INTRODUCTION

The CARE (Community. Academic. Research. Education) Oncology Faculty is a national group of specialists from across Canada who meet and discuss various topics at key conferences. The common vision of the CARE Oncology Faculty is enhancing education with the explicit goal of improving patient outcomes.

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CARE — CANADIAN PERSPECTIVES FROM ECC 2013 & IASLC 2013

The CARE Oncology Faculty recently met at ECC (European Cancer Congress) 2013 in Amsterdam, Netherlands (September 27–October 1, 2013). The congress covered a wide range of oncology disciplines; this report focuses on lung cancer, breast cancer and gastrointestinal cancer. Canadian authors are highlighted by symbol.

The CARE Faculty also attended IASLC (International Association for the Study of Lung Cancer) 2013 in Sydney, Australia (October 27–30, 2013). There was a large Canadian presence at the conference this year with the presentation of many posters led by leading Canadian opinion leaders. The lung cancer section of the report includes an update from this conference, including an overview of two Canadian poster presentations made by CARE Faculty members:

Approach to Biomarker Testing: Perspectives From Various Specialties
Natasha Leighl, Peter Ellis, Sunil Verma

Afatinib in Advanced Pretreated NSCLC — A Canadian Experience
Barbara Melosky, Manstein Kan, Roxana Tudor, Stephanie Lin, Anthea Lau, Tony Panzarella, Natasha Leighl

More information on these presentations can be found in the “CARE Update From IASLC 2013” section of the report.

The following commentary and perspectives have been provided by the CARE Oncology Faculty. Information and visuals are in the language in which they were presented.

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Unresectable Stage III NSCLC

F. Shepherd et al.

**Background:** START is a phase III trial of MUC1-specific cancer immunotherapy L-BLP25 in patients with stage III unresectable non-small cell lung cancer who did not progress after primary chemoradiotherapy (CRT). While the primary objective of overall survival prolongation was not met, pre-defined subgroup analyses revealed a clinically meaningful prolongation of OS in pts previously treated with concurrent CRT. Sensitivity analyses suggested the observed treatment effect was underestimated due to a clinical hold. L-BLP25 was well tolerated, with no safety concerns identified. Here we report pre-defined subgroup analyses for secondary endpoints. Updated OS data, available in Q3 2013, also will be presented.

**Conclusions:** While the primary objective of the trial to prolong survival time significantly was not met, detailed secondary endpoint analyses of pre-defined subgroups support a potential benefit of L-BLP25 in patients receiving prior concurrent CRT.

**CARE Faculty Perspective:**

The effect of a passive immunization with BLP-25 (a MUC-1-based vaccine) in patients with tumour control with chemoradiation therapy for stage III NSCLC was first discussed at ASCO 2013, with the START trial (Abstract #7500). The START trial did not achieve the primary objective of increasing median OS by 6 months, however an encouraging increase in OS was observed in the patient group who received concurrent CRT. This study was then updated at ECC 2013 and showed similar results. More information/confirmation is needed to determine which patient population may benefit from this form of therapy.

Therapeutic Targets in Advanced NSCLC

**EGFR TARGETED THERAPIES**

Targeted therapy with an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) has become the standard of care for patients whose tumours harbour an EGFR receptor mutation (EGFR M+). Second-generation EGFR TKIs now available form covalent bonds at kinase domains and inhibit more members of the EGFR family. The LUX-Lung 3 study presented at ASCO 2012 demonstrated that afatinib, a second-generation EGFR TKI, performed better than its comparator, cisplatin + pemetrexed, in the first-line treatment of EGFR mutated patients. Afatinib significantly improved PFS (13.6 mo vs. 6.9 mo) and quality of life, and was established as a clinically relevant first-line treatment option. Questions concerning drug-related adverse events (AEs) were raised, specifically with ≥ grade 3 diarrhea. This issue was then addressed with the presentation of LUX-Lung 6 at ASCO 2013. Results from this study showed that afatinib was significantly better than gemcitabine/cisplatin (GC) in terms of PFS and tumour response, with a more favourable safety profile. It is important to note that the rate of grade 3 diarrhea was only 5%. This is a dramatic difference in the rate of grade 3 diarrhea compared with what was seen in the LUX-Lung 3 trial, which does need to be taken into consideration. Close monitoring and proactive management can help minimize common adverse events.

This story was again updated at ECC 2013, with data presented from the LUX-Lung 4 trial. This study further investigated gastrointestinal adverse effects in patients using EGFR inhibiting agents. Information on this trial can be found below.

**ECC 2013 Abstract #3478: Individualized Dose Adjustments Facilitate Continuous Treatment With Afatinib, Allowing Patients With Advanced NSCLC Previously Treated With Chemotherapy and Erlotinib or Gefitinib to Maintain Clinical Benefit. Inoue et al.**

**Background:** Gastrointestinal adverse events – in particular, diarrhea – are characteristic of epidermal growth factor receptor-inhibiting agents and guidance on their effective management can facilitate continuous treatment, allowing pts to obtain maximum therapeutic benefits. Afatinib (A) is an oral, irreversible, ErbB family blocker that blocks signaling from EGFR (ErbB1), human epidermal growth factor receptor 2 (HER2; ErbB2) and ErbB4.
In LUX-Lung 4, A was effective in third- or fourth-line NSCLC Japanese pts with acquired resistance to erlotinib/gefitinib (median progression-free survival of 4.4 months based on central independent review at the primary endpoint analysis [data cut-off Feb. 14, 2011]). Here, in a subsequent exploratory analysis, we show that appropriate dose interruptions facilitate continuous A treatment.

**Conclusions:** In LUX-Lung 4, individualized A dose adjustments allowed pts to remain on treatment for as long as they had clinical benefit.

**CARE Faculty Perspective:**

**In this trial it is important to consider that only two patients discontinued therapy due to grade 3 diarrhea. An individualized dose reduction allowed most patients to continue afatinib treatment and prevent disease progression.** These results emphasize that proactive management is essential for successful treatment with afatinib. As new targeted agents become available, a patient management process using a “team approach” needs to be considered.

**Supporting ECC 2013 Abstract:**

**ECC 2013 Abstract #895:** Epidermal Growth Factor Receptor (EGFR)-Mediated Adverse Events in Patients With EGFR Mutation Positive (EGFR M+) Non-Small Cell Lung Cancer Treated With Afatinib.

J. Chih-Hsin Yang et al.

**Background:** Afatinib (A) is an oral, irreversible ErbB family blocker showing superior efficacy to first-line pemetrexed/cisplatin (PC) in EGFR M+ pts. In the LUX-Lung 3 trial, median progression-free survival was 11.1 months for A and 6.9 months for PC (HR = 0.58; p = .0004). A similar phase 3 trial, LUX-Lung 6, comparing A with gemcitabine/cisplatin in Asian pts was recently reported (ASCO 2013). Here, we present the data on common EGFR-mediated AEs from both phase 3 trials.

**Conclusions:** The most common AEs observed with A were characteristic of EGFR-inhibiting agents. G3 AEs were short-lived, and responded to dose interruptions/reductions with little recurrence at a lower dose of A. Treatment discontinuation due to EGFR-related AEs was low, which indicates that A has a manageable safety profile and is suitable for the long-term treatment of EGFR M+ lung cancer pts.

**CMET PATHWAY**

**ECC 2013 Abstract #3410:** MARQUEE: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial of Tivantinib (ARQ 197) Plus Erlotinib Versus Placebo Plus Erlotinib in Previously Treated Patients With Locally Advanced or Metastatic, Non-Squamous, Non-Small-Cell Lung Cancer (NSCLC).

G. Scagliotti et al.

**Background:** The CMet pathway is felt to be one mechanism by which resistance develops to EGFR inhibitors. It thus may be desirable to inhibit both EGFR and CMET. One of the first trials to look at this dual inhibition in NSCLC was a phase 2 trial OAM4558g. The monoclonal antibody MetMab added to erlotinib was compared to erlotinib alone. Met high was defined as > 50% staining of the MET protein by IHC. In Met high tumors, progression-free survival was doubled (1.5 mo to 2.9 mo HR = 0.53, p = .04). More interesting, overall survival was tripled (3.8 mo to 12.6 months (HR 0.37, p = .002). The phase 3 results are to be presented ASCO 2014 and are anticipated to be positive.

**Conclusions:** Addition of tivantinib to erlotinib did not achieve the primary endpoint of improved OS. However, the combination is well tolerated and biologically active with substantial improvement in PFS and ORR. Analysis of molecular subgroups, including MET expression, is ongoing.

**CARE Faculty Perspective:**

Tivantinib (ARQ 197) is an oral tyrosine kinase inhibitor of CMet. 1,048 patients with non-squamous NSCLC in the second- or third-line setting were randomized to the combination of tivantinib (ARQ 197) and erlotinib versus erlotinib alone. Although the PFS was increased (3.6 mo vs. 1.9 mo; HR 0.74; p < .001), the primary endpoint of OS was not met (8.7 mo vs. 7.8 mo; HR 0.98; p = 0.81). A negative trial was reported to the media.

**This trial’s importance lies in the biomarker of Met high by IHC.** Staining for Met IHC was available in only 40% of the patients so far. In the Met high patients, the PFS paralleled the ITT group. However the OS was impressively positive. Erlotinib alone in this patient population had an overall survival of 5.9 months. When tivantinib was combined with erlotinib in the Met high patients, overall survival was increased to 9.3 months (HR 0.70; p = 0.81).

When the trial was designed, the biomarker as defined by the OAM4558g trial was not known. Although this biomarker was not prospectively defined in MARQUEE, the results are intriguing and confirm initial findings of the Metmab trial. A new biomarker has arrived! Our understanding of the CMet pathway, the impact of its inhibition and best biomarker to measure it by continues to evolve.
ANGIOKINASE INHIBITORS

LUME Lung 1 was first presented at ASCO 2013 (LBA #8011) by M. Reck et al., which looked at nintedanib (N) plus docetaxel (D) in NSCLC patients progressing after first-line chemotherapy. This phase 3 trial found that N + D significantly improved PFS independent of histology, and prolonged OS for adenocarcinoma patients. AEs were generally manageable with dose reductions and symptomatic treatment. This data was then updated at ECC 2013, this time focusing on overall survival in adenocarcinoma NSCLC patients.

ECC 2013 Abstract #3409: Analysis of Overall Survival in Adenocarcinoma NSCLC Patients Receiving 2nd Line Combination Treatment With Nintedanib (BIBF 1120) + Docetaxel in the LUME-Lung 1 Trial: A Randomized, Double-Blind, Placebo-Controlled Phase 3 Study.

A. Mellemgaard et al.

Background: Nintedanib is an oral inhibitor of VEGFR, FGFR, and PDGFR. LUME Lung 1, a placebo-controlled phase 3 trial investigated nintedanib + docetaxel in locally advanced/metastatic NSCLC patients progressing after first-line chemotherapy.

Conclusions: Second-line treatment with N + D improved OS for adeno NSCLC pts significantly and consistently over time. AEs were generally manageable with dose reductions and symptomatic treatment.

CARE Faculty Perspective:

Nintedanib with docetaxel significantly prolonged PFS vs. docetaxel alone, with a median of 3.4 mo vs. 2.7 mo (HR 0.79; p = .0019) regardless of histology. Overall survival was significantly prolonged in patients with adenocarcinoma histology 12.6 mo vs. 10.3 mo (HR 0.83; p = .0359). A trend for improved OS was seen in all, median 10.1 mo vs. 9.1 mo (HR 0.94; p = .272), and although the primary endpoint of PFS was improved only slightly, it was statistically significant. A survival of over 1 year in a second-line trial is encouraging and increases anticipation for antiangiogenesis therapies in NSCLC.

OTHER TARGETED THERAPIES

ECC Abstract #3408: Clinical Activity, Safety and Biomarkers of PD-L1 Blockade in Non-Small Cell Lung Cancer (NSCLC): Additional Analysis From a Clinical Study of the Engineered Antibody MPDL3280A (Anti PD-L1).

J.C. Soria et al.

Background: Antitumor immune response may be inhibited by PD-L1 expression. MPDL3280A is a human monoclonal antibody that contains an engineered Fc-domain whose aim is to restore tumor specific T cell immunity by blocking PD-L1 from binding with its receptors.

Conclusions: Treatment with MPDL3280A was well tolerated, with no pneumonitis-related deaths. Rapid and durable responses were observed, and PD-L1 tumor status correlated with response to MPDL3280A. In addition, preliminary data suggest that the number of responders was numerically higher for former/current smokers versus never smokers.

CARE Faculty Perspective:

This study demonstrates a number of very interesting and provocative aspects of this novel agent. First, the tolerability of this agent. The significant efficacy especially in heavily pretreated patients as well as patients with squamous cell carcinoma. It appears that there is a predictive biomarker for this agent with evidence that increasing PD-L1 expression correlates with a higher efficacy of the compound. Finally, there appears to be differential activity of this agent in patients who are current or previous smokers.

This is the first time that evidence of smokers benefiting from a targeted agent has been documented. The theory behind the benefit in smokers relates to the mutational load in tumour cells which is significantly higher in smokers versus nonsmokers and the relationship between mutational load and immunogenicity. Thus, this agent is very promising from the early phase I data. There are rapid and durable responses observed and it is well tolerated. Results of further investigations are eagerly anticipated as we try to improve the outcome of patients with advanced NSCLC.
CARE LUNG CANCER FACULTY UPDATE FROM IASLC 2013

There was a strong Canadian presence at IASLC 2013 with the presentation of multiple exciting posters led by leading Canadian OLs. A summary of two Canadian posters led by CARE Faculty members, as well as additional abstracts of interest from IASLC 2013 identified by the CARE Lung Cancer Faculty can be found in this section.

The CARE Lung Cancer Faculty will next meet at CLCCO 2014 in Vancouver, Canada (February 6–7, 2014). More details to follow.

CARE Faculty Poster Presentations

The CARE Lung Cancer Faculty reviews content on the management and treatment of lung cancer with emphasis to date on the development and implementation of a CARE Molecular Testing at Diagnosis Initiative. The CARE Medical Oncology Lung Cancer Faculty first met in 2011 to discuss testing at diagnosis. There was an agreement that molecular status impacts patient outcomes and influences treatment decision, and that testing at diagnosis allows for molecular status at first presentation. It was then decided that all stakeholders (medical oncologists, pathologists, respiratory medicine) along the patient pathway needed to be involved in this process. Meetings were subsequently held with each of these groups, and it was identified that there was a need for a national strategy or algorithm for biomarker testing. To better understand current treatment protocol for biomarker testing a national survey of Canadian specialists was conducted by CARE Faculty members Drs. Leighl, Verma, and Ellis. The results of this survey then formed the basis for a poster presentation by Dr. Leighl at IASLC.

**IASLC 2013 Abstract #2426: Approach to Biomarker Testing: Perspectives from Various Specialties.**

*N. Leighl, P. Ellis, S. Verma*

**Background:** Currently, biomarker testing for lung cancer is not uniformly integrated into the Canadian public health care system, despite its clear importance for patient outcomes. In order to better understand the current practice pattern for lung cancer biomarker testing, we assessed physician perspectives by specialty and region.

**Results:** The overall response rate for the survey was 36%, (38% of medical oncologists, 24% of pathologists, and 40% respirologists). It is understood that knowing tumour genotyping results at the time of the initial medical oncology consultation impacts patient outcome and influences the treatment decision (98%). To date, medical oncologists most commonly initiate molecular testing (67%), however, most respondents suggested a shared model for initiating the testing involving medical oncologists and pathologists is needed. The current perception is that less than two-thirds of patients have testing results available at the time of initial medical oncology consultation. Barriers identified to routine testing for all advanced lung cancer patients include cost, lack of funding for molecular testing, tissue availability and the quality of the tumour sample.

**Conclusions:** There was clear agreement that biomarker testing is important in determining the most appropriate initial treatment for patients with advanced NSCLC. There is a need for national consensus on who should initiate molecular testing. Moving forward, clear clinical guidance for pathologists needs to be established for molecular testing as part of the lung cancer diagnostic process. This includes defining the population to be tested, timing, and the tests to be performed. This may be facilitated by including more information on diagnostic sample requisitions, such as clinical suspicion of lung cancer primary (versus metastasis from another site), other cancer history, and other samples collected (and tested) previously or planned (e.g., planned resection). Pathologists need to incorporate routine EGFR, ALK testing into diagnostic lung cancer algorithm. This and greater clinical information on sample requisitions will minimize unnecessary tissue sections and allow the most efficient use of available tumour tissue for molecular testing. Incremental laboratory funding is required throughout the Canadian public health care system in order to provide the current standard of molecular testing required for NSCLC. Turnaround times need to be clearly established and monitored. Implementation of the College of American Pathologists (CAP) guidelines for transport from diagnostic lab to molecular testing lab (3 days), and turnaround for test results (10 days) will also improve the proportion of patients with test results available at initial consultation. Finally, feedback to clinicians, including sample quality, volume, whether or not testing was successful, and molecular results is necessary in a timely manner.

The results of this survey supported the thought that there is a need to establish a national framework to address biomarker testing with multiple stakeholders. A suggested ‘testing at diagnosis’ algorithm was then created by the CARE Faculty. This algorithm showed the collaborative effort between all of the major stakeholders, from the collection of the pathology sample through to its handling and processing. As a result, biomarker testing has been made more accessible at many centres across Canada. The CARE Faculty is now working to adapt/enhance this algorithm to be tailored for each stakeholder at not only large centres, but also local and tertiary centres. More on this initiative is to follow.
Another exciting poster was produced by CARE Oncology Faculty member Dr. Barbara Melosky at IASLC 2013 which further updated and gave a Canadian perspective on the use of afatinib for EGFR mutation-positive patients from the authors’ experience. Similar to the LUX-Lung 6 and LUX-Lung 4 data that was discussed earlier in this report, this Canadian study showed that the most common AE was diarrhea (≥ grade 3 in 10%). For some patients a dose reduction was necessary due to toxicity.

**IASLC 2013 Abstract P3.11-049:** Afatinib in Advanced Pretreated NSCLC – A Canadian Experience.
B. Melosky, M. Kan, R. Tudor, S. Lin, A. Lau, T. Panzarella, N. Leigh

**Background:** Afatinib is an oral, irreversible pan-EGFR inhibitor with demonstrated superiority over first-line chemotherapy in advanced EGFR mutation-positive NSCLC. It is also active after failure of chemotherapy and reversible EGFR tyrosine kinase inhibitor therapy, with higher response rate and better progression-free survival than placebo (LUX-Lung 1, Miller et al. Lancet Oncol. 2012). Through a national special access program (SAP), Canadian patients with advanced NSCLC, similar to those in the LUX-Lung 1 trial, may access afatinib after exhausting all other available therapies. We report our Canadian experience with afatinib at the two largest centres participating in the SAP.

**Results:** From July 2010 to the present, 54 patients at the two sites were treated with afatinib through the SAP. Median age was 59.5 (range 37 to 88 years), 57% were female, 52% were never smokers (7% current, 35% former smokers), 67% had adenocarcinoma histology and 28% were East Asian. 26% had known EGFR mutations (7% wild type, 67% unknown), most commonly exon 19 deletions. Patients received a median of three previous therapies (range two to five). All had received prior EGFR TKI therapy (81% erlotinib, 11% gefitinib, 6% both, 2% dacomitinib). Half (47%) had a response to prior EGFR TKI therapy, and 37% experienced grade ≥ 2 rash and 9% grade ≥ 2 diarrhea on prior EGFR TKI. The median time from metastatic diagnosis to starting afatinib was 23.1 months. The median treatment duration was 2 months (range 0–26 months). 21% of patients had a response (tumour reduction) to afatinib, 20% stable disease and 50% disease progression as their best response. Median survival from the time of afatinib start was 5 months (95% CI: 2–12 months).

The average starting dose of afatinib was 40 mg (6% 50 mg, 94% 40 mg), with 11% requiring dose reduction. One-third of patients (34%) stopped treatment for disease progression, 17% for toxicity, 30% for clinical deterioration and 19% for other or unknown reasons. The rate of grade ≥ 2 diarrhea, rash, paronychia, or stomatitis with afatinib was 17%, 20%, 9%, and 9% respectively (grade ≥ 3 in 10%, 11%, 5% and 5%). Response (non-RECIST) to afatinib was seen in EGFR wild type (2/4) and mutation positive (3/13) patients. Response to erlotinib or gefitinib was non-significantly associated with response to afatinib (OR 3.3; p = 0.22). A similar non-significant association was seen with rash (OR 1.7; p = 0.22), but not with diarrhea, (OR 0.37; p = 0.45).

**Conclusion:** Afatinib demonstrates activity in clinical practice similar to that reported in LUX-Lung 1. While some required dose reduction, toxicity from afatinib appeared manageable for the majority. Although not significant, there was a propensity to experience response or rash on afatinib if seen with prior EGFR TKI, although this was not seen with diarrhea.

**Other Abstracts of Interest from IASCL 2013**

**IASLC 2013 Abstract P1.11-018:** An Open-Label, Multicenter, Randomized, Phase II Study of Cisplatin and Pemetrexed With or Without Cixutumumab (IMC-A12) as First-Line Therapy in Patients With Advanced Non-Squamous Non-Small Cell Lung Cancer. G. Scagliotti et al.

**Background:** Pemetrexed combined with cisplatin is an approved first-line treatment regimen for patients with advanced/metastatic non-squamous non-small cell lung cancer. New targets are needed to further improve first-line therapy outcomes. Cixutumumab, a fully human IgG1 monoclonal antibody, specifically blocks the insulin-like growth factor-type 1 receptor, inhibiting its activation and signal transduction. Early studies have reported clinical efficacy and safety with cixutumumab. However, the clinical benefit of adding cixutumumab to conventional chemotherapy is yet to be established. This study assessed whether pemetrexed and cisplatin combined with cixutumumab was superior to pemetrexed and cisplatin as first-line therapy.

**Conclusion:** Superior PFS was not achieved in non-squamous NSCLC patients when cixutumumab was added to the pemetrexed and cisplatin treatment regimen, and no significant improvement for any other endpoint was observed. Pemetrexed combined with cisplatin and cixutumumab was tolerable, with no new safety concerns reported.

**IASLC 2013 Abstract P2.11-024:** Efficacy Analysis for Molecular Subgroups in MARQUEE: a Randomized, Double-blind, Placebo-Controlled, Phase 3 Trial of Tivantinib (ARQ 197) Plus Erlotinib Versus Placebo Plus Erlotinib in Previously Treated Patients With Locally Advanced or Metastatic, No. S. Novello et al.

**Background:** MARQUEE, a Phase 3 study which investigated the role of tivantinib, a c-MET inhibitor, in previously treated non-squamous NSCLC, collected EGFR and KRAS genotype on >90% of randomized patients, and MET expression was determined for 42%. In the ITT population, addition of tivantinib to erlotinib significantly improved PFS and ORR but did not show benefit in OS. Additional efficacy analyses in the pre-defined molecular subgroups are presented.

**Conclusion:** Tivantinib significantly improved PFS and OS in the prospectively defined MET High subgroup. Further investigation of tivantinib in MET High selected, non-squamous NSCLC is warranted.
Prognostic and Predictive Biomarkers / Pathways

PIK3CA mutations are a poor prognostic factor in HER2-positive breast cancer (both early and advanced stage) and may be predictive of lack of substantial benefit for the combination of dual anti-HER2 therapy (trastuzumab and lapatinib).

Conversely, the PIK3CA wild-type HER2-positive breast cancers may be the subgroup that derives the greatest benefit from dual anti-HER2 therapies, and thus maximize the therapeutic efficacy and cost-effectiveness ratio in favour of combination therapy in this cohort of patients.

Activation of the PI3K-Akt-mTOR pathway (as measured by low PTEN or high pS6) may possibly identify the subgroup that derives greater clinical benefit of everolimus in combination with vinorelbine and trastuzumab in BOLERO-3. Further validation however is required — both in additional studies with higher proportional collection of contemporary tissue and in determining the appropriate reproducible methodology and cut-points for measuring low PTEN and high pS6.

It is likely in the future some HER2-positive breast cancers will require single upstream blockade, some will require dual upstream blockade, and others yet will require blocking both upstream and downstream of the activated HER2 pathway.

ECC 2013 LBA #16: Evaluation of Everolimus in HER2+
Advanced Breast Cancer With Activated PI3K/mTOR Pathway:
Exploratory Biomarker Observations From the BOLERO-3.
G. Jerusalem et al.

Background: In BOLERO-3 (NCT01007942; Novartis), a randomized, double-blind, placebo-controlled, phase 3 trial (n=569), EVE 5 mg daily combined with weekly trastuzumab and vinorelbine significantly prolonged progression-free survival vs. placebo in patients with trastuzumab-resistant HER2+ advanced BC previously treated with a taxane (HR = 0.78, 95% CI: 0.65–0.95). Correlations between key members of the PI3K/mTOR pathway and EVE efficacy were explored in a subset of patients for the identification of potential predictive biomarkers.

Conclusions: Patients in BOLERO-3 with biomarkers indicative of PI3K/mTOR pathway activation may derive greater benefit from addition of EVE to trastuzumab and vinorelbine. These observations are consistent with the hypothesis that mTOR inhibition attenuates trastuzumab resistance resulting from PI3K/mTOR pathway activation. The results and clinical implications of this exploratory analysis need further validation and investigation.

ECC 2013 Abstract #1859: PIK3CA Mutations and Correlation
With pCR in NeoALTTO Trial (BIG 01-06).
J. Baselga et al.

Background: Understanding the mechanism of resistance to human epidermal growth factor receptor 2 (HER2)-targeted agents is a critical step toward identifying the best therapy for individual patients with HER2-positive breast cancer. Activation of the PI3K/ Akt survival pathway is one of the molecular mechanisms that contribute to trastuzumab resistance.

Conclusions: These data provide further evidence of the role of PIK3CA mutations in resistance to trastuzumab and lapatinib-based therapies. Thus, assessment of PIK3CA status might be an important tool in identifying patients unlikely to derive substantial benefit from these treatments.

CARE Faculty Perspective:
The overall study demonstrated a statistically significant, but modest clinical benefit in PFS in favour of the everolimus arm (HR = 0.78; 95% CI: 0.65–0.95). In this correlative study, there were only 262 patient samples (46%) (predominantly archival from the primary tumour) with sufficiently available tumour for DNA sequencing for PIK3CA mutations and IHC assessment of pS6 and PTEN levels.

CARE Faculty Perspective:
The Neo-ALTTO study was a randomized phase 2 study (n = 455) in the neoadjuvant setting of a 6-week run in of lapatinib (L), trastuzumab (T) or the combination (LT) followed by combination with weekly paclitaxel x 12 weeks followed then by primary surgery. The primary end-point of the study, pCR (breast only), was significantly higher in the combination (LT) arm: 27.7%, 29.5% and 51.3% respectively (p = .001). In the correlative study, 355 patient samples (78%) were suitable for genotyping by mass spectrometry for PIK3CA, Akt, KRAS AND BRAF (V600E) mutations. In total, 23% of the correlative study population had a PIK3CA mutation, with no BRAF and very infrequent KRAS (one patient) mutations were found.
Unresectable / Recurrent HER2+ Metastatic Breast Cancer

**ECC 2013 LBA15: T-DM1 for HER2-Positive Metastatic Breast Cancer (MBC): Primary Results From TH3RESA, a Phase 3 Study of T-DM1 vs. Treatment of Physician’s Choice.**

H. Wildiers

**Background:** T-DM1, an antibody-drug conjugate comprising the cytotoxic agent DM1 linked to trastuzumab, is approved in the U.S. for patients with MBC previously treated with trastuzumab and a taxane. There is no clear standard of care for pts with progressive disease after ≥ 2 HER2-directed regimens for MBC. TH3RESA is an ongoing phase 3 study evaluating T-DM1 vs. treatment of physician’s choice (TPC) in this pt population.

**Conclusions:** T-DM1 resulted in a statistically significant improvement in PFS, with fewer grade ≥ 3 AEs than TPC in pts previously treated with ≥ 2 HER2-directed regimens for HER2-positive MBC.

**CARE Faculty Perspective:**

T-DM1 resulted in an improved PFS with fewer grade ≥ 3 AEs compared to TPC in pts previously treated with ≥ 2 HER2-directed regimens for HER2-positive MBC. PFS improvement was present even though TH3RESA patients were heavily pre-treated (median four regimens), with 75% having visceral disease burden and most (83%) patients in the TPC arm continued to receive HER2 directed therapies. Although median OS was not reached in the T-DM1 arm, a reported trend was noted. Given the allowed and likely continued crossover to T-DM1 in the TPC arm, it would seem less likely that definitive OS benefit will be seen with longer follow-up. Overall the side-effect profile and PFS benefit seen in the T-DM1 reaffirms the results from the EMILIA trial.

For our patients, having access to less toxic and more efficacious treatment options is a good thing. T-DM1 in HER2+ positive MBC seems to continue to fit this description. For clinicians, with the increasing number of HER2 directed agents and supportive studies, the complexity of treatment decision is reflected in the ongoing discussion as to what should be considered the ideal or ‘standard’ HER2+ MBC treatment algorithm. The TH3RESA study adds to and supports the use of T-DM1 and the clinical practice of continued HER2 directed therapy in the HER2-positive MBC setting. T-DM1 is not yet publicly funded in Canada.

For our Canadian health care system, the same question remains, how can we afford to fund all of these increasingly expensive next generation therapeutics? Although future correlative or bio-marker studies may help to decide how best to treat, we are not quite there.

Locoregional Recurrence Post Surgery

**ECC 2013 Abstract #1855: The 70-Gene Signature Predicts the Risk of Locoregional Recurrence After Adequate Breast Surgery.**

M.V. Nijenhuis et al.

**Background:** The possibility of predicting the risk of ipsilateral locoregional recurrence (LRR) after adequate surgery will allow individually tailored treatment. With the 70-gene signature (70-GS) it is possible to predict the risk of distant metastases in breast cancer and select those patients who will have benefit in survival from adjuvant treatment. Given the strong association between LRR and distant metastases, we hypothesize that the 70-GS will also be predictive for LRR.

**Table 1: Results**

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<td></td>
<td>70-GS high risk (n = 492)</td>
<td>70-GS low risk (n = 561)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 years</td>
<td>10 years</td>
<td>5 years</td>
<td>10 years</td>
</tr>
<tr>
<td>Entire group (n = 1053)</td>
<td>9.5%</td>
<td>13.0%</td>
<td>2.7%</td>
<td>6.1%</td>
</tr>
<tr>
<td>Breast-conserving treatment (n = 481)</td>
<td>7.7%</td>
<td>13.2%</td>
<td>1.6%</td>
<td>5.8%</td>
</tr>
<tr>
<td>Node positive (n = 211)</td>
<td>6.5%</td>
<td>11.6%</td>
<td>1.0%</td>
<td>6.6%</td>
</tr>
<tr>
<td>Node negative (n = 264)</td>
<td>9.0%</td>
<td>15.4%</td>
<td>2.0%</td>
<td>4.9%</td>
</tr>
<tr>
<td>Mastectomy (n = 567)</td>
<td>11.2%</td>
<td>13.0%</td>
<td>3.4%</td>
<td>6.0%</td>
</tr>
<tr>
<td>Node positive (n = 323)</td>
<td>13.8%</td>
<td>15.2%</td>
<td>0.6%</td>
<td>2.0%</td>
</tr>
<tr>
<td>Node negative (n = 244)</td>
<td>7.5%</td>
<td>9.8%</td>
<td>6.8%</td>
<td>11.1%</td>
</tr>
</tbody>
</table>

**Conclusions:** The 70-GS is able to predict the risk of LRR. Patients with 70-GS high risk breast cancers may benefit from more extensive adjuvant treatment to reduce the risk of LRR while patients with 70-GS low risk breast cancers may benefit from more limited treatment strategies.
GASTROINTESTINAL CANCER

The abstract and presentation content/visuals that follow are drawn from ECC 2013 and augmented with commentary from the CARE Gastrointestinal Cancer Faculty.

Topics covered in this section include:
▶ Colorectal Carcinoma
▶ Vitamin D and Inflammation
▶ Gastroesophageal Adenocarcinoma

Colorectal Carcinoma (CRC)

Over the past decade, evolution of systemic therapy for mCRC has achieved marked improvements in survival. In randomized controlled trials, median OS approaching 2 years has been observed with the addition of novel targeted agents like bevacizumab, cetuximab, and panitumumab, to contemporary chemotherapy regimens including: FOLFIRI (irinotecan, 5-FU, and leucovorin) and FOLFOX (oxaliplatin, 5-FU, and leucovorin). Figure 1 below shows the improvements over the past decade with the introduction of new treatment regimes.

**Figure 1:** Improvements in OS in mCRC Over the Past Decade

![Figure 1](image_url)

**ECC 2013 LBA #17:** Analysis of KRAS/NRAS and BRAF Mutations in FIRE-3: A Randomized Phase III Study of FOLFIRI Plus Cetuximab or Bevacizumab as First-Line Treatment for Wild-Type (WT) KRAS (Exon 2) Metastatic Colorectal Cancer (mCRC) Patients. V. Heinemann et al.

**Background:** The FIRE-3 study (AIO KRK-0306) was designed as a randomized multicenter trial to compare the efficacy of FOLFIRI plus cetuximab (cet) to FOLFIRI plus bevacizumab (bev) as first-line treatment in KRAS WT mCRC patients. FOLFIRI plus cet as first-line treatment of KRAS WT mCRC patients resulted in comparable overall response rates (ORR) and progression-free survival when compared to FOLFIRI plus bev. Overall survival was significantly longer in the FOLFIRI plus cet arm.

**Conclusions:** ORR and OS were increased in patients with cet plus FOLFIRI as compared to bev plus FOLFIRI in patients without RAS mutations. Exclusion of patients with RAS mutations identifies a population which is more likely to benefit from cetuximab.

**CARE Faculty Perspective:**

The findings from FIRE-3 were met with great interest as this study represents the first randomized clinical trial of FOLFIRI + bevacizumab vs. FOLFIRI + cetuximab in metastatic colorectal cancer where objective response rate (ORR) was selected as the primary endpoint. Despite comparable progression free survival (PFS) in both study arms, there was close to a 4 month difference in overall survival (OS) favoring the cetuximab group. The lack of PFS benefit makes the OS benefit difficult to explain and underscores the need to further explore the subsequent lines of therapies used among the participants.

**ECC 2013 Abstract #2151:** Intensified Follow-Up in Colorectal Cancer Patients Using Frequent Carcino-Embryonic Antigen (CEA) Measurements and CEA-Triggered Imaging. C. Verberne et al.

**Background:** The ultimate goal of post-surgical follow-up is to identify relapsing patients as early as possible and to offer appropriate individuals the potential for curative salvage procedures. Advances in local therapy is leading to a change in the pattern of recurrences and the options for subsequent treatment. While guidelines exist to assist clinicians, the optimal strategy is unknown. CEA is an inexpensive, sensitive, valid and readily available test. The CEA Watch Trial describes an intensive follow-up protocol with the hypothesis that identification of the trend of rise rather than the absolute value of CEA may lead to earlier detection of relapsing patients.

**Conclusions:** The CEA watch protocol was more likely than standard care follow-up to detect recurrent disease at a stage treatable with curative intent.

**CARE Faculty Perspective:**

This trial used an interesting trial design in which the randomization occurred at the hospital rather than the individual level. The results suggest that monitoring CEA trends more frequently with decisions to evaluate radiographically based on a specified rise over time rather than an absolute CEA value has the potential to both identify more patients with recurrences as well as offer them subsequent therapy with curative intent. It is still too early to identify whether this will, in fact, result in a difference in cure rates between the groups or whether there will be an influence of lead-time bias and so longer follow-up is needed. Also, given that CEA values may begin to rise many months before abnormalities are detectable by traditional imaging modalities, it is not clear whether assessments are required every 2 months, or if a 3-month schedule might be sufficient with confirmatory assessments 4 weeks later as performed in this study. A key element is to ensure that these patients are discussed with experienced individuals at multidisciplinary cancer conferences. In addition, in Canada’s public payer health care system, it will be necessary to evaluate the cost-effectiveness of this strategy.
Vitamin D and Inflammation

**ECC 2013 Best Abstract #3: Vitamin D Status and Inflammation in Cancer and Other Diseases.**
*P. Autier et al.*

**Background:** Several observational studies have identified an apparent association between 25-hydroxy-vitamin D levels and various disease states including poor bone health and malignancy. However, what is not known is whether this is apparent effect is correlative or modifiable.

**Conclusions:** Vitamin D status appears to represent a consequence rather than a cause of poor health and is likely due to underlying systemic inflammatory processes.

**CARE Faculty Perspective:**

This was a massive review of prospective patient data that attempted to discern if vitamin D levels were associated with malignancy (among other health states) and if the effect was modifiable. While the authors did identify that elevated levels of vitamin D were associated with a reduction of colorectal cancer, this did not appear to be the case for any other malignancy. Importantly, they also identified that lower levels of vitamin D appeared to be associated with poor health states involving higher states of systemic inflammation and that this was not a modifiable effect by vitamin D supplementation. This observation led them to conclude that the observed lower levels of vitamin D and the resulting increased risk of cancer were likely a consequence of inflammation rather than a direct cause of the disease.

These findings will have a significant implication for the design of preventative and adjuvant cancer studies and suggests that the focus of such interventions should be aimed at modifying the inflammatory process rather than via manipulation of vitamin D. Certainly, there is a suggestion that nonsteroidal anti-inflammatory medications may be effective in reducing the incidence of polyps and possibly colorectal cancer and is currently a focus of the ongoing CRC-6 clinical trial sponsored by the NCIC CTG. Interestingly however, there was a suggestion from this analysis that the vitamin D/inflammatory correlation did not appear to be dependent on COX-2 activation. This observation may affect the results of the CRC-6 trial given that the anti-inflammatory being evaluated is the COX-2 specific inhibitor celecoxib. **Overall, this study highlights the importance of assessing medical observations in a prospective fashion and we will await the outcome of the CRC-6 trial with interest.**

Gastroesophageal Adenocarcinoma

**ECC 2013 Abstract #2588: Tolerability and Quality-of-Life (QoL) Results From the Phase 3 REGARD Study: Ramucirumab Versus Placebo in Patients With Previously Treated Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma.**
*I. Chau et al.*

**Background:** Ramucirumab (RAM) was associated with significantly longer survival and progression-free survival versus placebo (Fuchs et al., GI Cancer Symposium 2013). Here we present assessments of tolerability and QoL from REGARD.

**Conclusions:** In addition to improved survival and PFS for RAM versus placebo, RAM was well tolerated. Rates of serious AEs were similar between arms; for RAM, the incidence of any individual severe toxicity was low and supportive care requirements were modest. For pts who received at least four cycles of therapy, more pts maintained their QoL with RAM. Performance status was maintained for a significantly longer time with RAM.

**CARE Faculty Perspective:**

Gastric cancer continues to be a leading cause of cancer-related morbidity and mortality, underscoring an unmet need for more effective therapies. Ramucirumab is a fully human IgG1 monoclonal antibody that targets the VEGF-receptor 2. In the REGARD trial that was previously presented at ASCO, investigators demonstrated statistically significant overall survival and progression-free survival improvements with ramucirumab alone in metastatic gastric adenocarcinoma patients who failed first-line platinum- and/or fluoropyrimidine-containing combination therapy. Because the treatment intent is palliative, significant concerns exist about ramucirumab’s toxicity and how it might negatively affect quality of life of patients who are nearing the end of life.

In the current analysis of the REGARD data, authors focused on QoL measures and revealed that **ramucirumab was well tolerated** with rates of serious adverse events being similar between ramucirumab and placebo. Importantly, more patients who received ramucirumab maintained their QoL and sustained their performance status for longer. While the OS and PFS benefits that were observed with ramucirumab were modest over best supportive care (only 1.4 months and 0.8 months, respectively), these should be interpreted within the context of a cancer in which prognosis is estimated to be in the range of only 6 months without treatment. The current QoL findings reassure clinicians that ramucirumab can be safely delivered. In the absence of severe toxicities, the modest but incremental survival advantages of ramucirumab may be clinically meaningful for selected patients. Economic analysis of the cost impact of ramucirumab must take into account the favorable QoL data.
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