ESMO 2016 Congress

7-11 October, 2016

Copenhagen, Denmark

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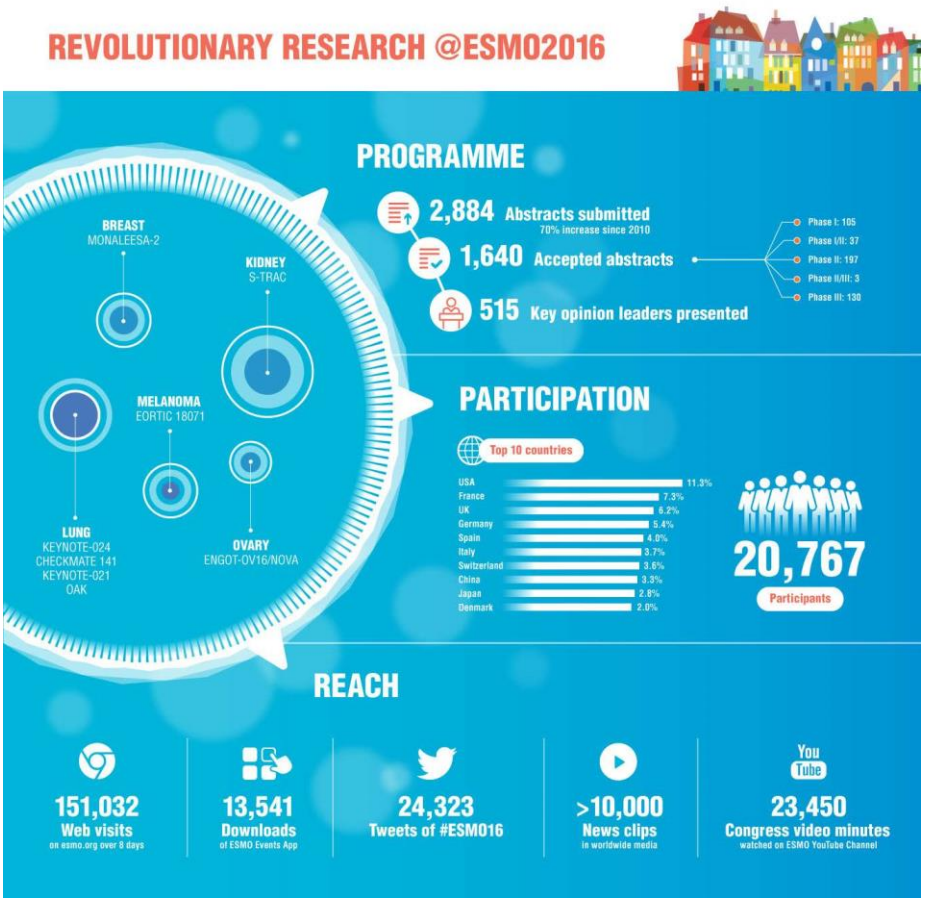
Summary

The European Society for Medical Oncology (ESMO) 2016 Congress, held October 7 to 11 in Copenhagen, Denmark, was a record-breaker on all levels. It was resounding success and in a dedicated infographic you can find the congress programme statistics. A primary emphasis in the scientific programme was placed on two areas: precision medicine and immunology and immunotherapy across multiple tumour types and how these advances change the treatment landscape in oncology. 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 2016 scientific programme, as well as advances in oncology.



ESMO 2016 record breaking Congress

ENDOCRINE AND NEUROENDOCRINE TUMOURS

Everolimus and pasireotide LAR alone or in combination significantly improved outcome in patients with advanced lung and thymic carcinoids

Piero Ferolla of the Multidisciplinary NET Group and the Department of Medical Oncology, Umbria Regional Cancer Network and University of Perugia in Perugia, Italy and co-investigators conducted LUNA, the first randomised trial specifically designed for patients with progressive lung and thymic carcinoids that assessed the efficacy and safety of pasireotide LAR and everolimus alone and in combination. The LUNA phase II trial randomised 41 patients to pasireotide LAR at 60 mg/month intramuscular, 42 patients to oral everolimus at 10 mg/day orally, and 41 patients to pasireotide LAR plus everolimus at the same single-agent doses. The patients' median age was 64 years; atypical carcinoid was present in 68.5% of patients while 31.5% of the patients had typical carcinoid. The primary tumour site was the lung in 93.5% of patients, and thymus in 6.5%. WHO performance status was 0, 1, or 2 in 64%, 34%, and 2% of patients, respectively. Prior drug treatment had been administered to 44% of patients, radiotherapy to 27%, surgery/locoregional therapy to 97%, and 48% of patients had received prior somatostatin analogues.

The primary endpoint of the trial was the progression-free rate at 9 months (PFR-9), defined as the proportion of patients with documented complete response (CR), partial response (PR), or stable disease (SD) by RECIST v.1.1 criteria at 9 months. Secondary end points included progression-free survival (PFS), disease control rate (DCR), and safety.

Although the greatest response was observed with the combination, all 3 treatment arms of the LUNA study met the primary end-point: PFR-9, was achieved by 39.0% of patients on single agent pasireotide LAR (95% confidence interval [CI] 24.2, 55.5), 33.3% of patients on sole everolimus (95% CI 19.6, 49.5), and by 58.5% of patients on combined everolimus and pasireotide LAR (95% CI 42.1, 73.7). No CR was observed; the best overall response at 9 months was PR, which was achieved by 2% of patients in each treatment arm. The SD was attained by 34% of pasireotide LAR patients, 31% of everolimus patients, and by 49% of patients receiving the combination. Progressive disease (PD) occurred in 17% receiving pasireotide LAR monotherapy versus 2% of patients receiving sole everolimus. PD was not reported with the combined treatment.

No new safety signals were observed. Study treatment was discontinued by 65% of patients during the 12-month core phase. Discontinuation due to PD or adverse events (AEs) was each reported in 27% of patients. AEs were mostly grades 1/2 across treatment groups. The most common AEs (any grade) with combined pasireotide LAR and everolimus were hyperglycaemia, which was reported in 88% of patients, diarrhoea in 78%, weight decrease in 56%, asthenia in 37%, and stomatitis was reported in 34% of patients. EUDRACT number: 2011-002872-17. Ferula *et al.* Abstract 416O

Practice point and future research opportunities

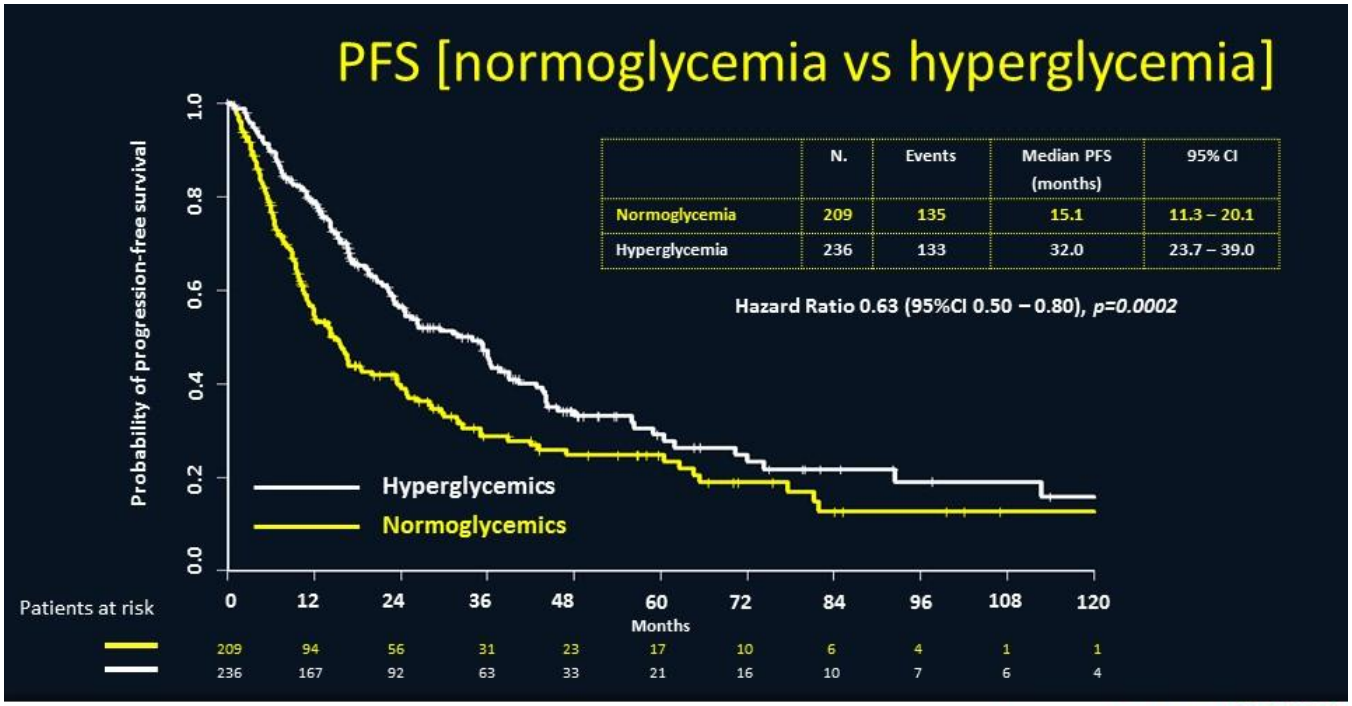
According to the current ESMO and ENETS guidelines, advanced carcinoid of the lung or thymus remains an area of high unmet medical need with few treatment options. Everolimus, which blocks the mTOR pathway, showed PFS benefit in patients with gastrointestinal/lung NET recently in the phase III RADIANT-4 study and the somatostatin analogue, pasireotide LAR, has also shown potential antitumour activity in NET studies. The investigators designed this phase II study entirely focused on patients with progressive advanced carcinoid of the lung or thymus and found clinical benefit and anti-tumour activity with everolimus and pasireotide LAR monotherapies that was greatest in the treatment arm that combined the two drugs. The combination of pasireotide LAR and everolimus had a statistically significant positive impact on the proportion of patients remaining progression free at 9 months. This combination warrants further study and looks promising to become a treatment option for patients with advanced lung and thymic carcinoids.

Risk of cancer progression in patients with diabetes and advanced pNETs significantly lowered by metformin treatment

Lead author Sara Pusceddu, Medical Oncology Department, Fondazione IRCCS - Istituto Nazionale dei Tumori in Milan, Italy presented findings from a multicentre, retrospective study that assessed the impact of hyperglycaemic versus normoglycaemic status on progression-free survival (PFS) in patients with pancreatic neuroendocrine tumours (pNETs), and evaluated the impact of concomitant metformin administered during everolimus and/or somatostatin analogue therapy. The investigators consulted the database of 24 Italian centres that included 445 patients who received everolimus and/or somatostatin analogue treatment for pNETs between 1999 and 2015. The patients' median age was 59 (range: 49 to 69) years and 53.5% of patients were male.

Of the patients with pNETs, 209 (46.7%) patients were normoglycaemic (non-diabetic) and 236 were hyperglycaemic (diabetic). Of the latter, 112 (25.2%) patients received metformin, 91 (20.4%) received insulin, and 33 (7.7%) patients were given dietetic counselling. The hazard ratio (HR) for risk of progression was calculated at 90% statistical power, with α error of 0.05 to detect risk of 0.67 in 445 hyperglycaemic versus normoglycaemic patients. The statistical power in the analysis of smaller subgroups of hyperglycaemic versus normoglycaemic patients on metformin and hyperglycaemic versus normoglycaemic on insulin was 77% to detect a hazard ratio [HR] of 0.67.

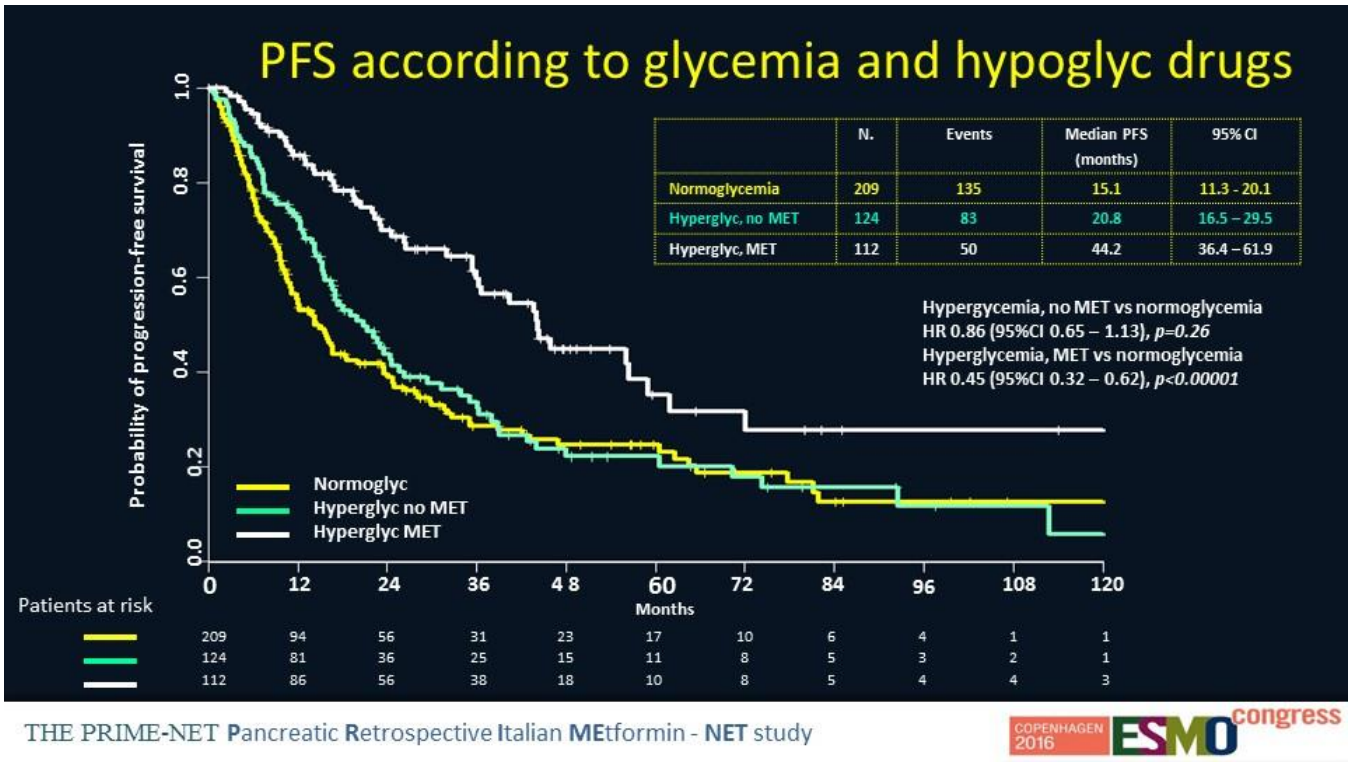
This analysis showed that patients with diabetes on metformin had longer PFS following treatment for pNETS than non-diabetic patients. In the overall population of patients treated for pNETs, median PFS was 23.4 months (95% confidence interval [CI] 19.1, 27.9). However, PFS was prolonged to 32 months in the subgroup of patients who had diabetes compared to just 15.1 months in normoglycaemic patients, HR 0.63; 95%CI 0.50, 0.80 (p = 0.0002).



*THE PRIME-NET **P**ancreatic **R**etrospective **I**talian **Me**tformin (**NET** study) - PFS (normoglycaemic vs hyperglycaemia).*

© Sara Pusceddu.

Patients receiving metformin for diabetes had the lowest risk of pNETs progression compared to non-diabetic patients. Subgroup analysis revealed that diabetic patients on insulin modulating therapy had a prognosis more similar to normoglycaemic patients, with a difference in PFS that was not statistically significant; the median PFS was 20.8 months (95% CI 15.6, 36.3) in patients receiving insulin versus normoglycaemic patients, HR 0.81; 95% CI 0.60, 1.1 (p = 0.18). However, diabetic patients on metformin showed the most prolonged PFS and lower risk of recurrence; PFS was 44.2 months (95% CI 36.4, 61.9) and the HR for progression versus normoglycaemic patients was 0.45; 95% CI 0.32, 0.62 (p< 0.0001).



*THE PRIME-NET **P**ancreatic **R**etrospective **I**talian **Met**formin (**NET** study) - PFS according to glycaemia and hypoglyc drugs.*

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Practice point and future research opportunities

Previous studies have suggested that patients with diabetes have an increased risk of developing cancer; however, metformin, the most widely used treatment in type 2 diabetes mellitus, has been associated with a decrease in cancer risk and has recently emerged as a potential anti-proliferation agent in cancer. Metformin acts by indirectly decreasing both glucose, insulin, and insulin-like growth factor 1 (IGF1) levels, and promoting both AMPK activation and mTOR inhibition by TSC1-2. This study has the limitations of any retrospective analysis but the findings from this large analysis were highly statistically significant and suggest that adding metformin to either everolimus or a somatostatin analogue may provide clinical benefit in patients with diabetes and advanced pNETs. These results warrant a prospective study to confirm these findings.

Genomic analysis of NETs facilitated by the NETwork! translational programme

Lead author Ben Lawrence, University of Auckland Faculty of Medical and Health Sciences in Auckland, New Zealand, presented the first findings of genetic analyses performed within

NETwork! a clinical and ethical framework that was established to support, interpret, and return genomic analyses of neuroendocrine tumours (NETs). This framework includes a national New Zealand registry of NETs that allows clinical annotation and is tethered to a NET-specific multidisciplinary meeting, which facilitates tissue collection. At ESMO 2016, findings were presented from genomic analyses of the first 61 pNETs done using this system. The investigators performed hybridisation capture DNA sequencing on 578 cancer-associated genes, which yielded greater than 750 times coverage, and microarray mRNA expression analysis was also done for all pancreatic NETs (pNETs). Additionally, whole genome sequencing, RNA sequencing, methylation, and microRNA (miRNA) expression analysis were done on 12 tumours. Clinical, pathological and genomic data were compared using a customised bioinformatic platform.

Dr. Lawrence and colleagues detected mutations in 75 cancer-associated genes, with 64 of these mutations being exclusive to individual tumours. Recurrent mutations were found at frequencies of 39% in MEN1 and 7% in ATRX genes. The driver genomic changes in pNETs were highly tumour-specific and included somatic mutations in the FANCA, APC, BRCA2, PTEN, EGFR, MDM4, MSH2 and VHL genes. The investigators also found mutations in ten additional genes that are not traditionally associated with cancer. A high rate of aneuploidy was observed in pNETs samples. Loss of heterozygosity (LOH) was detected in 18% of pNETs, which also showed an identical and previously undescribed pattern of LOH that involved the same ten whole chromosomes.

In depth analyses of the 12 tumours revealed gene expression profiles of immune activation. The investigators found that therapeutic choice as suggested using single biomarkers such as FANCA, and MSH2 could be further informed by multi-level genomics. An example was given of downstream activity negating a treatment decision, where the impact of a PTEN single nucleotide variation (SNV) was negated by LOH in downstream mTOR, thus reducing pathway activity. Another example was given of mTOR hypomethylation and expression changes being consistent with pathway activation. Lawrence *et al.* Abstract 418O

Practice point and future research opportunities

The NETwork! programme, facilitates largescale genomic analyses produced, which provide new insights into NET tumourigenesis. The endpoint is to enable rational and perhaps unexpected therapeutic choice to be applied in clinical trials. pNETs carry fewer genetic mutations compared with other tumour types, but demonstrate genomic alterations, including large-scale copy number, plus changes in epigenetic and gene expression. While mutations occur at a lower frequency in pNETs than other tumour types, the genomic variability uncovered in this study argues for multi-level sequencing of metastatic NETs, which may uncover potentially targetable alterations.

Landscape of pulmonary NETs defined by strategic use of whole-exome sequencing

I.G. Sullivan, Département d'Oncologie Médicale, Gustave Roussy, Villejuif, France,

and colleagues collected paired tumour/normal tissue fresh-frozen samples, including 35 typical carcinoid (TC), 4 atypical carcinoid (AC), and 9 large-cell neuroendocrine carcinoma (LCNEC) from consecutive patients attending 3 European centres between February, 2010 and November, 2013. The investigators selected specimens having more than 65% tumour cells on H&E staining by expert pathologists review, together with the paired sample for genomic DNA (gDNA) extraction. After normalization and quality control, gDNA was captured using in-solution enrichment methodology (Human All Exon V5+UTR–75 Mb, Agilent Technologies), and exome enriched libraries were sequenced on an Illumina HiSeq 2000 with a paired-end 2 x 100 bp protocol. Variants were identified using VarScan2 against the reference genome hg19 (GRCh37). After filtering based on frequency, variants were annotated using SnpEff and SnpSift with dbSNP and dbNSFP.

Typical and atypical carcinoid samples were from females in 59% of cases whereas 89% of LCNEC samples were from males; the patients overall were aged from 18 to 83 years. The samples were from 26 (54%) patients with stage I, 16 (24%) with stage II, 3 (6%) with stage III, and 3 (6%) patients with stage IV disease.

On average, 11.6 Gb of sequence were produced per sample, aiming a mean coverage of 72 X. A median of 277 (range: 10 to 8470) somatic variants per sample was observed, which may potentially represent an actionable target. Preliminary analysis revealed several somatic variants in histone modifiers, including 9 MEN1, 6 EZH2, and 5 HDAC5. Variants in genes involving the SWI/SNF complex, including ARID, BCL-2 and SMARCA were also found and several variants were observed in the PIK3 family of the mTOR pathway. Although, none of the detected alterations were enriched in any pulmonary NET subtype, 6 TP53 and 3 RB1 variants were observed exclusively in LCNEC samples. Sullivan *et al.* Abstract 419O

Practice point and future research opportunities

Treatment of pulmonary NETs remains a clinical challenge making the identification of targetable molecular alterations a priority. This whole exome sequencing study provides insight into the genomic landscape of pulmonary NETs that may open up offering future opportunities for precision medicine in these patients.

Comprehensive genomic profiling reveals paediatric, adolescent and young adult thyroid carcinomas harbour frequent and diverse therapeutically targetable genomic alterations

Lead author Pierre Vanden Borre, Biomedical Informatics, Foundation Medicine, Inc., Cambridge, USA, presented findings from an analysis using hybrid-capture based comprehensive genomic profiling (CGP) on 58 paediatric and young adult (PAYA) thyroid carcinomas. Overall, 64% of patients were female and the median age was 39 years or younger; the median age was 26 (range 7 to 39) years of 41 patients with papillary thyroid carcinoma (PTC), 33 years (range: 25 to 33) years in 3 patients with anaplastic thyroid carcinoma (ATC),

and 14 patients with medullary thyroid carcinoma (MTC) had a median age of 33 years, (range: 15-39).

Genomic alterations occurred at a high frequency and were detected in 93% of samples, with a mean of 1.4 genomic alterations per case. Genomic alterations that were clinically relevant, defined as being associated with at least one actively recruiting clinical trial or an FDA-approved therapy, were identified in nearly all (91%) cases. BRAF V600E was present in 46% of PTCs and in 33% of ATCs. PTC samples also harboured oncogenic fusions in 37% of cases, which were also present in and 33% of ATC cases. Fusions in RET, NTRK1, and NTRK3 had been previously observed in PAYA thyroid carcinoma; this analysis revealed 3 ALK fusions (EML4-ALK, STRN-ALK, and GTF2IRD1-ALK) in patients with PTC. RET mutation occurred in 93% of young adult patients with MTC, including the predominant RET M918T mutation, and 3 insertion/deletions in exons 6 and 11.

Vandetanib was given to 2 patients with MTC who harboured in-frame deletions in RET exons 6 and 11 that resulted in clinical benefit in both patients. Vanden Borre *et al.* Abstract 427PD

Practice point and future research opportunities

Diverse targetable genomic alterations are present at a high incidence in paediatric and young adult patients with thyroid carcinoma; of these, the majority of papillary thyroid cases harboured either activating kinase mutations or rearrangements, including three cases with ALK fusions. Findings from this genomic profiling data, taken together with clinical observations suggest that young patients with advanced thyroid carcinoma can often benefit from comprehensive genomic profiling to identify targetable genomic alterations. Additionally, several alterations were identified that offered the possibility for use of existing targeted therapies, including two cases where treatment was initiated and successful.

RELATED INFORMATION

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Save the date

ESMO 2017 Congress, Madrid, Spain, 8-12 September 2017.

Affiliations and Disclosure

Affiliation

Dr Svetlana Jezdic, ESMO Head Office.

Disclosure

No conflicts of interest to disclose.

Acknowledgment

ESMO would like to thank you Virginia Powers, PhD for editorial assistance in preparation of this report.

ESMO would like to thank you Drs Judith Balmaña, Mark Andrew Glaire, Pierre Laurent-Puig, Sara Pusceddu, Antoni Ribas, Phillipe Rochigneux, Alexa Schrock and Yibing Yan for giving their permission to publish the images from the studies presented during the ESMO 2016 Congress in the ESMO Scientific report.

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