O5 Impact of *BRCA* mutation status on tumor infiltrating lymphocytes (TILs), response to treatment and prognosis in breast cancer patients treated with neoadjuvant chemotherapy

Beatriz Grandal [1,7], Clémence Evrevin [1], Eric Daoud [7], Elise Dumas [7], Nadir Sella [7], Clara Sebbag [1], Sonia Rozette [1], Isabelle Jardin [1], Lucie Laot [1], Florence Coussy [2], Claire Saule [3], Dominique Stoppa-Lyonnet [3], Sophie Franck [3], Claire Sénéchal [4], Enora Laas [1], Marick Lae [5,6], Diane De Croze [5], Fabien Reyal [1,7], Anne-Sophie Hamy[7]

1.Surgery Institut Curie, Translational Research Department Institut Curie, **2**.Medical Oncology Institut Curie, **3.**Genetics institut Curie, INSERM U830, **4.**Genetics Institut Bergonié Bordeaux, **5.**Pathology Institut Curie St Cloud, **6.**Pathology Henri Becquerel, INSERM U1245 Rouen, **7.**Residual Tumor & Response to Treatment Laboratory, RT2Lab, INSERM U932

Introduction

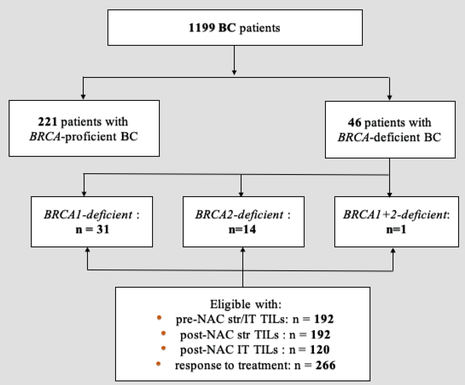
- Nearly 5 to 10 % of breast cancers (BC) occur in a context of genetic predisposition, mostly represented by germline mutations of *BRCA1*, *BRCA2* or *PALB2* genes[1]
- Tumors associated with germline or somatic *BRCA1/2* pathogenic mutation display different patterns when compared with sporadic BCs[2-8].
- The role of tumor infiltrating lymphocytes (TILs) in BC has been extensively studied over the last decade. High levels of TILs before NAC are associated with higher pathologic complete response (pCR) rates and better survival in TNBC and *HER2*-positive BC[9,10].
- Little is known about immune tumor infiltration and response to standard neoadjuvant chemotherapy (NAC) according to *BRCA* status.

Objectives

- The objective of the current study is to analyze if pre and post-NAC TILs, chemosensitivity and prognosis differ according to *BRCA* status in a cohort of BC patients treated with NAC.

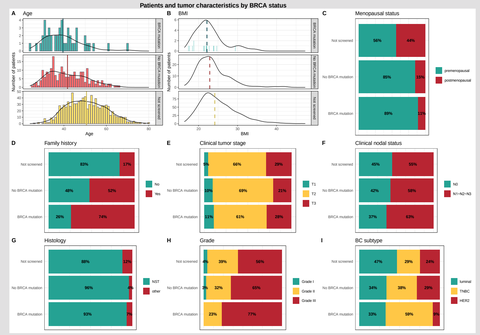
Materiels and Methods

- Out of **1199 T1-T3NxM0 invasive BC** patients treated with **NAC** between **2002 and 2012** at Institut Curie (**NEOREP cohort**).
- We retrospectively identified **267 patients** tested for a germline *BRCA* pathogenic variant.
- We evaluated **pre and post-NAC TILs**, defined as intra-tumoral TILs if in direct contact with tumor cells, and as stromal TILs if in the peri-tumoral areas (IT TILs and str TILs, respectively).
- A **pCR** was defined as the absence of invasive residual tumor in breast and axillary node (ypT0/is N0).
- **Survival analyses** were performed for the following end points : relapse free survival (RFS) and overall survival (OS) .

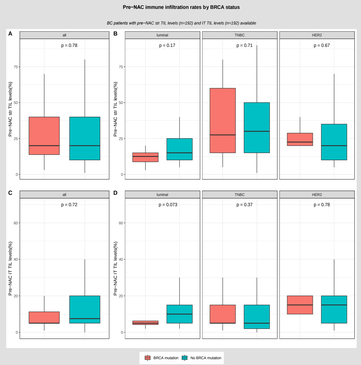


Results

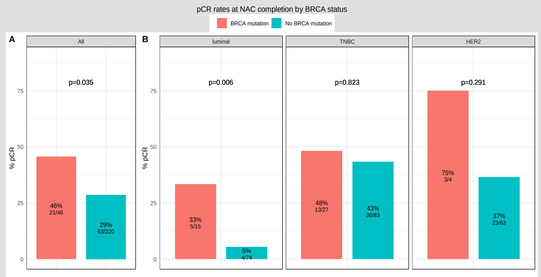
- Among the **1199 BC patients** : **221 (83%)** were considered as ***BRCA*-proficient** or wild type (WT) and **46 (17%)** were ***BRCA*-deficient** (*BRCA1*-deficient, n=31 (67.39%); *BRCA2*-deficient, n = 14 (30.43%) and *BRCA1+2*-deficient, n=1 (2.17%)).



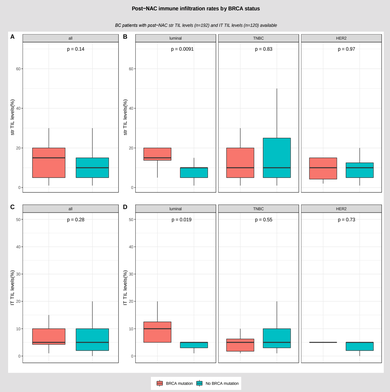
- Patients with **available *BRCA* status** were significantly different from patients with BRCA status unknown. They were younger, had lower body mass index, were more likely to be diagnosed with grade III, TNBC and no specific type (NST) than patients not screened ($p< 0.001$)
- BC patients with ***BRCA* pathogenic mutation** were more likely to be diagnosed with **TNBCs** than patients with WT BC (58.7% vs 37.6%, p=0.006). No other pattern was significantly different according to *BRCA* variant status.
- Neither **pre-NAC str TIL levels** nor **IT TILs** were significantly different by *BRCA* status , nor in each BC subtype.
- **pCR rates** were significantly **higher in patients with *BRCA*-deficient breast cancers** (45.7% (21/46) versus 28 % (63/221) in *BRCA*-proficient, $p< 0.035$. After the subgroup analysis of BC subtype, this was confirmed only in the **luminal BC subtype** (33.3% (5/15), p= 0.006).



- The **interaction** test **between BC subtype and *BRCA* status** was nearly significant (*Pinteraction*=0.056). However, *BRCA* status was not significantly associated with pCR after multivariate analysis.



- **Post-NAC str or IT TILs were not significantly different** between *BRCA*-deficient and *BRCA*-proficient carriers.
- **In the luminal BC group,** both str and IT **post-NAC TIL levels were significantly higher in *BRCA*-deficient BC** when compared with *BRCA*-WT (median str TIL levels: 15% vs. 10%, p= 0.009 and median IT TIL levels : 10% vs. 5%, p= 0.019, respectively)



- With a median follow-up of 92 months, **RFS and OS were not different** between *BRCA*-carriers and non-carriers.

Conclusion

- ***BRCA* mutation status** is associated with **higher pCR rates and post-NAC str TILs** in patients with **luminal BC**.
- Carriers of ***BRCA* pathogenic mutations with luminal BCs** could represent a subset of patients deriving **a higher benefit from NAC** than non-carriers with luminal BCs.
- As post-NAC TILs seem to be higher in case of *BRCA*-deficiency, **second line** therapies including **immunotherapy** could be of interest for non-responders to NAC.

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beatriz.grandalrejo@curie.fr