EORTC
Current Clinical Trials

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Medical Oncology

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EORTC 40085-75083

Treatment of patients with KRAS and NRAS wild type advanced colorectal cancer with 5-fluorouracil (5-FU) or 5-FU plus an Epidermal Growth Factor Receptor inhibitor (cetuximab) based on a Comprehensive Geriatric Assessment

Study Coordinator: Prof. Marc Peeters (BE)
Study Co coordinator: Dr. Ulrich Wedding (DE)
Rationale

- 5-Fluorouracil (5-FU) has activity in mCRC
  - overall, it’s well tolerated
  - used in combination regimens such as FOLFIRI and FOLFOX

- Associations with biologicals such as bevacizumab or EGFR inhibitors (KRAS wild type only) improve the outcome

- In general, older and/or frail patients are not investigated in clinical trials

Therefore, in this study we want to evaluate the tolerance of an active 5-FU regimen in combination with cetuximab in KRAS WT elderly/frail patients.
Endpoints

Primary:
- The primary endpoint is PFS
  - Progression will be defined according to the “RECIST V1.1”

Secondary:
- Overall Survival
- Response Rate (according to the RECIST V1.1)
- Comprehensive geriatric assessment (CGA) as evaluated by the elderly minimal dataset (MDS): G8 instrument, IADL and social situation questionnaires and by the short physical performance battery (SPPB)
- Quality of Life (EORTC-QLQ C30 and QLQ-ELD14)
- Safety profile
- Health Economics assessments
Main eligibility criteria

- Male or female pts with pathologically confirmed metastatic colorectal cancer
- KRAS and NRAS wild type colorectal cancer
- No prior systemic chemotherapy for metastatic disease
- No previous exposure to EGFR or VEGF/VEGFR targeted therapy
- Age $\geq 80$ or $\geq 70$ in combination with functional restrictions defined as limitation in at least 2 of 8 IADL
- Measurable disease according to RECIST V1.1. (CRC metastatic patients with non-measurable disease will be reviewed on a case by case basis by SC and EORTC HQ study sponsor)
Treatment

Randomization (1:1) of 150 KRAS/NRAS WT elderly frail patients
Treatment starts as soon as possible after randomization

Stratification Factors
- Institution
- WHO performance status (0-1 vs 2)
- Age category (≥ 80 years vs <80 years)

Arm 1
Day 1:
- Cetuximab 500 mg/m², Q 14 days.
  followed by:
  - Racemic leucovorin 400 mg/m²
    or l-leucovorin 200 mg/m²
  - 5-FU 400 mg/m²
  - 5-FU 2400 mg/m², 46 hrs IV, Q 14 days.

Arm 2
Day 1:
- Racemic leucovorin 400 mg/m²
  or l-leucovorin 200 mg/m²
  - 5-FU 400 mg/m²
  - 5-FU 2400 mg/m², 46 hrs IV Q 14 days.
**Statistical design**

- **Primary objective:**
  to detect 50% increase in median PFS between the 2 arms from 3 months in the control arm to 4.5 months in the experimental arm

- **Sample size:**
  n=150 patients
Participating countries

- UK (13 sites)
- Belgium (10 sites)
- France (9 sites)
- Germany (6 sites)
- Italy (3 sites)
- Spain (2 sites)
- Cyprus (1 site)
Accrual graph (on 21/10/14)

Expected today: 27
Observed today: 5
Current status (21/10/2014)

- The trial is open in Belgium (since May 2013), Cyprus, Italy, Spain, UK and Germany
- 22 sites open
- 5 patients enrolled only
Special issues

- The protocol has been amended to extend the testing of KRAS/NRAS to exons 2, 3 and 4 and redefine adequate renal function.

- Future of this trial will be re-discussed during EORTC GI meeting end of November

- EORTC team can be contacted at 40085@eortc.be
EORTC 75111 – 10114

Pertuzumab + trastuzumab (PH) versus PH plus metronomic chemotherapy (PHM) in the elderly HER2+ metastatic breast cancer population: an open-label multicentre randomized phase II selection trial of the EORTC Elderly Task Force and Breast Cancer Group.

Hans Wildiers, Leuven, Belgium
Etienne Brain, Saint-Cloud, France
**Trial design**

80 pts HER2+ MBC ≥ 70 Years

(≥65/≥60y with co-morbidity)

Pertuzumab + Trastuzumab

Pertuzumab + Trastuzumab + metronomic CT

Primary endpoint:
PFS at 6 months of PH or PHM

Secondary endpoints: OS, BCSS, toxicity,
RR according RECIST v 1.1, HRQoL,
evolution of geriatric assessment during treatment

Pertuzumab: 840 mg loading dose, further 420 mg q3w iv
Trastuzumab: 8 mg/kg loading dose, further 6 mg/kg q3w iv
Chemotherapy: Metronomic chemotherapy: cyclophosphamide 50 mg/d po continuously
On progression: option to have T-DM1 (3.6 mg/kg iv q3w) till progression

Stratification: ER and/or PR pos vs both negative, previous HER2 treatment (none vs adj only vs metastatic), G8< or equal 14 vs G8>14
Inclusion Criteria

- ≥ 70 years of age, or ≥ 60 years old with required number of dependencies:
  - 65 – 69 + functional restriction defined as limitation in ≥ 2/8 iADL or 1/6 ADL or Charlson Comorbidity Score > 2
  - 60 – 64 + functional restriction defined as limitation in ≥ 3/8 iADL or 2/6 ADL or Charlson Comorbidity Score > 3
- Histologically proven metastatic HER2 positive (IHC 3+ or FISH pos) breast cancer, based on local laboratory results
- Measurable (by RECIST 1.1) or evaluable disease
- No previous chemotherapy for metastatic disease
- Up to one line of anti-HER therapy (trastuzumab or lapatinib) is allowed in combination with hormone therapy
- Glomerular filtration rate ≥ 30 ml/min
- Liver function: AST/ALT and ALP ≤ 2.5 x ULN (for alkaline phosphatase limit applies in the absence of bone metastases)
- LVEF ≥ 50% within 28 days of randomization
Trial Status

- Open in Belgium, France, Italy
- Other countries (GB, NL, PL, PT) to follow as soon as possible
# Trial Status

<table>
<thead>
<tr>
<th>Site Description</th>
<th>Activated</th>
<th># Patients randomized</th>
<th>First patient in</th>
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<td>7</td>
<td>03/12/2013</td>
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<td>147. U.Z. Gasthuisberg (BE)</td>
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<td>02/07/2013</td>
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<td>1201. CMSE Namur (BE)</td>
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<td>252. Centre Rene Huguenin (FR)</td>
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<td>234. Centre Oscar Lambret (FR)</td>
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<td>223. Ctre Paul Strauss (FR)</td>
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<tr>
<td>9141. AZ Nikolaas (BE)</td>
<td>18/02/2014</td>
<td></td>
<td>n/a</td>
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</tbody>
</table>

- Open in Belgium, France, Portugal and Italy
- Other countries (UK, NL, PL, SW) to follow as soon as possible
Per recent amendment !!!!

• Patients that experience disease progression only in brain while the peripheral disease remains stable or even responds are allowed to continue on the treatment that were allocated prior to brain disease progression.

• Treatment should restart at the latest within 3 weeks after the completion of local therapy for brain disease.
Cancer in elderly nursing home residents in Belgium: prospective cohort study

H Wildiers, M Janssen-Heijnen, J De Wolf, M Elseviers, J De Lepeleire, F Buntinx and EORTC Headquarters Team
Why nursing home population?

- tend to be older and frailer than the community dwelling population
- Often not even referred to cancer centres (?)
- Nearly no data on occurrence, diagnostic and therapeutic approach of cancer in this population
- Probably severely ‘undertreated’.
- Optimal setting to study ‘ageing biomarkers’ (in blood)
Aims

1. To prospectively perform a **descriptive study** in nursing homes of patients with (suspected, new or already diagnosed active invasive) cancer where a diagnostic or treatment decision has to be taken.

2. To evaluate the prognostic impact of **ageing biomarkers** in order to:
   - Learn more about the biology of ageing
   - Develop better prognostic tools (for survival) to help aid treatment decisions in the elderly
Methodology

- Prospective observational clinical and translational research study.
- 'cancer patient cohort': Nursing home residents who will be identified with a suspicion or diagnosis of a new cancer event (new cancer or progression of a previously known cancer) where a diagnostic or therapeutic decision needs to be taken.
- 'control cohort' consisting of non-cancer patients.
  - 120 residents willing to give a blood sample (biomarker cohort)
  - 380 residents not giving a blood sample.

- After enrollment in the study, patients will be prospectively followed for evolution in ADL, cognition and QoL; new cancer events and treatments, and survival. Participants in all cohorts will be followed until death or exit from the nursing home or for a maximum of 2 years.
Study populations

- **Cancer patient cohort**: patients will be selected from about 34 Armonea nursing homes (all except the 6 for the control cohort described below). Main inclusion criteria:
  - Patients with a **new cancer event** (new cancer or progressive disease) where a diagnostic/treatment decision has to be/has been taken. Estimated number of participants is 225.
  - Patients with **strong clinical suspicion** of a new cancer event (new cancer or progressive disease), but where the decision is taken not to take further diagnostic or therapeutic steps. Estimated number of participants is 100.

- **Control cohort**: the other 6 Armonea nursing homes in the area of Leuven. Main inclusion criteria:
  - Nursing home residents without active invasive cancer or a strong clinical suspicion of cancer (**control cohort**). A control group of 500 participants will be included.
  - Within these 500 participants, 120 participants will be included who agree to give a blood sample for biomarker research (**biomarker cohort**).
Endpoints

• Primary endpoint:
  - demographics, referral patterns and motives for non-referral, anti-cancer treatments and outcome (evolution in ADL, cognition and QoL; and survival) in nursing home patients with cancer or with strong clinical suspicion of cancer
  - Prognostic capacity of p16INK4a expression in T lymphocytes on OS in the biomarker cohort.
Endpoints

Secondary endpoints:

- Comparison of baseline parameters and outcome (evolution in ADL, cognition and QoL; new cancer events, and survival) between nursing home cancer patients (cancer patient cohort) and nursing home non-cancer patients (control cohort).
- Comparison between demographics, anti-cancer treatments and outcome (survival) between nursing home patients with cancer (cancer patient cohort), versus elderly cancer patients from the Eindhoven cancer registry (cancer registry cohort). This will only be done for cancer types that occur in more than 10 patients in the nursing home cancer group.
- Prognostic capacity of baseline clinical markers (ADL, MMSE, weight and BMI, polymedication, Charlson comorbidity index), and Porock scale on OS, separately in nursing home cancer group (cancer patient cohort) and non-cancer group (control cohort).
- Prognostic capacity of baseline clinical markers (ADL, MMSE, weight and BMI, polymedication, Charlson comorbidity index), and Porock scale on functional decline (at least 2 points increase in ADL scale at 3 months), separately in nursing home cancer group (cancer patient cohort) and non-cancer group (control cohort).
- Prognostic capacity of baseline clinical markers (ADL, MMSE, weight and BMI, polymedication, Charlson comorbidity index), and Porock scale on cognitive decline (at least 2 points increase in the sum of the 2 cognitive questions related to the Belgian Katz scale at 3 months), separately in nursing home cancer group (cancer patient cohort) and non-cancer group (control cohort).
- Prognostic capacity of baseline clinical markers (ADL, MMSE, weight and BMI, polymedication, Charlson comorbidity index), and Porock scale on change in QoL (at least 2 points increase in the sum of the 2 QoL questions at 3 months), separately in nursing home cancer group (cancer patient cohort) and non-cancer group (control cohort).
- Prognostic capacity of other biomarkers of ageing on OS in the control group of nursing home patients without cancer (biomarker cohort).
- Evaluation of the additional impact of promising biomarkers of ageing to baseline clinical markers (ADL, MMSE, weight and BMI, polymedication, Charlson comorbidity index), and Porock scale on OS, functional decline, cognitive decline, and QoL decline at 3 months (definitions see above). (biomarker cohort)
- Describe advance care planning and its evolution in nursing homes during follow-up (cancer patient cohort and control cohort), and compare both groups.
For the primary objective "Description of the nursing home cancer group", we estimate to enter 250 patients with new diagnosis of cancer events and 100 patients with suspected (but not further diagnosed) cancer events during an accrual period of 1 year among home residents from about 34 Armonea nursing homes in Belgium (all except the 6 for the control cohort) (+/- 4000 residents). The accrual period for the cancer patient group can be prolonged in case an unexpected low number of events is observed.

For the co-primary objective "Prognostic capacity of p16INK4a expression in T lymphocytes on OS" in the biomarker cohort, 90 deaths are needed in order to detect a hazard ratio of 0.5 with 90% power between patients with low and high p16INK4a levels (cut-off at median) using a log-rank test with a two-sided type I error of 5%. Assuming a median OS of 12 months in these patients (8 months for patients with high p16INK4a levels and 16 months for patients with low p16INK4a levels), an enrollment period of 5 months, 120 non-cancer patients will have to be enrolled in order to observe the 90 needed deaths within a total study duration of 26 months.
## Data collection

<table>
<thead>
<tr>
<th>Cancer patient cohort and control cohort</th>
<th>Baseline</th>
<th>During study (every 3 months)</th>
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</thead>
<tbody>
<tr>
<td>Informed consent (patient and/or proxy)</td>
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<td></td>
</tr>
<tr>
<td>Patient characteristics (CRF for nurse and GP)</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Height</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>ADL (Belgian Katz scale + 2 linked cognitive questions)</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>MMSE</td>
<td>X</td>
<td>q6 mo</td>
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<tr>
<td>QoL (questions 29 and 30 from EORTC QLQ C-30 questionnaire) (if the patient is able to complete this)</td>
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</tr>
<tr>
<td>Porock 6-month mortality predictor scale (questions for nurse and GP)</td>
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<tr>
<td>Cancer specific aspects #</td>
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<td></td>
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<tr>
<td>Medical/Specialist reports#</td>
<td>X (if available)</td>
<td>X (if available)</td>
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<tr>
<td>Survival</td>
<td>X</td>
<td></td>
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<tr>
<td>Blood sample for biomarkers testing *</td>
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</table>
Expected outcomes

• The descriptive analysis will provide high quality prospective data on diagnostic, referral and treatment patterns for elderly cancer sufferers resident in nursing homes
• This will help identify areas where cancer diagnosis and treatment can be better tailored to the specific needs of these elderly
• The study will increase insight in the biology of ageing
• The study will show if any of the ageing biomarkers can predict survival (in addition to geriatric assessment)
Status

- PRC approval
- CRFs finalized
- EC approved
- Leaflets approved for family and residents
- 2 pilot control nursing homes and 2 pilot ‘cancer’ nursing homes
- First ‘resident’ in: 10-2014
Evaluation of the renal function in patients with solid tumors receiving targeted therapies

Collaborative research project EORTC- KUL-Service ICAR

| EORTC         | ¹UZ Leuven - Belgium  
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<tr>
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<th>²Service ICAR - Pitié-Salpêtrière Hospital – Paris - France</th>
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<tbody>
<tr>
<td>S. Marreaud</td>
<td>B. Sprangers¹</td>
</tr>
<tr>
<td>Statistician to be appointed</td>
<td>H. Wildiers¹</td>
</tr>
<tr>
<td></td>
<td>V. Launay-Vacher²</td>
</tr>
</tbody>
</table>

Project initiated and lead by B. Sprangers

Presented by V. Launay-Vacher
Objectives

- To evaluate renal function in patients with solid tumors - treated with classical chemo- and targeted therapies - at inclusion (baseline), during follow-up, and end of study (depending on available data)

- To determine how nephrotoxicity affects the treatment of patients and patients’ outcome

- To recommend a minimal renal monitoring plan to be included in future EORTC trials

- This project is not focused on elderly population however extension to the geriatric population is foreseen
Workplan

① To determine which data are available in EORTC database

Identification of renal data of interest:

- Email exchanges B. Sprangers, H. Wildiers, V Launay-Vacher
- Final proposal sent to EORTC last week (Sandrine Marreau)
- Meeting B. Sprangers and V. Launay-Vacher Oct. 29th.
Workplan

② Retrospective analysis of existing data:

- to assess the prevalence of CKD at the time of initiation of chemotherapy/ targeted therapy.
- to evaluate whether kidney function is associated with outcome:
  - side effect, dose reduction and treatment modification,...
- Formulae: Cockcroft-Gault, aMDRD (4-variables MDRD equation), CKD-EPI, Schwartz formula for children, with and without correction for BSA
Based on initial findings a minimal renal monitoring plan will be proposed to be included in every future EORTC trial.

Prospective data collection to allow for more detailed studies regarding incidence of CKD and AKI, and their impact on outcomes.
STBSG

• Dr. Olivier Mir & Axel Le Cesne (IGR)
• Randomized proof of concept study of CPA vs DXR as first line chemo in elderly patients w/ advanced or M+ STS
  – Histologically proven advanced and/or metastatic STS any grade
  – STS arising in pre irradiated field
  – No prior chemo regimen for advanced or metastatic disease
  – Presence of measurable disease (according to RECIST 1.1)
  – Progressive disease at entry based on investigator’s judgment
  – Patients amenable to receive DXR according to investigators’ judgment
  – Age ≥ 65 years of age
  – WHO performance status 0-2
Criteria

1. Progression free survival (RECIST 1.1)
2. Secondary
   - OS
   - QoL
   - Safety (according to CTCAE v4.0)
   - GA: G8 score at baseline, Lee’s score and CCI
   - Pharmacodynamics: evaluation of body composition by CT-scan (thorax abodmen pelvis), assessment of the impact of sarcopenia/lean body mass on toxicity and survival (PFS and OS) in both treatment arms
Treatment

• Multi-center open label randomized proof of concept study
  – Patients **fit** for DXR (based on physician’s judgment and a normal cardiac function) will be randomized between
    • Experimental arm: CPA 100mg twice daily, given from day 1 to day 7 of a 14-day cycle, until progression, unacceptable toxicity, patient’s refusal or second malignancy
    • Control arm: DXR (60 to 75 mg/m²), 6 cycles + up to 3 cycles (Q3W) according to local practice
  – Patients **unfit** for DXR (based on physician’s judgment)
    • Will be able to receive CPA 100mg twice daily, given from day 1 to day 7 of a 14-day cycle, until progression, unacceptable toxicity, patient’s refusal or second malignancy; other treatment or strategy (BSC) will be recorded
Statistics

- **Patients fit for DXR** - 1:1 randomization
  - $\alpha=0.05$ (one sided), Power 80%
  - PFS in the control arm: 4 months to 6 months: HR= 0.67
  - Standard Korn design $\rightarrow$ about 190 patients and 154 events, w/ null hypothesis rejected if the observed HR is 0.77 or more
  - $\rightarrow$ Extension of Korn design by allowing 3 possible outcomes; w/ same number of events and sample size, 3 outcomes
    - HR > 0.77 then reject H0, i.e. the difference is significant
    - HR < 0.87 then no significant difference
    - HR is in between 0.77 and 0.87 then the outcome is inconclusive with respect to efficacy, and toxicity and quality of life should be taken into account for the final evaluation of the trial
    - Of note: in this scenario the interpretation of the type I error and the power of the study are slightly different compared to that of classical designs as they are specific to the testing procedure based on PFS and do not take into account decisions in the grey zone based on secondary endpoints

- **Patients unfit for DXR**: it is expected that 30% of the registered patients will not be fit to receive doxorubicin

- Given that only 70% of registered patients are expected to be fit for randomization between DXR and CPA, approximately **275 patients** will need to be registered in this study

- Stratification factors: PS (0-1 vs 2), radiation-induced tumor (yes/no), center
Teach the treaters

- Dr. Andrea Meier and Dr. Monique-Slee Valentijn (Netherlands)
- Educational program that aims to increase public awareness of the worldwide cancer in the elderly epidemic and the need for a specific approach to address the problem and integrate geriatric oncology in the curricula for medical and nursing education both during studies and postgraduate education
- It will focus on improving the understanding of future treaters (oncologists and hematologists) on aspects of geriatric population and mainly geriatric oncology patients
- This started as a local project in the Netherlands, but EORTC ETF expressed is high interest – They will further elaborate this and also proposed to write a paper on education of young physicians in geriatric oncology
Protocol ASTER 2
GERICO XXX

Adjuvant systemic therapy in the elderly HER2+ early breast cancer population
Proposal from the Unicancer GERICO group and the EORTC Cancer in Elderly Task Force

EUDRACT N° XXX

Etienne BRAIN MD PhD, Hans Wildiers, MD PhD, Franck Bonnetain PhD
Rationale - 1

1. Population 70+ in adjuvant setting
   - ER+ HER2-: ASTER 70s (GERICO 11 / PACS 10)
     • Adjuvant chemo in HER2- ER+ population according to genomic grade
     • ~ 1,200 patients screened in 30 mths, ~ 600 randomized for 700 planned
     • 80 centres (F and B)
     • Unique network opportunity in adjuvant setting for extension to an HER2 strategy (national, European and beyond via EORTC, BIG & SIOG)
ASTER 70s - Design

EBC ≥70 yo Surgery →

ER+ HER2-Lee’s score§
G8 score

informed consent

Group I
high GG
by RT-PCR

pN (pN0 vs pN+)
G8 (≤ vs > 14)
Centre

Arm A = HT**
350

Arm B = CT + HT**
350

Group II
low GG
by RT-PCR

HT
hormonotherapy 5 years

CT
4 cycles (TC, AC or MC) + GCSF

± XRT according to standard guidelines

NO CHEMOTHERAPY IS RECOMMENDED
Follow up + inclusions in other studies (e.g ELD15 validation)
- Low GG
- Other causes for non inclusion (refusal, geriatrics, etc.)
Patients will be offered HT according to standard guidelines

Phase III w/ 4-yr OS
Hypothesis B > A
Δ 7.5% (A 80% vs B 87.5%) HR 0.60
Inclusion period 4 years
170/year
Follow up 4 years
129 events
α 5% β 20%
340 pts/arm

700 pts (+ 1100-1300 not included i.e. low GG or other causes followed up)

1/ 4-yr OS 2/ Tolerance, DFS, QoL (ELD15), Q-TWiST, G8,
cost-effectiveness analysis, GG/RT-PCR, TR, geriatrics

§ 4-yr mortality rate

4-yr mortality rate

≤

≥
**GERICO 11**
(EUDRACT N° 2011-004744-22, PHRC national 2011, NCT01564056)

All patients
Lee Score
G8, CCI
Polymedications

Genomic Grade (GG) evaluation

Group I**
High GG

Arm A = HT

Arm B = CT + HT

Cy1 + GCSF
Cy2 + GCSF
Cy3 + GCSF
Cy4 + GCSF

q3w q3w q3w

HT 5 yr

Group II
Low GG

NO CHEMOTHERAPY IS RECOMMENDED - Follow up

MMSE, IADL
QLQ C30 & ELD15
LVEF
Socioeconomic
Standard Lab

1 blood + serum

Chemo tolerance
Standard Lab

Polymedications
MMSE, IADL
QLQ C30 & ELD15
LVEF
Socioeconomic
Willingness
Standard Lab
1 blood + serum

G8, CCI
Polymedications
MMSE, IADL
QLQ C30 & ELD15
LVEF
Socioeconomic
Willingness

Standard Lab every year
1 blood + serum (M12 & M48)

Events

*Randomization stratified on pN, G8 and centre

** Group I include both high and equivocal GG cases

*Complete curative surgery

*Screening

16 weeks

1, 2, 3 & 4 year

1, 2, 3 & 4 year

1, 2, 3 & 4 year

time
1. Population 70+ in adjuvant setting

- ER+ HER2-: ASTER 70s (GERICO 11 / PACS 10)
  - Adjuvant chemo in HER2- ER+ population according to genomic grade
  - ~ 1,200 patients screened in 30 mths, ~ 600 randomized for 700 planned
  - 80 centres (F and B)
  - Unique network opportunity in adjuvant setting for extension to an HER2 strategy (national, European and beyond via EORTC, BIG & SIOG)

- HER2+ (ER+ and ER-)
  - Standard chemo + trastuzumab (TRASTU): 4 TC q3w (Jones Lancet Oncol 2013) or PTX qw x 12 (Tolaney SABCS 2013)
  - Options? TRASTU alone (cf. St Gallen)
  - **Only part of them (70-80%) receive TRASTU (85-90% with chemo)** AND
    - 15-40% require delays (either permanent or temporary cessation)
    - LVEF decrease ≥ 10% ± hospitalization for cardiac events in the year following completion of TRASTU occur in up to 30% and 10% respectively, influenced by age strata and comorbidity score (Barthelemy ASCO 2012, Vaz-Luis JCO 2014)
2. Competing risks for mortality
   - Impaired G8 → Strong prognosticator for mortality: from x 5 at 6 months to 30% at 1 year (Canoui Poitrine & ELCAPA; Oncodage; Kenis JCO 2014)
   - Adjuvant online "invalid", overestimates OS (de Glas Lancet Oncol 2014)

3. Low grade toxicity + different goals for different ages
   - May have an impact on treatment compliance, even with soft treatment (Kalsi ECCO 2013)
   - T-DM1 in MBC
     - EMILIA = T-DM1 vs X+ lapatinib (LAP) second line
       - Uncertain benefit for 75+ (decreased from 65) BUT very limited nb of pts
       - Age/nb pts/HR (95%CI): <65/853/0.52 (0.62-0.74), 65-74/113/0.89 (0.53-1.45), 75+/25/3.51 (1.22-10.13) (Verma NEJM 2012)
     - Integrated safety analysis
       - Same low representation of 75+ & higher risk of toxicity (Diéras JCO 2014)
4. Can we avoid chemo? → “multi” blockade (ER/HER2 ± dual HER2)
   - Hormonotherapy (HT) + anti-HER2? (some cases in SafeHer)
   - Dual HER2 blockade wo/ chemo: LAP or PERTU+TRASTU
     • Metastatic setting
       - LAP+TRASTU approved for ER- HER2+ population in case of progression
         > TRASTU+chemo (08/2013)
       - Trials 1st line PERTU+TRASTU ± chemo (Pernetta, EORTC 75111-10114)
     • (Neo) adjuvant setting
       - NeoALTTO (w/ chemo): LAP+TRASTU ↗ pCR rate in ER+ & ER-
         compared with either mono, and pCR ↗ EFS and OS in ER- (Baselga
         Lancet 2012, Piccart SABCS 2013)
       - NeoSphere: 16.8% of pCR w/ PERTU+TRASTU alone (Gianni Lancet
         Oncol 2012)
   - Dual HER2 blockade + HT
     • TBCRC-0006: TRASTU+LAP±LET → pCR = 27% (21% in ER+, 36% in ER-) in
       neoadjuvant setting (Rimawi JCO 2013)
5. **Next HER2+ trials in adjuvant setting**
   - APHINITY (chemo + TRASTU ± PERTU) → results in 2017?
   - **Next** = KAITLIN
     - 3 FEC 100 → 3 TXT + TRASTU + PERTU (= APHINITY arm) vs 3 FEC 100 → T-DM1 + PERTU (based on MARIANNE)
     - **No limit for age BUT elderly patients included will not be representative of the general population**

→ Need for a specific trial for elderly!!
Proposal

70+ HER2+ Adjuvant*

1,200 patients, 3-yr recruitment
Stratification for ER, stage and G8
Two coprimary
1/ iDFS (80% vs 74.8%, HR 1.3)
2/ HrQoL
α 5% β 20% non inferiority
Cohort for those not included

* No high selection according to previous medical history + as long as local curative surgery is complete and that adjuvant systemic treatment is discussed:
✓ Contralateral BC, invasive BC after ductal carcinoma in situ or isolated local invasive relapse are eligible
✓ Patients with multifocal or bilateral disease are eligible
Main Inclusion Criteria

- Women aged ≥ 70 yo
- Histologically proven invasive breast cancer
- Complete curative surgery performed before enrollment
- Any N status (pN+ or pN0, ± SLND)
- No clinically or radiologically detectable metastases (M0)
- Any ER status (ER+ or ER-)
- HER2+++ (or FISH+/CISH/SISH)

- Like in ASTER 70s, no high selection according to previous medical history
- As long as local surgical treatment is complete and that adjuvant systemic treatment is discussed
  - Controlateral BC, invasive BC after DCIS, or isolated local invasive relapse are eligible
  - Patients with multifocal or bilateral disease are eligible
Objectives

- **Primary Objective**
  Evaluation of the benefit of an adjuvant treatment wo/ chemotherapy on invasive DFS

- **Secondary Objectives**
  - To evaluate benefit on
    - Overall survival (OS) taking into account competing causes for mortality (e.g. cormorbidities, functional status, nutritional status)
    - Specific and non specific survival
    - Health-related quality of life (QLQ C30 and specific elderly scale QLQ-ELD15)
    - Disease-free survival (DFS)
    - Event-free survival (EFS)
  - Toxicity (NCI-CTC V4.0)
  - Geriatric assessment; G8 validation in a specific elderly breast cancer population
  - Q-TWiST analysis, treatment acceptability (willingness test questionnaire), cost-effectiveness analysis (medico-economic impact of de-escalation for chemotherapy)
  - Follow-up of a cohort of elderly BC patients not enrolled (no chemo, no anti-HER2 treatment)
  - Tumour banking, ageing biomarkers (telomeres length and telomeres dysfunction factors)
Statistics non inferiority

• **Co-primary**
  – iDFS
    • 3-yr iDFS w/ chemo+TRASTU = 80% (vs 74.8% dual blockade)
  – HrQOL
    • 3-yr QoL deterioration free survival (+1 and 2 yr)
      – > 10-point decrease QoL (targeted dimensions: global health, role or social functioning of EORTC QLQ C-30) (cf. GERICO 06)
      – Death all causes

• **Hypothesis**
  – HR iDFS = 1.3 (reject threshold i.e. DFS ≥ 74.8%)
  – α 5%, β 20%
  – 384 events are expected
    • 270 pts/yr x 3 years → 810 pts (study duration: 10 years > 1st inclusion)
    • **400 pts/yr x 3 years → 1,200 pts (study duration: 6-7 years > 1st inclusion)**
    • 500 pts/yr x 3 years → 1,500 pts (study duration: 5-6 years > 1st inclusion)
  – If non inferiority, HrQOL will be determinant for treatment choice

• **Feasibility**
  – Curie/St-Cloud: 30-35 patients 70+ yearly, 20-25 w/ chemo + TRASTU
Questions & comments

1. Support for PERTU development in adjuvant setting in this specific population (YES)
2. Primary endpoint: alternative to iDFS = OS as in ASTER 70s (?), dDFS (?)
3. Separate cohort for those not included (YES)
4. Include neoadjuvant cases (?)
5. Superiority (NO)
6. TRASTU subcutaneous (?)
7. Other partners (biosimilars) (?)
8. Choice for standard chemo: TC (YES) and PTX qw (?)

• Feasibility
  – Through SIOG, EORTC and BIG support
    + Unicancer (GERICO/UCBG), LACOG breast group, Italy (IRST/Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori), Chinese Breast Cancer Study Group (CBCSG, Fudan University), ABCSG, Germany (DETECT III)
    ? Australia/NZ, US (Alliance, SWOG), Sweden, Finland
  – With a 3-year recruitment period, we should seek
    • 400 pts/yr → length of study = 6-7 years, i.e. 1,200 pts
    • 500 pts/yr → length of study = 5-6 years, i.e. 1,500 pts