SMARTANALYST®

SMARTONCOLOGY

THE ONCOLOGY E-NEWSLETTER FROM SMARTANALYST

www.smartoncology.com

Volume 6, Issue 4 | Oncology E-newsletter – ESMO Special Edition | 2013

INTELLIGENT INSIGHTS. SMART RESULTS

Spotlight 1:

Moving Towards Personalized Medicine in Cancer

At the ESMO-ECCO 2013, participants showed excitement based on the continuing trend towards genomic unraveling of tumors and its potential application to more individualized treatment. The idea is that more tailored the therapy is to the genetic complement of the tumor, the greater the chance for better outcomes. Use of circulating tumor DNA has made the process easier.

Circulating Tumor DNA Sequencing: From Targeted Mutations to Whole Genome Resolution

The field has moved on from the pre-genome-era identification of single gene variants associated with hereditary cancers. Advances in sequencing technology have enabled the use of a whole-genome approach to examine the differences between genomes. In addition, the analysis of RNA expression patterns of tumor and patient DNA using next generation sequencing continues and epigenetic regulation of tumor and patient DNA complements the whole genome analysis. Tumors classified by organ of origin may be composed of multiple molecular subsets.

Read more...

SPOTLIGHT 2:

Prostate Cancer: Where are We Today and What is the Path Forward?

Today:

Prostate cancer is the most common tumor in men, with ~240,000 men expected to be diagnosed with the disease in the U.S. in 2013.[1] With screening for prostate cancer well established in the developed countries, the majority of the cases are detected in early stages (>80%) and have a good prognosis with 100% relative 5-year survival.[1] However, a small proportion of the patients progress to metastatic castration resistant stage, which is defined as progressive prostate cancer despite a castrate level of serum testosterone (<50 ng/dL). Until 2010, Docetaxel was the only approved drug which improved the survival of metastatic castration-resistant prostate cancer (mCRPC). These patients had a progressive and morbid disease process, with a median survival of 18-20 months.[2]

Read more...

Non Small Cell Lung Cancer

FDA backs continued study of Belagenpumatucel-L for NSCLC based on data from Phase III STOP trial

Read More...

Ovarian Cancer

Cediranib significantly improves OS and PFS as maintenance therapy in recurrent platinum-sensitive ovarian cancer patients in Phase III ICON6 trial

Read More...

Renal Cell Carcinoma

Dovitinib fails to show a clinical benefit over sorafenib in 3rd line RCC patients

Read More...

Hepatocellular Carcinoma

Impact on treatment practices in hepatocellular carcinoma

Read More...

CLICK HERE to visit SMARTANALYST

The E-newsletter team: Dr. Andrew Bush, Dr. Loveleen Taneja, Dr. Shirish Kumar, Dr. Vinamrata Bhatia, Monica Tuli

Spotlight 1

Moving Towards Personalized Medicine in Cancer

At the ESMO-ECCO 2013, participants showed excitement based on the continuing trend towards genomic unraveling of tumors and its potential application to more individualized treatment. The idea is that more tailored the therapy is to the genetic complement of the tumor, the greater the chance for better outcomes. Use of circulating tumor DNA has made the process easier.

Circulating Tumor DNA Sequencing: From Targeted Mutations to Whole Genome Resolution

The field has moved on from the pre-genome-era identification of single gene variants associated with hereditary cancers. Advances in sequencing technology have enabled the use of a whole-genome approach to examine the differences between genomes. In addition, the analysis of RNA expression patterns of tumor and patient DNA using next generation sequencing continues and epigenetic regulation of tumor and patient DNA complements the whole genome analysis. Tumors classified by organ of origin may be composed of multiple molecular subsets. This molecular makeup of a tumor may evolve over time and space, and molecular profiling offers the opportunity to apply targeted therapy and personalized treatment.

An alternative approach to tissue biopsy is the analysis of blood samples for cell-free circulating tumor DNA (ctDNA), which can be performed repeatedly and which might allow real-time monitoring of cancer therapies. Elevated concentrations of cell-free ctDNA fragments have been found in blood plasma and serum of cancer patients. ctDNA fragments mainly originate from apoptotic or necrotic tumor cells which discharge their DNA into the circulation. With the development of next generation sequencing technologies, the field of ctDNA analysis is focused on genomic aberrations relevant to targeted therapy in patients with cancer.

Y. Lo, *et al.* *(ESMO-ECCO 2013: Abstract # 299)* explored the use of techniques capable of detecting targets at single DNA molecule resolution for analyzing plasma DNA in patients with lung cancer and hepatocellular carcinoma (HCC). Digital PCR was used to detect epidermal growth factor receptor (EGFR) mutations in lung cancer patients. Shotgun massively parallel sequencing (MPS) was used to analyze plasma DNA from the HCC patients' plasma. Digital PCR allowed the sensitive, specific, and quantitative detection of EGFR mutations in the plasma of lung cancer patients, and such detection demonstrated a good correlation with clinical course. MPS analysis of plasma DNA from HCC patients allowed genome-wide copy number aberrations and single nucleotide variations of the tumor genomes to be detected from the patients' plasma. MPS also allowed the fractional circulating tumoral DNA concentration for each patient to be measured. The researchers concluded that digital PCR and MPS are powerful methods for the analysis of tumor-derived DNA in the plasma of cancer patients.

Although the evaluation of plasma samples (ctDNA) is convenient, conditions for ctDNA analysis remain to be standardized. In addition, larger prospective trials are needed to demonstrate clinical utility. Future studies need to show whether ctDNA detected in blood is representative of all relevant cell clones located at different sites and whether the information obtained by molecular analyses of ctDNA might contribute to better choice of therapy and hence, improved clinical outcome.

Noninvasive monitoring of cancer dynamics using circulating tumor DNA

Cancer is a genetic disease caused and characterized by variable patterns of genomic alterations. It is difficult to treat since each cancer is different and, importantly, the disease evolves over time and response to treatment. Improved methods for detection of residual disease, quantification of tumor burden, and molecular characterization will help management of cancer care. Current diagnostic modalities are limited as protein markers and imaging estimate tumor burden, but can't assess genomic status, whereas biopsies give a snapshot of genomic changes, but are rarely used repeatedly. Improved

Back to top of Spotlight Section 1 | Back to Top of Document

Spotlight Report 1
(Cont'd)

techniques to study genomic tumor evolution holds enormous promise for molecular insight.

Patient plasma contains DNA fragments originating from the tumor that carry tumor-specific genomic alterations. These short cell-free fragments found in body fluids can be used as a "liquid biopsy". The mechanisms through which tumor DNA reaches blood circulation are unclear, although fragmentation patterns of DNA in the plasma suggest it may originate from cell death. Overall levels of circulating DNA are higher in cancer patients compared with healthy controls but are variable and generally low; 2 mL of plasma may contain as many as 10,000 copies of DNA from healthy cells but only a few dozen copies of the tumor genome.

Only recently have technologies matured that allow these entities to be effectively studied and exploited as diagnostic tools. Different analysis methods can work together, allowing noninvasive assessment of both levels and genetic characteristics of circulating tumor DNA (ctDNA). Because this analysis relies on readily accessible blood samples, those can be collected serially over clinical follow-up, providing a window into tumor dynamics. Analysis of mutation patterns in ctDNA can help select suitable therapies, and can help identify novel resistance mechanisms in patient cohorts or the emergence of resistance in individual patients. Accumulating evidence suggests that the level of ctDNA can be an informative prognostic factor in advanced epithelial cancers, and that changes in the levels of ctDNA correlate with disease progression and response to treatment. High levels of ctDNA suggest poor prognosis and changes in ctDNA levels may indicate response to therapy or disease progression, and indeed may prove to be the earliest indicator of changes to tumor burden. Studies in cohorts of patients with advanced metastatic cancers show that in many patients, serial analysis of ctDNA provides the earliest indication of disease progression or response, preceding changes in other parameters, such as tumor growth.

The molecular characterization of ctDNA may take a targeted or unbiased approach. In the former, the assay is tumor or patient specific, it examines the genetic status of one or a few crucial drivers of tumorigenesis, is less costly, and is feasible even with low disease burden. It is better suited for non-enriched samples like plasma. In the unbiased approach, the whole exome is sequenced and this is feasible only when the disease burden is high in the blood. The procedure is better suited for enriched samples like circulating tumor cells (CTCs). Compared to the former, the procedure has a higher cost.

Using these techniques may reduce dependence on obtaining a tumor biopsy, which involves invasive procedures *(ESMO-ECCO 2013: Abstract # 300)*. In certain clinical scenarios where obtaining a biopsy is not possible, analysis of blood samples may yield important diagnostic information. Such analysis can also be done more frequently, and in the future may be incorporated as part of a clinical routine analysis. Furthermore, cancer biologists need to understand the role of tumor heterogeneity and evolution on drug response and resistance. Historically, this work depended on collection of multiple biopsy samples from cooperative patients, which limits its applicability and adds complexity and costs. Genomic techniques can provide data in a noninvasive manner and can greatly enhance the pace of research. Application of ctDNA as a diagnostic aid can span a wide range of clinical scenarios, as ctDNA has been observed in most tumors to date. However, further studies are needed to establish the clinical utility, limitations, and performance characteristics. As these methods become more widely used, we are likely to come to appreciate their importance, and their limitations, in the coming years.

Spotlight 2

Prostate cancer: where are we today and what is the path forward?

Today:

Prostate cancer is the most common tumor in men, with ~240,000 men expected to be diagnosed with the disease in the U.S. in 2013.[1] With screening for prostate cancer well established in the developed countries, the majority of the cases are detected in early stages (>80%) and have a good prognosis with 100% relative 5-year survival.[1] However, a small proportion of the patients progress to metastatic castration resistant stage, which is defined as progressive prostate cancer despite a castrate level of serum testosterone (<50 ng/dL). Until 2010, Docetaxel was the only approved drug which improved the survival of metastatic castration-resistant prostate cancer (mCRPC). These patients had a progressive and morbid disease process, with a median survival of 18-20 months.[2]

Approval of the therapeutic vaccine Provenge (sipuleucel-T) in the asymptomatic docetaxel-naïve

Spotlight Report 2
(Cont'd)

mCRPC and cytotoxic Jevtana (cabazitaxel) in symptomatic docetaxel-treated mCRPC patients in 2010,[3,4] prolonged survival in mCRPC. However, approval of hormonal therapies—CYP17 inhibitor Zytiga (abiraterone acetate [AA])[5] in 2011 and anti-androgen Xtandi (enzalutamide)[6] in 2012—changed the treatment landscape significantly with the survival of docetaxel-naïve patients extending to nearly 35 months.[5,7]

The evolving landscape has raised a series of questions. Urologists and medical oncologists are the primary caregivers in prostate cancer and the main questions they face are:

1.Is there cross-resistance between the anti-androgens and CYP-17 inhibitors? Do abiraterone-treated patients respond to anti-androgens?

2.Can responders be rechallenged with the same drug or the same class of hormones?

3.How should the "newer hormonal therapies" be given? Sequentially or in combination?

4.What is the role of chemotherapy (docetaxel)? Where would cabazitaxel fit in?

5.Is there a space or unmet need for the newer anti-androgens/CYP17 inhibitors in development?

6.What is the role of immunotherapies in prostate cancer? Can they be used in combination?

Multiple presentations at the ESMO-ECCO 2013 directly or indirectly tried to address some of these issues.

Sequencing versus combination:

Data was presented by Efstathious et al from MD Anderson Cancer Center, who observed that in patients treated with abiraterone, testosterone levels decreased; however, androgen receptor (AR) copy number increased due to an "adaptive response." In patients treated with enzalutamide, AR decreased; however, marrow testosterone levels increased. Hence, they designed a proof-of-concept (POC) study to test the hypothesis that co-targeting both pathways will be synergistic and safe. Sixty patients were started on enzalutamide and 8 weeks later abiraterone (with prednisone) was added. The combination was well tolerated, with <20% incidence of Grade 3 increase in liver enzymes being the main side effect. The combination resulted in both decrease of testosterone levels and AR copy number. These are potentially significant results, although, the combination will need to be tested in a large randomized trial against sequential use to ascertain whether there are response rate and survival benefits.

Source: The effect of enzalutamide in combination with AA in patients with bone-metastatic castration-resistant prostate cancer (ESMO-ECCO 2013: Abstract #2854)

Rechallenge with same drug and/or class:

In a presentation of data from an open label Phase I/II study of ODM-201 (a new anti-androgen), Fizazi K showed that ODM-201 was active in pretreated mCRPC patients. However, on subgroup analysis, greatest benefit was seen in chemotherapy and CYP17-naïve patients, followed by chemotherapy-treated (but CYP17-naïve) patients with least benefit in CYP17-treated patients (⩾50% PSA decrease was 65% vs. 32% vs. 9%, respectively). Similarly, CTC response at 12 weeks was also lower in CYP17-treated patients. This study supports the hypothesis of development of cross-resistance or "adaptive response" seen with newer hormones and, therefore does not support rechallenge of patients with the same class/molecule.

Source: ESMO-ECCO 2013: Abstract#2853

Upfront use of AA/CYP17 inhibitors in hormone-naïve prostate cancer (HNPC) patients

Smith MR presented data from a Phase II study of enzalutamide in HNPC patients. High level of PSA responses were seen (93% of men had a PSA response [⩾80% decline in PSA] at week 25) and the responses were maintained beyond week 25. Since it has a lower impact on bone mineral density than that seen historically with Androgen Deprivation Therapy (ADT), enzalutimide makes an attractive alternate to ADT in this setting.

Source: ESMO-ECCO 2013: abstract # 2852

However, plenty of questions remain unanswered. Should these potent therapies be used up-front or kept in reserve until patient develops aggressive disease? Will upfront use deplete the options available in docetaxel-failed patients? Will giving a drug holiday (using chemotherapy between two hormones) decrease the risk of cross-resistance?

We look forward to the ASCO 2014 GU Symposium (Jan 30 to Feb 1, 2014) where hopefully more of our questions will get answered.

Back to top of Spotlight Section 2 | Back to Top of Document

Other tumors

Non-small cell lung cancer (NSCLC)

FDA backs continued study of Belagenpumatucel-L for NSCLC based on data from Phase III STOP trial

Phase III STOP trial of therapeutic tumor cell vaccine, belagenpumatucel-L (Lucanix™, NovaRx Corporation), failed to meet its predefined endpoint of improving OS in patients with late-stage NSCLC (maintenance after frontline chemotherapy). However, the trial identified subgroups of patients who derived notable clinical benefit. Significantly prolonged OS with belagenpumatucel-L were demonstrated in stage IIIB/IV patients who began belagenpumatucel-L within 12 weeks of the completion of frontline platinum-based chemotherapy. A significant, clinically meaningful prolongation of OS was also observed in the non-adenocarcinoma subset.

This Phase III study evaluated vaccination with belagenpumatucel-L as maintenance therapy for patients with stages IIIA-IV NSCLC who did not progress after frontline chemotherapy. STOP did not meet its predefined primary endpoint in the entire patient population; mOS was 20.3 months with the vaccine compared to 17.8 months with placebo (HR 0.94; p = 0.594). Factors prognostic of better outcome were starting maintenance treatment within 12 weeks of therapy, disease stage, prior radiation therapy, and histology.

- The OS was improved by 7.3 months with belagenpumatucel-L in 305 stage IIIB/IV patients who were randomized within 12 weeks of chemotherapy completion. In this cohort the mOS was 20.7 months with belagenpumatucel-L compared to 13.4 months with placebo (HR 0.75; p = 0.083).
- Patients pretreated with radiation showed a substantial improvement of 29.8 months in the OS; patients receiving belagenpumatucel-L following radiation showed mOS of 40.1 months compared to 10.3 months with placebo (HR 0.45; p = 0.014).
- Analysis of OS by disease subtype showed that 99 patients with stage IIIB/IV non-adenocarcinoma, who were randomized within 12 weeks of the completion of chemotherapy, experienced mOS of 19.9 months with belagenpumatucel-L versus 12.3 months with placebo—a difference of 7.6 months (HR 0.55; p = 0.036).

Subset analysis and identification of the specific subgroups of patients who achieved marked improvement in survival lead to an investigators meeting with USFDA that confirmed interest in continuing study of belagenpumatucel-L in the specific subsets of patients. The approximate four fold difference in survival when the vaccine is combined with radiation provides encouragement for cancer vaccine approaches to lung cancer.

Source: ESMO-ECCO 2013: Abstract# LBA 2; ESMO Sep 28, 2013 news; NCT00676507

ALK inhibitor Alectinib shows activity in crizotinib refractory ALK fusion gene positive unresectable, recurrent/ advanced NSCLC

Alectinib (RO5424802/CH5424802), a 2nd generation anaplastic lymphoma kinase (ALK) inhibitor, had earlier reported activity from a Phase I/II Japanese trial in crizotinib-naïve, chemotherapy-treated NSCLC patients (presented at ASCO 2013 with mPFS >14 months). Ou S. presented data from an American Phase I dose-escalation study of patients with ALK fusion gene positive NSCLC whose disease had progressed on crizotinib therapy. Alectinib has activity against the ALK mutations as well as point mutations identified as a cause for crizotinib resistance.

Preliminary efficacy was assessed in 47 evaluable patients across all cohorts with an overall response rate (ORR) of 54.5% (median duration of treatment >4 months). The RP2D was determined to be 600 mg BID unlike 300 mg BID in Japanese patients. Of the 47 evaluable patients, 21 (54%) had preexisting brain metastasis at enrollment. Clinical activity in 13 patients showed a partial response (PR 62%), whereas 6 had a stable disease (SD). Alectinib was well-tolerated with the most common adverse events (AEs) being fatigue (30%), myalgia (17%), and peripheral edema (17%). Grade 3-4 AEs included γ-GGT increase, neutropenia, and hypophosphatemia (4% each).

Based on the results from the Japanese and US trials, alectinib was granted the Breakthrough Therapy Designation by USFDA on June 26, 2013. A global Phase II single-arm trial in crizotinib-refractory NSCLC has been initiated (NCT01801111).

On September 13, 2013, alectinib for the treatment of "ALK fusion gene positive unresectable, recurrent/advanced NSCLC" was designated as orphan drug by Ministry of Health and Labour Welfare

Back to Top of NSCLC Section | Back to Top of Document

Non-small cell lung cancer (NSCLC)
(Cont'd)

(MHLW), Japan. Chugai filed a new drug application with MHLW on October 7, 2013, based on the results from the Japanese Phase I/II clinical trial.

Source: ESMO-ECCO 2013: Abstract#LBA 44; Roche News Sep 23, 2013; Chugai News Oct 8, 2013; NCT01801111

Impact on treatment practices in NSCLC:

Early-stage NSCLC:

- Currently adjuvant treatment in stage I NSCLC is not recommended despite approval of UFT (tegafur-uracil) in eastern countries. Pazopanib (in full dose of 800 mg) in adjuvant setting was found to have high toxicity with reduced compliance.
  - Compliance with Pazopanib (800mg) was 38% vs. 87% with placebo
  - Dose modifications were seen in 44% patients; 53% patients had at least one G3/4 toxicities (vs. 13% in placebo)
- Reduced-dose Pazopanib (400mg) demonstrated better compliance and tolerance
  - Compliance with pazopanib (400mg) : 69% vs. 93% with placebo
  - Dose modifications were required in 34% patients; 38% patients had at least one G3/4 toxicities (vs. 27% in placebo) *(ESMO-ECCO 2013: Abstract #LBA19)*
  - The study demonstrates that full dose pazopanib is not suitable for adjuvant setting, however compliance and tolerance with reduced dose may be acceptable.

Advanced-stage NSCLC:

- In EGFR-positive patients:
  - Although EGFR TKIs are the 1st line recommended treatment in EGFR mutants, most patients develop resistance in 10-11 months with development of various mutations in the receptor itself. The most frequent is T790M.
- In EGFR TKI pretreated patients, promising clinical activity (~50% response rate) and tolerability is shown by AZD9291, an irreversible inhibitor of EGFR activating (EGFRm+) and resistant (T790M) mutations - *(ESMO-ECCO 2013: Abstract# LBA33)*
- Addition of tivantinib to erlotinib failed to improve OS in previously treated patients with locally advanced or metastatic, non-squamous NSCLC in a Phase III trial - (MARQUEE trial) *(ESMO-ECCO 2013: Abstract# 3410)*
- VeriStrat (VS) serum protein test status is predictive of differential OS benefit for Erlotinib versus chemotherapy in 2nd line mNSCLC patients in a Phase III PROSE Trial – *(ESMO-ECCO 2013: Abstract# 3421)*
- ALK-positive patients:
  - Data from ongoing Phase III trial in 2nd line patients showed that crizotinib therapy in ALK+ve NSCLC significantly improves quality of life (QOL – as measured by patient-reported symptoms and EORTC QLQ-C30 questionnaire) compared to docetaxel/pemetrexed *(ESMO-ECCO 2013: Abstract#3400).* Crizotinib demonstrated an ORR of ~60% in 1st and 2nd Line NSCLC patients harboring ALK mutations. Studies are ongoing to demonstrate overall survival benefit of crizotinib in ALK+ NSCLC
- Biomarkers:
  - PD-L-1 status of tumor correlated with responses to MPDL3280A (anti-PDL1 from Roche) in Phase I trial of NSCLC patients - *(ESMO-ECCO 2013: Abstract#879)*
  - ERCC1 (HR 0.26) and XRCC1 (HR 0.37) SNPs independently predict OS in metastatic NSCLC patients in retrospective analysis of 145 patients - *(ESMO-ECCO 2013: Abstract#3522)*
  - MED12, a component of the transcriptional MEDIATOR complex, could be a potential biomarker of chemoresistance, and inhibition of TGF-β signaling can restore chemotherapy response in patients with low MED12 - *(ESMO-ECCO 2013: Abstract#3514)*
- Proof-of-concept study demonstrates activity with cabazitaxel in docetaxel-resistant metastatic NSCLC patients - *(ESMO-ECCO 2013: Abstract# 3486)*
- Nintedanib (with docetaxel) significantly improved OS (HR 0.83) for 2nd line adenocarcinoma NSCLC patients (LUME-Lung 1 trial). Patients in whom the time to start of 1st line therapy was <9 months had higher benefit (HR 0.75) – *(ESMO-ECCO 2013: Abstract#3409)*

Ovarian cancer

Cediranib significantly improves OS and PFS as maintenance therapy in recurrent platinum-sensitive ovarian cancer patients in Phase III ICON6 trial

Cediranib is a potent oral inhibitor of VEGFR-1,-2,-3 and inhibits VEGF signaling. ICON6 is an international three-arm, double-blind, placebo-controlled randomized trial. Platinum-sensitive ovarian cancer patients were randomized (2:3:3) to receive platinum-based chemotherapy with either placebo (reference: Arm A), cediranib 20mg/day during chemotherapy followed by placebo for up to 18 months (concurrent: Arm B), or cediranib 20mg/day followed by maintenance cediranib (Arm C). The

Back to Top of NSCLC Section | Back to Top of Ovarian Cancer | Back to Top of Document

Ovarian Cancer
(Cont'd)

primary endpoint was PFS in the reference versus maintenance arm. Secondary endpoints were OS, toxicity, and QoL.

A total of 456 eligible patients were enrolled. Results were as follows:

Parameter	Arm A (reference arm)	Arm C (concurrent + maintenance)	*p* Value
mPFS	8.7 months	11.1 months	p = 0.00001; HR: 0.57 (0.45 -0.74)
mPFS (restricted means)	**9.4 months**	**12.5 months**	
mOS	20.3 months	26.3 months	p = 0.042; HR: 0.70 (0.51 -0.99)

As non-proportional hazards (p = 0.0237 for PFS and p = 0.0042 for OS) were seen, survival time was estimated using restricted means (RM) and HRs given for completeness. The RM estimates an increased time to progression of 3.1 months from 9.4 to 12.5, during 2 years. Similarly using RM, OS increased by 2.7 months from 17.6 to 20.3 (HR 0.70; p = 0.0419). PFS using RM for the reference versus concurrent arms saw an increase of 2.0 months, from 9.4 to 11.4 months (HR 0.68; p = 0.0022). Significantly more common side effects seen in the cediranib-maintenance arm were hypertension, diarrhea, hypothyroidism, hoarseness, hemorrhage, proteinuria, and fatigue.

However, in Sept 2011, AstraZeneca ceased the development of cediranib. The decision to discontinue development of cediranib in CRC, gastric cancer, GBM, and NSCLC was based on disappointing results from pivotal Phase II and Phase III studies in the HORIZON program. Even though the decision to discontinue development of cediranib had been made, several ongoing studies were allowed to complete. Based on the favorable efficacy data from Cediranib trial in Ovarian Cancer, AstraZeneca is in discussions with UK's Medical Research Council (MRC) to fully understand the potential for this drug in patients with platinum-sensitive, relapsed ovarian cancer

Source: ESMO-ECCO 2013: Abstract #LBA10

Final analysis of ICON7 trial confirms lack of OS benefit with bevacizumab in women with newly diagnosed ovarian cancer, although high-risk patients may benefit

Anti-angiogenic therapies have shown promise in ovarian cancer in early stage trials. ICON7 investigated safety and efficacy of adding bevacizumab to standard chemotherapy in women with newly diagnosed ovarian cancer. Primary analysis of PFS demonstrated benefit from addition of bevacizumab to chemotherapy; however, there was no OS benefit (presented at ESMO 2010, updated ASCO 2011). Final analysis of OS was presented at ESMO 2013.

Back to Top of Ovarian Cancer | Back to Top of Document

Eligible women with high-risk early (FIGO stage I-IIa) or more advanced (stage IIb-IV) epithelial ovarian, primary peritoneal, or fallopian tube cancer were randomized (1:1) to 6 cycles of 3 weekly carboplatin and paclitaxel alone, or the same chemotherapy given concurrently with bevacizumab for 5 or 6 cycles followed by continued 3-weekly single-agent bevacizumab for 12 additional cycles or until progression. Total 1,528 women were randomized from 263 centers in seven GCIG groups.

Restricted Mean Survival Time (RMST) was used as the primary estimate rather than the hazard ratio; the proportional hazards (P-H) test as well as the log-rank test is reported. With median follow-up of 49 months, 714 women died (352 control, 362 bevacizumab), median OS with RMST showed an improvement of 0.9 months, from 44.6 to 45.5 months (log-rank p = 0.85, P-H test p = 0.02). Updated mPFS was 19.9 months versus 17.5 months in placebo arm (HR: 0.93; p = 0.25). In the poor prognosis group (patients with suboptimal debulking defined as residual disease >1 cm), 332 of 502 patients died (174 control, 158 bevacizumab), with an improvement of 4.8 months in RMST from 34.5 to 39.3 months (log-rank p = 0.03, P-H test = 0.007); mPFS (restricted mean) was 20.0 months versus 15.9 months. There were no new safety concerns on long-term follow-up. *Source: ESMO-ECCO 2013: Abstract #LBA6*

Impact on treatment practices in ovarian cancer:

Recurrent/relapsed ovarian cancer:

- Trebananib (AMG386, angiopoietin inhibitor) added to weekly paclitaxel significantly improved PFS (by 52%, HR = 0.66; p<0.001) from a median of 5.4 to 7.2 months in recurrent epithelial ovarian cancer in Phase III trial (TRINOVA-1) – *(ESMO-ECCO 2013: Abstract #LBA41)*
  - Treatment effect was seen irrespective of age, previous VEGF therapy, or platinum-free interval.
  - OS data showed a trend to improvement, final data is awaited (expected to be available in 2014).
  - Well tolerated with incidence of AEs similar to placebo. VEGF-related AEs were not seen. However, major AE with Trebananib was local edema.
  - Based on patient-reported outcomes, quality of life was maintained.
- BMN673 (PARP inhibitor) demonstrated high objective (44%) and clinical benefit response rates in heavily pretreated ovarian cancer patients with BRCA mutation in Phase I. Although higher ORR was seen in platinum-sensitive patients, 20% ORR was seen even in platinum-resistant patients. A

Ovarian Cancer (Cont'd)

Phase III trial in breast cancer was initiated in September 2013, and further development in ovarian cancer is awaited - *(ESMO-ECCO 2013: Abstract #LBA29; NCT01945775)*

- Interim OS analysis of Olaparib plus chemotherapy, followed by maintenance olaparib monotherapy, showed a clinical benefit (OS improvement) in patients with BRCA-mutated platinum-sensitive recurrent ovarian cancer in Phase II. MAA has been accepted by EMA for olaparib in this indication based on PFS improvement reported at ASCO 2012 - *(ESMO-ECCO 2013: Abstract #3002)*
- In a Phase IIb study, Cvac (autologous dendritic cell therapy targeting mucin 1 target) given as maintenance therapy shows positive trends in PFS for ovarian cancer patients in 2nd remission, although not in patients in 1st remission. OS data is awaited to assess the clinical benefit of this vaccine - *(ESMO-ECCO 2013: Abstract #3000)*

Biomarkers:

- Expression of 4 genes—RTF1, FUBP1 MAP2K1, CSDE1, and CNOT8—on microarray analysis correlated to platinum resistance in ovarian cancer - *(ESMO-ECCO 2013: Abstract #3083)*
- IL-17, a new pro-inflammatory cytokine and a marker of poor prognosis in ovarian cancer, acts by promoting self-renewal of CD133+ cancer stem-like cells in ovarian cancer; IL-17 is a novel treatment target in ovarian cancer - *(ESMO-ECCO 2013: Abstract #3010)*
- $p70^{S6\ kinase}$ promotes a rate-limiting step in ovarian cancer metastasis by modulating tumor-mesothelial cell adhesion through P-cadherin-beta1-integrin crosstalk - *(ESMO-ECCO 2013: Abstract #3015)*

Renal cell carcinoma

Dovitinib fails to show a clinical benefit over sorafenib in 3rd line RCC patients

Superior efficacy was not demonstrated by dovitinib in a head-to-head comparison with sorafenib in patients with clear cell metastatic renal cell carcinoma (mRCC) who had progressed following therapies targeting the VEGF and mTOR pathways.

Dovitinib is a multi-targeted receptor tyrosine kinase inhibitor that offers broader inhibition of the FGFR by binding FGFRs 1, 2, and 3, plus it also targets the PDGFR, FLT3, and cKIT, in addition to the VEGFR. In Phase II, dovitinib demonstrated promising anti-tumor activity in heavily pretreated RCC patients. The GOLD trial (Global Oncologic Leanings for Dovitinib) was an open-label, randomized, multicenter Phase III trial. The GOLD enrolled 570 patients with clear cell mRCC. The trial's primary endpoint was PFS by central review. Secondary endpoints included OS, response rate, and safety. The trial did not meet the primary endpoint; median PFS was 3.7 and 3.6 months in the dovitinib and sorafenib arms, respectively (HR 0.86; $p = 0.063$). Median OS was also nearly the same at 11.1 months with dovitinib and at 11.0 months in the sorafenib arm (HR 0.96; $p = 0.357$). The best overall response was the same in both arms; 4% of patients receiving each treatment demonstrated partial response and stable disease was achieved by 52% of patients in each arm. Different safety profiles were seen with each treatment. The AEs most commonly reported by patients receiving dovitinib versus sorafenib were diarrhea (68% vs. 45%), nausea (53% vs. 29%) and vomiting (44% vs. 16%).

Although the trial failed to show improvement in survival endpoints, it did confirm a role of tyrosine kinase inhibitors in 3rd line RCC patients. Dovitinib, while inhibiting many of the same kinases as sorafenib, is generally well-tolerated, and thus may offer an additional alternative in this group with limited treatment options.

Source: ESMO-ECCO 2013: Abstract# LBA34; ESMO @ ECC 2013, Sep 29; NCT01223027

Impact on treatment practices in renal cell carcinoma

Advanced RCC:

- Everolimus provides clinical benefit with promising OS (21.0 months in ITT population) in patients with 1st line papillary mRCC (final analysis of Phase II RAPTOR trial)– *(ESMO-ECCO 2013:Abstract# 2706)*

Biomarkers:

- In a pooled analysis of eight Phase II and Phase III trials, maximal tumor shrinkage was an independent predictor of prolonged OS in mRCC patients - *(ESMO-ECCO 2013: Abstract#2702)*
- Angiopoietin 2 (Ang-2) may be an independent prognostic marker associated with a worse outcome in clear cell RCC - *(ESMO-ECCO 2013: Abstract#2806)*

Back to Top of Ovarian Cancer | Back to Top of RCC Section | Back to Top of Document

Renal Cell Carcinoma
(Cont'd)

- Multiple biomarkers are being evaluated in an attempt to develop predictive/prognostic markers in advanced patients, especially in sunitinib-treated patients. These include:
  - Development of hand-foot syndrome (HFS), identified a subset of patients that manifested highly favorable efficacy results with sunitinib - *(ESMO-ECCO 2013: Abstract#2738)*
  - Other genes such as cMyc/HIF2a, FAK, and PTEN might be predictive biomarkers for sunitinib in mRCC - *(ESMO-ECCO 2013: Abstract#2803)*

Hepatocellular carcinoma

Impact on treatment practices in hepatocellular carcinoma

Early HCC:

- Sorafenib with TACE in unresectable HCC in Chinese population demonstrated mTTP of 12.3 months and mOS of 25.1 months, consistent with earlier results in other Asian populations *(ESMO--ECCO 2013:Abstract#2492, NCT00990860).*
- In phase I trial, Idarubicin-loaded beads for chemoembolization were found to be safe *(ESMO-ECCO 2013:Abstract # 876).*

Advanced HCC:

- GIDEON is the largest (>3200 patients) global, prospective, non-interventional study of unresectable HCC (uHCC) patients treated with sorafenib under real-life practice conditions *(ESMO-ECCO 2013:Abstract#2581, 2594).* The data from this trial allows for the evaluation of the safety and efficacy of sorafenib in a diverse range of settings and patient groups where the data are currently limited, including patients with Child-Pugh B disease and those with poor prognostic factors. Although sorafenib is recommended at a dose of 800 mg/day, real-life data suggest that physicians tend to start uHCC patients with poorer prognostic factors on the lower sorafenib dose (400 mg/day).
  - However, the GIDEON study suggested dose reduction is not necessary as AEs with 800 mg/day are similar to those who started with the lower dose.
  - Patient outcomes with 800 mg/day were better as compared with 400 mg/day dose (mOS: 26 vs. 18 months, mPFS: 6.5 vs. 6.2 months).
  - ECOG PS, Child-Pugh status, and CLIP and MELD scores were confirmed to be useful prognostic factors for OS.
- In the Phase II GoNext trial, Sorafenib combined with Gemcitabine and Oxaliplatin (GEMOX) versus Sorafenib alone in 1st line HCC patients failed to demonstrate an OS benefit (mOS of 13.5 months vs. 13.0 months) despite an increase in mPFS (6.2 months vs. 4.6 months) and meeting its primary endpoint of 4-month PFS ⩾ 50% - *(ESMO-ECCO 2013:Abstract # 2467)*
- In a Phase I/II SHELTER study, Resminostat (a pan HDAC inhibitor) in 2nd line mHCC patients demonstrated mOS of 8.1 months *(ESMO-ECCO 2013:Abstract # 2601).* Patients with Child-Pugh-A, ECOG 0, or absence of vascular invasion had a statistically significant lower risk of death. Currently, there is no established benchmark for 2nd line mHCC (median overall survival is 4-6 months with best supportive care).
- Phase II trial of Nintedanib, an oral angiokinase inhibitor targeting VEGFRs, PDGFRs, and FGFRs, versus sorafenib in Asian population, reported non-significant outcomes (mTTP 2.7 vs. 3.7 months, mOS 10.7 vs. 9.5 months) - *(ESMO-ECCO 2013:Abstract # 2580)*
- Preliminary results (25 patients study) with stereotactic body radiotherapy (SBRT) demonstrated that it can be an effective alternate modality in inoperable HCC patients with vascular invasion who are unsuitable for other therapies. Promising local control (CR: 83.3% within 6 months) with mOS of 9.5 months and mPFS of 6 months was seen *(ESMO-ECCO 2013:Abstract# 1117).* Another study reported OS rate of 76.8% at 2 years in TACE + SBRT in HCC patients without vascular invasion *(ESMO-ECCO 2013:Abstract# 2552).* Together, these two reports reveal that radiation therapy continues to improve in the treatment of advanced HCC.

Phase I/II study of S-1 (Thymidylate synthase inhibitor, from Taiho Pharmaceuticals) in combination with sorafenib failed to demonstrate a clinical benefit (the median TTP and OS were 2.4 and 10.5 months, respectively as compared to the current benchmark of mTTP of 5.5 months and mOS of 10.7 months with sorafenib alone) over sorafenib alone. Its toxicities were slightly severe and its effect does not seem to be improved than sorafenib alone. *(ESMO-ECCO 2013:Abstract#2624).*

Back to Top of RCC Section | Back to Top of HCC Section | Back to Top of Document

- **A SMART Synopsis of Today's Oncology Headlines. We find the stories that matter most, *so you don't have to.***
- **An E-Newsletter that both educates *and* informs.**
- **SmartAnalyst is a strategic consulting firm** that has supported multiple pharma client engagements **over a ten-year history. Oncology has been a core indication of analytical focus.**
- **SMARTOncology is a reflection of SmartAnalyst's Oncology experience and expertise.** We inform our readers **about headlining news that matters most,** while also supplementing issues **with our spotlight articles.**

SmartOncology E-Newsletter

Product of SmartAnalyst

SMARTANALYST®
INTELLIGENT INSIGHTS. SMART RESULTS.

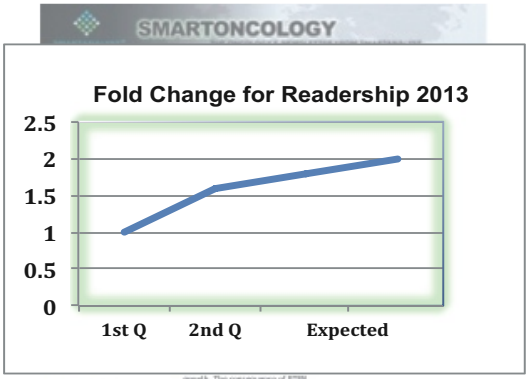
Become A SmartOncology Sponsor

Offering Biotech and Pharma companies a viable opportunity to share their products and services with their key target market.

Please review our sponsorship rates and placement choices. Feel free to contact our team at any point in time. We would be more than happy to answer any questions. mtuli@smartanalyst.com

Readership 3,000+ and Growing… Targeting:

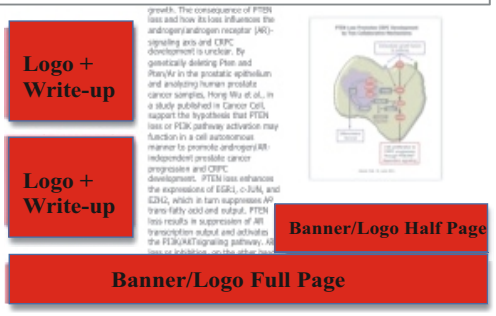
- Academics
- Physicians
- KOLs
- Pharma
  - Marketing
  - R & D



Key Sponsors include:

- Advocacy groups
- Vendors
- Congresses

.



Ad Type	Size	Price/Issue	Price/Quarter	Price/6-month	Price/Anum
Banner/Logo	Full Page (7"x0.7")	$650	$1625	$2925	$5200
Banner/Logo	Half Page (3.5"x0.7")	$325	$800	$1450	$2600
Logo + 1-3 sentences (~50 Words)	(Approx. 2.7"x1.5")	$825	$2025	$3650	$6500

Back to top of Newsletter Sponsorship Section | Back to Top of Document