ESMO 2014 Congress Scientific Meeting Report – Gynaecological Cancers Extract

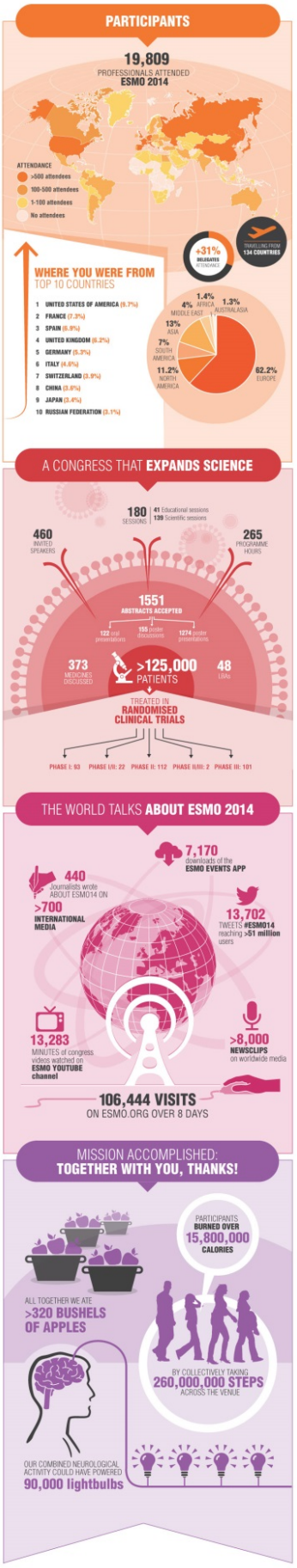
26-30 September 2014

Madrid, Spain

Summary

The European Society for Medical Oncology (ESMO) Congress, held September 26 to 30 in Madrid, Spain, was a record-breaker on nearly all levels. It was resounding success and in a dedicated infographic you can find the congress statistics. A primary emphasis in the scientific programme was placed on precision medicine and how it will change the future treatment landscape in oncology. In addition, a number of scientific presentations were dedicated to cancer immunology and immunotherapy across multiple tumour types. This report is an overview of key scientific presentations made during the congress by leading international investigators. It attempts to represent the diversity and depth of the ESMO 2014 scientific programme, as well as advances in oncology.

Infographic (right): ESMO 2014 record breaking Congress



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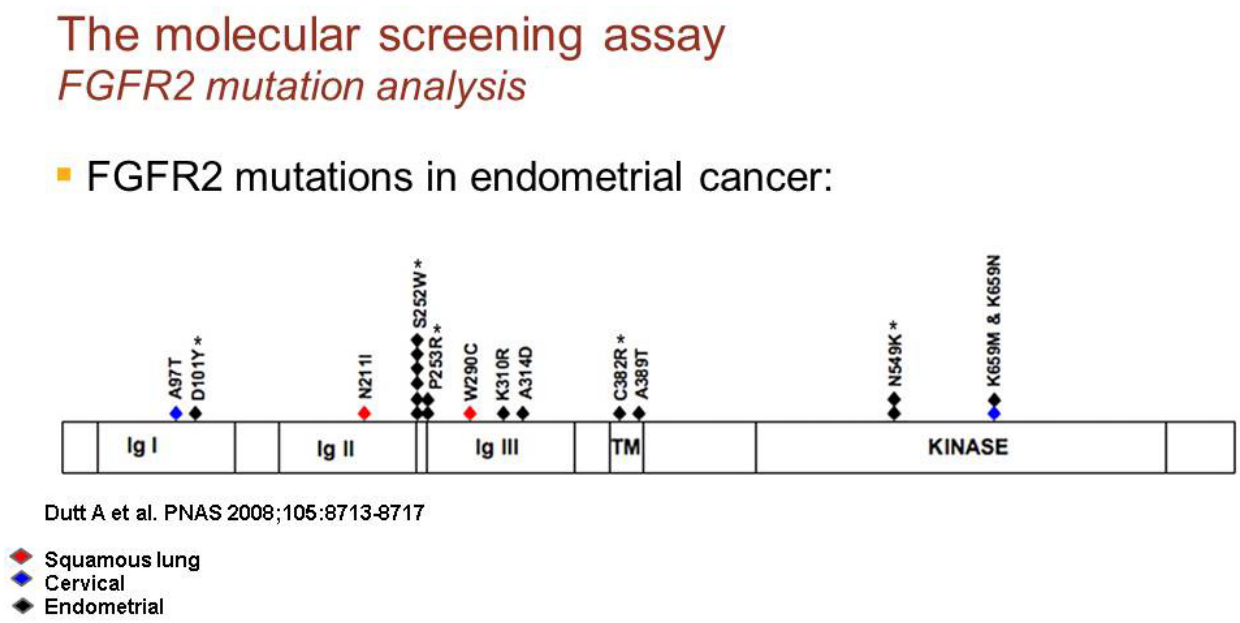
Gynaecological Cancers

Activity of second-line dovitinib in advanced and/or metastatic endometrial cancer

The single-agent dovitinib demonstrated clinically meaningful activity in second-line treatment of patients with fibroblast growth factor receptor 2 (FGFR2)-mutated or -non-mutated advanced and/or metastatic endometrial cancer and a trend toward greater median PFS and OS in the FGFR2-mutated group. The results of a phase II study were presented by Prof. Gottfried Konecny of the Gynecologic Oncology Unit, UCLA Westwood Oncology Hematology, Los Angeles, USA.

Activating mutations in FGFR2, identified in 10%-15% of primary endometrial cancers, are associated with disease progression and poor outcome.



Caption: FGFR2 mutation analysis in endometrial cancer. © Gottfried Konecny

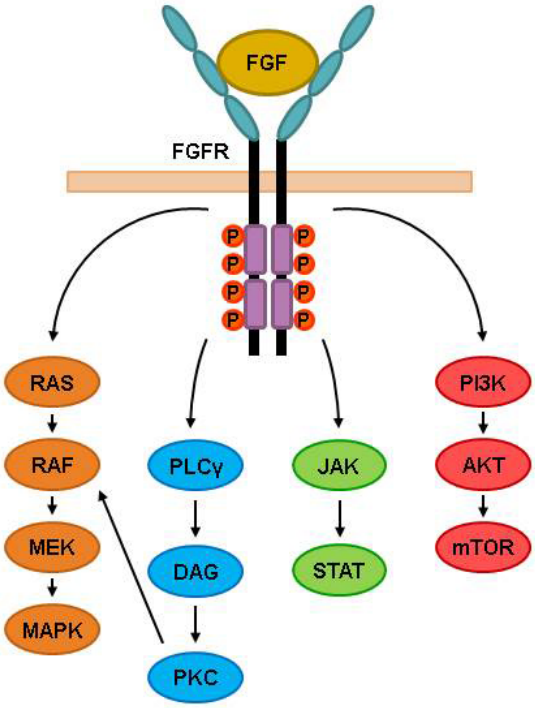
Dovitinib (TKI258) is a potent TKI that targets FGFR, vascular endothelial growth factor receptor (VEGFR) and platelet derived growth factor receptor (PDGFR) and other kinases. Dovitinib demonstrated dose-dependent growth inhibition of FGFR2-mutated and FGFR2-non-mutated xenografts.

In this phase II study, researchers evaluated dovitinib as a second-line therapy in patients with FGFR2-mutated or –non-mutated disease. Women who progressed after first-line chemotherapy for advanced and/or metastatic endometrial cancer underwent molecular prescreening for FGFR2 status and then clinical screening if eligible for the study (ECOG PS ≤ 2). Then they were treated with oral dovitinib on a 5-days-on/2-days-off schedule.

The primary endpoint was percentage of patients who are progression-free by investigator assessment after 18 weeks. The trial used a 2-stage design for each group; stage 2 could proceed if ≥ 8 of the first 20 treated patients (40%) met the primary endpoint. Secondary endpoints

included ORR, DCR, DoR, PFS, OS, safety, tolerability, pharmacokinetics, and pharmacodynamics.

- FGF/FGFR system
  - Receptors: 4 FGFRs
  - Ligands: 22 FGFs
  - Each FGFR has specificity for particular FGFs
- Context-dependent signaling through various intracellular pathways
- Regulates normal biological processes
  - Protein synthesis
  - Cell growth and proliferation
  - Cell motility, migration, invasion
  - Cell differentiation
  - Resistance to cell death
  - Angiogenesis



Turner N, et al. *Nat Rev Cancer.* 2010;10(2):116-129.
Itoh N, Ornitz DM. *J Biochem.* 2011;149(2):121-130.

Caption: The fibroblast growth factor (FGF) pathway. © Gottfried Konecny

A key eligibility criterion was progressive disease after first-line antineoplastic treatment for advanced and/or metastatic endometrial cancer. Eligible histologies were endometrioid, serous, clear cell, mucinous, adenosquamous, and mixed types. Prior antineoplastic treatment should have included at least one cytotoxic agent and prior hormonal therapy was not considered as a line of treatment.

Response was assessed by local investigator every 6 plus/minus 1 weeks according to RECIST v1.1 criteria. Adverse events were assessed according to CTCAE v4.03.

FGFR2 analysis was performed on archival tumour blocks or fresh fixed tumour biopsies. FGFR2-mutated status was identified by Sanger sequencing of the 5 main hotspot mutation sites reported for endometrial cancer.

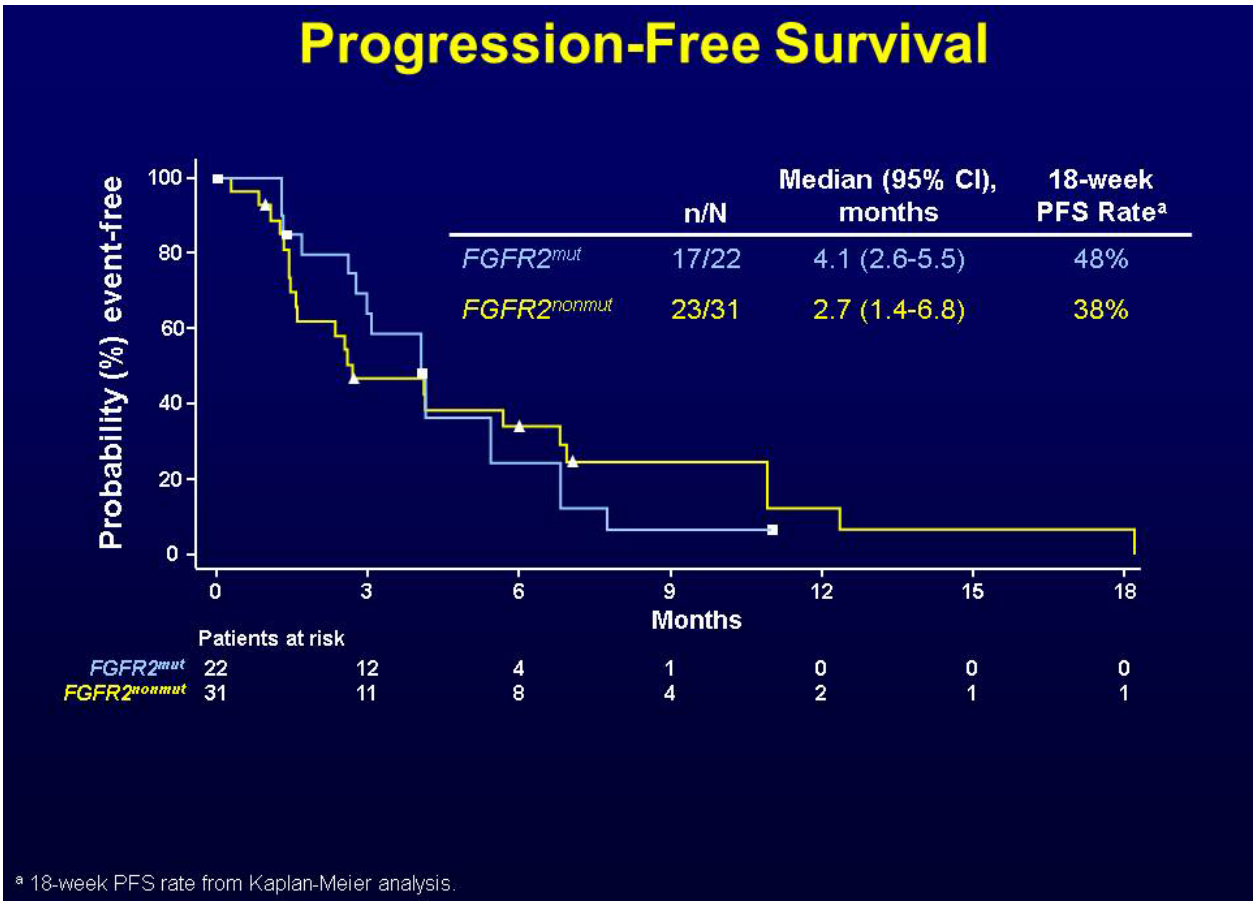
Of 248 pre-screened patients, 27 had FGFR2-mutated tumours (11%). The study enrolled 53 patients, of which 22 had FGFR2-mutated disease and 31 FGFR2-non-mutated.

Among patients with FGFR2-non-mutated tumours, 17 had ECOG PS 1 vs. 7 patients with mutated tumours. In the same group there were also slightly more patients with serous and clear cell adenocarcinoma histology and poorly differentiated tumours. Median relative dose intensity was similar.

All patients discontinued the treatment mostly due to progressive disease (66%) or adverse events (26%). Most frequent adverse events leading to discontinuation were deep vein thrombosis, pulmonary embolism, and small intestinal obstruction.

The observed 18-week PFS rates were 32% in patients with FGFR2-mutated tumours and 29% in patients with FGFR2-non-mutated. The 18-week PFS rate in the first 20 patients was 35% and 25% in the FGFR2-mutated and FGFR2-non-mutated groups, respectively. However, the study did not proceed to stage 2 based on the predefined criteria.

The 18-week PFS rates from a Kaplan Meier analysis were 48% in FGFR2-mutated and 38% in FGFR2-non-mutated group.



Caption: PFS in study patients with endometrial cancer (FGFR2-mutated and FGFR2–non-mutated). © Gottfried Konecny

The DCR (≥ SD) was 64% (59% SD, 5% PR) in the FGFR-2 mutated group and 51% (35% SD, 16% PR) in the FGFR2-non-mutated groups, respectively.

Median PFS (4.1 vs. 2.7 months) and OS (20.2 vs. 9.3 months) trended to be higher in the FGFR2-mutated group.

Adverse events suspected to be study drug related were similar between the groups. The most common grade 3/4 adverse events were hypertension (17%) and diarrhoea (9%). Of the 5 on-treatment deaths, 4 were due to endometrial cancer and 1 was due to cardiac arrest. The safety profile was similar to that observed in other dovitinib trials.

Prof. Konecny concluded that single-agent dovitinib demonstrated clinically meaningful activity in both groups. There was a trend toward greater median PFS and survival in the FGFR2-mutated group. The overall safety profile was similar to that observed in other dovitinib trials. However, the incidence of thrombosis appeared more common in this patient population.

Dr Michael Bookman of the University of Arizona Cancer Center, Tuscon, USA, who discussed the study results, said that accrual was biased toward high-grade and advanced-stage tumours with increased risk of recurrence. 40-50% of patients have already received pelvic radiation, with impact on haematologic reserve. Recurrent disease within the pelvis is less responsive to many treatments, due to prior surgery and/or radiation. Historical controls are necessary to define the primary study hypothesis, but the reference population may not have the same molecular profile as the enrolled population.

According to Dr Bookman, the investigators have provided a well-designed and carefully-conducted phase II experiment with dovitinib in endometrial cancer. Patients were allowed one prior treatment, plus/minus pelvic radiotherapy, and appear similar to patients enrolled on GOG 229 phase II trials, contributing to a broader experience. As a multi-targeted tyrosine kinase inhibitor, dovitinib also inhibits VEGFR2. Without randomised combinations or stratification for prior anti-VEGF therapy, it is uncertain which pathway(s) accounted for the observed outcomes.

FGFR2 is mutated in 10% of early-stage endometrioid (type I) tumours, and associated with risk of recurrence. The prognostic significance of mutations in recurrent or metastatic disease is uncertain. However, in this trial, patients with FGFR2-mutated tumours had an improved prognosis, compared to non-endometrioid (type II) tumours.

Type I endometrial cancer is associated with frequent (non-overlapping) mutations in KRAS, CTNNB1, FGFR2, and PIKC3A, with associated pathway activation. In recurrent disease, targeting VEGF (with bevacizumab) demonstrates activity that appears equal or superior to multi-targeted TKIs, including anti-FGFR2. Some TKIs may not be effective in the setting of common activating mutations within the kinase domain of FGFR2. Understanding, and optimising, the net contribution of each pathway awaits randomised trials that incorporate stratification based on prior treatment and analysis of biospecimens.

The study sponsor was Novartis Pharmaceuticals.

Reference

LBA27: Phase 2 study of second-line dovitinib (TKI258) in patients with fibroblast growth factor receptor 2 (FGFR2)-mutated or -nonmutated advanced and/or metastatic endometrial cancer

Final OS analysis of the phase III randomised trial of chemotherapy with and without bevacizumab for advanced cervical cancer

Final OS data from the NRG Oncology - Gynecologic Oncology Group (GOG) study of chemotherapy with and without bevacizumab for advanced cervical cancer has showed that the benefit conferred by the incorporation of bevacizumab is sustained beyond 50 months as evidenced by the survival curves remaining separated. The results were reported during the ESMO 2014 by Prof. Krishnansu Tewari of the Department of Obstetrics & Gynaecology, University of California, Irvine Medical Center, Orange, USA.

On 14 August, 2014, the USA Food and Drug Administration approved bevacizumab with chemotherapy for women with recurrent, persistent, or metastatic cervical cancer. This regulatory milestone was due to GOG protocol 240 that met its primary endpoint with the arm administering chemotherapy plus bevacizumab resulting in significantly improved OS compared to

chemotherapy alone. These results were publicly announced following a data freeze on 12 December, 2012 when 271 deaths had occurred.

At ESMO 2014, the study investigators reported planned final analysis of OS and a detailed updated toxicity analysis based on the protocol-specified 346 events. The study results that were previously presented during the ASCO 2013 were from the second analysis. These results were also published in the New England Journal of Medicine on 20 February 2014.

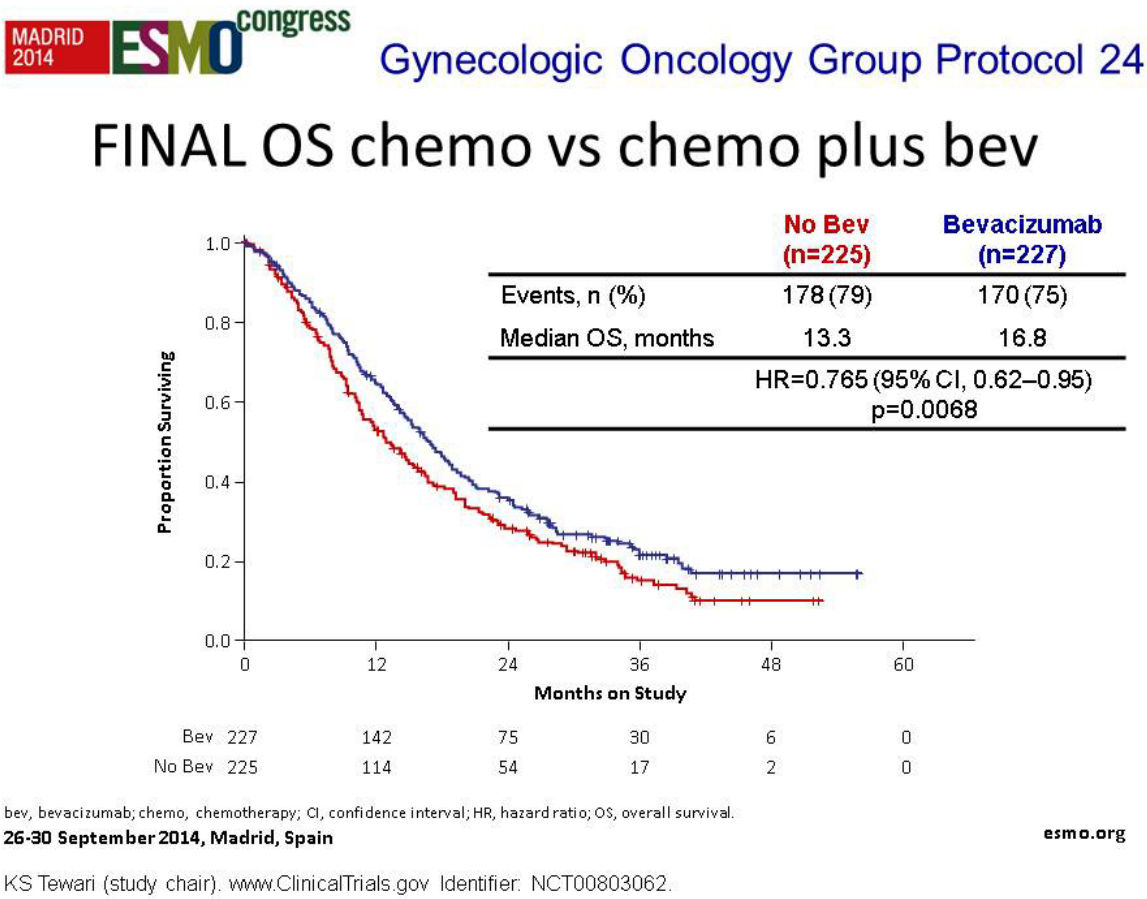
The GOG 240 is a phase III randomised clinical trial using a 2x2 factorial design to determine whether chemotherapy plus bevacizumab and/or the non-platinum chemotherapy doublet (topotecan plus paclitaxel) improves OS in women with recurrent/persistent and metastatic cervical cancer.

The primary endpoints were OS and toxicity and secondary endpoints PFS and response.

The study investigators calculated that they would have to enrol approximately 450 patients with approximately 346 deaths expected to provide the study with 90% power to detect a reduction in the risk of death of at least 30% with either experimental treatment, with the one-sided type I error rate limited to 2.5% for each regimen.

The median age was 49 years and groups were well-balanced for disease status (70-73% recurrent), prior chemoradiation (74-75%), and in-field pelvic recurrence (53-54%).

When 348 events had occurred (2 more than the pre-specified number estimated for final analysis), the regimens administering bevacizumab continued to demonstrate a significant improvement in OS over chemotherapy alone: 16.8 vs. 13.3 months (HR 0.765; p=0.0068). The benefit conferred by the incorporation of bevacizumab is sustained beyond 50 months as evidenced continued separation of the survival curves.



Caption: Final OS analysis in the GOG240 study shows significant improvement in the bevacizumab/chemotherapy arm vs. chemotherapy alone. © Krishnansu S. Tewari

GI perforations were reported in 3.2% of patients receiving bevacizumab, all of whom had prior radiotherapy. GI-vaginal fistula occurred in 8.2% of patients treated with bevacizumab vs. 0.9% of those treated with chemotherapy alone. Grade 3 plus venous thromboembolic events were reported in 10.6% in the chemotherapy plus bevacizumab arm vs. 5.4% in the chemotherapy alone arm.

Bevacizumab is the first targeted agent to be granted regulatory approval in the USA for treatment of cervical cancer.

Dr Sandro Pignata of the Istituto Nazionale Tumori – I.R.C.C.S - Fondazione Pascale, Naples, Italy, who discussed the study results, said that strengths of the study are the first improvement in OS after several years in this setting, first biological drug approved for cervical cancer, and clear demonstration that targeting angiogenesis is important in this disease.

However, there was a significant toxicity rate in the study with GI fistula in 8.6%, GI perforations in 3.2%, thromboembolism > grade 3 in 8.2% of patients, bleeding > grade 3 in 4.5% and death in 3.3% of patients. There was no analysis reported for risk factors related to toxicity and it is urgently needed in term of disease in the pelvis, previous radiotherapy, PS, etc. Dr Pignata said that the use of the drug in patients unselected for clinical trials may require special attention.

Bevacizumab is a significant advance in the therapy of metastatic cervical cancer, but management of toxic events is still an open issue. The question is if the results could be

generalizable in high incidence, but poor resource countries. According to Dr Pignata, resources still need to be directed with priority on screening and prevention of cervical cancer.

The GOG 240 was sponsored by the USA National Cancer Institute (NCI). Genentech, the drug manufacturer, provided support for the trial under the Cooperative Research and Development Agreement with the NCI for the clinical development of bevacizumab.

Reference

LBA26: Final overall survival analysis of the phase III randomized trial of chemotherapy with and without bevacizumab for advanced cervical cancer: A NRG Oncology - Gynecologic Oncology Group Study

RELATED INFORMATION

Click here to access the Conference abstracts.

Click here to access the meeting webcast page.

Save the date

European Cancer Congress 2015 (ECC 2015), Vienna, Austria, 25-29 September 2015.

Affiliations and Disclosure

Affiliation

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Disclosure

No conflicts of interest to disclose.

Acknowledgment

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