CLINICAL STUDY REPORT

ICE II: An investigational randomized phase II-(III) study on epirubicin plus cyclophosphamide (or CMF) vs. nab-paclitaxel plus capecitabine as adjuvant chemotherapy for elderly non frail patients with an increased risk for relapse of a primary carcinoma of the breast

A Study of the German Breast Group (GBG)

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Investigational Products:	
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Phase:	II (–III)
Report Version:	2
First Patient Enrolled:	22.05.2009
Last Patient Completed:	31.11.2013

Co-ordinating Investigator:
Prof. Dr. Gunter von Minckwitz
GBG Forschungs GmbH
Martin-Behaim-Str. 12
63263 Neu-Isenburg, Germany

Sponsor:
GBG Forschungs GmbH
Martin-Behaim-Str. 12
63263 Neu-Isenburg, Germany

Date of this report: January 10th, 2020

APPROVAL SIGNATURES

STUDY TITLE: An investigational randomized phase II-(III) study on epirubicin plus cyclophosphamide (or CMF) vs. nab-paclitaxel plus capecitabine as adjuvant chemotherapy for elderly non frail patients with an increased risk for relapse of a primary carcinoma of the breast

STUDY NUMBER: GBG 52

I, the undersigned, have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

SIGNATURE: ..... DATE: 21.01.2020

Prof. Dr. Sibylle Loibl
Chief Executive Officer (CEO)
GBG Forschungs GmbH

..... 21.01.2020

Dr. Valentina Nekljudova
Head of Medicine and Research
GBG Forschungs GmbH

..... 20.01.2020

Dr. Nicole Buchardi
Study Biostatistician
GBG Forschungs GmbH

1. SYNOPSIS

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Name of active ingredient: (1) Capecitabine (2) nab-Paclitaxel (3) Epirubicin (4) Cyclophosphamide (5) 5-Fluorouracil (6) Methotrexat		

Title of Study:

ICE II: An investigational randomized phase II-(III) study on epirubicin plus cyclophosphamide (or CMF) vs. nab-paclitaxel plus capecitabine as adjuvant chemotherapy for elderly non frail patients with an increased risk for relapse of a primary carcinoma of the breast

Investigators:

Prof. Dr. Gunter von Minckwitz, Co-ordinating Investigator, GBG Forschungs GmbH, Neu-Isenburg

Study Center(s):

The study was conducted at 81 centers in Germany.

- Marienhospital Aachen, Frauenheilkunde und Geburtshilfe, Zeise 4, 52066 Aachen (PI: Prof. Dr. Manfred Kusche)
- Karolinen-Hospital Hüsten, Abt. für Gynäkologie und Geburtshilfe, Stolte Ley 5, 59759 Arnsberg (PI: Dr. Norbert Peters)
- Praxis Brudler/Heinrich/Bangerter, Gynäkologie und Geburtshilfe, Halderstr. 29, 86150 Augsburg (PI: Dr. Bernhard Heinrich)
- Ev. Krankenhaus Bergisch Gladbach, Gynäkologie, Ferrenbergstr. 24, 51465 Bergisch Gladbach (PI: Prof. Dr. Bernhard Liedke)
- Helios-Kliniken Berlin Buch, Brustzentrum, Schwanebecker Chaussee 50, 13125 Berlin (PI: Keil)
- Sana Klinikum Lichtenberg Oskar-Ziehten Krankenhaus, Frauenklinik, Fanninger Str. 32, 10365 Berlin, (PI: Dr. Jutta Krocker)
- Evangelisches Waldkrankenhaus, Innere Abteilung, Stadtrandstr. 555-561, 13589 Berlin (PI: Dr. Jochem Potenberg)
- Fachärzte für Frauenheilkunde und Geburtshilfe, Wönnichstr. 64-66, 10317 Berlin (PI: Dr. Jörg Schilling)
- Studiengesellschaft Onkologie Bielefeld, Teutoburger Str. 60, 33604 Bielefeld (PI: Dr. Marianne Just)
- Städt. Klinikum Brandenburg, Klinik für Gynäkologie und Geburtshilfe, Hochstr. 29, 14770 Brandenburg an der Havel (PI: Dr. Peter Ledwon)

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- Onkologische Schwerpunktpraxis, Schwachhauser Heerstr. 50, 28209 Bremen (PI: Dr. Gabriele Doering)
- Klinikum Bremerhaven Reinkenheide, Frauenklinik. Postbrookstr. 103, 27574 Bremerhaven (PI: Dr. Doraid Mouarrawy)
- Allg. Krankenhaus Celle, Frauenklinik, Siemensplatz 4, 29223 Celle (PI: Dr. Michael Berghorn)
- Klinikum Darmstadt, Frauenklinik, Grafenstr. 9, 64283 Darmstadt (PI: PD Dr. Sven Ackermann)
- Klinikum Dortmund, Klinikzentrum Mitte, Frauenklinik, Beurhausstr. 40, 44137 Dortmund (PI: Dr. Nurgül Acar)
- Krankenhaus St. Joseph-Stift, Klinik für Gynäkologie, Wintergartenstr. 15-17, 01307 Dresden (PI: Dr. Axel Gatzweiler)
- Diakonissen Krankenhaus Dresden, Klinik für Gynäkologie und Geburtshilfe, Holzhofgasse 29, 01099 Dresden (PI: Dr. Andreas Werner)
- Europäisches Brustzentrum Luisenkrankenhaus, Senologische Onkologie, Hans-Günther-Sohl-Str. 6-10, 40235 Düsseldorf (PI: Dr. Mahdi Rezai)
- Kreiskrankenhaus Ebersberg, Gynäkologie, Pfarrer-Guggetzer-Str. 3, 85560 Ebersberg (PI: Prof. Dr. Cornelia Höß)
- Städt. Kliniken Esslingen, Frauenklinik, Hirschlandstr. 97, 73730 Esslingen (PI: Prof. Dr. Thorsten Kühn)
- Klinikum der J. W. Goethe Universität, Zentrum der Frauenheilkunde und Geburtshilfe, Theodo-Stern-Kai 7, 60590 Frankfurt am Main (PI: Dr. Eugen Ruckhäberle)
- Klinikum Frankfurt Höchst, Klinik für Gynäkologie und Geburtshilfe, Gotenstr. 6-8, 65929 Frankfurt (PI: Prof. Dr. Volker Möbus)
- Uniklinikum Freiburg, Frauenklinik, Hugstetter Str. 55, 79106, Freiburg im Breisgau (PI: Prof. Dr. Elmar Stickeler)
- Kreiskrankenhaus Freudenstadt, Gynäkologische Abteilung, Karl-von-Hahn-Str. 120, 72250 Freudenstadt (PI: Dr. Yvonne Fauster)
- Schwerpunktpraxis Gyn. Onkologie, Domgasse 1, 15517 Fürstenwalde (PI: Dr. Georg Heinrich)
- Main-Kinzig-Kliniken, Frauenklinik / Brustzentrum, Herzbachweg 14, 63571 Gelnhausen (PI: Dr. Kristina Scheerer)
- Klinikum Gifhorn, Interdisziplinäres Brustzentrum, Campus 6, 38518 Gifhorn (PI: Dr. Thomas

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Dewitz)

- Universität Greifswald, Klinik für Frauenheilkunde und Geburtshilfe, Ferdinand-Sauerbruch-Str., 17475 Greifswald (PI: Dr. Antje Belau)
- Onkodok GmbH, Dres. med. Rösel und Depenbusch, Brunnenstr. 14, 33332 Gütersloh (PI: Dr. Siegfried Bernhard Rösel)
- Sana Klinikum Hameln-Pyrmont, Frauenklinik / Brustzentrum, Saint-Maur-Platz 1, 31785 Hameln (PI: Dr. Thomas Noesselt)
- Diakovere Henriettenstift, Frauenklinik, Schwemannstr. 17, 30559 Hannover (PI: Dr. Kristina Lübbe)
- Kreiskrankenhaus Bergstraße, Gynäkologie und Geburtshilfe, Viernheimer Str. 2, 64646 Heppenheim (PI: Dr. Ursula Hurst)
- Gynäkologisch-onkologische Gemeinschaftspraxis, Bahnhofsplatz 5, 31134 Hildesheim (PI: Dr. Christoph Uleer)
- Universitätsklinikum des Saarlandes, Frauenklinik, Kirrberger Str. 9, 66421 Homburg (PI: Prof. Dr. Erich-Franz Solomayer)
- Universitätsklinikum Jena, Klinik für Frauenheilkunde und Geburtshilfe, Bachstr. 18, 07743 Jena (PI: Prof. Dr. Ingo Runnebaum)
- Westpfalz-Klinikum Kaiserslautern, Frauenklinik, Hellmut-Hartert-Str. 1, 67655 Kaiserslautern (PI: Prof. Dr. Hartmut Link)
- Städtisches Klinikum, Frauenklinik, Moltkestr. 90, 76133 Karlsruhe (PI: Dr. Gabriele Kaltenecker)
- St. Vincentius Kliniken, Frauenklinik, Edgar-von Gierke-Str. 2, 76135 Karlsruhe (PI: Dr. Oliver Tomé)
- Klinikum Kassel, Gynäkologische Ambulanz, Mönchebergstr. 41-43, 34125 Kassel (PI: Dr. Gabriele Feisel-Schwickardi)
- Elisabeth-Krankenhaus, Brustzentrum, Weinbergstr. 7, 34117 Kassel (PI: Dr. Sabine Schmatloch)
- Universitätsklinikum Schleswig-Holstein, Klinik für Gynäkologie und Geburtshilfe, Arnold-Heller-Str. 3, Haus 24, 24105 Kiel (PI: Dr. Holger Eidtmann)
- St. Elisabeth-Krankenhaus, Senologie, Biedermannstr. 84, 04277 Leipzig (PI: Dr. Dagmar Langanke)
- Klinikum Ludwigsburg, Frauenklinik, Posilipostr. 4, 71640 Ludwigsburg (PI: Dr. Gabriele Ziemendorff)

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- Ev. Krankenhaus Ludwigsfelde-Teltow, Brandenburgisches Brustzentrum, Albert-Schweitzer-Str. 44, 14974 Ludwigsfelde (PI: Dr. Andreas Kohls)
- Städtisches Klinikum Lüneburg, Frauenklinik, Bögelstr. 1, 21339 Lüneburg (PI: Prof. Dr. Peter Dall)
- St. Vincenz und Elisabeth-Hospital, Frauenklinik, An der Goldgrube 11, 55131 Mainz (PI: Prof. Dr. Wolfgang Wiest)
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- Klinikum Fichtelgebirge, Frauenklinik, Schillerhain 1-8, 95615 Marktredwitz (PI: Dr. Maria Dietrich)
- Klinikum Meiningen, Frauenklinik, Bergstr. 3, 98617 Meinigen (PI: Dr. Heiko Graf)
- Klinikum Minden, Zentrum für Innere Medizin, Klinik für Hämatologie / Onkologie, Hans-Nolte-Str. 1, 32429 Minden (PI: Dr. Martin Grieshammer)
- Dietrich-Bonhoeffer Kliniken, Frauenklinik, Salvador-Allende-Str.30, 17036 Neubrandenburg (PI: Dr. Katy Roterberg)
- Klinikum Nürnberg Nord, Brustzentrum/Frauenklinik, Prof.-Ernst-Nathan-Str. 1, 90419 Nürnberg (PI: Prof. Dr. Cosima Brucker)
- Klinikum Nürtingen, Brustzentrum, Auf dem Säer 1, 72622 Nürtingen (PI: Dr. Elke Faust)
- Sana Klinikum Offenbach, Frauenklinik, Starkenburgring 66, 63069 Offenbach (PI: Prof. Dr. Sibylle Loibl)
- Ortenauklinikum Offenburg-Gengenbach, Frauenklinik mit Brustzentrum, Ebertplatz 12, 77654 Offenburg (PI: Dr. Matthias Frank)
- Paracelsus Krankenhaus Ruit, Brustzentrum, Hedelfingerstr. 166, 73760 Ostfildern (PI: Dr. AnjaTuczek)
- Krankenhaus Siloah, Gynäkologie, Wilferdingerstr. 67, 75179 Pforzheim (PI: Dr. Michael Wagner)
- Klinikum Pforzheim, Frauenklinik, Kanzlerstr. 2-6, 75175 Pforzheim (PI: Dr. Stefanie Buchen)
- Onkologische Praxis Pinneberg, Innere Medizin, Hämatologie, intern. Onkologie, Fahltskamp 74, 25421 Pinneberg (PI: Dr. Stefan Moegling)
- Elbsandsteinkliniken Meißen-Radebeul, Frauenklinik, Heinrich-Zille-Str. 13, 01445 Radebeul (PI: Dr. Barbara Richter)
- Studienzentrum Onkologie Ravensburg, Elisabethenstr. 19, 88212 Ravensburg (PI: Prof. Dr. Thomas

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Decker)

- Klinikum Rosenheim, Gynäkologie und Geburtshilfe, Pettenkoferstr. 10, 83022 Rosenheim (PI: Prof. Dr. Thomas Beck)
- Klinikum Südstadt, Universitätsfrauenklinik, Südring 81, 18059 Rostock (PI: Prof. Dr. Toralf Reimer)
- Gemeinschaftspraxis für Gynäkologie und Geburtshilfe, Albert-Schweitzer-Str. 18, 38226 Salzgitter (PI: Dr. Wolfgang Dietz)
- Helios Klinik Schkeuditz, Brustzentrum Nordsachsen, Leipziger Str. 45, 04277 Schkeuditz (PI: Dipl. Med. Henning Eichler)
- Leopoldina-Krankenhaus, Frauenklinik, Gustav-Adolf-Str. 8, 97421Schweinfurt (PI: Prof. Dr. Michael Weigel)
- Marienkrankenhaus, Brustzentrum, Goethestr. 19, 58239 Schwerte (PI: Dr. Anna Elisabeth Balwanz)
- Hunsrück Klinik Kreuznacher Diakonie, Gynäkologie und Geburtshilfe, Holzbacher Str. 1, 55469 Simmern (PI: Dr. Barbara Kipp)
- Klinikum Schaumburg, Kreiskrankenhaus Stadthagen, Gynäkologie und Geburtshilfe, Am Krankenhaus 1, 31655 Stadthagen (PI: Dr. Sabine Lemster)
- Johanniter Krankenhaus Genthin-Stendal, Klinik f. Frauenheilkunde und Geburtshilfe, Bahnhofstr. 24-26, 39576 Stendal (PI: Dr. Andrea Stefek)
- Kreiskrankenhaus Torgau, Gynäkologie, Christianistr. 1, 04860 Torgau (PI: Dr. Eike Simon)
- Universitätsklinikum Tübingen, Frauenklinik, Calwerstr. 7, 72076 Tübingen (PI: Prof. Dr. Eva-Maria Grischke)
- Universitätsklinikum, Frauenklinik, Prittwitzstr. 43, 89075 Ulm (PI: Prof. Dr. Wolfgang Janni)
- Schwarzwald-Baar-Klinikum, Frauenheilkunde und Geburtshilfe, Klinikstr. 11, 78052 Villingen-Schwenningen (PI: Dr. Wolfgang Bauer)
- GRN Klinik Weinheim, Gynäkologie und Geburtshilfe, Röntgenstr. 1, 69469 Weinheim (PI: Dr. Leila Bauer)
- Marien-Hospital, Brustzentrum, Pastor-Janßen-Str. 8, 46483 Wesel (PI: Dr. Doris Sprengnetter)
- Dr.-Horst-Schmidt-Kliniken, Klinik für Gynäkologie und gyn. Onkologie, Ludwig-Erhard-Str. 100, 65199 Wiesbaden (PI: Dr. Tanja Neuhöffer)
- St.-Josefs-Hospital, Gynäkologie und Geburtshilfe, Beethovenstr. 20, 65189 Wiesbaden (PI: Prof.

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Dr. Gerald Hoffmann)

- Asklepios Paulinen Klinik, Frauenklinik, Geisenheimer Str. 10, 65197 Wiesbaden (PI: Dr. Volker Heyl)
- Marienhospital, Brustzentrum, Marienplatz 2, 58452 Witten (PI: Dr. John Hackmann)
- Gemeinschaftspraxis Dr. Joachim Haessner , Hämatologie und Internistische Onkologie, Kaufhofpassage 5, 38440 Wolfsburg (PI: Dr. Joachim Haessner)

Publication (reference):

von Minckwitz G, ICE II: An investigational randomized phase II study on epirubicin (E) plus cyclophospamide (C) (or CMF) versus nab-paclitaxel plus capecitabine (PX) as adjuvant chemotherapy for elderly nonfrail patients with an increased risk for relapse of a primary carcinoma of the breast. J Clin Oncol 28(15S):8s, 2010 (suppl; abstr TPS 104), ASCO 2010

von Minckwitz G, Conrad B, Decker T et al.: Final results from a randomized phase II study comparing epirubicin plus cyclophosphamide (EC) or CMF versus nab-paclitaxel plus capecitabine (PX) as adjuvant chemotherapy for elderly non-frail breast cancer patients with an increased risk of relapse. Abstract Nr. 228, EBCC9-Programme book web-v2, Page 81, 2014

von Minckwitz G, Conrad B, Decker T et al.: A randomized phase II study comparing EC or CMF versus nab-paclitaxel plus capecitabine as adjuvant chemotherapy for non-frail elderly patients with moderate to high risk early breast cancer (ICE II – GBG 52). Submitted.

Studied Period (years):

Date of the first patient enrolled: 22.05.2009
Date of the last patient completed: 31.11.2013

Phase of Development:

Phase II (-III)

Objectives:

Primary Objective:

Phase II:
To determine the compliance and safety of epirubicin plus cyclophosphamide or CMF (EC/CMF) and nab-

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paclitaxel in combination with capecitabine (PX).

Secondary Objectives:

1. To compare the disease-free survival (DFS) and distant disease free survival (DDFS) with epirubicin plus cyclophosphamide or CMF (EC/CMF) vs. nab-paclitaxel in combination with capecitabine (PX).
2. To compare the overall survival (OS) with epirubicin plus cyclophosphamide or CMF (EC/CMF) vs. nab-paclitaxel in combination with capecitabine (PX).
3. To analyze the efficacy of treatments in subgroups according to clinical stratification factors.
4. To determine prognostic factors on tumor tissue collected from primary surgery and to correlate them with study treatment effect.
5. To compare the geriatric assessments scores (Charlson, VES-13, IADL, G8) at baseline and end of therapy.

Methodology:

Multicentre, open, randomized Phase II-(III) trial comparing epirubicin plus cyclophosphamide (EC) or CMF with a combination of capecitabine and nab-paclitaxel in patients with primary breast cancer.

Number of patients (planned and analyzed):

planned: 400 enrolled: 400 randomized: 400, analyzed (safety): 391 analyzed (efficacy): 391

Diagnosis and Main Criteria for Inclusion:

Histological confirmed unilateral or bilateral primary carcinoma of the breast, written informed consent, female and male breast cancer patients with age at first histologically diagnosis ≥ 65 years, adequate surgical treatment with complete resection (R0) of the tumor and ≥ 10 axillary nodes, no evidence for distant metastasis, estimated life expectancy of at least 5 years and ECOG Performance Status ≤ 2.

Test Products, Dose and Mode of Administration, Batch Number:

Patients will be randomized to receive either

- 4 cycles of chemotherapy with epirubicin plus cyclophosphamide (EC) on day 1 q22
  or
- 6 cycles CMF on days 1 and 8 q29

or

- 6 cycles of weekly nab-Paclitaxel 100 mg/m^2 on days 1, 8, 15 q22 with a week of rest every 6 weeks in combination with capecitabine 2000 mg/m^2, days 1 - 14 orally, divided into 2 daily doses every 3 weeks for 6 cycles (nPX).

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Duration of Treatment:

EC: 12 weeks

CMF: 24 weeks

PX: 18 weeks

Reference Therapy, Dose and Mode of Administration, Batch Number:

EC or CMF were the reference therapies. See above for details on therapy and dose.

Nab-Paclitaxel Batch Numbers: 6001468A, 6001710A, 6002205A

Capecitabine Batch Numbers: B106301, X0111B01, X1007B01, X9043B01, X9071B01

Criteria for Evaluation:

Efficacy:

Disease-free survival (DFS) is defined as time from randomization to any invasive breast cancer event, contralateral invasive breast cancer, second primary cancer, or death due to any cause according to the invasive disease free survival (IDFS).

Additionally there is a distant disease free survival defined as time from randomization to any distant recurrence, second primary non breast cancer or death due to any cause.

Overall survival (OS) is defined as the interval between the date of randomization and the date of death due to any cause. If a patient is lost to follow-up, that patient will be censored as of the date of last contact.

Safety:

Adverse events are graded according to the NCI-CTC.

Statistical Methods:

The Intent-to-treat (ITT) set (modified) includes all patients that were randomized to the chemotherapy treatment and received at least one dose of study medication. Patients are analyzed according to their treatment group assignment irrespective of their actual treatment. Patients who did not start study treatment are listed together with the reason for not starting treatment.

The Safety Analysis Set includes all patients that were randomized to the chemotherapy treatment and received at least one dose of study medication. Patients are analyzed according to their actual study treatment.

SUMMARY

Efficacy Results:

From April 2009 to April 2013, 400 out of 423 screened patients were randomized to the ICE II trial in 63 centers of the German Breast Group (Figure 2). A total of 391 patients started treatment, 182 with EC, 16 with

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CMF and 193 with nPX. Nine patients (4 in the EC/CMF and 5 in the nPX arm) did not start treatment and were therefore not included into the intent-to-treat population. The as-treated safety population was identical with the intent-to-treat population as no cross-over occurred between arms. After 78 patients had been recruited impurities of nab-paclitaxel were detected in one center and shortly thereafter accrual was temporarily stopped for a period of nine months (2009/11-2010/08) before nab-paclitaxel became available again.

Baseline characteristics of the 391 study participants with a median age of 72 (range 65-84) years were balanced between treatment arms (Table 1). Two third of the patients fulfilled the eligibility of having clinicopathological medium to high risk early stage breast cancer. Geriatric assessment tools identified moderately fit patients in 3.3% (Charlson Comorbidity Index 2), 13.3% (VES-13 score ≥2), 5.4% (IADL score ≤7) and 16.7% (G-8 score ≤14). Distribution of breast cancer subtypes was comparable to that expected in younger patients (65.5% hormone-receptor-positive/HER2-negative, 16.9% HER2-positive, and 17.6% triple-negative breast cancers). Mastectomy was performed in 32.5% of patients.

Patients treated with EC/CMF and with nPX showed a median relative dose-intensity of 97.5% and 85.4%, respectively (P=<0.001). Overall geriatric assessments changed from before to after chemotherapy (Charlson Comorbidity Index decreased in 7.3% and increased in 13.6%; VES-13 score decreased in 38.4% and increased in 8.8%; IADL decreased in 2.0% and increased in 20.9%; G-8 score decreased in 42.9% and increased in 5.2%). Treatment arm, performance status, hemoglobin level; VES-13 and G8 score predicted treatment discontinuations; however, only treatment arm provided independent information in the multivariate model. Treatment arm, performance status prior to start of therapy, number of co-medications predicted grade 3-5 toxic events, however, only treatment arm and performance status were independent factors. (Table 3)

Up to March 21th 2014 and after a median follow up of 22.8 months, 39 iDFS events (21 in the EC/CMF arm and 18 in the nPX arm) and 23 OS events (11 in the EC/CMF arm and 12 in the nPX arm) were recorded. Hazard ratios were 0.91 for iDFS and 1.18 for OS with broad 95% confidence intervals (0.49-1.71; log rank P=0.776 for iDFS and 0.52 to 2.66 ; log rank P=0.699 for OS),

Safety Results:

Overall, thirteen (6.6%) of 198 patients discontinued EC/CMF and 69 (35.8%) of 193 discontinued nPX (P<0.001). Main reasons in both arms were adverse events. Dose reductions were necessary in 9 (4.5%) and 112 (58.0%) patients treated with EC/CMF or nPX, respectively (P<0.001). Grade 3-5 adverse events were more frequent with EC/CMF (90.9%) than with nPX (64.8%) (P<0.001) with hematological toxicities being more frequent with EC/CMF (88.4% vs. 22.3%, P<0.001), but non-hematological toxicities (hand-foot-syndrome, diarrhea, mucositis, fatigue, sensory neuropathy, thromboembolisms, metabolic disorders) being more frequent with nPX (58.5% vs. 18.7%, P<0.001).

Deaths during treatment occurred in 1 patient due to pulmonary embolism in the EC/CMF arm and in 5

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patients in the nPX arm (2 thromboembolism, 1 cardiac event, 1 febrile neutropenia, 1 dihydropyrimidine dehydrogenase insufficiency).

CONCLUSIONS:

Even if ICE II trial did not continue as phase III mainly due to slow recruitment, as well as lack of funding despite the independent data-monitoring committee (IDMC) approved continuation based on the interim safety analysis results, it showed that non-frail, elderly patients with moderate or high risk breast cancer can be treated with taxane-based polychemotherapy; however, compound-specific toxicities, in particular non-hematological toxicities, lowered relative dose intensity and therefore potential survival benefits. Moreover it has been shown that treatment arm and performance status are independent predictive factors of grade 3-5 toxicities. As the trial stopped after completion of the phase II part, statistical power of the survival analysis is limited so that the risks cannot be related to the benefits of both treatments.

Date of the Report:

10.01.2020

Annex 1

Amendment to Protocol

There was one Substantial Amendment to the protocol of ICE2 pertaining in the main to study medication:

After the delivery of the study medication nab-paclitaxel encountered difficulties, the CA had suspended the approval under Section 42 (1) AMG.
After the delivery difficulties had been eliminated, the application was made to continue with an amendment. This also included the addition of two further questionnaires on the “Quality of Life” to the geriatric survey. After approval, the recruitment phase continued.