Conference Highlights from ASCO 2014

Including conference content and supporting commentary from the CARE Oncology Faculty and perspective from CCOCO 2014.

Members of the CARE Oncology Faculty recently met at the annual ASCO (American Society of Clinical Oncologists) 2014 conference held in Chicago, IL from May 30th – June 3rd. The CARE at ASCO education event was held with trainees and community oncologists from across Canada and covered various topics in oncology. Perspectives from the CCOCO (Canadian Conference of Community Oncology) 2014 held in Collingwood, ON (June 13th – June 15th) are also included in this report.

ABOUT THE CARE ONCOLOGY FACULTY

The CARE (Community, Academic and Research Education) Oncology Faculty are a national group of oncologists across Canada who gather, discuss and address gaps in knowledge, to develop education initiatives framing news from a Canadian perspective.

The vision of the CARE Oncology Faculty is to share opinions and update Canadian specialists with key news and developments from key conferences framed in a Canadian perspective.

The mission of the CARE Oncology Faculty is to enhance medical education with the explicit goal of improving patient outcomes.

The report content that follows is drawn from ASCO 2014 and is augmented with the CARE Oncology and Supportive CARE Faculties perspectives and commentary.

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Information and visuals in this report are in the language in which they were presented.
HR+ Breast Cancer


FIRST RESULTS FROM THE PHASE III ALTTO TRIAL (BIG 2-06; NCCTG [ALLIANCE] N063D) COMPARING ONE YEAR OF ANTI-HER2 THERAPY WITH LAPATINIB ALONE (L), TRASTUZUMAB ALONE (T), THEIR SEQUENCE (T→L), OR THEIR COMBINATION (T+L) IN THE ADJUVANT TREATMENT OF HER2-POSITIVE EARLY BREAST CANCER (EBC).

Marine J. Piccart-Gebhart et al.

Background: Lapatinib (L) is a HER1-Her2 tyrosine kinase inhibitor. The Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation (ALTTO) Trial is a randomised, phase III trial comparing 3 oral L-containing regimens with T, each given for 1 year.

Conclusion: L+T has lower risk of a DFS event compared with T, and T→L appeared non-inferior to T, but neither finding was statistically significant. The first DFS results of dual HER2 blockade in the adjuvant ALTTO at 4.5 years MFU are unexpected considering the effect shown by doubling the pCR rate with L+T vs. T in the NeoALLTO trial.

The combined analysis of these two large RCTs of ovarian suppression in premenopausal women with early stage ER+ breast cancer comparing an aromatase inhibitor (AI) versus tamoxifen parallels the results seen in postmenopausal women trials (BIG 1-98 and ATAC) of improvements in DFS in favour of the AI over tamoxifen without a clear improvement in OS to date.

ASCO 2014. LBA 1.

RANDOMIZED COMPARISON OF ADJUVANT AROMATASE INHIBITOR (AI) EXEMESTANE (E) PLUS OVARIAN FUNCTION SUPPRESSION (OFS) VS TAMOXIFEN (T) PLUS OFS IN PREMENOPAUSAL WOMEN WITH HORMONE RECEPTOR-POSITIVE (HR+) EARLY BREAST CANCER (BC): JOINT ANALYSIS OF IBCSG TEXT AND SOFT TRIALS.

Olivia Pagani et al.

Background: Adjuvant endocrine therapy with AI vs T improves outcomes in postmenopausal HR+BC. TEXT and SOFT were designed to test whether adjuvant AI improves outcomes in premenopausal women with HR+BC treated with OFS (AI question) and to determine the value of OFS in women who remain premenopausal and are suitable for adjuvant T (OFS question).

Conclusion: In premenopausal women with HR+BC, adjuvant treatment with E+OFS significantly reduced the risk of recurrence compared to T+OFS.

The side effect profiles are different across the two regimens, with a greater discontinuation rate for the OFS + exemestane arms, but an adverse event profile consistent with AIs in postmenopausal women (more musculoskeletal symptoms, decreased bone density, vaginal dryness and dyspareunia) and no difference in QoL as measured in the trials.

The lack of results from the tamoxifen only arm (in SOFT) precludes direct comparison to the general standard of care of today, which is tamoxifen alone in the majority of such patients.

These results do suggest that ovarian function suppression with exemestane is an option for premenopausal women with early stage ER+ breast cancer, particularly those intolerant to or with a contra-indication to tamoxifen.

Widespread publicly funded adoption of this therapeutic strategy (OFS + exemestane) would benefit from the identification of the subset of patients that derive the greatest benefit to this treatment strategy, a survival signal benefit, knowledge of the results of tamoxifen alone as a therapeutic strategy (forthcoming from SOFT), and a well performed cost-effective analysis.

— CARE Faculty Perspective
Background: T-DM1, an antibody–drug conjugate comprising trastuzumab, DM1 (microtubule inhibitor), and a stable linker, is approved for patients (pts) with HER2-positive metastatic BC previously treated with trastuzumab and a taxane. In two phase 3 studies, T-DM1 prolonged progression-free survival (PFS; EMILIA, TH3RESA) and overall survival (EMILIA) vs control arms. Here we examine the relationship between tissue BM related to the HER2 pathway and PFS in TH3RESA (NCT01419197).

Conclusion: Similar to previous results, T-DM1 prolonged PFS in all BM subgroups analyzed with a greater benefit observed for pts with tumours expressing >median HER2 mRNA levels. Although PIK3CA mutation status was not associated with decreased PFS in the control arm, benefit was seen with T-DM1 regardless of mutation status.

--- CARE Faculty Perspective

--- Perspective from CCOCO 2014

**ASCO 2014. Abstract 605.**

**RELATIONSHIP BETWEEN TUMOUR BIOMARKERS (BM) AND EFFICACY IN TH3RESA, A PHASE 3 STUDY OF TRASTUZUMAB EMTANSINE (T-DM1) VERSUS TREATMENT OF PHYSICIAN’S CHOICE (TPC) IN HER2-POSITIVE ADVANCED BREAST CANCER (BC) PREVIOUSLY TREATED WITH TRASTUZUMAB AND LAPATINIB.**

Sung-Bae Kim et al.

**ASCO 2014. Abstract 645.**

**META-ANALYSIS OF STOMATITIS INCIDENCE IN EVEROLIMUS (EVE) CLINICAL STUDIES AND ITS RELATIONSHIP WITH EFFICACY.**

Hope S. Rugo et al.

--- CARE Faculty Perspective

--- Perspective from CCOCO 2014

**EVOLVING STORY THAT HOLDS INTEREST:**

**mTOR Pathway**

**ASCO 2014. Abstract 645.**

**META-ANALYSIS OF STOMATITIS INCIDENCE IN EVEROLIMUS (EVE) CLINICAL STUDIES AND ITS RELATIONSHIP WITH EFFICACY.**

Hope S. Rugo et al.

--- CARE Faculty Perspective
HR- Breast Cancer

**ASCO 2014. LBA505.**

PHASE III TRIAL (PREVENTION OF EARLY MENOPAUSE STUDY [POEMS]-SWOG S0230) OF LHRH ANALOG DURING CHEMOTHERAPY (CT) TO REDUCE OVARIAN FAILURE IN EARLY-STAGE, HORMONE RECEPTOR-NEGATIVE BREAST CANCER: AN INTERNATIONAL INTERGROUP TRIAL OF SWOG, IBCSG, ECOG, AND CALGB (ALLIANCE).

Halle C. F. Moore et al.

**Background:** Premature ovarian failure (POF) is a common toxicity of CT. Risk depends on type and amount of CT, age, and perhaps ovarian cycling at the time of CT. POEMS is a SWOG-coordinated phase III randomized study to evaluate whether LHRH analog administration with CT for early-stage breast cancer (BC) would reduce POF.

**Conclusion:** LHRH analog administration with CT was associated with less POF and more pregnancies. In an exploratory analysis, GN use in premenopausal ER-negative BC was associated with improved DFS and OS.

Compared to historical controls, other smaller studies reported potential ovarian protection with concomitant LHRH analog. Previous smaller randomized studies reported mixed results and commonly only used return of menses as an endpoint with few data on pregnancy outcomes.

The POEMS study is the largest phase III study that demonstrates the benefit of LHRH analog therapy for potential ovarian protection (and pregnancy outcomes) in this breast cancer patient population with the main benefit seen at year 2. An expected increase in vasomotor symptoms was noted while on LHRH treatment with no other unexpected serious events.

Of note, the trial was closed prior to full accrual (original target 416 patients) due to slow accrual and loss of drug funding, and post-hoc power calculations were required. Endpoint data was also missing for 38% and patients were not stratified for other disease risk factors (stage, HER2, nodal status), however stage adjustment did not significantly alter DFS or OS.

Intriquingly, in a planned exploratory analysis the investigators reported an improvement in 4yDFS (78% → 89%) for those receiving LHRH analog therapy (HR 0.47, p=0.04) and a trend in OS as well. But one has to remember that this was a secondary endpoint of the trial with immature follow-up and methodologic issues as noted above.

Although not definitive, given the overall risk-benefit profile in this ER negative patient population, clinicians should at least discuss and patients should consider the option of concomitant LHRH analog therapy during chemotherapy for potential ovarian protection. This approach, for ovarian preservation purposes however, cannot be translated to patients with ER+ disease. The potential therapeutic role of ovarian suppression in ER+ breast cancer patients (TEXT/SOFT) was also presented at ASCO 2014 and is the subject of another CARE Faculty Commentary.

— CARE Faculty Perspective
**MELANOMA**

The abstract content/visuals that follow are drawn from the presentation made by Dr. Winson Cheung during CORE at ASCO 2014 and are augmented with content from the ASCO 2014 conference, and Canadian perspectives from the CARE Oncology Faculty.

**ASCO 2014. Abstract LBA9003.**

**SURVIVAL, RESPONSE DURATION, AND ACTIVITY BY BRAF MUTATION (MT) STATUS OF NIVOLUMAB (NIVO, ANTI-PD-1, BMS-936558, ONO-4538) AND IPILIMUMAB (IPI) CONCURRENT THERAPY IN ADVANCED MELANOMA (MEL).**

Mario Sznol et al.

*Background:* We report updated survival and clinical activity in initially enrolled cohorts and activity by BRAF MT status in a phase I trial of concurrent and sequenced NIVO+IPI.

*Conclusion:* Concurrent NIVO + IPI therapy showed encouraging survival and a manageable safety profile in advanced MEL pts. Responses were observed regardless of BRAF MT status and were durable in the majority of pts. Forty additional pts were enrolled (last pt: Nov 2013) on a cohort of NIVO 1 mg/kg + IPI 3 mg/kg q3wk × 4 doses, followed by NIVO 3mg/kg Q2Wk (the selected regimen for phase II/III trials).

<table>
<thead>
<tr>
<th>NIVO (mg/kg) + IPI (mg/kg) [n]</th>
<th>1-Y OS rate, % [pts at risk]</th>
<th>Median OS, mo</th>
<th>ACAR, %</th>
<th>ACAR by BRAF MT status,* % [n]</th>
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<td>Pos</td>
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</table>

n: no. response-evaluable pts. ACAR: aggregate clinical activity rate = CR+PR+uCR+uPR+irCR+irPR+SD ≥24 wk+ irSD ≥24 wk. *Retrospective analysis. †Pts began NIVO Q2Wk × 48 doses within 4-12 wk after last IPI dose.

**Ipilimumab is an approved agent for melanoma, with a 20% 5 year survival and a plateau at 3 years.** It boosts the immune response against cancerous cells in the body. The response rate to nivolumab in ipi-naïve patients is 31-40%; in ipi refractory patients at Moffitt it is 25%. Responses in ipilimumab naïve and – refractory patients can be long lasting – median 24 months. Nivolumab failures that are ipilimumab-naive can respond to subsequent ipilimumab. PD-L1 tumour staining associated with but not a reliable predictive marker for response to nivolumab. Nivolumab + ipilimumab yields high proportion of rapid and deep responses of long duration.

— CARE Faculty Perspective

**ASCO 2014. Abstract 9005.**

**BRAF<sup>v600</sup> MUTATION LEVELS AND RESPONSE TO VEMURAFENIB IN METASTATIC MELANOMA.**

Celeste Lebbe et al.

*Background:* Resistance mechanisms acquired during BRAF inhibitor (BRAFi) treatment were shown to involve multiple signalling pathways including MAPK, PI3K pathways and tumour microenvironment. They may also be complicated by intra-tumour heterogeneity of BRAF mutational status which paradoxically enhances wild-type BRAF cells proliferation. We therefore wanted to evaluate using a quantitative pyrosequencing assay whether the level of BRAF<sup>v600</sup> mutation in tumour tissue could predict clinical response and outcome of BRAF<sup>v600</sup> melanoma patients treated with the BRAFi, vemurafenib.

*Conclusion:* We show that quantification of BRAF mutant allele (V600E and V600K) is a predictive marker of BRAFi response in metastatic melanoma patients. This preliminary study constitutes a first step in the identification of surrogate biomarkers of melanoma response to BRAFi and provides a promising tool that might help in the management of metastatic melanoma.
The abstract content/visuals that follow are drawn from the presentation made by Dr. Barbara Melosky during CORE at ASCO 2014 and are augmented with content from the ASCO 2014 conference, and Canadian perspectives from the CARE Lung Cancer Faculty.

**THERAPEUTIC TARGETS IN NSCLC**

**EGFR Targeted Therapies**

**ASCO 2014. Abstract 8004.**

**OVERALL SURVIVAL (OS) IN PATIENTS (PTS) WITH ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC) HARBOURING COMMON (DEL19/L858R) EPIDERMAL GROWTH FACTOR RECEPTOR MUTATIONS (EGFR MUT): POOLED ANALYSIS OF TWO LARGE OPEN-LABEL PHASE III STUDIES (LUX-LUNG 3 [LL3] AND LUX-LUNG 6 [LL6]) COMPARING AFATINIB WITH CHEMOTHERAPY (CT).**

James Chih-Hsin Yang et al.

**Background:** Afatinib (A) is an oral, irreversible ErbB family blocker of EGFR, HER2, ErbB3 and ErbB4 signalling. LL3 compared A with cisplatin/pemetrexed in 345 pts recruited globally and LL6 compared A with gemcitabine/cisplatin in 364 Asian pts. The primary analysis (2012) showed improved progression-free survival (PFS) with A versus CT in the overall EGFR mut positive population (HR=0.58 [LL3], HR=0.28 [LL6]) and pts with common (Del19/L858R) EGFR mut (HR=0.47 [LL3], HR=0.25 [LL6]). The FDA has approved A for the first-line treatment of pts with advanced NSCLC harbouring common EGFR mut. Here we present a pooled analysis of mature OS data among such pts.

**Conclusion:** This pooled analysis reveals that first-line A significantly improves OS in pts with advanced NSCLC harbouring common EGFR mut (Del19/L858R) compared with CT. This is the first analysis to show that genotype-directed therapy for EGFR mut pts can improve survival.

The use of EGFR TKI inhibitors in patients whose tumours harbour an EGFR mutation has become standard of care in Canada.

First generation TKI’s such as gefitinib and erlotinib showed improvement in PFS over chemotherapy in the pivotal trials IPASS and EURTAC. OS (21-22 months) was not different and an expected finding given the high rate of crossover for both arms in both trials.

The second generation EGFR TKI, afatinib was tested in the first line setting in LUX Lung 3 and LUX Lung 6. The PFS of 13.6 months and 11 months were impressive. As a pan HER inhibitor which also blocks the acquired T790 mutation, the results were explained.

The overall survival was presented as a pooled analysis at this year’s ASCO. Patients treated with afatinib had an OS of 27.3 months compared to chemotherapy 24.3, p<0.037 (Figure 1). This was even more pronounced in patients who had the common mutation of deletion 19. An outstanding survival of 31.7 months was found. This is the first EGFR TKI in the first line setting to have a benefit in OS. This will be practice changing in my patients.

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**ASCO 2014. Abstract 8008.**

**A RANDOMIZED, MULTICENTER, OPEN-LABEL, PHASE III STUDY OF GEMCITABINE-CISPLATIN (GC) CHEMOTHERAPY PLUS NECITUMUMAB (IMC-11F8/LY3012211) VERSUS GC ALONE IN THE FIRST-LINE TREATMENT OF PATIENTS (PTS) WITH STAGE IV SQAMOUS NON-SMALL CELL LUNG CANCER (sq-NSCLC).**

Nick Thatcher et al.

**Background:** Necitumumab (N), a human IgG1 anti-EGFR monoclonal antibody, inhibits ligand-binding and receptor activation. EGFR is detectable in the vast majority of advanced sq-NSCLC tumours.

**Conclusion:** The addition of N to GC statistically significantly improved OS, PFS, and DCR. The safety profile of GC+N is acceptable.

Although squamous cell lung carcinoma is decreasing in its incidence, it still remains a clinical challenge. Our understanding of the driver mutations and treatment thereafter lacks far behind adenocarcinoma.

The Squire Trial was presented at this year’s ASCO on Monday June 2 as an oral presentation.

Necitumumab is a monoclonal antibody to EGFR. Squire randomized patients with stage IV NSCLC squamous cell histology to chemotherapy with cisplatin/gemcitabine with or without necitumumab.
The primary endpoint of overall survival was met. Progression free survival was significantly improved. More importantly necitumumab prolonged overall survival to 11.5 months vs 9.9 with chemotherapy alone p<0.001.

Is a two month improvement in survival meaningful? It does not meet the current 4 month bar set by ASCO this year. Nonetheless squamous cell carcinoma is a group that is challenging and need new therapeutic treatments. Personal opinion is yes.

This is an unmet need. This will be a new option for first line treatment in patients with this histology.

— CARE Faculty Perspective

Testing for EGFR mutation is extremely important in order to provide a patient with the best possible treatment. EGFR mutations were tested across Canada, and the results showed that the amount of patients with EGFR mutation was higher in Canada’s western provinces\(^5\). Oncologists should consider this when testing for mutations.

— Perspective from CCOCO 2014

**ALK + Targeted Therapies**

**ASCO 2014. Abstract 8002.**

FIRST-LINE CRIZOTINIB VERSUS PEMETREXED–CISPLATIN OR PEMETREXED–CARBOPLATIN IN PATIENTS (PTS) WITH ADVANCED ALK-POSITIVE NON-SQUAMOUS NON-SMALL CELL LUNG CANCER (NSCLC): RESULTS OF A PHASE III STUDY (PROFILE 1014)

Tony Mok et al.

**Background:** The efficacy of the oral ALK inhibitor crizotinib as 1st-line treatment for advanced ALK-positive NSCLC compared with standard chemotherapy is unknown. A multicenter, randomized open-label phase III study was conducted to compare the efficacy and safety of crizotinib vs. pemetrexed–platinum chemotherapy (PPC) in this setting.

**Conclusion:** First-line crizotinib treatment showed significant improvements in PFS and ORR compared with standard chemotherapy and had an acceptable safety profile. These findings establish crizotinib as the standard of care for pts with previously untreated advanced ALK-positive non-squamous NSCLC.

The ALK fusion as a driver mutation in NSCLC is well known. The immediate approval of crizotinib by both the FDA and Health Canada following the high response rate in patients with an ALK mutation was understood and accepted. NCCN guidelines quickly followed to recommend crizotinib in the first line setting. Canada was more conservative asking for survival efficacy.

Last year’s ESMO meeting 2013, the second line trial showed crizotinib to have survival advantage over chemotherapy in this setting. The pan Canadian Drug Review Panel recommendation followed restricting crizotinib to the second line setting.

At this year’s ASCO the first line trial was presented. Patients with an ALK mutation randomized to crizotinib had a progression free survival of 10.9 months vs pemetrexed/cisplatin doublet of 7.0 months (p< 0.0001). This was not a surprise. This was an ASCO poster highlight as US practice was adopted long ago.

We look forward to this abstract changing the Canadian practice.

— CARE Faculty Perspective
**CERITINIB IN ADVANCED ANAPLASTIC LYMPHOMA KINASE (ALK)-REARRANGED (ALK+) NON-SMALL CELL LUNG CANCER (NSCLC): RESULTS OF THE ASCEND-1 TRIAL.**

Dong-Wan Kim et al.

**Background:** ALK + NSCLC is sensitive to crizotinib (CRZ) but patients (pts) invariably progress. Ceritinib (LDK378) is a novel ALK inhibitor (ALKi) more potent than CRZ in enzymatic and cell-based assays and CRZ-resistant animal models. Prior results from this Phase I study (ASCEND-1) established a MTD of 750 mg/d.

**Conclusion:** Ceritinib 750 mg/d has rapid, durable and high antitumour activity in ALK+ NSCLC pts, regardless of prior treatment with ALKi, providing effective treatment in this pt population.

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>ALKi PT N=121</th>
<th>ALK naive N=59</th>
<th>All N=180</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, n (%) [95% CI]</td>
<td>67 (55.4%)</td>
<td>41 (69.5%)</td>
<td>108 (60.0%)</td>
</tr>
<tr>
<td>DOR [Median [95% CI]]</td>
<td>7.4 mos</td>
<td>NE*</td>
<td>9.7 mos</td>
</tr>
<tr>
<td>Time to first response [Median [min, max]]</td>
<td>6.1 wks (4.6, 24.1)</td>
<td>6.1 wks (3.0, 24.1)</td>
<td>6.1 wks (3.0, 24.1)</td>
</tr>
<tr>
<td>PFS [Median [95% CI]]</td>
<td>4.9 mos</td>
<td>NE*</td>
<td>7.0 mos</td>
</tr>
</tbody>
</table>

Abbreviation: NE, not estimable. * DOR rate at 12 mos: 71.1% (95% CI: 49.8, 84.6). ** PFS rate at 12 mos: 58.1% (95% CI: 41.6, 71.6).

There are more toxicity challenges associated with ceritinib than with crizotinib. Using ceritinib increases the risk of getting diarrhea, nausea, vomiting, and ALT/AST. Oncologists must dose-reduce early to manage these toxicities. Dr Mark Vincent suggests using this ceritinib for third line treatment.

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**Angiogenesis Inhibitors**

**ASCO 2014. Abstract 13862.**

ANTIANGIOGENIC-SPECIFIC ADVERSE EVENTS (AEs) IN PATIENTS WITH NON-SMALL CELL LUNG CANCER (NSCLC) TREATED WITH NINTEDANIB (N) AND DOCETAXEL (D): SUBSET ANALYSIS OF LUME-LUNG 1

Reck M et al.

**Background:** Antiangiogenic treatments, including monoclonal antibodies and TKIs, have shown activity in tumours; however, their use is limited in part by their characteristic side effects (eg, bleeding, thrombosis, perforation, serious skin reactions, hypertension). N is an oral, twice-daily, triple angiokinase inhibitor. Here we extend our investigation of the LUME-Lung 1 study (ClinicalTrials.gov NCT00805194) and evaluate whether adding N to standard second-line D increases the frequency of characteristic adverse events (AEs) associated with antiangiogenic agents and whether these AEs restrict the use of N.

**Conclusion:** We demonstrated that adding N to standard second-line D for NSCLC therapy did not increase the frequency of AEs associated with antiangiogenic treatment to a relevant extent, except for grade 1-2 bleeding events in SCC patients. These AEs were balanced regardless of histology in LUME-Lung 1.

**Immunotherapy: PD-1 in NSCLC**

**ASCO 2014. Abstract 8112.**

NIvolumab (ANTI-PD-1, BMS-936558, ONO-4538) IN PATIENTS (PTS) WITH ADVANCED NON-SMALL-CELL LUNG CANCER (NSCLC): SURVIVAL AND CLINICAL ACTIVITY BY SUBGROUP ANALYSIS.

Julie R. Brahmer et al.

**Background:** Nivolumab, a fully human IgG4, PD-1 immune-checkpoint inhibitor antibody, has shown durable clinical activity in a large phase I trial of pts with advanced solid tumours. For NSCLC pts in this trial, we report overall survival (OS) by dose and histology and clinical activity of pt subgroups including PD-L1 tumour status.

**Conclusion:** Nivolumab continues to demonstrate an encouraging survival profile and clinical activity across NSCLC pt subgroups with a manageable safety profile. Ongoing phase III trials are evaluating 3 mg/kg nivolumab in NSCLC pts and PD-L1 as a potential predictor of clinical outcomes.

PD-1 is a receptor (immune checkpoint pathway) expressed on activated T-cell ligands. The PD-1 pathway normally plays a protective role, however can be exploited by cancer cells to protect...
Other Novel Therapies

**ASCO 2014. Abstract LBA8006.**
REVEL: A RANDOMIZED, DOUBLE-BLIND, PHASE III STUDY OF DOCETAXEL (DOC) AND RAMUCIRUMAB (RAM; IMC-1121B) VERSUS DOC AND PLACEBO (PL) IN THE SECOND-LINE TREATMENT OF STAGE IV NON-SMALL CELL LUNG CANCER (NSCLC) FOLLOWING DISEASE PROGRESSION AFTER ONE PRIOR PLATINUM-BASED THERAPY. 
Maurice Perol et al.

**Background:** RAM is a human IgG1 monoclonal antibody that targets the extracellular domain of VEGFR-2. The REVEL study evaluated the efficacy and safety of RAM+DOC vs. PL+DOC (DOC) in patients (pts) with stage IV nonsquamous (NSq) and squamous (Sq) NSCLC after platinum-based therapy.

**Conclusion:** REVEL demonstrated a statistically significant improvement in ORR, PFS, and OS for RAM+DOC vs DOC in NSCLC pts with stage IV NSCLC as second-line treatment after platinum-based therapy. Benefits were similar in NSq and Sq pts, and no unexpected AEs were identified.

Despite the recent advancements in the understanding of lung cancer biology and resultant treatment in certain subsets, the majority of lung cancer patients have not benefited from the addition of targeted therapy to the backbone of standard chemotherapy.

While there was some initial enthusiasm for the addition of anti-VEGF monoclonal antibody treatment with bevacizumab to carboplatin-doublet chemotherapy in the 1st line setting, subsequent studies with cisplatin and an increased understanding of the importance of histology in treatment decisions have made the option debatable and as such, it is not considered standard of care in Canada.

In the phase III REVEL study, ramucirumab, a human IgG1 monoclonal antibody directed against the extracellular domain of VEGFR-2, when added to docetaxel, led to statistically improved ORR (13.6% → 22.9%), PFS (HR 0.762, 3.0 m → 4.5 m) and OS (HR 0.857, 9.1 m → 10.5 m). Although the study was well balanced, two-thirds of tumour EGFR mutation status was unknown. Similar benefits were seen in all subgroups (including squamous cell), and there was similar use of post-discontinuation treatment in both arms. More thrombocytopenia, neutropenia and febrile neutropenia, minor epistaxis and hypertension was seen in the ramucirumab containing arm, but no SAEs or AEs leading to increased death were noted.

While the REVEL investigators should be applauded for identifying a novel antiangiogenic molecule that statistically improves outcomes in the second-line NSCLC setting, the clinical significance of these findings are unlikely to be practice changing in the Canadian health system.

Although there appears to be a signal for benefit for ramucirumab, a signal alone is not enough, and further efforts to try and identify predictive biomarkers are needed.

In the past, this type of positive finding may have generated more excitement but the bar has been set much higher in terms of therapeutic expectations in the age of molecularly targeted therapy. We should be striving to do even better, and our patients deserve it.

— CARE Faculty Perspective

Many of these novel agents look promising, however traditional chemotherapy still need to be considered. We need to optimize chemotherapy while incorporating novel agents where applicable.

— Perspective from CCOCO 2014
The CARE faculty was pleased to have an international speaker, Dr. Jeffrey Weber (Moffit Cancer Centre) present at the resident CORE at ASCO 2014 meeting. What follows is a summary of his presentation on immuno-oncology.

Immuno-Oncology (I-O) is a new area of therapy being studied for its potential to fight against cancer. It has been successful in melanoma and renal cell carcinoma, however more research needs to be done in lung cancer and other tumour sites.

There is an ongoing need for therapeutic modality for advanced cancers. Most treatments such as radiation, surgery, chemotherapy and novel targeted therapies, target the cancer tumour. However, I-O targets the immune system and not the cancer, which can be beneficial because it has the potential to target various disease/tumour sites.

The foundation of I-O is understanding how the cancer cells invade the immune system. Knowing the fundamentals of cellular and molecular tumour immunology has identified ways in which the immune system can be amplified to treat cancer, such as boosting the immune system, T-cell modulation, reducing immunosuppression in the tumour microenvironment, and enhancing adaptive immunity.

The immune checkpoint is a competing mechanism with T-cell activation where it protects tissues from damage if the immune system response to pathogenic infection is out of control. Under normal physiological conditions, immune checkpoints are crucial for the maintenance of self-tolerance. There is an association between cancer cell growth and imbalance of the natural feedback mechanisms that modulate the immune response.

The recognition that immune checkpoint blockade including antibodies against cytotoxic T lymphocyte antigen-4 (CTLA-4) and programmed death-1 (PD-1) or its ligand programmed death ligand-1 have excellent clinical activity against metastatic melanoma. This has spawned a large variety of trials using that class of antibodies in other histologies like renal cell cancer, non-small cell lung cancer and ovarian cancer.

The figure below shows the CTLA-4 and PD1 Blockades.

**CTLA-4**
- The **CTLA-4 blocking antibody ipilimumab** has been approved by the FDA and European authorities for patients with metastatic melanoma, and has a 10-20% response rate, but more importantly 20% of patients will be alive at 3 years, and that rate of survival plateaus, with patients likely being cured of their disease that previously would have died.
- Unusual kinetics of response, including prolonged partial responses of slow onset over months, or progression followed by regression have been observed with ipilimumab and with PD-1 antibodies. In contrast, ipilimumab has been shown to be associated with immune related adverse events (irAE) that are auto-inflammatory in nature and mechanism based.

**PD-1**
- When PD-1 and PD-L1 interact with tumours, they prevent immune cells from attacking cancer cells. This allows them to escape immune surveillance, and multiply. Therefore, therapeutics that block immunocheckpoint molecules can allow the immune system to react effectively to tumours.
- The **PD-1 antibodies nivolumab and pembrolizumab** and the PD-L1 antibody MPDL 3280A have been shown to induce responses in melanoma, renal cell cancer and non-small cell lung cancer. Nivolumab and pembrolizumab have response rates of 30-40% in unresectable melanoma, with a low rate of irAEs, and prolonged duration of response.
- Combining ipilimumab and nivolumab resulted in high response rates of approximately 50% with rapid onset of regression, albeit with a significant rate of irAEs.
- Current trials include combinations of PD-1/PD-L1 blocking antibodies with other biologics and with adoptive cell therapy as well as targeted therapies to achieve higher response rates and prolonged survival.

While it is still a relatively new area in most solid tumour groups, there is enough data available from clinical trials to show that it has proven efficacy. There are new agents entering the clinic as well as previously available agents that are being investigated in new areas that look especially promising. I-O may have the potential to transform the future of cancer treatment, which would ultimately improve patient outcomes/prognosis. There is an ongoing need for more research into this area, in order to offer new therapeutic modalities for patients with advanced cancers.

The CARE Oncology Faculty believes there is value in raising awareness to this novel treatment modality. They are currently developing a need assessment questionnaire that will look to address gaps in knowledge and the level of understanding of I-O concepts. For more details on this needs assessment as well as other initiatives that the CARE Oncology Faculty are doing, please see the CARE Update section.
In early fall of 2013, a needs assessment focused on maintenance therapy and patient communication was created by CARE Lung Cancer Faculty members Drs. Barb Melosky (British Columbia Cancer Agency) and Normand Blais (Centre hospitalier de l’Université de Montréal). A questionnaire was distributed to Canadian medical oncologists that are directly involved with lung cancer patient diagnosis and treatment (n=100). The aim of the needs assessment was to identify gaps in knowledge regarding patient communication protocol along the patient pathway, with a focus on addressing patient knowledge/access to maintenance therapy. We were pleased to get a good response rate to the questionnaire at 32%.

Earlier this year, the results of the first half of this needs assessment were included in the CARE Conference Report from CLCCO 2014. The questions included in this report focused on the discussion physicians have with their patients regarding treatment options, and who is involved in these discussions.

Key Takeaways included:
- **Discussing all options at first consultation** was identified as being ideal, but may be too overwhelming for the patient to take in so much information at once.
- Physicians often involve various supportive care workers in both treatment discussions as well as with the management of disease.
- **Multidisciplinary care** offers benefits to both patients and to the team, including promotion of evidence-based care and opportunities for both continuing education and quality assurance.
How involved is the patient in making treatment decisions?

- Not involved: 8%
- Moderately involved: 4%
- Highly involved: 56%

Do you make it explicit that patients should be involved in treatment choices?

- Yes: 100%
- No: 0%

It is positive to see that a large majority of responders (89%) involve the patient in making treatment decisions, and that all make it explicit that the patient should be involved. Involving the patient is especially important given the non-curative context of metastatic NSCLC. The benefits of maintenance therapy need to be weighed against factors such as cumulative toxicity, cost, and patients’ compliance. An important part of patient-centric care is involving the patient in decision making. Most patients want to be fully informed of their disease, and want to be actively involved in making treatment decisions.1

Do you explain why recurrence or metastases in lung cancer happens?

- Yes: 100%
- No: 0%

All responders explain why recurrence or metastases happens in lung cancer. It is important that this is done as the patient and their families are often finding out that they are palliative. It is important not to give false hope. Poor communication with patients can lead to adverse psychological outcomes for patients. It can lead to the patient being dissatisfied with care, increase anxiety, and cause long-term maladjustment.1

Do you explain the benefits/disadvantages of waiting for second line versus the benefits/disadvantages of maintenance?

- Yes: 95%
- No: 5%

Do you explain the different maintenance options with benefits and inconveniences of each?

- Yes: 62%
- No: 38%

It is surprising that not all responders (5% responded “No”) explain the benefits/disadvantages of waiting for second line vs. going on maintenance therapy. Even more surprising was that only 62% of responders discuss the different maintenance options with their patients. As seen with the response to earlier questions, there is agreement that it is important to have the patient involved in therapy decision and choices. This is not possible if the patient does not have all of the information on the available therapies. It is important for the patient to understand this information in order to be involved in and be comfortable with the treatment decisions and therapy choices.

What physician-patient communication strategies do you think are most valuable for successful patient communication? (Please rank the following from 1-most valuable to 8-least valuable)

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Weighted Average of Ranking*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Audio taping the consultation</td>
<td>28%</td>
</tr>
<tr>
<td>Information Booklets</td>
<td>51%</td>
</tr>
<tr>
<td>Internet Resources</td>
<td>39%</td>
</tr>
<tr>
<td>Interactive CDs</td>
<td>27%</td>
</tr>
<tr>
<td>Question Prompt Sheets</td>
<td>36%</td>
</tr>
<tr>
<td>Decision Aids</td>
<td>39%</td>
</tr>
<tr>
<td>Treatment Algorithms</td>
<td>46%</td>
</tr>
<tr>
<td>Direct one-on-one interview exchange</td>
<td>73%</td>
</tr>
<tr>
<td>Other</td>
<td>15%</td>
</tr>
</tbody>
</table>

* Most weight given to responder ranking of 1, least given to ranking of 8

Responders believe that the most valuable resource is direct one-on-one interview exchange with a weighted average of 73%. This is not surprising as the faculty emphasized that communication with different patients is so individualized. Although this may be the most valuable resource, it is clear from the information gathered in this needs assessment that it may not be viable to discuss all therapy choices, including maintenance therapy options.

The poor rating of CD/internet services for patient education should serve as a reminder to companies providing these resources that direct patient oriented approaches are more effective, rather than developing interactive material that are seldom consulted.

References:

**Prostate Cancer**

The management of advanced prostate cancer is dramatically changing. A number of new therapies are in development.

**ASCO 2014. LBA 2.**

**IMPACT ON OVERALL SURVIVAL (OS) WITH CHEMOMHOROMINAL THERAPY VERSUS HORMONAL THERAPY FOR HORMONE-SENSITIVE NEWLY METASTATIC PROSTATE CANCER (mPrCa): AN ECOG-LED PHASE III RANDOMIZED TRIAL.**

Christopher Sweeney et al.

**Background:** Docetaxel (D) improves OS of men with mPrCa who have progressed on androgen deprivation therapy (ADT). We aimed to assess the benefit of upfront chemohormonal therapy for metastatic PrCa.

**Conclusion:** ADT + D improves OS over ADT alone in men with HV mPrCa. Longer follow-up is needed for men with LV mPrCa.

<table>
<thead>
<tr>
<th>Intent to treat analysis</th>
<th>ADT</th>
<th>ADT + D</th>
<th>P value</th>
<th>Hazard ratio (95%CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA &lt; 0.2 at 12 mos</td>
<td>9.4%</td>
<td>19.7%</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Median OS (mos)</th>
<th>ADT</th>
<th>ADT + D</th>
<th>P value</th>
<th>Hazard ratio (95%CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=790</td>
<td>42.3</td>
<td>52.7</td>
<td>0.0006</td>
<td>0.63 (0.48, 0.82)</td>
</tr>
<tr>
<td>N=520-HV</td>
<td>32.2</td>
<td>49.2</td>
<td>0.0012</td>
<td>0.62 (0.46, 0.83)</td>
</tr>
<tr>
<td>N=270-LV</td>
<td>NR**</td>
<td>NR</td>
<td>0.0836</td>
<td>0.58 (0.31, 1.08)</td>
</tr>
</tbody>
</table>

* CI: confidence intervals; **NR: not reached.

The results of this randomized phase 3 study will drastically change our management of men who present with metastatic disease. Because of the very statistically significant and highly clinically relevant 17-month improvement in overall survival observed when six cycles of docetaxel was added to ADT, the standard of care has changed overnight and these men should be considered for chemotherapy. Although it appeared that men with a higher burden of disease at presentation were the ones who benefited most from docetaxel, the large majority of patients who presented with a lower burden are still alive in both arms and it may very well be too early to see a separation of the curves and to conclude that only the high burden group should be offered chemotherapy. Because of the CHAARTED results, virtually all patients with prostate cancer who present with metastatic disease (unless very frail or sick) should now be referred to a medical oncologist for consideration of docetaxel chemotherapy, in addition to ADT. This highlights the need for strong multi-disciplinary collaboration for the optimal treatment of patients diagnosed with this highly complex and heterogeneous disease.

— CARE Faculty Perspective

**ASCO 2014. Abstact 5007.**

**PRIMARY, SECONDARY, AND QUALITY-OF-LIFE ENDPOINT RESULTS FROM PREVAIL, A PHASE 3 STUDY OF ENZALUTAMIDE IN MEN WITH METASTATIC CASTRATION RESISTANT PROSTATE CANCER (mCRPC).**

Andrew J. Armstrong et al.

**Background:** Enzalutamide (ENZ), an androgen receptor inhibitor, improved overall survival (OS) in men with mCRPC who had received prior docetaxel therapy (Scher, N Engl J Med 2012;367:13). The PREVAIL study examined whether ENZ could prolong OS and radiographic progression-free survival (rPFS) in men with mCRPC who had progressed on androgen deprivation therapy (ADT).

**Conclusion:** In men with mCRPC who progress on ADT, treatment with enzalutamide has a favorable safety profile and significantly improves OS, rPFS, and secondary measures of disease response and progression.

This presentation updated the results of PREVAIL first presented at GU ASCO this past winter and confirms the considerable clinical efficacy of enzalutamide in patients who have not yet received docetaxel. The authors confirmed the 29% improvement in survival experienced by patients receiving enzalutamide compared to the men who received placebo. A highly statistically significant and clinical relevant 81% improvement in time to radiographic progression was also confirmed. These data support the use enzalutamide, along with abiraterone acetate...
plus prednisone, as one of the two main standard of care treatment options in docetaxel-naïve patients. Although at first hand the impressive HR of enzalutamide might suggest that it is more effective than abiraterone/prednisone, it is important to take note that the comparator was placebo for PREVAIL and was placebo plus prednisone for study COUGAR-302. As a matter of fact, the comparator rPFS estimate in the PREVAIL study was only 3.9 months, compared to 8.3 months in the COUGAR-302 study. Without wanting to make any definitive conclusions from cross-trial comparisons, it appears that both abiraterone/prednisone and enzalutamide may offer similar effects given the median OS estimates of 35 months for abiraterone/prednisone and 32.4 months for enzalutamide, compared to 30 months for the comparator arms of both studies. For patients who are suffering from a high burden of measurable disease, enzalutamide might be the agent of choice, given its high objective response rate of 59% of which 20% were complete radiologic responses, a degree of disease regression not previously observed in prior phase 3 studies of CRPC patients.

— CARE Faculty Perspective

Renal Cell Carcinoma

**ASCO 2014. Abstract 4505.**

**EVEROLIMUS VERSUS SUNITINIB PROSPECTIVE EVALUATION IN METASTATIC NON-CLEAR CELL RENAL CELL CARCINOMA (THE ESPN TRIAL): A MULTICENTER RANDOMIZED PHASE 2 TRIAL.**

Nizar M. Tannir et al.

**Background:** In a single-arm phase II trial of sunitinib in non-clear cell RCC (nccRCC) we previously reported (Tannir et al. Eur Urol 2012), objective response rate [ORR] was 5% and median progression-free survival [PFS] was 2.7 months. Temsirolimus was previously shown to produce overall survival (OS) benefit in poor-risk RCC including nccRCC (Hudes et al. NEJM 2007).

**Conclusion:** Based on futility analysis for PFS and inferior OS with E compared to S in 1L, the DSMB recommended termination of further pt accrual on this trial. E cannot be recommended as 1L option in ccRCC.

Pure clear cell or a clear cell component in RCC represent the great majority of cases of renal cancer (>80%). Therefore, very few trials have specifically addressed this population of patients with papillary, chromophobe sarcomatoid and other rare non clear cell histology subtypes excluding urothelial origin.

In this trial, two targeted therapies known to be active in metastatic ccRCC for response and PFS were tested with the assumption that everolimus would fare better. This was hypothesized based on data obtained for sunitinib, from a phase II trial in a non-clear cell mRCC patient population showing limited efficacy and from a trial with an mTOR inhibitor other than everolimus showing efficacy that compared favorably. The presented study allowed cross-over to the other therapy ad progression. This was a small trial with fewer than 100 patients, but a high event rate of progression and deaths.

Very few responses were seen in both treatment groups and mainly for chromophobe or translocation histology patients. No difference was seen in mPFS for first line or second line.

However, the HR for survival was statistically significant in advantage of sunitinib at the second interim analysis, but only shows a trend at the latest analysis. The OS advantage was more striking for patients with histologies other than sarcomatoid.

This trial therefore shows a negative endpoint as it did not demonstrate its primary objective of superiority of the mTOR inhibitor and that current targeted agents used for ccRCC have limited activity in patients suffering from metastatic non clear cell RCC, both for response, PFS and OS. However, it is reasonable to consider their use, with a possible preference for sunitinib. Moreover, it calls for more research with new agents for these patients.

— CARE Faculty Perspective
**ASCO 2014. Abstract 4520.**

A PROSPECTIVE OBSERVATIONAL STUDY OF METASTATIC RENAL CELL CARCINOMA (mRCC) PRIOR TO INITIATION OF SYSTEMIC THERAPY.

Brian I. Rini et al.

**Background:** The biology of mRCC includes a subpopulation of patients (pts) with indolent growth. Because of the toxicity and non-curative nature of current systemic therapy, select pts may be better served with initial surveillance. A prospective phase II observation trial was conducted in pts with mRCC prior to initial systemic treatment.

**Conclusion:** A subset of mRCC pts can be safely observed for a period of time before starting systemic therapy.

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**ASCO 2014. Abstract 4521.**

OUTCOMES OF TREATMENT CESSION IN SELECT METASTATIC RENAL CELL CARCINOMA (mRCC) PATIENTS.

Kriti Mittal et al.

**Background:** Tyrosine kinase inhibitors (TKIs) demonstrate efficacy in mRCC, but may cause significant adverse effects (AEs). We have previously evaluated outcomes in patients (pts) receiving prolonged treatment breaks on TKIs and expand and update this experience herein.

**Conclusion:** A treatment break is feasible in selected pts, especially after achievement of CR with TKIs. This strategy may be associated with acceptable overall disease control and reduced toxicity.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number of pts starting treatment</th>
<th>Median duration of therapy in months (95% CI)</th>
<th>Number of pts on treatment break</th>
<th>Median duration of break in months (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>112</td>
<td>13.5 (11.1-16.4)</td>
<td>112</td>
<td>16.8 (12.5-26.4)</td>
</tr>
<tr>
<td>B</td>
<td>68</td>
<td>16.1 (14.4-20.1)</td>
<td>26</td>
<td>9.5 (4.6-10.1)</td>
</tr>
<tr>
<td>C</td>
<td>43</td>
<td>14.8 (12.1-17.2)</td>
<td>10</td>
<td>7.1</td>
</tr>
<tr>
<td>D</td>
<td>15</td>
<td>13.8 (5.7-19.4)</td>
<td>3</td>
<td>15.9</td>
</tr>
</tbody>
</table>

The results from the above abstracts (4520, 4521) are not practice changing, as “watch and wait” and treatment holidays were already in use, but they give some guidance as to whom it should be offered.

Considering withholding therapy for patient with metastatic disease, the results do seem to indicate that patients can enjoy a long period without therapy inducing side effects. However, the results presented by Rini et al provide insight into the fact that patients selected by the tumour bulk at diagnosis of metastatic disease is indicative. In fact, the “watch and wait” attitude was particularly relevant for patients with a tumour bulk of less than 3.0cms. These data could therefore guide physicians at identifying patients for whom “watch and wait” is an adequate clinical option and to partly predict the period of time that patients can expect to enjoy without initiating therapy.

The data on drug holidays was obtained from retrospective data and is therefore exploratory in nature. There is therefore a bias in patient selection. Patients had previously stopped therapy because of adverse events or reasons other than tumour progression. These patients basically represent a population of good responders for whom continuation of therapy was not deemed necessary when the treatment was terminated. The period without therapy was rather long, especially after cessation of first line therapy. Data on patients offered a drug holiday in second and further lines of therapy was rather minimal and is representative of the fact that this clinical option of drug holiday is a rather rare occurrence after first line therapy, as second and third line agents are linked with rather low response rates of 5 to 10%. This study is therefore informing us on the fact that for patients with a good response to first line therapy could be offered a drug holiday, especially if the patient is experiencing significant adverse events, and that reinitiation of therapy at disease progression or when treatment becomes necessary is associated with adequate response rates.

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— CARE Faculty Perspective
Colorectal Cancer (CRC)

Over the past decade, evolution of systemic therapy for mCRC has achieved marked improvements in survival. In randomized controlled trials, median OS approaching two 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).

ASCO 2014. LBA 3.

CALGB/SWOG 80405: PHASE III TRIAL OF IRINOTECAN/5FU/LEUCOVORIN (FOLFIRI) OR OXALIPLATIN/5FU/LEUCOVORIN (mFOLFOX6) WITH BEVACIZUMAB (BV) OR CETUXIMAB (CET) FOR PATIENTS WITH KRAS WILD-TYPE UNTREATED MCRC.

Alan P. Venook et al.

Background: Irinotecan/5-FU/leucovorin (FOLFIRI) or oxaliplatin/5-FU/leucovorin (mFOLFOX6), combined with bevacizumab (BV) or cetuximab (CET), are first-line treatments for metastatic adenocarcinoma of the colon or rectum (MCRC). The optimal antibody combination is unknown.

Conclusion: Chemo/CET and chemo/Bv equivalent in OS in pts KRAS wt (codons 12 + 13) MCRC; either is appropriate in first line. Overall OS of 29 + mos and 8% long-term survivors confirms progress in MCRC. The preference for FOLFOX limits chemotherapy comparison. Expanded RAS and other molecular and clinical analyses may identify subsets of pts who get more or less benefit from specific regimens.

This study suggests bevacizumab or cetuximab in combination with FOLFOX or FOLFIRI are acceptable regimens. The primary endpoints and PFS were similar between bevacizumab and cetuximab. In order to differentiate between which regimen is better, toxicity/side effect profiles will have to be looked at. Further analyses of select patient subsets needs to be examined.

— CARE Faculty Perspective


RAINBOW: A GLOBAL, PHASE III, RANDOMIZED, DOUBLE-BLIND STUDY OF RAMUCIRUMAB (RAM) PLUS PACLITAXEL (PTX) VERSUS PLACEBO (PL) PLUS PTX IN THE TREATMENT OF METASTATIC GASTROESOPHAGEAL JUNCTION AND GASTRIC ADENOCARCINOMA (mGC) FOLLOWING DISEASE PROGRESSION ON FIRST-LINE PLATINUM-AND FLUOROPYRIMIDINE-CONTAINING COMBINATION THERAPY—EFFICACY ANALYSIS IN JAPANESE AND WESTERN PATIENTS.

Shuichi Hironaka et al.

Background: RAINBOW, a global phase III trial, demonstrated significant improvements in overall survival (OS), progression-free survival (PFS), and objective response rate (ORR) in patients (pts) with mGC receiving RAM, a human IgG1 VEGF-receptor-2 targeted antibody, plus PTx compared with PL plus PTx. In global trials for mGC, regional differences in survival outcomes have been reported. Here, we analyzed clinical outcomes of Japanese (JP) pts and Western (Europe, US, Australia) pts.

Conclusion: Benefit was seen in PFS, ORR, and the 6-mos OS rate in the JP population, which was consistent with the Western population. Prolonged post-progression survival in JP pts may be due to higher use of post-discontinuation treatment (PDT) and may have masked the potential OS benefit.


PREOPERATIVE CHEMORADIOThERAPY AND POSTOPERATIVE CHEMOTHERAPy WITH 5-FLUOROURACIL AND OXALIPLATIN VERSUS 5-FLUOROURACIL ALONE IN LOCALLY ADVANCED RECTAL CANCER: RESULTS OF THE GERMAN CAO/ARO/AIO-04 RANDOMIZED, PHASE III TRIAL.

Claus Rödel et al.

Background: The CAO/ARO/AIO-94 trial established preoperative chemoradiotherapy (CRT), total mesorectal excision (TME) surgery, and adjuvant chemotherapy with 5-FU as standard treatment for locally advanced rectal cancer. The goal of the CAO/ARO/AIO-04 trial was the integrating of more effective systemic treatment. First results of early secondary endpoints have been published (Rödel et al., Lancet Oncol 2012). Here we present the primary endpoint, disease-free survival (DFS) at 3 years.

Conclusion: Adding oxaliplatin to 5-FU-based neoadjuvant CRT and adjuvant chemotherapy in locally advanced rectal cancer significantly improved DFS.

COMBINED EPIREGULIN (EREG) AND AMPHIREGULIN (AREG) EXPRESSION LEVELS AS A BIOMARKER OF PROGNOSIS AND PANITUMUMAB BENEFIT IN RAS-WT ADVANCED COLORECTAL CANCER (aCRC).

Jenny F. Seligmann et al

Background: RNA expression of epiregulin (EREG) ligands EREG and/or amphiregulin (AREG) has shown correlation with the efficacy of EGFR-targeted therapy in advanced colorectal cancer (aCRC). This finding requires validation, and interaction with MEK-AKT pathway mutations clarified. We examined both ligands and mutations in patients (pts) in a large randomised trial of panitumumab. The a priori hypothesis was that high expression of either AREG or EREG, in RAS-wild type (wt) pts, would predict panitumumab benefit.

Conclusion: The hypothesis was confirmed: high ligand expression predicts panitumumab benefit on PFS in RAS-wt pts; there was no evidence of benefit with low ligand expression. Optimisation of the ligand model for clinical use is needed, however this work confirms that EREG and AREG are potentially useful biomarkers for anti-EGFR therapy.

Predictive biomarkers for anti-EGFR therapies are evolving. Until recently, KRAS exon 2 status was the only validated predictive biomarker in metastatic colorectal cancer with KRAS exon 2 mutated tumours demonstrating resistance to anti-EGFR inhibitors. Recent expanded mutational analysis showed that about 20% of KRAS exon 2 wild type patients also harboured other RAS mutations (such as in KRAS exons 3 and 4, NRAS exons 2, 3, and 4, and BRAF exon 15), all of which were associated with worse progression-free and overall survival, suggesting that only patients with all RAS wild type status will have the highest potential to benefit from anti-EGFR treatments. The current abstract demonstrates that additional biomarkers may further enrich patient selection, with high ligand expression of amphiregulin and epiregulin predicting panitumumab benefit. The panel of predictive biomarkers available for anti-EGFR therapies continues to grow and how to best fit and use all of this information in the treatment paradigm of metastatic colorectal cancer in Canada is the main focus of current and ongoing research.

— CARE Faculty Perspective


MAINTENANCE STRATEGY WITH FLUOROPYRIMIDINES, (FP) PLUS BEVACIZUMAB (BEV), BEV ALONE, OR NO TREATMENT, FOLLOWING A STANDARD COMBINATION OF FP, OXALIPLATIN (OX), AND BEV AS FIRST-LINE TREATMENT FOR PATIENTS WITH mCRC: A PHASE III NON-INFERIORITY TRIAL (AIO KRK 0207)

Dirk Arnold et al

Background: The optimal maintenance strategy following combination chemotherapy plus Bev is still controversial. AIO KRK 0207 investigates whether after a 24-week standard induction with F/Ox/Bev, no continuation of therapy or continuation with Bev alone are non-inferior to FP plus Bev.

Conclusion: Following 24 weeks of induction, active maintenance with both, FP plus Bev or Bev alone, show prolonged TFS over no treatment. Only a minority of patients received re-induction treatment as planned. With currently limited follow up, the different maintenance strategies had no impact on OS.

Noncolorectal Cancer


IMPACT OF CHEMORADIOThERAPY (CRT) ON LOCAL CONTROL AND TIME WITHOUT TREATMENT IN PATIENTS WITH LOCALLY ADVANCED PANCREATIC CANCER (LAPC) INCLUDED IN THE INTERNATIONAL PHASE III LAP 07 STUDY.

Florence Huguet et al

Background: In the LAP07 multicenter randomized study, administration of CRT in patients with LAPC controlled with induction chemotherapy (IT) was not superior to continuing CT alone in terms of overall survival. However, whether CRT should have an impact on locoregional tumour control remains unknown.

Conclusion: Even though the OS was not improved in the CRT arm, patients with non-progressive LAPC after 4 months of induction IT had a longer time without treatment in the CRT arm with significantly less local tumour progression which could translate into a better quality of life.


PHASE III STUDY OF APATINIB IN ADVANCED GASTRIC CANCER: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL

Shukui Qin et al

Background: Molecular targeted therapy has made great progress in the treatment of gastric cancer. This paper reports the outcome of a phase III clinical study of apatinib, as an oral small molecular of VEGFR-2 tyrosine kinase inhibitor, in the treatment of patients with advanced gastric cancer who prior failure to second-line chemotherapy. This study may provide a new treatment options and leading a new hope for these patients.

Conclusion: This study further confirmed the efficacy and safety of apatinib in the patients with advanced gastric cancer. 850 mg, qd is the recommended dose for clinical use.
References:
5. Ellis et al. Poster presented at 14th World Conference Lung Cancer, 2011. Amsterdam, The Netherlands; July 3-7
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