 weeks until disease progression

****EDTA tubes are collected on C1D1 and C4D1

*****Streck tubes are collected on C1D1, C4D1 and End of Treatment

******PROs (FACT-B and EQ-5D) are assessed on C1D1, C4D1 and every 12 wks until

TREATMENT PLAN / INTERVENTION

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- Histologically confirmed invasive breast cancer that is metastatic or not amenable for resection or radiation therapy with curative intent
- Histologically confirmed HER2+ and hormone receptor-positive (ER+ and/or PR+) metastatic breast cancer
- A representative formalin-fixed paraffin-embedded (FFPE) tumor tissue block (preferred) or at least 15 unstained slides along with a pathology report documenting HER2 positivity and hormone receptor positivity must be submitted to the study's central biorepository
- An optional, representative tumor specimen obtained from metastatic disease is recommended if clinically feasible. This could include tumor obtained from metastatic biopsies performed for diagnostic purpose or biopsies performed as part of the current study
- ECOG performance status 0–1
- Patients must have received an acceptable, standard, chemotherapy containing anti-HER2-based induction therapy for the treatment of metastatic breast cancer prior to study enrollment. For this study, chemotherapy is limited to a taxane or vinorelbine (only for trastuzumab-based regimen). Eligible patients are expected to have completed 6 cycles of chemotherapy containing anti-HER2 therapy treatment. A minimum of 4 cycles of treatment is acceptable for patients experiencing significant toxicity associated with treatment as long as they are without evidence of disease progression (i.e., CR, PR, or SD)

KEY ELIGIBILITY CRITERIA

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FUNDING SUPPORT

This trial (PATINA | AFT-38) is funded by Pfizer, Inc.

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