NUOVE PROPOSTE

Sottogruppi HER2-positivi e Triplo Negative in stadio avanzato

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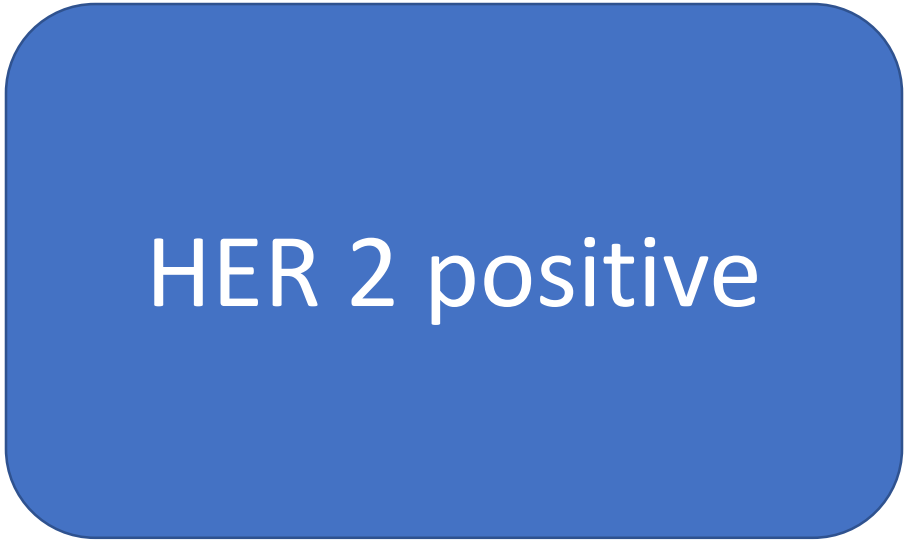
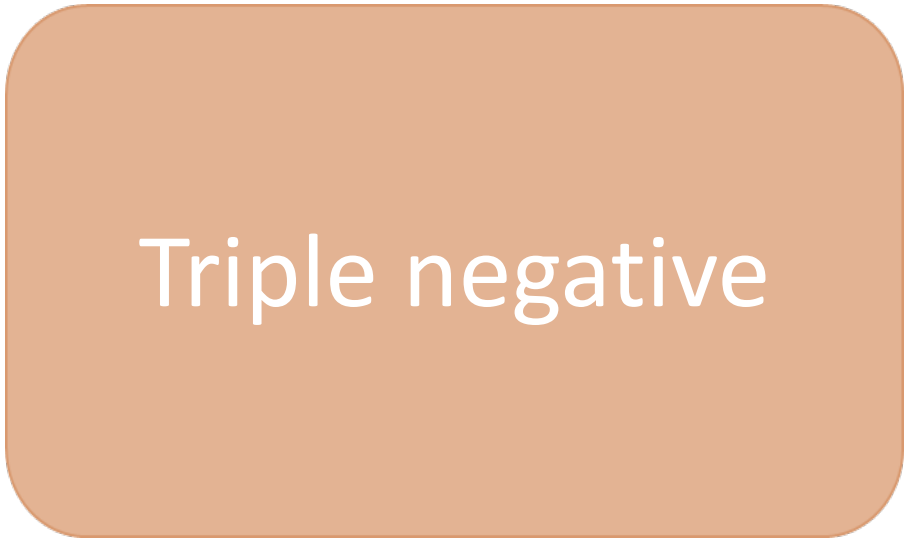


1 study proposal



2 study proposals

HER 2 positive

Triple negative

A phase 2a/2b Multicenter Study to evaluate the efficacy of the combination of Elacestrant and Neratinib in ER+/HER2+mut mBC

Dott. Daniele Generali

ASST Cremona

A phase 2a/2b Multicenter Study to evaluate the efficacy of the combination of Elacestrant and Neratinib in ER+/HER2+mut mBC

Background 1

- Acquired HER2 mutations lead to endocrine resistance in a proportion of patients with ER+ MBC
- Hotspot mutations in HER2 (D769Y, L755S, and S310Y) are more common in acquired endocrine resistant tumors
- Mutations within the HER2 gene lead to E2 independence and resistance to the first line endocrine therapy (tamoxifen, fulvestrant and palbociclib)
- ER-directed drug in combination with neratinib demonstrated to be effective in these patients

A phase 2a/2b Multicenter Study to evaluate the efficacy of the combination of Elacestrant and Neratinib in ER+/HER2+mut mBC

Background 2

- The Y537S and D538G mutant forms of *ER*α demonstrated to drive endocrine resistance and metastasis
- Novel SERD, AZD9496, *in vitro* downregulates the D538G/ Y537S/ Y537N/ Y537C containing ERα proteins and was more effective than fulvestrant in suppressing the growth of tumors driven by $ER\alpha^{WT}$ and $ER\alpha^{MUT}$ (Y537S)
- Elacestrant (RAD1901), a novel orally bioavailable SERD, inhibits cell proliferation in ER+ BC cell lines and was associated with good responses in heavily pretreated ER+/ER mutant and HER2 negative MBC patients

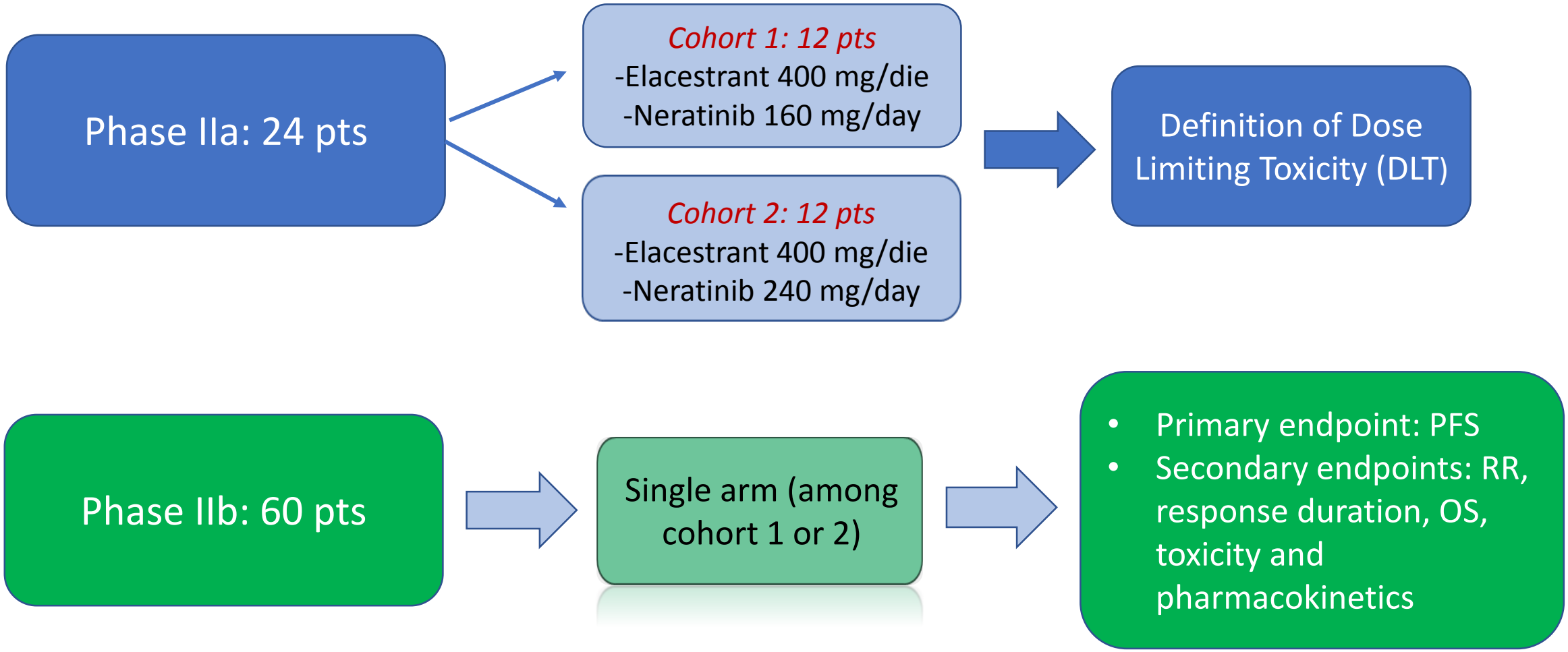
A phase 2a/2b Multicenter Study to evaluate the efficacy of the combination of Elacestrant and Neratinib in ER+/HER2+mut mBC

Study Aim:

- To test the safety and the efficacy of the combination of Elacestrant and Neratinib in ER+/HER2+mut 1st line mBC

A phase 2a/2b Multicenter Study to evaluate the efficacy of the combination of Elacestrant and Neratinib in ER+/HER2+mut mBC

Study Design:



Triple negative

A phase II Trial of Atezolizumab plus Carboplatin plus Paclitaxel as first-line therapy in metastatic Triple-negative PD-L1 positive BC patients: the GIM25-CAPT trial

Dott.ssa Claudia Bighin

IST San Martino, Genova

A phase II Trial of Atezolizumab plus Carboplatin plus Paclitaxel as first-line therapy in metastatic Triple-negative PD-L1 positive BC patients: the GIM25-CAPT trial

Background

- Taxane-based chemotherapy currently represents the preferred first-line treatment in TNBC
- TNT trial: confirmed the activity of single agent taxane chemotherapy in this setting, although median PFS was only 4.4 months
- IMpassion130: the combination of atezolizumab + nab-paclitaxel significantly reduced the risk of disease worsening or death in the ITT and PD-L1+ population, showing also encouraging OS results
- TNACITY trial: nab-paclitaxel + carboplatin seems the best first-line schedule in terms of median PFS in metastatic TNBC patients (8.3 months)
- Efficacy of carboplatin, paclitaxel and atezolizumab in NSCLC, without any detrimental interaction between atezolizumab and steroid premedication of paclitaxel

A phase II Trial of Atezolizumab plus Carboplatin plus Paclitaxel as first-line therapy in metastatic Triple-negative PD-L1 positive BC patients: the GIM25-CAPT trial

Study Aim:

- To demonstrate that addition of an anti-PDL1 (Atezolizumab) to 1st line therapy (Carboplatin + Paclitaxel) in metastatic PD-L1+ TNBC patients is associated with a clinically relevant 2-year increase in OS over what expected based on historical data (54%)

A phase II Trial of Atezolizumab plus Carboplatin plus Paclitaxel as first-line therapy in metastatic Triple-negative PD-L1 positive BC patients: the GIM25-CAPT trial

Statistical considerations:

- Power 80% and α error 0.05 (1-sided)
- Null hypothesis: 2yrsOS in mTNBC treated with atezolizumab plus carboplatin and paclitaxel is 54%
- Alternative hypothesis: atezolizumab increases this percentage by 12% (i.e. to 66%)
- Number of pts needed: 97
- With 97 patients, the estimated 2yrsOS will have a precision (= width of the 95% CI) equal to +/-11% and the minimal observed 2yrsOS% allowing rejection of the null hypothesis at the 1-sided 5% significance level is 62%.

A phase II Trial of Atezolizumab plus Carboplatin plus Paclitaxel as first-line therapy in metastatic Triple-negative PD-L1 positive BC patients: the GIM25-CAPT trial

Study Design:

Metastatic Triple-Negative PD-L1 positive Breast Cancer

N=97

1) Not previously treated for metastatic disease

2) Eligible for chemotherapy

3) PD-L1≥1%

Carboplatin AUC 2 dd 1,8,15 q 28 dd

+

Paclitaxel 90 mg/m^2 dd 1,8,15 q 28 dd

+

Atezolizumab 840 mg dd 1,15 q 28 dd

(until PD or unacceptable toxicity)

Objectives:

Primary: %OS at 24 months

Secondary: %OS at 30 months; %OS at 24 months in HR 1-10%; PPS; ORR; time to treatment failure; safety

Exploratory: NGS analysis of ctDNA and evaluation of a multiparametric Cancer agnostic circuLating ImmunOsignature (CLIO)

Enrollment period: about 24 months
Follow-up: 24 months (from the enrollment of the last patient)
Total Study Duration: 48 months approximately

Update al 25/09/2019 pranzo

- Previsto Investigator meeting 14-15 Novembre 2019
- 15/11/2019 è dedicato agli anatomo patologi per la corretta valutazione di PDL1 (metodo da definirsi), probabilmente a cura del Prof. Viale
- Per qualunque dubbio o perplessità è possibile contattare la dott.ssa Bighin al: claudia.bighin@hsanmartino.it o oncotech

Randomized phase III trial comparing the addition of BEvacizumab and /or STatin to the combination of immunotherapy and chemotherapy in advanced triple negative breast cancer: the BEST trial

Dott.ssa Piera Federico

Ospedale del Mare, Napoli

Randomized phase III trial comparing the addition of BEvacizumab and /or STatin to the combination of immunotherapy and chemotherapy in advanced triple negative breast cancer: the BEST trial

Background 1

- Poor prognosis of metastatic TNBC
- Impassion 130: efficacy of immunotherapy in 1st line TNBC treatment
- p53 mutations are frequent in TNBC and associated with higher number of TILs
- p53 mutations are associated with reduced expression of miR30 and increased levels of ZEB2 → increased cell motility and possibility of metastasis
- This could represent the rationale for the association of immunotherapy with bevacizumab

Randomized phase III trial comparing the addition of BEvacizumab and /or STatin to the combination of immunotherapy and chemotherapy in advanced triple negative breast cancer: the BEST trial

Background 2

- Tumour-associated p53 mutants have been also associated with drug resistance (gain of function)
- Mutant p53 protein stabilization is a prerequisite for this gain-of-function occurrence
- Intermediates of the mavelonate pathway contribute to mutant p53 accumulation, inhibiting its ubiquitin-mediated proteolysis
- Statins inhibit cholesterol synthesis acting on HMG-CoA reductase, blocking mevalonate pathway, potentially inhibiting the stabilization of p53 mutants
- Statins have been associated with reduced overall and breast cancer specific mortality
- This represents the rationale for including statins in TNBC treatment

Randomized phase III trial comparing the addition of BEvacizumab and /or STatin to the combination of immunotherapy and chemotherapy in advanced triple negative breast cancer: the BEST trial

Study aim

- To demonstrate that addition of Bevacizumab and/or statins to 1st line therapy (Paclitaxel + Atezolizumab) in metastatic BRCA wt TNBC patients is associated with increase in PFS and OS

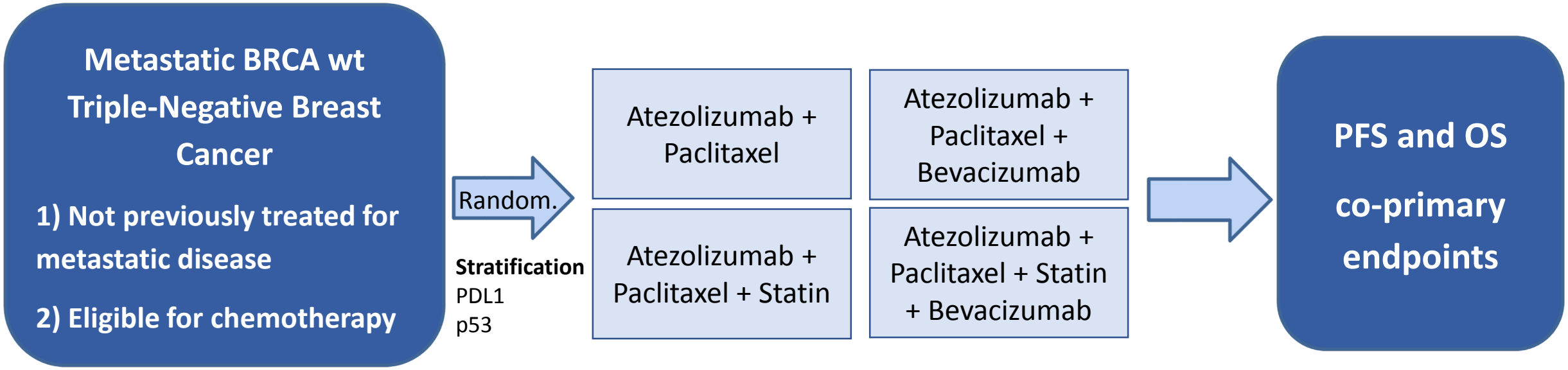
Randomized phase III trial comparing the addition of BEvacizumab and /or STatin to the combination of immunotherapy and chemotherapy in advanced triple negative breast cancer: the BEST trial

Statistical considerations

- 2 x 2 factorial design
- PFS and OS co-primary endpoints
- PDL1 (≥1% vs. 0) and p53 (mut. vs. wt) as stratification criteria
- Pre-specified subgroup analysis according to PDL1 and p53 status

Randomized phase III trial comparing the addition of BEvacizumab and /or STatin to the combination of immunotherapy and chemotherapy in advanced triple negative breast cancer: the BEST trial

Study Design:



Let’s start the discussion