ICON: A randomized phase IIb study evaluating immunogenic chemotherapy combined with ipilimumab and nivolumab in patients with metastatic hormone receptor positive breast cancer

Jon Amund Kyte (jonky@ous-hf.no)
Department of Oncology, Oslo University Hospital, Oslo, Norway; Department of Cancer Immunology, Oslo University Hospital https://orcid.org/0000-0002-2854-3694

NK Andresen
Department of Oncology, Oslo University Hospital, Oslo, Norway; Department of Cancer Immunology, Oslo University Hospital

HG Russnes
Dept. Pathology, Oslo University Hospital; Department of Cancer Genetics, Oslo University Hospital

Signe Øien Fretland
Department of Clinical Cancer Research, Oslo University Hospital

RS Falk
Oslo Centre for Biostatistics and Epidemiology, Oslo University Hospital

OC Lingjærde
Department of Cancer Genetics, Oslo University Hospital

B Naume
Department of Oncology, Oslo University Hospital, Oslo, Norway; Institute of Clinical Medicine, University of Oslo, Oslo, Norway

Protocol

Keywords: Breast cancer, hormone receptor positive, immunotherapy, checkpoint inhibitor, immunogenic cell death, PD-1, CTLA4, antracyclin, cyclophosphamide

Posted Date: April 23rd, 2020

DOI: https://doi.org/10.21203/rs.3.rs-21888/v1

Version of Record: A version of this preprint was published on July 3rd, 2020. See the published version at https://doi.org/10.1186/s12967-020-02421-w.

Abstract

Background: Immunotherapy with checkpoint inhibitors (CI) targeting PD-1 or CTLA-4 has emerged as an important treatment modality for several cancer forms. In hormone receptor positive breast cancer (HR+ BC), this therapeutic approach is largely unexplored. We have started a clinical trial, ICON (CA209-9FN), evaluating CI combined with selected chemotherapy in patients with metastatic HR+ BC. The tumor lymphocyte infiltration is predictive for the effect of chemotherapy in BC. In ICON, we use antracyclins, which are considered as “immunogenic” chemotherapy, and low-dose cyclophosphamide, which has been reported to counter immunosuppressive cells.

Methods: ICON is a randomized exploratory phase IIb study evaluating the safety and efficacy of combining nivolumab (nivo; anti-PD-1) and ipilimumab (ipi; anti-CTLA-4) with chemotherapy in subjects with metastatic HR+ BC. Primary objectives are aassessment of toxicity and progression-free survival.

The trial will enrol 75 evaluable subjects, randomized 2:3 into two arms (A:B). Patients in Arm A receive only chemotherapy, i.e. pegylated liposomal doxorubicin (PLD 20mg/m2 intravenously every 2nd week) + cyclophosphamide (cyclo; 50 mg per day, first 2 weeks in each 4 week cycle). Patients in Arm B receive PLD + cyclo + ipilimumab (1mg intravenously every 6th week) + nivolumab (240mg intravenously every 2nd week). Patients in arm A will be offered ipi+nivo after disease progression.

Discussion: ICON is among the first clinical trials combining chemotherapy with PD-1 and CTLA-4 blockade, and the first in BC. There is a strong preclinical rationale for exploring if antracyclins, which are considered to induce immunogenic cell death, synergize with CI, and for combining PD-1 and CTLA-4 blockade, as these checkpoints are important in different phases of the immune response. If the ICON trial suggests acceptable safety and provide a signal of clinical efficacy, further studies are warranted. The sub-cohort from Arm A receiving ipilimumab/nivolumab without concomitant chemotherapy represents the first BC cohort receiving this therapy. The ICON trial includes a series of translational sub-projects addressing clinically important knowledge gaps. These studies may uncover biomarkers or mechanisms of efficacy and resistance, thereby informing the development of novel combinatory regimes and of personalised biomarker-based therapy.

Trial registration: NCT03409198, Jan 24th 2018; https://clinicaltrials.gov/ct2/show/record/NCT03409198

1 Background

Immunotherapy with PD-1 and CTLA-4 inhibitors has shown remarkable clinical efficacy against several cancer forms [1–6] and now show activity in breast cancer [7, 8]. This includes durable responses in metastatic breast cancer (BC) patients, amid minimal adverse effects. Intriguingly, the host immune response is strongly predictive for the effect of chemotherapy (chemo) in BC[9]. We have started the trial ICON (CA209-9FN), a randomized phase IIb trial evaluating the effect of adding PD-1 and CTLA-4 checkpoint blockade to immunogenic chemotherapy in patients with metastatic hormone receptor positive BC (mBC). The strategy is to release the brake on the chemo-induced immune response. We have

selected chemotherapeutic agents shown to be potent inducers of immune responses. Further, the chosen drugs are accepted as 1st line therapy. This allows for including patients that have not received multiple lines of therapy and are may be more likely to respond.

PD-1 blockade has shown activity against metastatic breast cancer, but only in a minority of patients when used as monotherapy [7]. The proportion of responders is greater when PD-1/PD-L1 blockers are given in the first line, rather than after several lines of chemotherapy (Schmid P ASCO 2017; Adams S ASCO 2017). The first randomized study comparing chemotherapy +/- PD-L1 blockade against mBC, IMPASSION130, was published October 2018[8]. This study showed significant clinical benefit of adding atezolizumab (a-PD-L1) to taxans. Based on this study, atezolizumab has been approved by the FDA and EMA in combination with taxans for metastatic triple negative breast cancer. Further, in early studies of preoperative therapy, the combination of PD-1 blockade and chemotherapy has produced a substantial increase in response rates, compared to chemotherapy alone, for both ER+/HER-2 negative and triple negative BC patients [10, 11]. Our study rationale is in line with these findings, combining checkpoint blockade with a carefully selected chemotherapy regimen, as 1st / 2nd line metastatic treatment.

We utilize selected chemotherapy for inducing immunogenic cell death, which represents a personalized in vivo vaccination covering the entire repertoire of antigens expressed in each individual tumor. Such antigen release does not necessarily lead to an effective immune response. However, the chemotherapeutic agents chosen in ICON, doxorubicin and cyclophosphamide, induce “danger signals” that trigger the immune system [12]. In BC patients, these drugs are reported to induce a type I interferon response [9, 13], which suggests that they may turn an immunologically “cold” tumor into a tumor that responds to checkpoint blockade. There is also evidence from follow-up of BC patients, indicating that the survival effect of doxorubicin and cyclophosphamide depends on the host immune response [9, 14]. The IMPASSION130 trial used taxans and did not show an effect of aPD-L1 in the PD-L1 negative group[8]. This highlights the need to explore if more immunogenic chemotherapy, as employed in ICON, can make “cold” tumors responsive to PD1-blockade.

ICON is to our knowledge the first clinical trial combining chemotherapy with PD-1 and CTLA-4 blockade in breast cancer. There is a strong preclinical rationale for combining PD-1 and CTLA-4 blockade, as these checkpoints are important in different phases of the immune response, and this drug combination has shown remarkable clinical efficacy in melanoma and lung cancer [2, 6]. In breast cancer, animal studies have demonstrated a substantial advantage by adding anti-CTLA-4 to anti-PD-1 and chemotherapy [15]. Taken together, there is a strong rationale for synergy between doxorubicin/cyclophosphamide and PD-1/CTLA-4 blockade [16].

2 Methods

2.1 Objectives

Primary
Assessment of toxicity
Assessment of progression-free survival (PFS)
Secondary
Assessment of clinical response in ipi/nivo/chemo group compared to chemo only group: Objective tumor response rate (ORR), duration of response (DR), durable tumor response rate (DRR; >6 months), clinical benefit rate (CBR), overall survival (OS)
Assessment of toxicity of ipi/nivo (without chemotherapy) in cross-over arm
Assessment of ORR, DR, DRR, CBR, PFS and OS in cross-over arm receiving ipi/nivo (without chemotherapy)
Assessment of PD-L1 expression, mutation load and immune gene expression as biomarkers for clinical response
Comparison of clinical and biological response in molecular subtypes of breast cancer
Assessment of patient reported outcomes, as measured by the Chalder Fatigue Questionnaire (FQ), an 11 point Numerical Rating Scale (NRS) for pain intensity and EORTC QLQ-C15-PAL
Exploratory
Assessment of immunological response
Identification of biomarkers for clinical response, toxicity and immune response
Characterization of tumor evolution and changes in immunological milieu induced by the combination therapy (ipi/nivo/chemo), as compared to chemo only, and by ipi/nivo without concomitant chemotherapy

2.2 Study design

This is a randomized phase IIb study evaluating the safety and efficacy of combining nivolumab and ipilimumab with immunogenic chemotherapy in subjects with metastatic HR+ breast cancer. The patients will be randomized 2:3 into two arms (A:B):

- Arm A: Chemotherapy only (pegylated liposomal doxorubicin + cyclophosphamide)
- Arm B: Chemotherapy + ipilimumab + nivolumab
- Upon progression, patients may continue study treatment until loss of clinical benefit.
- The patients in arm A will be offered nivo/ipi (without chemotherapy) after disease progression..

2.3 Study treatment

- Nivolumab 240mg intravenously (i.v.) every 2nd week until disease progression or for a maximum of 24 months (flat dose of 240mg recommended by BMS)

- Ipilimumab 1mg v. every 6th week until disease progression (maximum 24 months)
    - If toxicity unacceptable, apply dose-1 level for ipilimumab of 1mg every 12th week
- Pegylated liposomal doxorubicin (PLD; Caelyx) 20mg/m2 i.v. every 2nd
- Cyclophosphamide tablets 50 mg per day, daily for 2 first weeks in each 4 week cycle.

Rationale for immunotherapy regime: The combination of CTLA-4 and PD-1 checkpoint blockade has shown high efficacy in melanoma, but also a relatively high frequency of grade 3 and 4 adverse events. This toxicity mainly correlates with the Ipilimumab dosage. We therefore use a low dosage of Ipilimumab (1 mg/kg vs 3 mg/kg in melanoma) and prolonged intervals between treatments (6 weeks). This regime has in recent studies shown good efficacy and a much safer toxicity profile [6, 17].

Rationale for chemotherapy regime: Doxorubicin and cyclophosphamide are particularly powerful inducers of immunogenic cell death and thus attractive for combination with immune checkpoint inhibitors. We employ a semi-metronomic regime, rather than a high dose regime administered every 3rd/4th week, to maintain the ability of the effector immune cells to respond. Further, metronomic cyclophosphamide has been used to counter regulatory T cells (Tregs) and myeloid suppressor cells (MDSCs) [18], and has also been applied against metastatic breast cancer [19]. We use pegylated liposomal doxorubicin to avoid steroids, minimize the adverse effects of antracyclins on the heart and allow for continued treatment beyond otherwise mandatory antracyclin limits.

2.4 Sample collection/biobanking

Samples are collected before, during and after therapy (time of progression/treatment discontinuation). Some of the biobanking procedures are not performed at all study centers. The following samles are collected: Biopsies, Peripheral blood mononuclear cells (PBMC), plasma, serum, urine, feces, circulating tumor cells.

2.5 Selected inclusion criteria

1. Metastatic hormone receptor positive breast cancer (primary or recurrent), defined as ER+ >1% in metastatic biopsy (archival material or study biopsy) or cytology and HER2 negative in the last biopsy or cytology evaluable for HER2.
2. Adequate core or excisional study biopsy of a tumor lesion.
3. Measurable metastatic disease according to RECIST
4. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
5. Signed Informed Consent Form
6. Women or men aged ≥ 18 years

7. A minimum of 12 months from adjuvant/neoadjuvant chemotherapy with antracyclins to relapse of disease.
8. A maximum of one previous line with chemotherapy in the metastatic setting
9. Previous endocrine and targeted therapy is allowed
10. Adequate organ function as defined in the protocol

2.6 Selected exclusion criteria

1. Malignancies other than breast cancer within 5 years prior to randomization, with the exception of those with a negligible risk of metastasis or death and treated with expected curative outcome
2. Spinal cord compression not definitively treated with surgery and/or radiation, or previously diagnosed and treated spinal cord compression without evidence that disease has been clinically stable for > 2 weeks prior to randomization
3. Known CNS disease, except for asymptomatic CNS metastases, provided all of the following criteria are met:

    a. Measurable disease outside the CNS
    b. Asymptomatic for CNS disease > 4 weeks
    c. No ongoing requirement for corticosteroids as therapy for CNS disease
    d. No radiation of brain lesions within 2 weeks prior to randomization
    e. No leptomeningeal disease
4. Uncontrolled pleural effusion, pericardial effusion, or ascites.
5. Pregnant or breastfeeding
6. Received treatment with immune checkpoint modulators
7. Received treatment with systemic corticosteroids or other systemic immunosuppressive medications within 2 weeks prior to randomization, or anticipated requirement for systemic immunosuppressive medications during the trial

    a. Patients who have received acute, low-dose, systemic immunosuppressant medications (e.g., a one-time dose of dexamethasone for nausea) may be enrolled in the study
    b. Patients with a history of allergic reaction to IV contrast requiring steroid pre-treatment should have baseline and subsequent tumor assessments performed using MRI
    c. The use of inhaled corticosteroids for chronic obstructive pulmonary disease, mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension, and low-dose supplemental corticosteroids for adrenocortical insufficiency are allowed
8. Received anti-cancer therapy (medical agents or radiation) within 2 weeks prior to study Cycle 1, Day 1. Palliative radiotherapy for bone lesions is allowed up to 7 days before start of therapy.

2.7 Outcome measures

2.7. 1 Safety Outcome Measures

The safety outcome measures will be evaluated in the ITT population, as follows:

- Incidence, nature, and severity of adverse events graded according to NCI CTCAE v4.0
- Changes in vital signs, physical findings, and clinical laboratory results

2.7.2 Efficacy Outcome Measures

The PFS is defined as the time from randomization to the time of radiographic progression (as assessed by RECIST v1.1) or death from any cause during the study. Data for patients with a PFS event who missed two or more assessments scheduled immediately prior to the date of the PFS event will be censored at the last tumor assessment prior to the missed visits. If no tumor assessment was performed after randomization, data will be censored at the date of randomization +1 day. Clinical deterioration without objective radiological evidence will not be considered as documented disease progression. The primary efficacy outcome measure (PFS) is to be assessed in patients evaluable per protocol (PP).

The secondary efficacy outcome measures will be assessed in the PP population, ITT population and in the PD-L1-positive subpopulation. The ITT population is defined as a full analysis set (FAS). The FAS is defined as all patients that have started therapy with at least one of the IMPs, and where data on the relevant endpoint is obtained. The safety will be evaluated in the ITT (FAS) population.

2.8 Statistics

A descriptive analysis of demographics, medical history, and clinical data will be performed.

The primary efficacy analysis will be an analysis of PFS in the combination arm(B), compared to the control arm(A). Comparison between treatment arms will also be given by HR for disease progression or death using a Cox proportional hazards model. The HR will be adjusted for the relevant variables (e.g. from list below). The confidence interval for the HR will be provided. Kaplan-Meier methodology will be used, and Kaplan-Meier curves will be produced.

Overall survival (OS) will be calculated from time of randomization until death. Patients alive at the time of data analysis will be treated as censored. OS will be estimated by the Kaplan Meier method.

Exploratory analyses will be carried out to evaluate the data of the immunological and molecular analyses (e.g. biomarker studies) carried out. The statistical analyses will be dependent on the biological

factors investigated and the analysis methodology used, and will be defined separately for each molecular study.

A data-driven time point for PFS-analysis has been defined, as 70 PFS events in the PP population. If this is not met within 24 months after inclusion of the last patient, the PFS-analysis will be performed at this time point.

The primary data analysis will be performed on the PP population and analyzed according to the following factors:

- Tumor PD-L1 status
- Disease free interval between end of (neo)adjuvant chemotherapy or surgery, whichever was last, and relapse
- Time from diagnosis of metastatic disease to start of therapy in the ICON-study
- Prior chemotherapy against metastatic disease (no previous chemo vs. previous chemo).
- Sites of metastases
- Molecular breast cancer profile, including PAM50 subtype, and immune gene profile

Exploratory analyses will be carried out to evaluate data from translational studies. Here, statistical methods will be defined separately for each study, as advised by the statisticians.

3 Discussion

3.1 Study organization and timeline

Oslo University Hospital, Oslo, Norway, is the study sponsor. We have established three study centers in Norway (Oslo University Hospital, Stavanger University Hospital, SSHF Kristiansand) and three in Belgium (Institute Jules Bordet Brussels, Cliniques Saint Luc Brussels, CHU UCL Namur). The study opened February 2018, expanded to more sites in 2019 and has included 63 patients as of March 1st 2020. We estimate a need to recruit 80 patients, to obtain the required 75 evaluable patients per protocol.

3.2 Funding

BMS supply nivolumab and ipilimumab free of charge and provide a funding contribution. The study is supported by a grant from the Norwegian Health Region South-East. Nanostring, Menarini and Thermo Fisher provide assays/kits free of charge for translational research. The expenses for chemotherapy, routine blood samples and radiology are covered by the national health care systems.

3.3 Comments on study design

The clinical development of novel drugs as add-ons to established therapy is challenging, as conventional one-armed phase I/II studies may not be suitable for providing information on the effect and toxicity of the add-on drug. In many patient populations, like the HR+ BC investigated in the ICON-trial, historic controls are heterogeneous and of limited value. In our case, neither the effect nor the toxicity of adding checkpoint inhibitors to chemotherapy could be properly assessed in a one-armed study. On the other hand, a full-scale phase III trial, powered to show clinical efficacy with a $p<0.05$, is not warranted, too resource demanding and ethically problematic, until basic clinical data have been generated. In the ICON-study, we therefore chose a randomized phase IIb design, with a limited number of patients. The aim is to assess the toxicity of the CIs as add-ons to the chemotherapy, and provide leads on potential clinical efficacy in the overall HR+BC patient population, as well as in subgroups identified by biomarkers. Accordingly, the study was not powered to demonstrate a statistically significant ($p<0.05$) clinical effect. If the study suggests acceptable toxicity and potential clinical benefit, a larger randomized study will be warranted.

The biomarker analyses and other translational projects included in ICON may inform the selection of patient subgroups for later studies and allow for more personalised therapy. Moreover, the ICON trial is designed to address the question of which chemotherapy should be added to checkpoint inhibitors. It is important to point out that the hypothesised beneficial effects of antracyclins (immunogenic cell death) and low-dose cyclophosphamide (counter Tregs/MDSCs) on the immune milieu have not yet been convincingly re-produced in patient cohorts. A critical evaluation of these hypotheses is among the listed objectives in the ICON trial, and may have implications for the choice of chemotherapy for combination with checkpoint inhibitors in future studies, both in BC and other cancer forms.

List Of Abbreviations

BC	Breast Cancer
CBR	Clinical Benefit Rate
CI	Checkpoint inhibitor
CNS	Central Nervous System
CR	Complete Response
CTC	Circulating Tumor Cells
CTCAE	Common Terminology Criteria for Adverse Event
CTLA-4	Cytotoxic T Lymphocyte Antigen 4
DOR	Duration of Objective Response
DR	Duration of response
DRR	Durable tumor Response Rate
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ER	Estrogen Receptor
FAS	Full analysis set
HER2	Human Epidermal growth factor Receptor 2
HR	Hazard Ratio
ICH	International Conference on Harmonization
IHC	Immunohistochemistry
IMP	Investigational Medicinal Product
ISH	In situ hybridization
ITT	Intention To Treat
IV	Intravenous
MDSC	Myeloid-derived Suppressor Cells
ORR	Overall Response Rate
OS	Overall Survival
PBMC	Peripheral Blood Mononuclear Cell
PD	Progressive disease
PD-1	Programmed Death 1

PD-L1	Programmed Death Ligand-1
PFS	Progression-free Survival
PLD	Pegylated liposomal doxorubicin
PP	Per protocol
PR	Progesterone Receptor
QLQ	Quality of Life Questionnaire
SD	Stable Disease

Declarations

Ethics approval and consent to participate: The ICON trial has been approved by the Norwegian and Belgian Medical Agencies and Ethics Committees. The study is performed in compliance with the World Medical Association Declaration of Helsinki and ICH E6 for Good Clinical Practice. Signed informed consent is obtained from all patients.

Consent for publication: All authors have consented to the publication. Approval has also been obtained from BMS.

Availability of data and material: Not applicable.

Competing interests: None.

Funding: Please see paragraph 3.2 in the manuscript.

Authors' contributions:

- JA Kyte: Principal investigator; concept, preparation of trial, writing of protocol and manuscript.
- NK Andresen: Study doctor; contribution to protocol revisions and manuscript.
- HG Russnes: Pathologist; contribution to preparation of trial, protocol revisions and manuscript.
- SØ Fretland: Project manager; coordination of trial set-up, contribution to protocol and manuscript
- RS Falk and OC Lingjærde: Study statisticians; contribution to protocol revisions and manuscript.
- B Naume: Co-investigator; contribution to protocol, trial preparations and manuscript.

Acknowledgements:

The authors thank doctors at the Breast Cancer Unit, study nurses at the Clinical Research Unit and pathologists at Department of Pathology for important input during the preparation of the trial. Special thanks to Dr. Elin Borgen and Dr. Olav Engebråten for valuable advice.

References

1. Robert, C., et al., *Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomised dose-comparison cohort of a phase 1 trial.* Lancet, 2014. **384**(9948): p. 1109-17.
2. Larkin, J., et al., *Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma.* N Engl J Med, 2015. **373**(1): p. 23-34.
3. Gibney, G.T., et al., *Safety, correlative markers, and clinical results of adjuvant nivolumab in combination with vaccine in resected high-risk metastatic melanoma.* Clin Cancer Res, 2015. **21**(4): p. 712-20.
4. Rizvi, N.A., et al., *Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer.* Science, 2015. **348**(6230): p. 124-8.
5. Ferris, R.L., et al., *Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck.* N Engl J Med, 2016. **375**(19): p. 1856-1867.
6. Hellmann, M.D., et al., *Nivolumab plus Ipilimumab in Lung Cancer with a High Tumor Mutational Burden.* N Engl J Med, 2018.
7. Emens, L.A., *Breast Cancer Immunotherapy: Facts and Hopes.* Clin Cancer Res, 2018. **24**(3): p. 511-520.
8. Schmid, P., et al., *Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer.* N Engl J Med, 2018. **379**(22): p. 2108-2121.
9. Sistigu, A., et al., *Cancer cell-autonomous contribution of type I interferon signaling to the efficacy of chemotherapy.* Nat Med, 2014. **20**(11): p. 1301-9.
10. Nanda, R., *Pembrolizumab plus standard neoadjuvant therapy for high-risk breast cancer (BC): Results from I-SPY 2.* J Clin Oncol, 2017. **35**(Suppl; abstr 506).
11. Schmid, P., et al., *Pembrolizumab for Early Triple-Negative Breast Cancer.* N Engl J Med, 2020. **382**(9): p. 810-821.
12. Bezu, L., et al., *Combinatorial strategies for the induction of immunogenic cell death.* Front Immunol, 2015. **6**: p. 187.
13. Kroemer, G., et al., *Natural and therapy-induced immunosurveillance in breast cancer.* Nat Med, 2015. **21**(10): p. 1128-38.
14. Apetoh, L., et al., *Toll-like receptor 4-dependent contribution of the immune system to anticancer chemotherapy and radiotherapy.* Nat Med, 2007. **13**(9): p. 1050-9.
15. Nolan, E., et al., *Combined immune checkpoint blockade as a therapeutic strategy for BRCA1-mutated breast cancer.* Sci Transl Med, 2017. **9**(393).
16. Pfirschke, C., et al., *Immunogenic Chemotherapy Sensitizes Tumors to Checkpoint Blockade Therapy.* Immunity, 2016. **44**(2): p. 343-54.
17. Goldman, J.W., et al., *Nivolumab (N) plus ipilimumab (I) as first-line (1L) treatment for advanced (adv) NSCLC: 2-yr OS and long-term outcomes from CheckMate 012.* Journal of Clinical Oncology, 2017. **35**(15_suppl): p. 9093-9093.

18. Ghiringhelli, F., et al., *Metronomic cyclophosphamide regimen selectively depletes CD4+CD25+ regulatory T cells and restores T and NK effector functions in end stage cancer patients.* Cancer Immunol Immunother, 2007. **56**(5): p. 641-8.
19. Munzone, E. and M. Colleoni, *Clinical overview of metronomic chemotherapy in breast cancer.* Nat Rev Clin Oncol, 2015. **12**(11): p. 631-44.