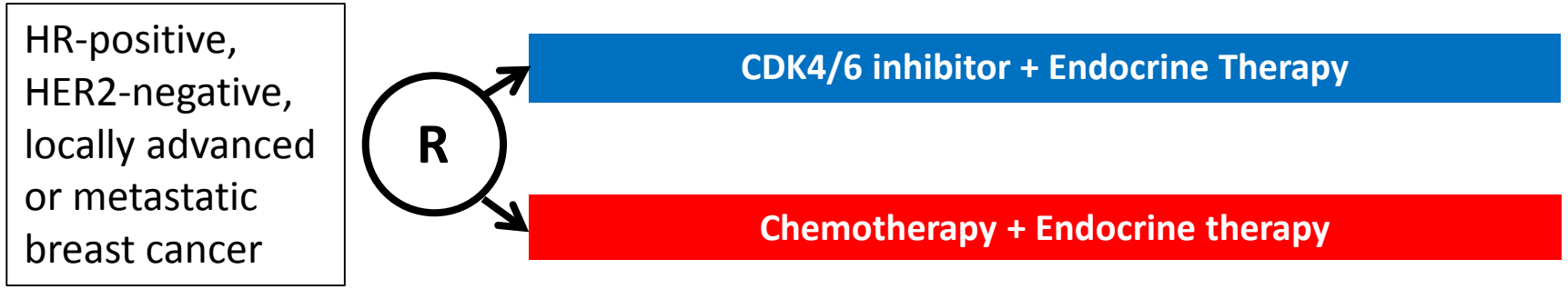
Group sequential response adaptive RCT of concomitant CT plus ET versus CDK4/6 inhibitor plus ET for HR+/HER2- MBC (KENDO)

- Background: advanced luminal breast cancer is usually initially treated with endocrine-based therapies, but it is uncertain what is the best treatment in case of primary endocrine resistance or doubtful endocrine sensitivity
- Prospective, open label, multicenter, group sequential, response adaptive, randomized phase 2 study, comparing two treatments for locally advanced or metastatic luminal breast cancer:
  - Arm A: concomitant **CDK4/6 inhibitor** (palbociclib, ribociclib or abemaciclib) **plus ET** (AI or fulvestrant)
  - Arm B: **chemotherapy plus endocrine therapy** (AI or fulvestrant, administered either concomitantly from the beginning of chemotherapy or sequentially after 4-6 months of chemotherapy)
- Cross-over to the other treatment arm is encouraged (although not mandatory) after disease progression



Patient population

HR+/HER2- MBC, **with primary endocrine resistance or doubtful endocrine sensitivity** or other signs of disease aggressiveness.

Main inclusion criteria:

- Histological diagnosis of HR+ (ER ≥10% of tumor cells), HER2- breast cancer
- Locally advanced (not susceptible to locoregional therapy) or MBC
- At least one of the following :
  - low expression of ER (10% ≥ ER < 50%) or
  - relapse while on the first 2 years of adjuvant ET or PD within the first 6 months of first-line ET for MBC, or
  - other tumor characteristics of aggressiveness that make the patient potentially candidate to chemotherapy, according to AIOM guidelines 2017: elevated Ki67 (preferably on a metastatic biopsy), low expression of hormone receptors (e.g. progesterone receptor <20%), extended visceral involvement or visceral involvement at risk for organ failure, uncontrolled symptoms
- Postmenopausal, or premenopausal women undergoing treatment with LHRH analogue, or men
- Measurable disease according to RECIST 1.1 criteria, or not measurable but evaluable disease
- No prior CT nor CDK4/6 inhibitor for MBC
- Up to one prior line of ET for MBC

Treatments

Chemotherapy regimen at the discretion of the treating physician chosen among those commonly accepted as "standard":

- anthracycline + taxane
- taxane
- anthracycline
- capecitabine / fluoropyrimidines
- Others

Endocrine therapy:

- NSAI or SAI, in women not pretreated with an AI
- NSAI in women pretreated with a SAI for MBC, or who relapsed while on adjuvant SAI
- SAI in women pretreated with NSAI for MBC, or who relapsed while on adjuvant NSAI
- fulvestrant in women not pretreated with fulvestrant for MBC

CDK4/6 inhibitor: palbociclib, ribociclib, abemaciclib

Objectives

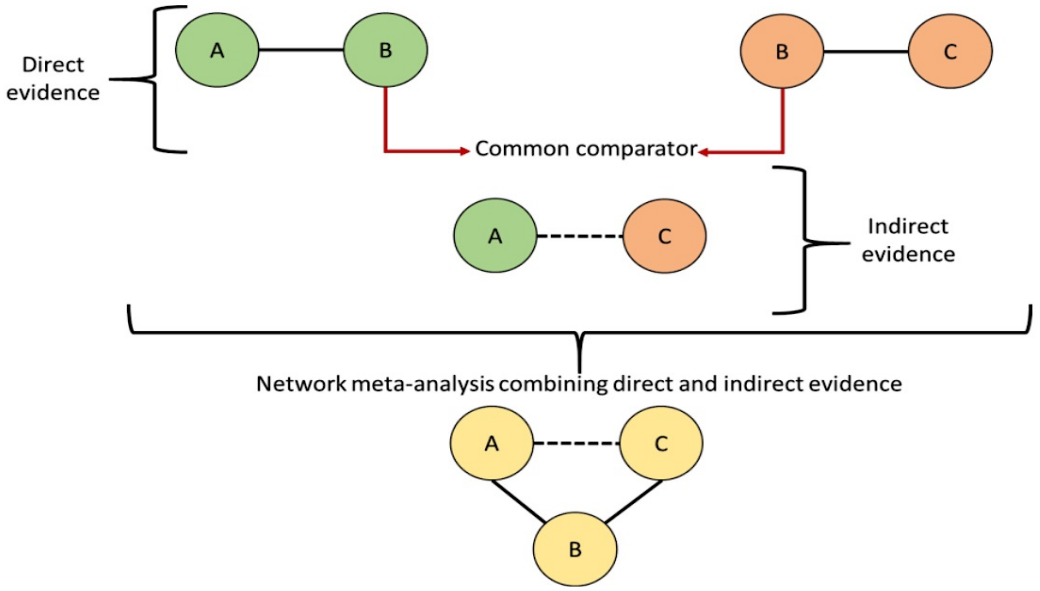
- **Primary**: to compare the efficacy of treatments in terms of PFS
- **Secondary**: to compare between treatment arms:
  - quality of life (EORTC QLQ-C30 and QLQ-BR23)
  - toxicity (CTCAE version 4.03)
  - time to treatment failure
  - best response rate
  - DoR
  - CBR
  - OS
  - correlative biomarkers of response to CDK4/6 inhibitors and chemotherapy:
    - tissue markers (on the primary tumor and / or metastatic tissue)
    - circulating markers (e.g. CTCs, ctDNA)
  - to compare, within the experimental arm, PFS with concomitant versus sequential administration of chemotherapy and ET (exploratory)

Hypotheses

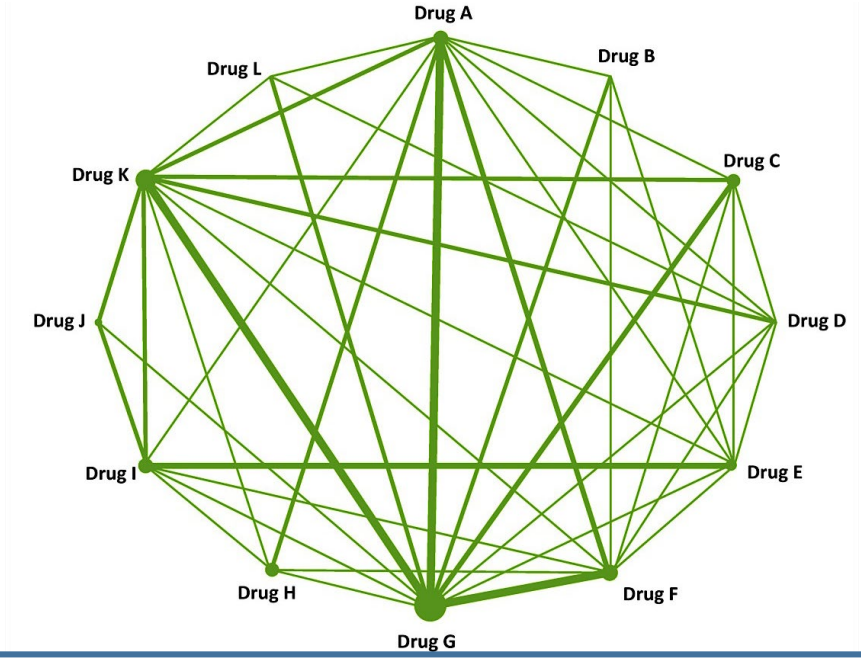
- Statistical hypothesis: chemotherapy + ET (considered in this context the experimental arm) yields better PFS compared to CDK4/6 inhibitors + ET
- Biological hypothesis:
  - Rb-proficient tumors respond better to CDK4/6 inhibitors + ET
  - Rb-deficient tumors respond better to chemotherapy

Network meta-analyses (NMA)
to compare two treatments never directly confronted in a RCT

To date, NMA represent the only statistical approach to indirectly compare treatments, providing that they have been compared to at least one common comparator

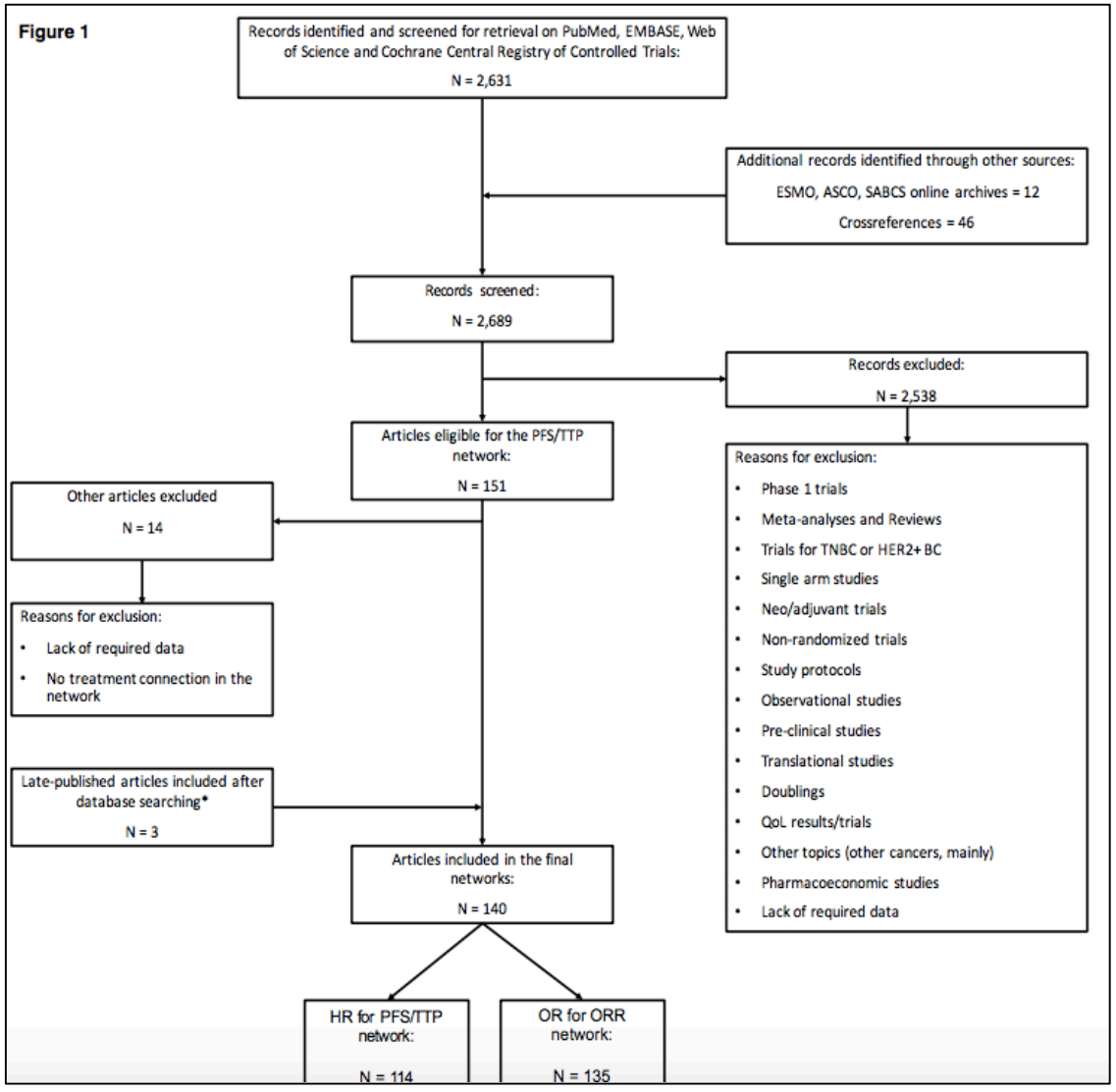


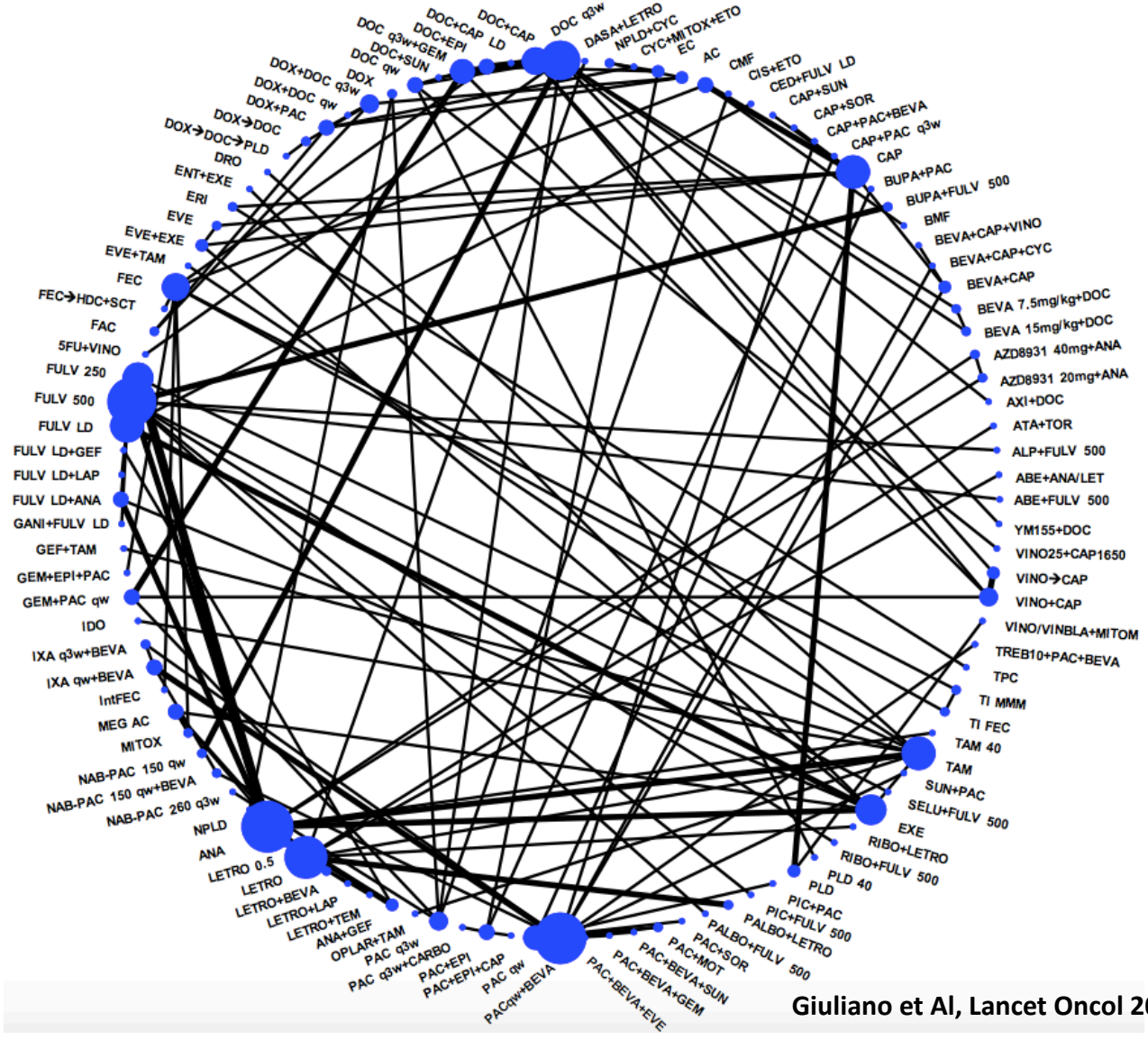
Network meta-analysis compares multiple interventions simultaneously by assessing in the same analysis the results of studies making different comparisons



Tonin FS et al., Pharmacy Practice 2017; 15(1):943

ET versus CT in postmenopausal women with HR+/HER2- MBC: a systematic review and network meta-analysis

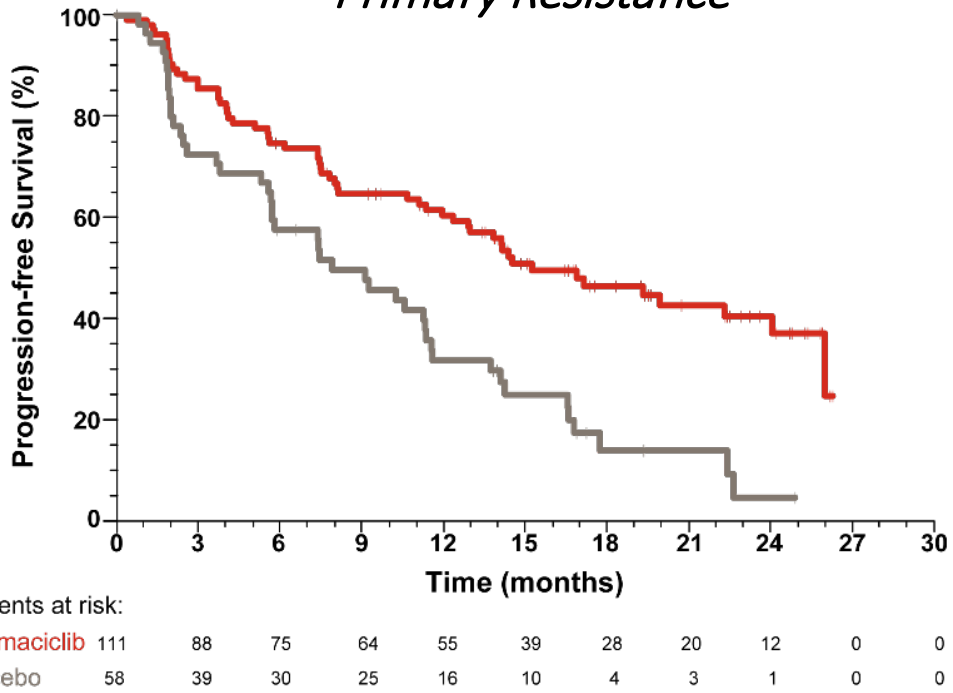




Giuliano et Al, Lancet Oncol 2019

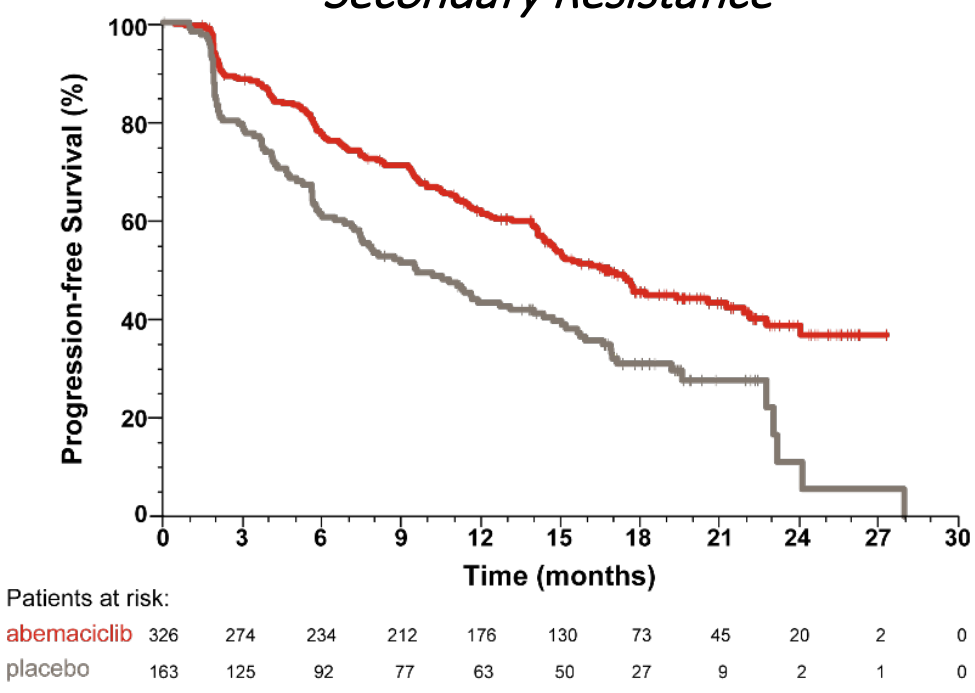
Subgroups from the MONARCH 2 study according to ET resistance: PFS

Primary Resistance



Median PFS
abemaciclib + fulvestrant: 15.3 months
placebo + fulvestrant: 7.9 months
HR (95% CI): .454 (.306, .674) p<.0001

Secondary Resistance

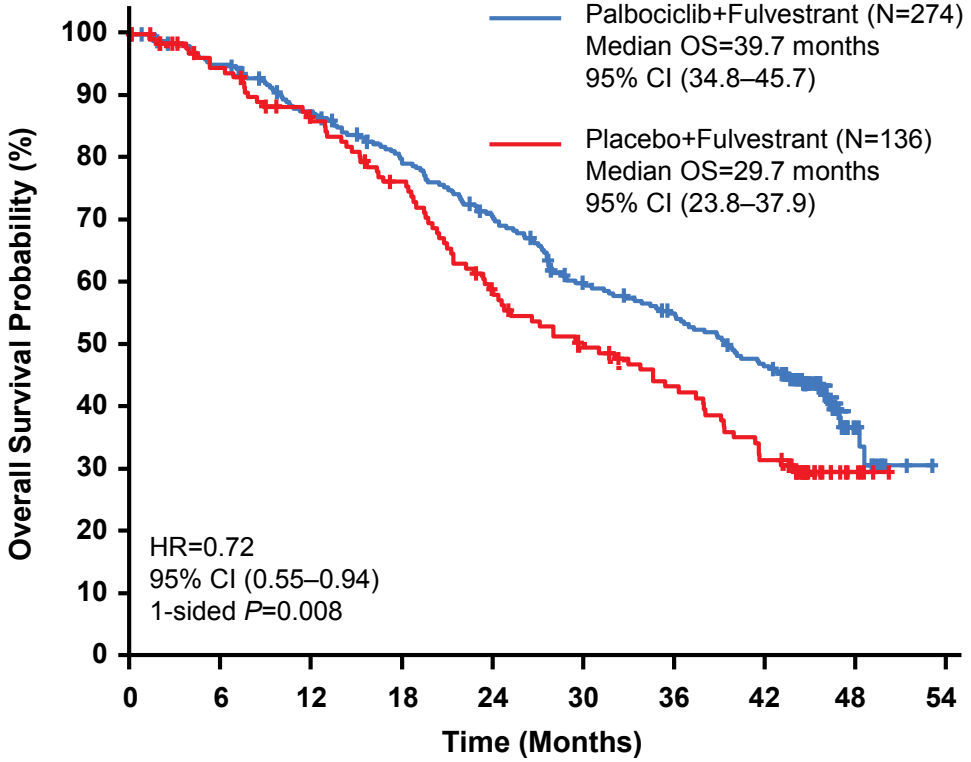


Median PFS
abemaciclib + fulvestrant: 16.6 months
placebo + fulvestrant: 9.6 months
HR (95% CI): .591 (.464, .754) p<.0001

Grischke M et al, ESMO 2018

PALOMA-3: OS by sensitivity to prior ET

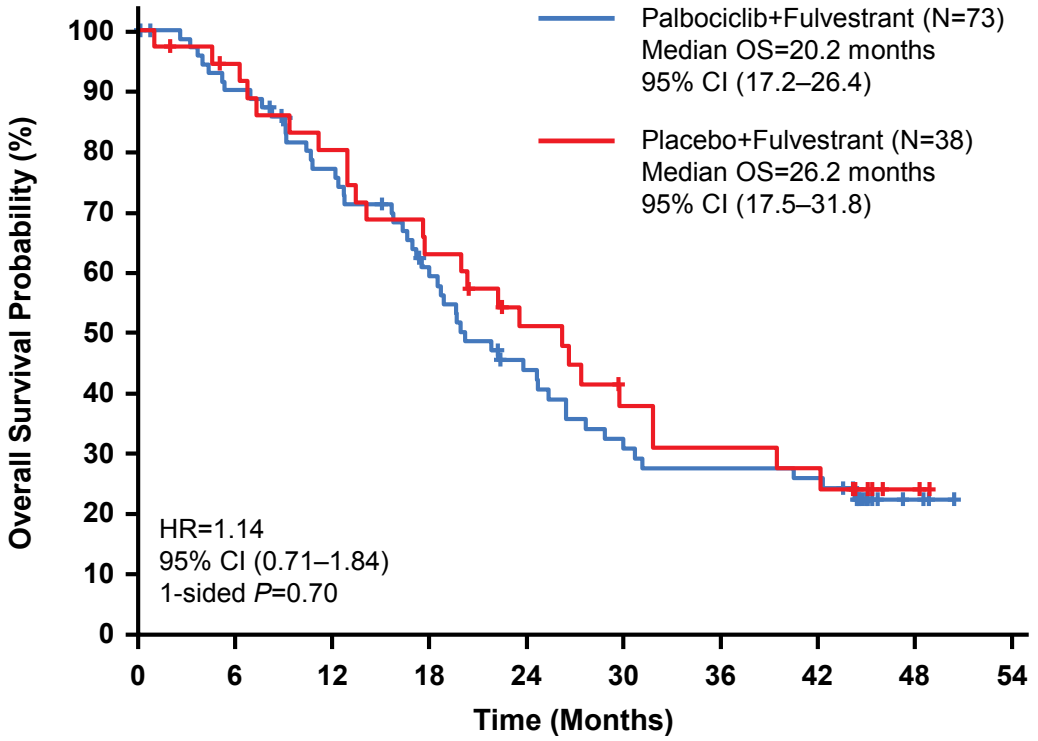
Pts With Sensitivity to Prior ET



Number of patients at risk

PAL+FUL	274	257	233	208	182	146	131	110	14
PBO+FUL	136	122	107	93	70	57	48	35	5

Pts Without Sensitivity to Prior ET



Number of patients at risk

PAL+FUL	73	64	53	39	27	19	17	16	3
PBO+FUL	38	33	28	22	16	11	9	8	2

Turner NC et al, NEJM 2018

My suggestions

- CDK4/6i maybe not be all equal in patients with primary endocrine resistance
- Define chemotherapeutic agent, at least choose monotherapy or combo
- Choosing just one between concomitant ET/CT or sequential CT→ ET might help with the statistical plan and sample size
- You may want to consider adding PFS 2 as secondary endpoint for those patients who cross over

Local Treatment in ER-positive/HER2-negative oligo-metastatic breast cancer treated with CDK4/6 inhibitors: the role of autoimmunity as biomarker of response

Alessandra Fabi

Michelangelo Russillo

Dir: F. Cognetti

BACKGROUND

- CDK4/6 inhibitors have recently been proven effective when combined with endocrine therapy (ET) also in oligometastatic breast cancer

- Surgical control of primary breast lesion could be considered as an option in the locoregional treatment of MBC, particularly in non-visceral oligometastastic breast cancer

Project plan and inclusion criteria

- This is an open-label, multicenter study in patients with oligometastatic pre-and post-menopausal breast cancer patients, who are candidates for standard first line treatment with CDK 4/6 inhibitor plus endocrine therapy

- Target accrual 30 patients

- HR+/HER2- primary tumor (diagnostic biopsy of the primary BC)
- Primary breast cancer with synchronous metastatic disease. Oligometastatic disease is defined as: ≤ 5 lesions in single organ or no more than 3 sites (lung, bone, liver, adrenal glands, distant LNs)
- Metastatic lesions amenable for local therapy (radiotherapy [Size≤3cm])
- Age>18 yrs
- no prior chemotherapy nor endocrine therapy in the metastatic setting
- PS≤2

Goals

- To evaluate the impact of surgery of the primary tumor in oligometastatic BC patients treated with CDK4/6 inhibitors + AI (+/- LHRHa) as first line therapy

- To identify biomarkers of response to CDK 4/6 inhibitors

Endpoints

- Primary Endpoints:
  - Response rate (primary and metastatic disease)
  - PFS

- Secondary Endpoints
  - Rate of patients undergoing surgery of the primary tumor
  - Time to response of primary tumor and metastases
  - Duration of response of metastasis after surgery

Biological objectives

- To study Lymphocyte subpopulations in peripheral blood (B CD19+, NK CD3-CD56+, ratio CD4+/CD8+, T cit. soppr.CD3+CD8+, T Help.ind.CD3+CD4+, T CD3+) at diagnosis and at the time of first disease progression

Treatment

CDK4/6 inhibitor (as per investigator's choice) + AI* for 6 months

↓

Surgery of the primary tumor**

↓

Continuation of CDK4/6 inhibitor + AI*

*Leuproline in case of premenopausal pts

** no surgery in case of standard clinical considerations

OLIGOMETASTATIC DISEASE

- 1–10% of newly diagnosed MBC are oligometastatic and might benefit from a more aggressive and integrated treatment strategiy (combining both systemic and locoregional therapies) to achieve long-lasting remission and potentially cure

- Selection bias and the retrospective nature of available data do not allow for generalization of the results, and the use of such approaches must be individualized and discussed in a multidisciplinary team

- Local treatment can be discussed in selected patients, taking into account several factors such as tumor subtype, DFS/PFS, number/size of lesions and response to previous therapies, performance status and comorbidity of the patients

Pagani O, et al. J Natl Cancer Inst. 2010; O`Shaughnessy J. Oncologist. 2005.
Cardoso F, et al. Annals Oncol. 2018; Hellman S, R.R. Weichselbaum. JCO. 1995

Safety and Efficacy of Palbociclib and Radiotherapy in Metastatic Breast Cancer Patients: Initial Results of a Novel Combination

Mudit Chowdhary[1], Neilayan Sen[1], Akansha Chowdhary[2], Lydia Usha[3], Melody Cobleigh[3], Dian Wang[1], Kirtesh R. Patel[4], Parul N. Barry[1], Ruta D. Rao[3]

Rush University Medical Center, Departments of Radiation Oncology[1] and Medical Oncology[3];
Northwestern University, Division of Medical Oncology[2]; Yale School of Medicine, Department of Therapeutic Radiology[4]

- 16 patients treated with concomitant palbociclib and RT
- First report of concomitant treatment
- Concomitant treatment resulted in minimal grade 1 and no grade 2+ toxicities

RT can be safely administered in symptomatic patients without discontinuing systemic treatment with palbociclib

The Breast 46 (2019) 70–74

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Original article

Concurrent radiotherapy with palbociclib or ribociclib for metastatic breast cancer patients: Preliminary assessment of toxicity

Edy Ippolito [a], Carlo Greco [a], Sonia Silipigni [a, *], Emanuela Dell'Aquila [b], Gian Marco Petrianni [a], Giuseppe Tonini [b], Michele Fiore [a], Rolando Maria D'Angelillo [a], Sara Ramella [a]

[a] *Radiation Oncology, Campus Bio-Medico University of Rome, Rome, Italy*
[b] *Medical Oncology, Campus Bio-Medico University of Rome, Rome, Italy*

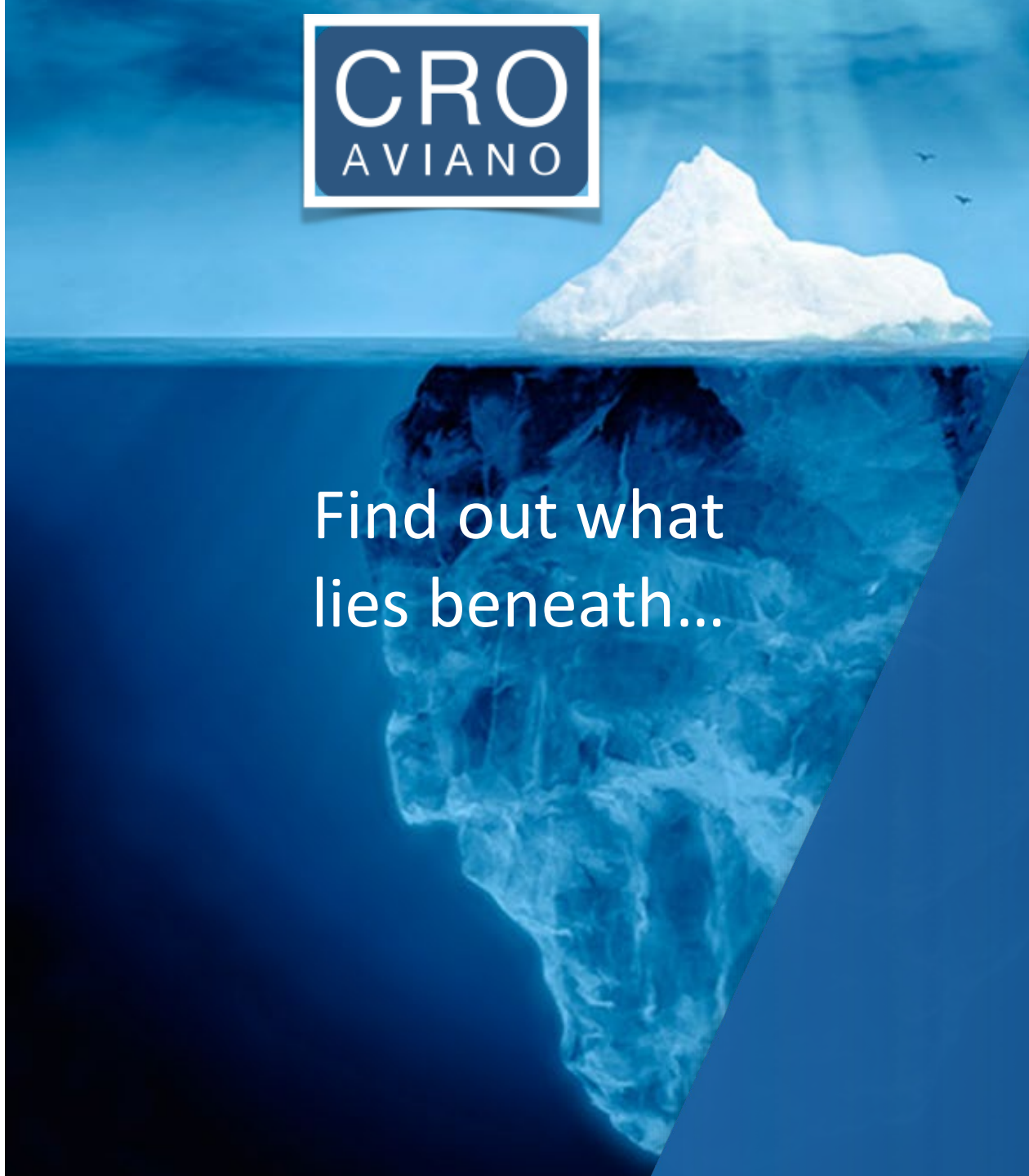
Concurrent radiotherapy with palbociclib or ribociclib for metastatic breast cancer patients: Preliminary assessment of toxicity

Type of Adverse Event	During CDK4/6 inhibitor cycle delivered concurrently with RT	During following CDK4/6 inhibitor cycle
Hematological		
Neutropenia		
Grade 1	0 (0.0%)	0 (0.0%)
Grade 2	2 (12.5%)	1 (6.3%)
Grade 3	4 (25.0%)	4 (25.0%)
Grade 4	1 (6.3%)	0 (0.0%)
Trombocitopenia		
Grade 1	2 (12.5%)	0 (0.0%)
Grade 2	0 (0.0%)	0 (0.0%)
Grade 3	0 (0.0%)	0 (0.0%)
Grade 4	0 (0.0%)	0 (0.0%)
Anemia		
Grade 1	3 (18.8%)	2 (12.5%)
Grade 2	0 (0.0%)	0 (0.0%)
Grade 3	0 (0.0%)	0 (0.0%)
Grade 4	0 (0.0%)	0 (0.0%)
Non Hematological		
Fatigue		
Grade 1	2 (12.5%)	2 (12.5%)
Grade >2	0 (0.0%)	0 (0.0%)
Skin		
Grade 1	1 (6.3%)	0 (0.0%)
Grade >2	1 (6.3%)	0 (0.0%)

"Conclusion: concomitant treatment of CDK4/6 and radiotherapy seems well tolerated; high grade hematological toxicity is common, but did not change treatment course in the majority of patients."

My suggestions

- I would clarify the role of RT in the therapeutic algorithm
- Timing is crucial: define when to perform surgery and/or RT



CRO AVIANO

UNIVERSITY OF UDINE
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Find out what lies beneath…

The MEASURE study

luMinal brEast cAncer; Skeletal muscle mass, subcUtaneous and visceRal fat measurement during Endocrine treatment

Debora Basile, MD

Department of Medicine (DAME) - The University of Udine

Unit of Clinical Oncology and Oncology Prevention -

CRO Aviano National Cancer Institute

• The MEASURE Study

• Background

Overweight is an established risk factor for development of breast cancer (BC) and an unfavorable prognostic factor with higher incidence of recurrence and cancer related deaths

- BMI is the most common measure of body size, and the relationship between obesity and BC survival has been widely studied.
- Data derived from clinical trials, pooling projects, and meta-analyses have consistently shown that BMI >35 was associated with worse survival.
- However, studies have shown mixed associations with overweight or lower levels of obesity.

The association between adiposity, poor treatment response and prognosis has been observed in HR positive, HER2 negative BC

Changes in adipose tissue after adjuvant treatment with aromatase inhibitors

Adipose Tissue Type	Before Therapy	After Therapy	Outcome
Total Abdominal Adipose Tissue, mm^3	16,280.3 ± 6953.3	17,763.6 ± 6850.8	Increased 9.1%
Abdominal Visceral Adipose Tissue, mm^3	9024.4 ± 4630.0	10,651.9 ± 4371.7	Increased 18 %
Abdominal Subcutaneous Adipose Tissue, mm^3	7255.8 ± 3376.6	7111.6 ± 3372.0	Decreased 1.9%

Munsell MF Epidemiol Rev 2014; Chan DS Ann Oncol 2014
Battisti S. 2014 Clin Breast Cancer; Smith IE N Engl J Med 2003

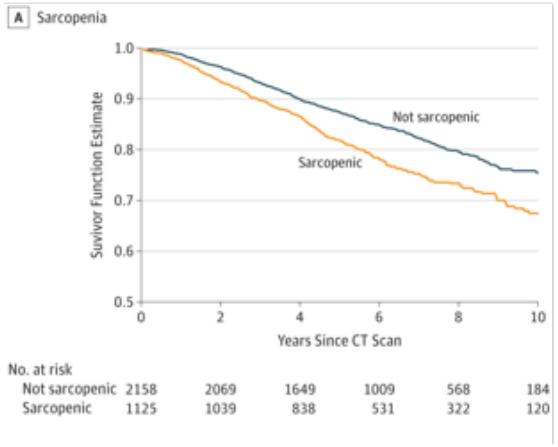
• The MEASURE Study

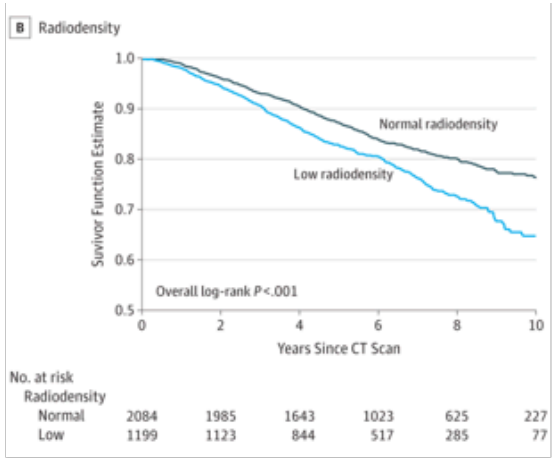
• Background

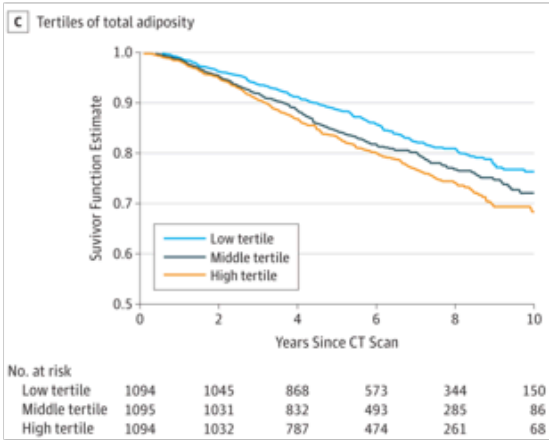
34% of patients had sarcopenic regardless of BMI and 37% had low muscle radiodensity

Patients with sarcopenia, high total adiposity (highest tertile) had worse OS (HR, 1.41; 95% CI, 1.18-1.69; p<.001; HR, 1.40; 95% CI, 1.04-1.88, P<.001, respectively).

However, only 18% of women who are overweight (BMI 25-30) and 73% of women who are class 1 obese (BMI 30-35) women fall into the highest adiposity category.







Caan BJ, et al; JAMA 2018

• The MEASURE Study

• Objectives and Endpoints

Prognostic impact of body composition in luminal mBC treated with endocrine treatment

Prognostic impact of variation in body composition in luminal mBC treated with endocrine treatment

Evaluation of anthropometric measure (eg. BMI, weight) in confront of CT scan

Association among body composition, high level of estrone sulfate and response to endocrine treatment

→ Primary endpoint:

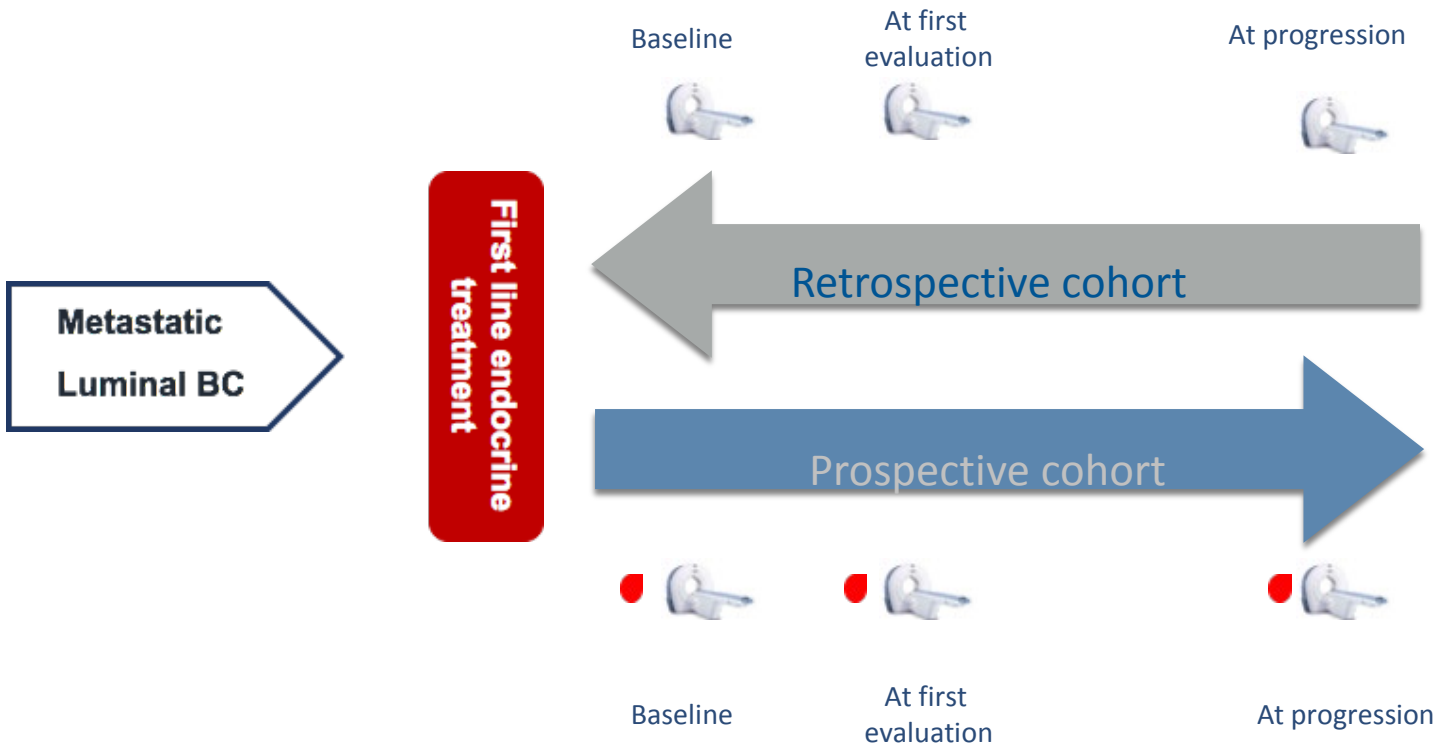
- PFS

→ Secondary endpoints:

- OS
- Accuracy

• The MEASURE Study

• Study Design



- Six months for the recruitment of the retrospective cohort
- Twelve months for the recruitment of the prospective cohort

• The MEASURE Study

• Procedures

Retrospective cohort

- Voluntary, written, dated and signed Informed Consent
- Enrollment with the assignment of a digits ID code
- Collection of anagrafic data, anthropometric measurements and information on life-style and job
- Send CT scan through AMBRA open source platform

Prospective cohort

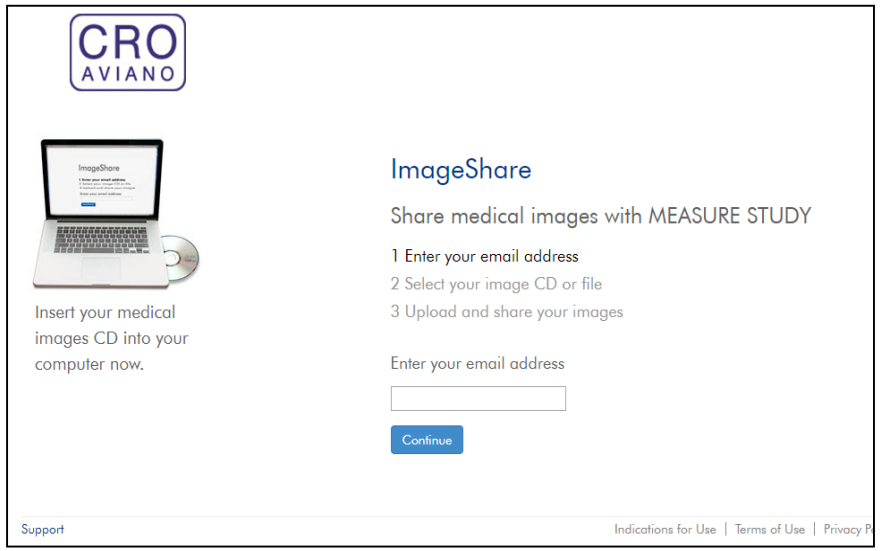
- Voluntary, written, dated and signed Informed Consent
- Enrollment with the assignment of a digits ID code
- Collection of anagrafic data, anthropometric measurements and information on life-style and job
- Request the blood analyses as requested on CRF at C1D1 of endocrine treatment, at first CT evaluation and at progression
- Send CT scan though AMBRA open source platform

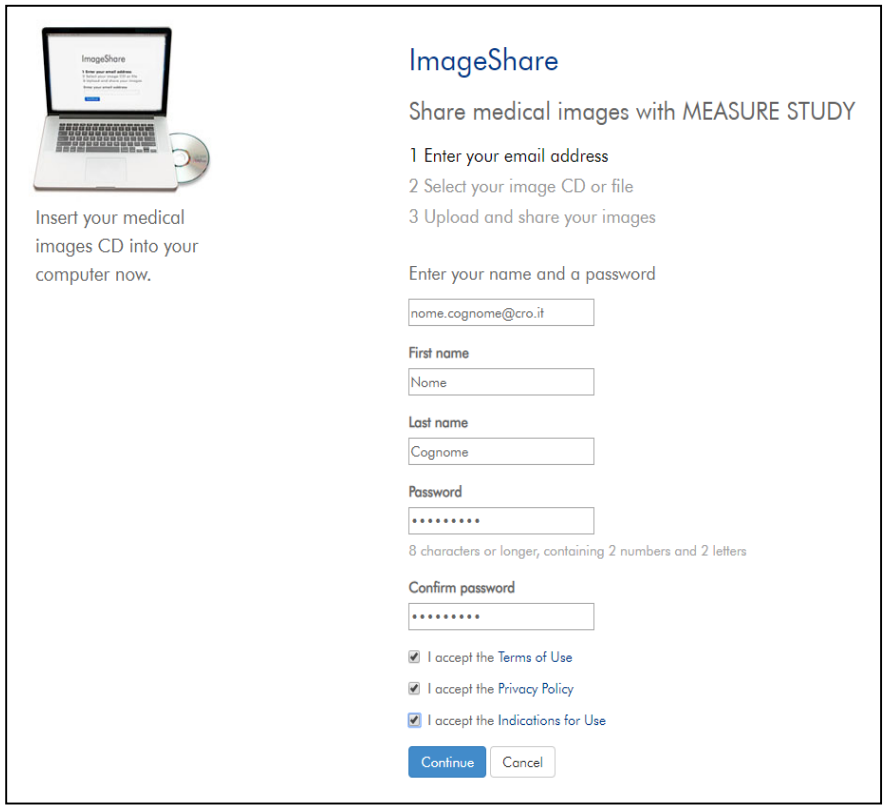
• The MEASURE Study

• Procedures

Send CT scan through AMBRA platform

https://croaviano.dicomgrid.com/share/MEASURE STUDY .

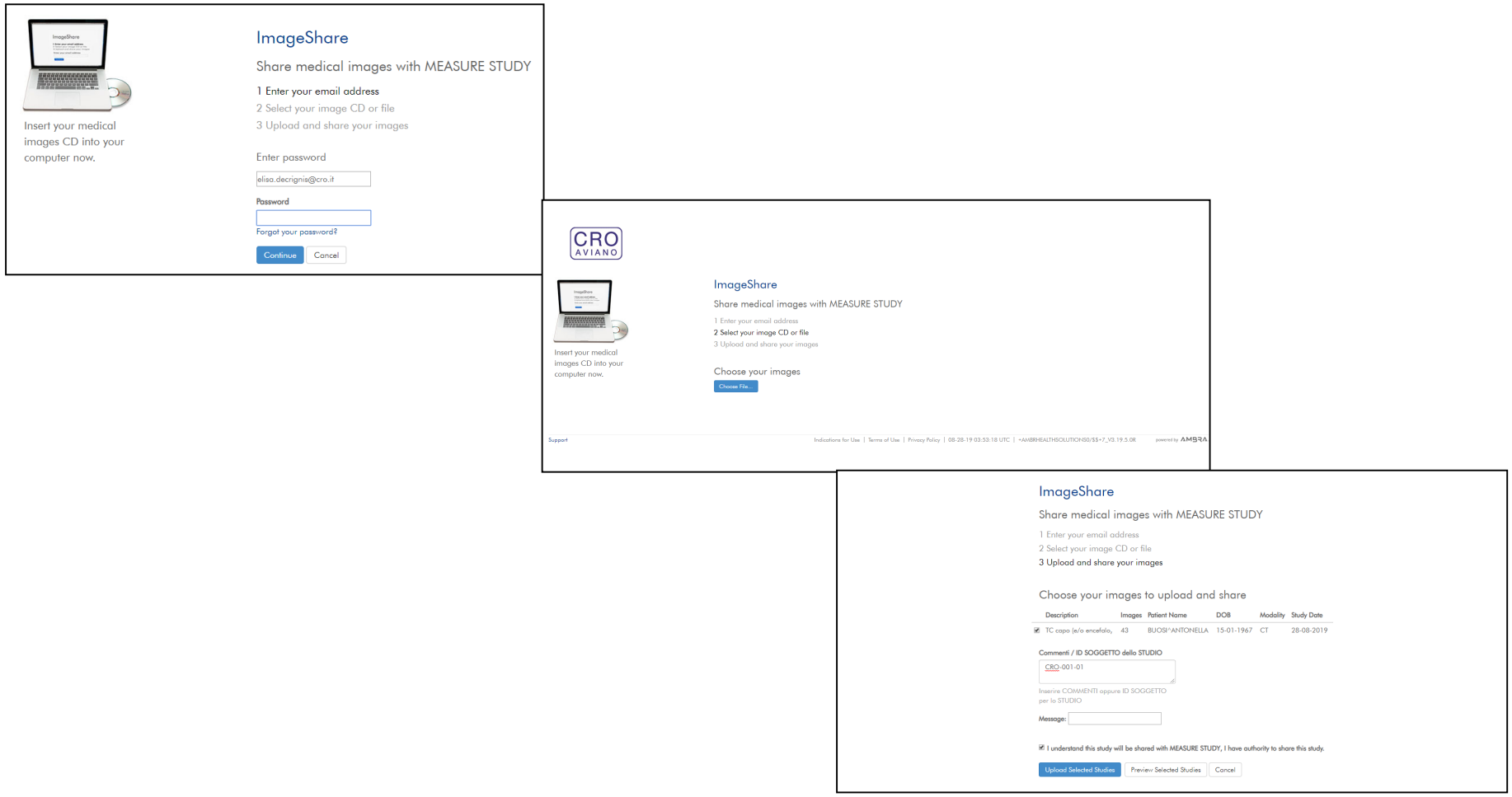




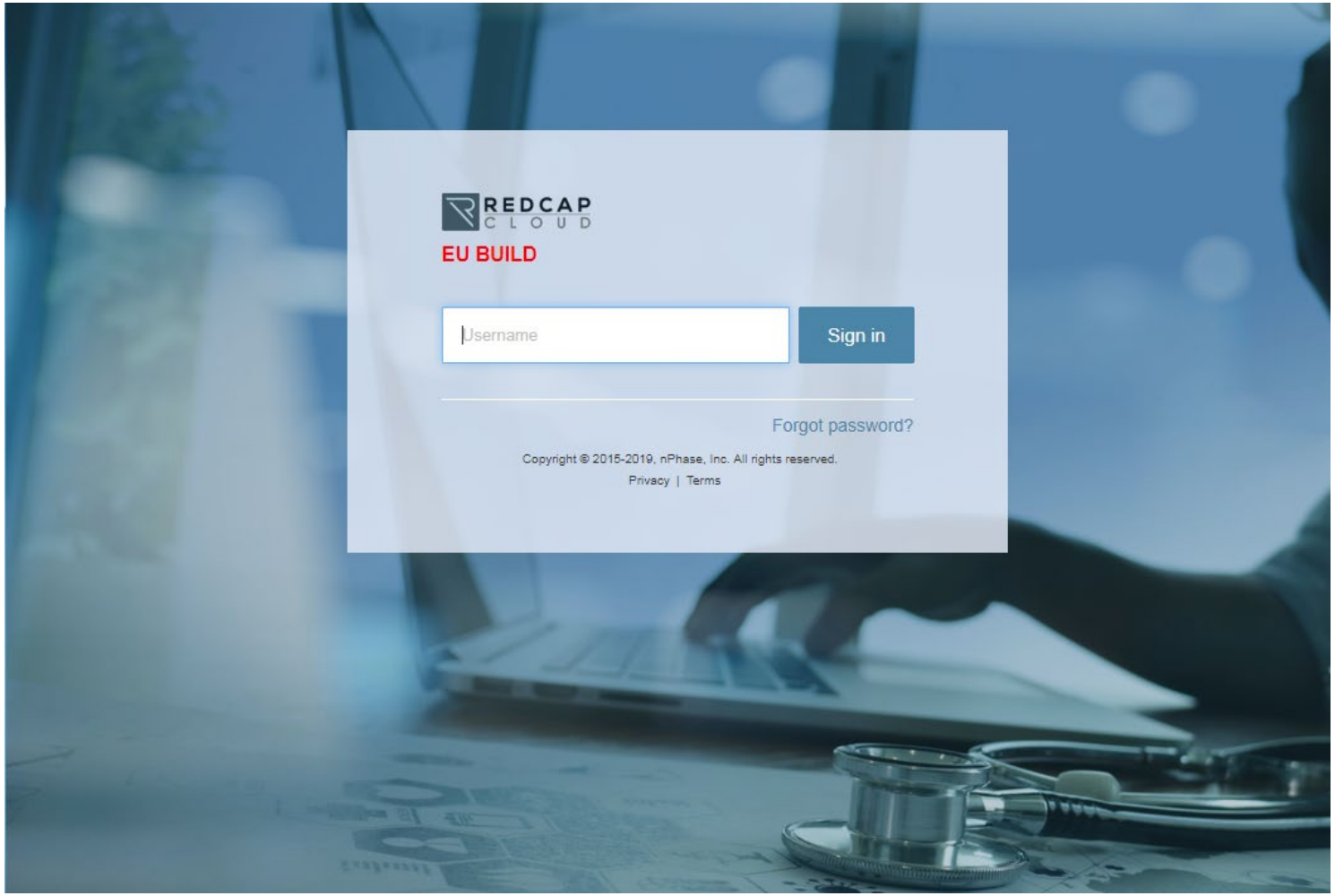
• The MEASURE Study

• Procedures

Send CT scan through AMBRA platform

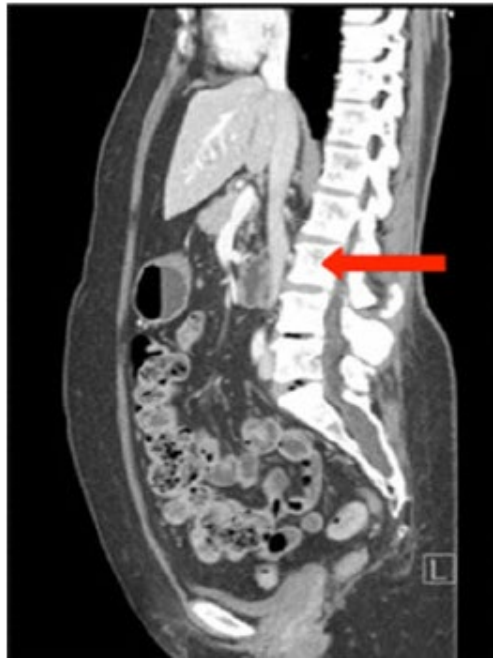


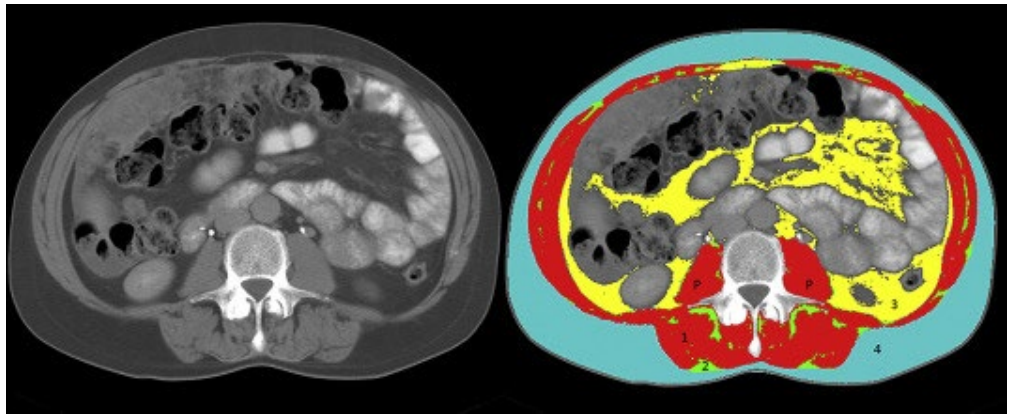
Send data through RedCap Cloud platform



- The MEASURE Study
- Body composition assessment

Skeletal muscle mass, subcutaneous and visceral fat index will be calculated as cross-sectional area of muscle (cm^2) at the L3 level





My suggestions

- Estimate the magnitude of the expected effect of the biomarker to better define the sample size
- I would suggest detailing the retrospective chohort
- Clarify how endpoints will be evaluated