Anticipating the Real-World Impact of Therapeutic Innovations in France by Transporting Evidence from the United States - *A Case Study in Metastatic Triple-Negative Breast Cancer (mTNBC) based on the Flatiron Health Database*

MSR54

LB. Simomia Mbowen[1], V. Machuron[1], G. Machuron[1], R. Jegou[2], C. Esnault[1]

1. Roche SAS, Boulogne-Billancourt, France; 2. Keyrus Life Science, Nantes, France

Context & Objectives

Approval of innovative treatments is often earlier in the US than in France, making US data particularly valuable for predicting potential impacts in France and supporting decision-making, including for Health Technology Assessment. Taking the example of mTNBC, this study aims to:

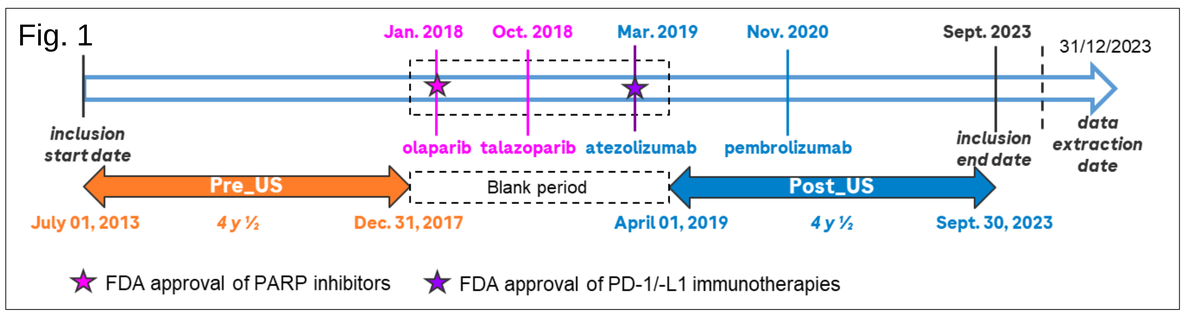
1. Estimate the impact of access to innovative medicines on overall survival (OS) of mTNBC patients in the US (including immunotherapies and targeted therapies)
2. Evaluate the transportability of OS estimates from the US to France *before* access to innovative medicines in mTNBC (validation with French data)
3. Predict the impact of access to innovative medicines on OS in France by extrapolating US data in mTNBC

Methods

Populations (figure 1):

- **Flatiron US data** of female adult patients treated for mTNBC(*) (n = 2126) (1)
  - Pre_US: metastatic diagnosis between 01/07/13 and 31/12/2017 (n = 812)
  - Post_US: metastatic diagnosis between 01/04/19 and 30/09/2023 (n = 1052)
- **Aggregate French data** of adult female patients treated for metastatic TNBC from the national ESME mBC database (diagnosis < 2017) (2). OS IPD were reconstructed (3).

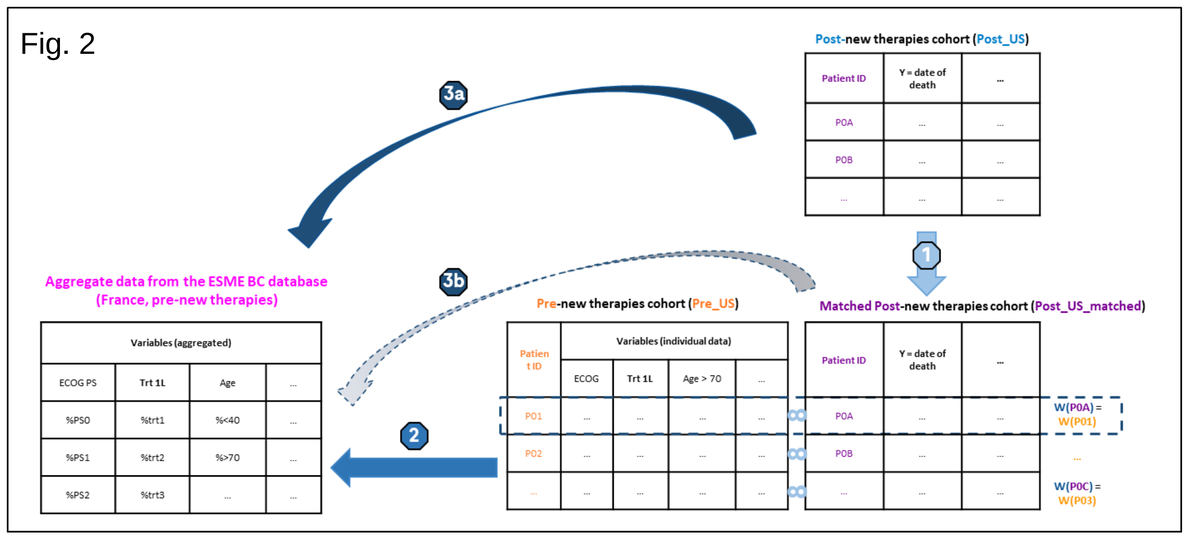
Fig. 1



Statistical considerations (figure 2):

- **Adjustment methods:**
  1. 1:1 k-NN matching with replacement between Pre_US and Post_US
  2. MAIC between Pre_US and ESME data (4)
  3. MAIC between ESME and either Post_US (3a), or the Post_US_matched population (3b) using the same weights estimated in analysis 2 (**)
- **Variables used for all adjustments:**
  Age *(<50, 50-60, 60-70, >70)*, ECOG PS *(0, 1, 2+)*, De novo status (y/n), Sites of metastases (Lung *(y/n)*, Bone *(y/n)*, Nodes *(y/n)*), Number of metastatic sites at diagnosis *(1, 2+)*.
  - Only for 2: 1L treatments use (Anthracyclines *(y/n)*, Taxanes *(y/n)*, Capecitabine *(y/n)*)
  - Missing values: single imputation randomly drawn from the distribution of missing data (FCS)
- **Overall Survival:** from 1L treatment initiation (index date). Censoring at extraction date.
- **Sensivity analyses (SA):**
  - for missing values: complete case analysis and missing values as a category
  - for the adjustment method: IPTW for 1
  - for the censoring rule in OS analyses: date of last known alive

Fig. 2



(*) defined as no positive and at least 1 negative test results for PR, ER, HER2 between +/-90 days around metastatic diagnosis. (**) The use in analysis 3b of the same weights as in analysis 2 attempts to give more importance to 'Post' patients whose theoretical management before the arrival of the new therapies corresponds to that of French patients.

Results

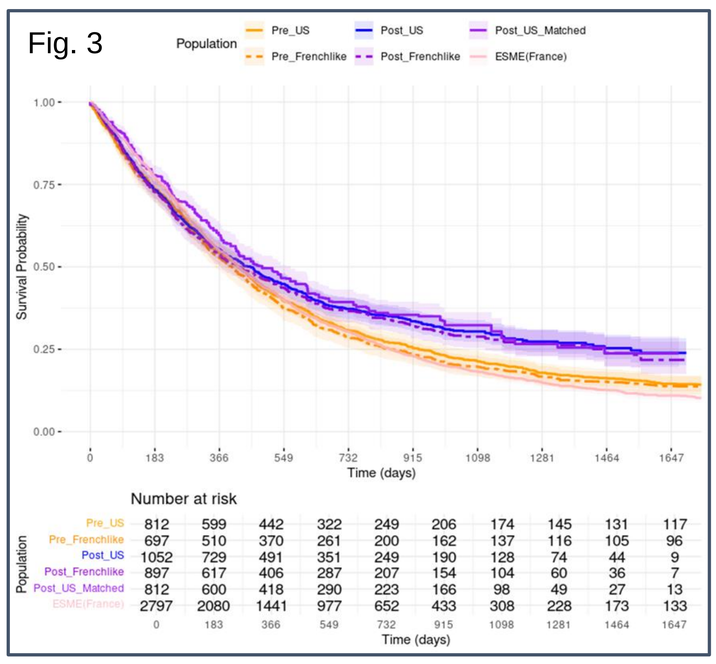
First Line Therapy Class	Pre_US, n=812	Post_US, n=1052
Immuno/PD1/PDL1	2 (0.2%)	311 (30%)
Anthracyclines	124 (15%)	78 (7.4%)
Parp Inhibitor	4 (0.5%)	16 (1.5%)
Anti-Trop2	0 (0%)	43 (4.1%)
Capecitabine	163 (20%)	155 (15%)
Taxanes	291 (36%)	461 (44%)
Platines	205 (25%)	245 (23%)

Table of 1L treatment use per class of therapies before (Pre_US) and after (Post_US) the arrival of new therapies in the US (multiple choices). Blue boxes are new therapies (immunotherapies and targeted therapies)

	1		2		3a
OS	Post_US	Post_US_matched	Pre_US	ESME	Pre_Frenchlike	Post_Frenchlike
1-year rate	0.55 (0.52 ; 0.59)	0.60 (0.56 ; 0.63)	0.54 (0.51 ; 0.58)	0.55 (0.53 ; 0.57)	0.53 (0.49 ; 0.57)	0.54 (0.50 ; 0.58)
2-year rate	0.37 (0.34 ; 0.41)	0.39 (0.36 ; 0.43)	0.31 (0.28 ; 0.34)	0.30 (0.29 ; 0.32)	0.29 (0.25 ; 0.33)	0.37 (0.33 ; 0.41)
3-year rate	0.30 (0.27 ; 0.34)	0.32 (0.29 ; 0.36)	0.21 (0.19 ; 0.24)	0.18 (0.17 ; 0.20)	0.20 (0.17 ; 0.23)	0.29 (0.25 ; 0.33)
median	14.9 (13.1 ; 16.4)	16.0 (13.9 ; 18.6)	13.8 (12.6 ; 15)	13.8 (13.2 ; 14.6)	13.2 (11.6 ; 14.6)	13.8 (12.1 ; 16.2)

Table of OS medians and rate estimates at fixed time points (95% CI).

Fig. 3



Adjusted HR(*) = 0.79 (0.65; 0.95), **p < 0.05**
(Post_US_matched vs Pre_US)

- **Around 36% of mTNBC Post_US patients are treated with immuno- or targeted therapies.**
- **Predicted impact of new therapies in the US:**
  - **OS: -21% of hazard rate**
    - *SA: HRs ranged from 0.78 to 0.85*
  - **2- and 3-year OS rates: +8% and +11%**
    - *SA at 2 years: from +6% to +7%*
    - *SA at 3 years: from +8% to +10%*

1

Very good transportability of Overall Survival data from the US to France. 2

- ***Pre_US, Pre_Frenchlike and ESME OS curves overlap strongly***

Adjusted HR(*) = 0.84 (0.74; 0.95), **p < 0.05**
(Post_Frenchlike vs Pre_Frenchlike)

Predicted impact of new therapies in France:

- **OS: -16% of hazard rate** *(SA: HRs = 0.80 to 0.89)*
- **2- and 3-year OS rates: +8% and +9%**
- ***Analysis 3b: HR = 0.79** (0.69; 0.90) **(p < 0.05)***

3a

Post_US_matched: Post_US patients are matched to resemble the Pre_US patients (SMDs < 0.05)

Pre_Frenchlike: Pre_US patients are weighted to resemble the ESME (France) patients (SMDs ≃ 0)

Post_Frenchlike: Post_US patients are weighted to resemble the ESME (France) patients (SMDs ≃ 0)

(*) Hazard ratios are estimated from Cox models using robust standard error estimation and, specifically for analysis 1, the procedure described by Austin and Cafri (2020) for valid inference with matching by replacement (5).

Conclusion

2 **This study provides evidence that the US Flatiron OS estimates in 1L mTNBC are transportable to French patients.**

1 3 **The predicted overall impact of new therapies on OS in mTNBC in France should be similar to that in the US: -15 to -20% in the OS hazard rate.**

Limitations

- The estimated increase in OS in the US may be due to introduction of new treatments in second and further lines (and not only in 1L).
- The estimated increase in OS in the mTNBC may be underestimated due to the impact of COVID-19 from 2020.
- Other differences between the US and France may affect the transportability of OS estimates, such as access to others treatments, local care management, centers expertise, etc.

FCS: Fully conditional specification
HR: Hazard Ratio
IPD: Individual Patient Data
IPTW: Inverse Probability of Treatment Weighting
k-NN: k-nearest neighbors
mTNBC: metastatic Triple-Negative Breast Cancer
MAIC: Matching Adjusted Indirect Comparison
OS: Overall Survival
SA: Sensitivity Analyses
SMDs: standardized mean differences
US: United States of America

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