The Causes and Consequences of Incomplete Paclitaxel Administration during the Neoadjuvant treatment of Early Triple negative and HER2 positive breast cancer (CIPNETH)

Marina Borges, Elise Dumas, Hailey Fenton, Eriseld Krasniqi, Gaber Plavc, Katarzyna Pogoda, Michal Uher, Mahéva Vallet, Cédric Van Marcke

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Early triple negative and HER2-positive BC : standard approach

- Chemotherapy administered in the **neoadjuvant setting** is the standard schedule for early TNBC and HER2-positive BC.[1]

- The sequential administration of anthracyclines and taxanes is the backbone of the treatment :
  - Adding taxanes to anthracyclines allows for improved surgical and long-term outcomes.[2,3]
  - The standard schedule for **taxanes** is the **weekly** administration of **12 cycles of paclitaxel**.[4]
  - Carboplatin can be added to paclitaxel in TNBC.[5]
  - HER2-directed therapies act synergistically with paclitaxel in case of HER2-positive disease.[6]

- Treatment schedules are homogeneous among European countries.

1. Cortazar P et al. The Lancet. 2014 ; 2. Mamounas EP et al. J Clin Oncol. 2005 ; 3. Sparano JA et al. J Clin Oncol. 2015 ;
4. Sparano JA et al. NEJM. 2008 ; 5. Poggio F et al. Ann Oncol. 2022 ; 6. Perez EA et al. J Clin Oncol. 2011

Early triple negative and HER2-positive BC : challenges in daily practice

- Despite these treatments, 20 to 40% of early breast cancer cases still relapse. [1]

- The assessment of the **pathological response** rate to neoadjuvant chemotherapy has an important **prognostic value**. In triple negative and HER2-positive disease, pathological complete response after neoadjuvant chemotherapy is a surrogate endpoint, being associated with excellent long-term outcomes. [1,2]

- **Peripheral neuropathy** is a main dose-limiting side effect of **paclitaxel** (up to 70% of cases) and a frequent reason for early **cessation** or **dose reduction** of chemotherapy (up to 40% of cases). [3-5]

- To the best of our knowledge, no study assessed the impact on treatment efficacy of reduced paclitaxel dose-intensity administration in early breast cancer.

- The impact of reduced paclitaxel administration in high-risk BC patients is a very **important question in daily practice, with treatment decisions being taken without strong evidence**.

1. Cortazar P et al. The Lancet. 2014 ; 2. I-SPY2 trial consortium et al. JAMA Oncol. 2020 ; 3. Sparano JA et al. NEJM. 2008 ;
4. Staff NP et al. Exp Neurol. 2020 ; 5. Nyrop K et al. Cancer. 2019

CIPNETH : real world data from 8 European cancer centres

Retrospective cohort of TNBC and HER2-positive EBC treated in the neoadjuvant setting with anthracyclines-cyclophosphamide and weekly paclitaxel or carboplatin-paclitaxel (with or without trastuzumab ± pertuzumab)

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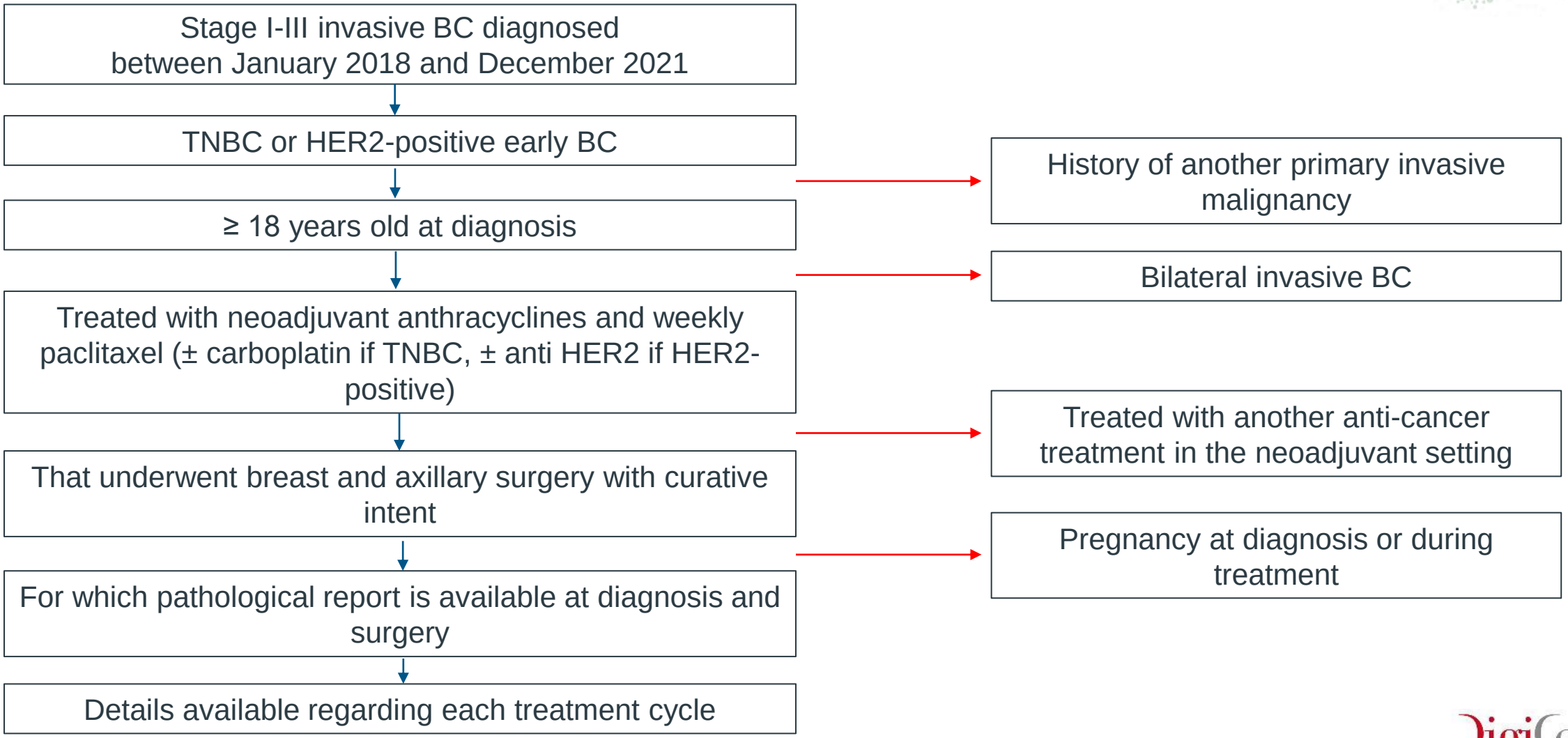
Study objectives

- **Primary objective**
  - highlight a **potential impact of reduced paclitaxel dose-intensity** on treatment effect (pCR and IDFS).

- **Secondary objectives**
  - Estimate if this impact differs according to the **BC subtype.**
  - Characterize our patients with respect to **main demographics** and **clinical characteristics** at diagnosis index date and treatment received.

- **Exploratory objectives**
  - Highlight a potential impact of reduced paclitaxel dose-intensity on OS.
  - Characterize the **clinical factors** and **side effects** associated with **early cessation** or dose-intensity reduction of paclitaxel administration.
  - Assess and quantify the **frequency of early cessation** and dose reduction of paclitaxel administration in patients presenting treatment-induced neuropathy.

Inclusion and exclusion criteria



Expected cohort sizes

	Scotland	Portugal	England	Belgium	Slovenia	Czech Republic	Poland	Italy
TNBC	60	160	40	120	40	90	200	70
HER2+	20	5	10	70	40	90	5	100

Around **50% of TNBC and HER2-positive** early BC patients achieve **pCR**.

We hypothesize :

- For **TNBC, pCR** rate to drop **to ≤ 40%** if paclitaxel dose-intensity is reduced. At an alpha of 0.05, a power of 0.842 could be achieved with 780 TNBC cases.
- For **HER2-positive** BC, **pCR** rate to be **non-significantly different**, given a high sensitivity to anti-HER2 treatments.

Data analysis

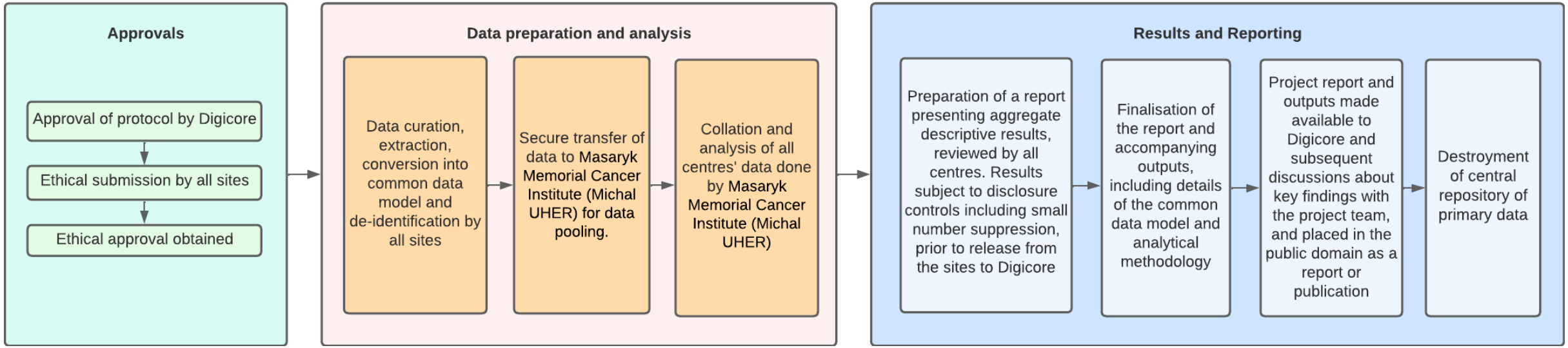
- **Descriptive statistics** for all demographic characteristics and clinical characteristics at diagnosis.
- Attrition tables for inclusion and exclusion criteria.

- **Time-to-event** analyses depicted with Kaplan-Meier curves and compared through Log-rank tests.

- Estimation of the **impact of reduced paclitaxel dose-intensity** :
  - on **pCR** by a logistic regression model
  - on **IDFS** by a Cox proportional hazard model
  - adjusting for baseline main characteristics ; main comorbidities ; treatment schedules ; main side effects

- Descriptive statistics of the **frequency** of patients experiencing **neuropathy** (with CTCAE grading), stratified by paclitaxel dose-intensity.
- Estimation of the associations between paclitaxel-induced neuropathy and reduced dose-intensity by a logistic regression model, adjusted for confounding factors at baseline.
- The analysis of the frequency of **other AEs** leading to **paclitaxel early cessation**.

General study design and Quality Control



- Manual data curation at each site from at least 20 randomly chosen patients.
- Between-site consistency of data will be checked by descriptive statistical analyses and graphical approaches.
- Thorough discussion and establishment of the common data model.

Tackling our main study limitations

- Retrospective, observational nature

  ➔Chart reviews, data curation, attrition tables

- Inconsistency / under-reporting of neuropathy

  ➔Understanding the causes of reduced paclitaxel dose-intensity is only an exploratory objective

- Small cohort sizes at some centres

  ➔Data pooling, heterogeneity checks

- Short follow-up

  ➔OS not a main objective

- Heterogeneity in estimation of events and outcomes ?

  ➔ Binary pathological event (pCR and not RCB scoring)

  ➔ Agreement on definition of IDFS

Building on our strengths

- Very complementary team
- Highly motivated
- Weekly short meetings since months

- Work on a frequent cancer, treated the same way across Europe

- Open mind to consensus and improvements

What could be the next steps?

- Validation by re-exploration of available randomized data :
  - CTNeoBC
  - BrighTNess
  - CALGB 40603
  - Keynote 522

- Validation by involving other centres through EORTC BC group

➔ Defining a cohort where testing shorter treatment duration could be safe.

OR

➔ Put chemotherapy-induced peripheral neuropathy at the forefront of side effects to prevent or tackle.

Thank you for your attention !

We’re happy to take your questions and comments