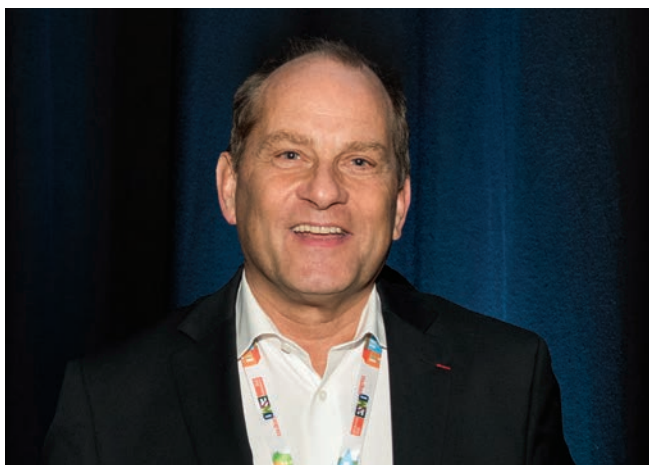
COPENHAGEN 2016 ESMO

SUNDAY 9 OCTOBER, 2016

FROM DISEASE TREATMENT TO PATIENT CARE

DAILY REPORTER



Ipilimumab for melanoma: New data show survival benefit in the adjuvant setting and dose–response in metastatic disease

Important new data from a phase III trial of ipilimumab versus placebo as adjuvant treatment for melanoma were reported in a Late-Breaking Abstract presentation yesterday by Dr Alexander Eggermont from Institut Gustave Roussy, Villejuif, France (Abstract LBA2_PR).

The study randomised 951 patients who had undergone complete resection of stage 3 melanoma to ipilimumab 10 mg/kg (every 3 weeks [q3w] for 4 doses and then every 3 months up to 3 years) or placebo (EORTC 18071). The primary endpoint was met, with a significant improvement in recurrence-free survival (RFS) previously reported.[1] According to the data presented yesterday, at a median of 5.3 years' follow-up, the RFS benefit with ipilimumab versus placebo translated into significant improvements in secondary endpoints, with a 28% reduction in the risk of death (overall survival [OS] hazard ratio [HR] 0.72; 95% confidence intervals [CI] 0.58–0.88; p=0.001) and a 24% reduction in the risk of distant metastases (HR 0.76; 95% CI 0.64–0.92; p=0.002). The 5-year OS rate was 11% higher in the ipilimumab arm (65%) than in the placebo arm (54%). Toxicities were similar to previous reports and included grade 3–4 gastrointestinal (16%), hepatic (11%) and endocrine (8%) adverse events.

Dr Ascierto noted that, "There was a marked improvement in OS with higher-dose ipilimumab in these patients." At a minimum follow-up of ~43 months, median OS (primary endpoint) was 15.7 months (95% CI 11.6–17.8) with 10 mg/kg versus 11.5 months (95% CI 9.9–13.3) with 3 mg/kg (HR 0.84; p=0.04).

"Ipilimumab adjuvant therapy brings a significant improvement of OS and has a favourable risk benefit ratio. It clearly represents a serious option for patients with stage 3 melanoma," commented Dr Eggermont.

"Although patients who received 10 mg/kg ipilimumab experienced higher rates of drug-related toxicity, the clinical utility of such a schedule in refractory patients warrants further evaluation," he added.

The study confirms earlier phase II data with ipilimumab in previously treated advanced melanoma.[2]

1. Eggermont AMM, et al. Lancet Oncol 2015;16:522–30
2. Wolchok JD, et al. Lancet Oncol 2010;11:155–64

Data from the first phase III study to directly compare ipilimumab 10 mg/kg and 3 mg/kg given q3w for 4 doses in patients (N=727) with stage 3–4 melanoma who had not received prior BRAF or immune checkpoint inhibitor therapy were also reported yesterday by Dr Paolo Ascierto from Istituto Nazionale Tumori Fondazione Pascale, Naples, Italy (Abstract 11060).

View the ESMO 2016 Broadcast on the youtube playlist here.

New kids on the block: ESMO début for novel targeted therapies

In spite of the tsunami of checkpoint inhibitors, other targeted agents continue to be developed and 2016 sees the first presentation at ESMO of promising new drugs with potential activity in a variety of solid tumours.

Ahmad Awada: *Jules Bordet Institute, Université Libre de Bruxelles, Belgium*

The aurora A kinase inhibitor, alisertib, was the subject of 3 presentations in sessions on Friday. Adding alisertib to paclitaxel as second-line therapy for small-cell lung cancer (SCLC) prolongs progression-free survival (PFS) compared with placebo plus paclitaxel (hazard ratio [HR] 0.72; 95% confidence interval [CI] 0.522–1.004; p=0.038), with overall survival (OS) and response rate trends also in favour of alisertib (Abstract 14230). In a further presentation, 6 novel MYCL1 fusions were identified by hybrid-capture-based comprehensive genomic profiling of 689 SCLC cases. Investigation of their role as oncogenic drivers is warranted, as well as the value of alisertib as potential treatment (Abstract 14240). Notably, a patient who had failed 3 previous lines of chemotherapy experienced an 18-month near-complete response to alisertib. This drug is also being investigated in neuroendocrine prostate cancer (NEPC), where N-myc and aurora A drive the NEPC phenotype. Single-agent alisertib in 56 evaluable patients with metastatic disease yielded a 6-month PFS rate of 16.3% in patients with pathologically confirmed NEPC (Abstract LBA29). Two patients achieved complete response of liver metastases and a third patient had stable disease at 39 months.

Modulation of the immune system is being used to improve the outcome of cancer patients. Survival and toxicity results from a randomised, double-blind study investigating the benefits of adding the TLR8 agonist, motolimod, to standard platinum/5-fluorouracil/cetuximab for metastatic squamous cell carcinoma of the head and neck showed that the novel combination was generally well tolerated but did not improve PFS or OS for the intent-to-treat population. However, in a subgroup of patients with immune-related motolimod injection-site reaction, addition of the TLR8 agonist significantly increased PFS (216 days versus 181 days, respectively; p=0.005) and OS compared with the standard regimen (Abstract LBA37). Final results from the randomised FAST trial will be presented today. They confirm the clinically relevant benefit of combining in the first-line setting the anti-CLDN18.2 antibody IMAB362 with epirubicin/oxaliplatin/capecitabine (EOX) in the 48% of patients with CLDN18.2-positive advanced/recurrent gastric and gastro-oesophageal junction adenocarcinomas, with significant improvements in PFS (HR 0.47; p=0.0001), OS (HR 0.51; p=0.0001) and ORR (43% versus 28%) compared with EOX alone (Abstract 6140).

Phase I data for a number of other agents are also encouraging. Yesterday, preliminary data for the antibody–drug conjugate PF-06647020 (comprising a humanised PTK7-directed monoclonal antibody, an auristatin microtubule inhibitor payload and a cleavable dipeptide linker) in advanced solid tumours were the subject of a Poster Discussion Session (Abstract LBA35). ORR was 27% in the platinum-resistant ovarian cancer cohort. Another presentation reported the safety of the pan-FGFR inhibitor, BAY 1163877, in patients with advanced solid tumours, and partial responses were recorded in 6/47 RECIST-evaluable patients with FGFR mRNA overexpressing tumours (particularly those with bladder cancer) while at least stable disease (>8 weeks) was documented in 39/47 patients (Abstract 3600_PR). These results are of particular interest due to the response profile that supports the selection of patients based on tumour FGFR mRNA levels. Today, in a Poster Discussion Session, the phase I results of single-agent treatment of advanced solid tumours with the p53/HDM2-protein–protein interaction inhibitor, NVP-CGM097, show clinical activity, with 40% of 50 patients achieving stable disease (range, 7.7–86.7 weeks), along with evidence of p53 pathway activation by induction of its downstream target, GDF-15 (Abstract 366PD).

Clinically relevant benefits can be confirmed with some novel targeted agents and it is hoped that their early promise will be realised in larger studies. Identification of targets involved in cell carcinogenesis, development of potent agents and importantly, patient and tumour enrichment, are cues for therapeutic innovation.

TARGETS OF NOVEL AGENTS

Targets are upregulated/overexpressed or dysfunctional in different cancers

- Aurora kinases are involved in cell-cycle regulation via microtubule formation and stabilisation of the spindle pole. They also interact with the *MYC* proto-oncogene in carcinogenesis.
- Toll-like receptors play a vital role in pathogen recognition and the activation of innate immunity.
- Claudins are involved in the regulation of paracellular permeability, via tight junctions, and cell polarity and signal transductions.
- PTK7 is a receptor tyrosine kinase in the Wnt signalling pathway, which is involved in determining cell function.
- Dysregulation of the fibroblast growth factor signalling pathway is a frequent oncogenic event in multiple tumour types.
- *TP53* is a tumour-suppressor gene frequently inactivated in multiple cancer types. Overexpression of the HDM2 protein is one of the mechanisms of loss of function.

ESMO 2016 DAILY BROADCASTS

Introducing ESMO 2016 Daily Broadcasts on You Tube!

Visit You Tube daily for an overview of sessions not to be missed. Highlights of the day are also captured in a selection of clips from around the congress, including footage of the experts discussing the day's hot topics. Yesterday, these included key sessions on the latest advances in melanoma and supportive and palliative care.

Highlights of the Opening Session are also featured and include a warm welcome from the Prime Minister of Denmark, as well as the recipients of the ESMO 2016 Awards.

Lapatinib in HER2-positive digestive tract cancers: **Moving on to phase III development?**

Combination platin-based perioperative chemotherapy plus surgery is the standard of care for patients with operable oesophagogastric adenocarcinoma.[1] For those patients with advanced gastric or gastro-oesophageal junction (OGJ) cancer who are positive for HER2, targeting it with trastuzumab improves survival.[2] Yesterday, Professor Eric Van Cutsem presented data from a poster by Dr Elizabeth Smyth at The Royal Marsden NHS Foundation Trust, London, UK (Abstract LBA26) that sought to determine whether adding the dual HER1/HER2 tyrosine kinase inhibitor, lapatinib, to epirubicin, cisplatin plus capecitabine (ECX) was feasible in HER2-positive patients with operable, gastric or OGJ cancer, or lower oesophageal adenocarcinoma.

In this phase II, open-label study, 46 patients were randomised to three pre- and three post-operative ECX cycles, or investigational treatment with ECX plus lapatinib 1,250 mg/day during each chemotherapy cycle and for 6 further maintenance cycles. In the ECX plus lapatinib arm, 4/20 patients required lapatinib dose reduction and 4/19 patients experienced diarrhoea of grade 3 or higher (versus no patients in the ECX arm). Although this regimen was feasible, whether lapatinib will proceed to phase III development in this setting is currently undecided.

While new potential cancer treatments are a cause for optimism, some caution should be exercised. Toxicity associated with lapatinib and ECX can be high, leading some clinicians to call into question its suitability as a combination therapy in new drug development; similar toxicity data were reported with adjuvant lapatinib in patients with HER2-positive early breast cancer (ALTTO trial).[3]

1. Glatz T, et al. Eur J Surg Oncol 2015;41:1300–7
2. Bang YJ, et al. Lancet 2010;376:687–97
3. Piccart-Gebhart M, et al. J Clin Oncol 2016;34:1034–42

ESMO Open Meet the Editor, Christoph Zielinski - today at 12.30 at the ESMO Booth

Shedding light on endocrine therapy sequencing for **advanced breast cancer**

Dr Nicholas Turner: Royal Marsden NHS Foundation Trust and Institute of Cancer Research, London, UK

The optimal sequencing of treatment for hormone therapy-naïve, post-menopausal women with hormone receptor-positive advanced breast cancer needs to be confirmed, particularly in view of practice-changing Late-Breaking Abstracts presented yesterday with results from two randomised phase III trials.

In the first presentation of results from the large MONALEESA-2 trial in 668 patients with untreated hormone receptor-positive/HER2-negative disease, Professor Gabriel Hortobagyi from the University of Texas MD Anderson Cancer Center, Houston, Texas, USA, reported progression-free survival (PFS) benefit with the addition of the selective CDK4/6 inhibitor ribociclib to letrozole (Abstract LBA1_PR). In a pre-planned interim analysis (after 243 PFS events) the hazard ratio (HR) was 0.556 (95% confidence interval [CI] 0.429–0.720; p=0.00000329) in favour of letrozole plus ribociclib. Ribociclib increased the rate of grade 3–4 neutropenia (59% versus 1%) and leukopenia (21% versus 1%) compared with letrozole alone.

The CDK4/6 inhibitors, including palbociclib (approved by the US FDA) and abemaciclib, are changing the breast cancer treatment landscape. "Testing combinations of ribociclib with other inhibitors of various signalling pathways might lead to additional progress in the management of several subtypes of breast cancer," suggested Professor Hortobagyi.

According to results from the large FALCON trial presented earlier in the day by Dr Matthew Ellis from Baylor College of Medicine, Houston, Texas, USA, fulvestrant is significantly more effective than anastrozole in hormone treatment-naïve patients with oestrogen receptor-positive and/or progesterone receptor-positive, locally advanced or metastatic breast disease (Abstract LBA14_PR). Among 462 patients randomised, fulvestrant significantly reduced the chance of progression compared with anastrozole (HR 0.797; 95% CI 0.637–0.999; p=0.0486), with median PFS times of 16.6 months and 13.8 months, respectively.

No significant difference in overall survival was observed. Health-related quality of life was similar in both arms.

The results of these two studies are practice changing, yet they propose two different standards for the initial treatment of hormone therapy-naïve disease, with fulvestrant or with aromatase inhibitor-CDK4/6 inhibitor combinations. Further studies are going to be required to establish the optimal sequence of these agents, and help clinicians select the most appropriate therapy.

Dr Ellis proposed: "For patients with non-visceral disease whose life isn't immediately threatened by breast cancer…it looks like fulvestrant could be a new standard of care compared to anastrozole."

Medscape ESMO 2016 live blog: Real-time expert perspectives

Top to bottom: **Dr Matthias Preusser** (Medical University of Vienna, Austria); **Dr Stefan Zimmerman** (HFR Fribourg-Cantonal Hospital, Switzerland); **Dr Floriana Morgillo** (Second University of Naples, Italy); **Dr Markus Joerger** (St Gallen Cancer Centre, Switzerland).

Throughout the congress this year, many esteemed experts, including members of the ESMO 2016 Daily Reporter Editorial Board will be contributing to the Medscape live blog that will feature personal experiences, highlights and must-see presentations at ESMO 2016. These multidisciplinary blog entries incorporate perspectives across disease areas and give concise personal observations about the data releases and events as they happen.

Blogs include an account of upcoming Young Oncologist (YO) Track activities and ongoing highlights of the central nervous system (CNS) track from YO Committee Chair, Dr Matthias Preusser (Medical University of Vienna, Austria). Dr Stefan Zimmerman (HFR Fribourg-Cantonal Hospital, Switzerland) gives a no-nonsense precis of the current status of biomarkers for immunotherapeutic outcomes, asserting that gene signatures offer the best hope for treatment tailored to the individual patient.

Dr Floriana Morgillo (Second University of Naples, Italy) discusses basic science and translational research, including the Personalised OncoGenomics study, as well as giving us a timely reminder that precision medicine comes at a high financial cost. Dr Markus Joerger (St Gallen Cancer Centre, Switzerland) summarises the importance of multi-institutional studies, and basket and umbrella trial designs to assess new therapies for rare and under-treated cancers.

Read the ESMO 2016 Medscape blog here.

Defining meaningful benefits: **Diverse contributions to treatment decision making**

Making treatment decisions requires consideration beyond efficacy and safety, with increasing importance placed on quality of life, cost-effectiveness and patient acceptance.

Professor Jean-Yves Blay:
Centre Léon Bérard, Lyon, France

The ESMO Magnitude of Clinical Benefit Scale (ESMO-MCBS) is a standardised, generic tool to stratify the magnitude of clinical benefit that can be anticipated with novel cancer treatments.

Value in healthcare, and particularly in cancer care, is a huge public policy issue and the ESMO-MCBS aims to assist with public policy making and accelerate patient access to the best new medications. A feasibility study of 77 regimens across 10 cancer types indicated that the ESMO-MCBS was a rational and useful rating system in this regard.[1]

Hear Dr Kiesewetter present the results from the real-life experience of applying the ESMO-MCBS to rare tumour treatment; 'Public health and health economics' Proffered Paper Session, Monday 16.30 – 18.00, Oslo.

Dr Barbara Kiesewetter of the Medical University of Vienna, Austria will report tomorrow on the use of the ESMO-MCBS to direct real-world practice by ranking medications used regularly to treat rare tumours ranging from neuroendocrine tumours and glioblastoma, to sarcomas and urothelial cancer (Abstract 1364O).

Unsurprisingly, data were sparse for some tumour types but rankings largely accorded with clinic-based experience, further validating the ESMO-MCBS.

While the ESMO-MCBS is a useful objective tool, it cannot consider the magnitude of clinical benefit from the patient's perspective. Involving patients in treatment choices is an essential aspect of the medical team's work. Patients differ wildly in what they are willing to tolerate for a given level of clinical improvement and subjective perceptions of risk and benefit are foremost in their treatment decision making.

As we continue to take giant steps in oncology, it is important that we take a holistic approach by considering the sensitivities of our patients to make the best therapeutic choices. Randomised clinical trials are essential to establish the magnitude of clinical benefit even in rare tumours.

1. Cherny NI, et al. Ann Oncol 2015;26:1547–73

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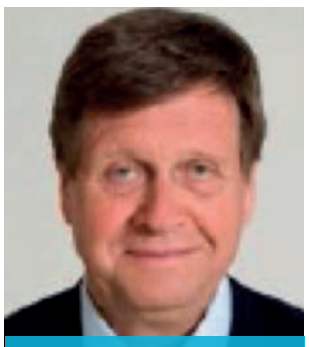
Continued advances in pulmonary and midgut neuroendocrine tumours



Professor Kjell Öberg: Department of Medical Sciences, Uppsala University, Sweden

Targetable molecular alterations have not been well defined in pulmonary neuroendocrine tumours (NETs) and treatment is challenging, with limited therapeutic options. The current available treatment options for pulmonary NETs have originally been developed from the treatment of small and non-small-cell lung cancer. Therapies that have also been developed for gastrointestinal NETs have been applied in different trials, but in general there are very few randomised trials concerning pulmonary NETs. Some of the pulmonary NETs are more aggressive than other NETs and very little is known about the genetic changes and molecular mechanisms responsible for their development. So far, in grouping together pulmonary NETs with gastrointestinal NETs, the results in terms of progression-free (PFS) and overall survival have been dismal.

I think it is very important to determine the driver mutations in most cancers and particularly so in pulmonary NETs, where there have been very limited therapeutic options in the past.

Advanced midgut NETs that have progressed on somatostatin analogue therapy are similarly challenging to treat. The Lu-177-labeled somatostatin analogue peptide, ^{177}Lu-DOTATATE (Lutathera®), a peptide receptor radionuclide therapy, was recently associated with significant improvements in PFS in the phase III NETTER-1 trial.[1] In a presentation tomorrow (Poster Discussion Session 'Endocrine and neuroendocrine tumours' 11.00 – 12.00, Berlin; Abstract 420PD), a poster by Dr Jonathan Strosberg from H. Lee Moffitt Cancer Center University of South Florida, Tampa, Florida, USA, will review additional analyses from this study. ^{177}Lu-DOTATATE therapy appears to be associated with a moderate improvement in global health status, suggesting that the observed clinically meaningful PFS benefit is not offset by a detrimental impact on patient quality of life. Notably, significant increases in PFS are seen with ^{177}Lu-DOTATATE regardless of prognostic factors, including tumour grade, age, gender, tumour marker levels, and levels of radiotracer uptake. ^{177}Lu-DOTATATE can also be considered a potential agent to be combined with immune checkpoint inhibitors. Its on-target activity and the potential for cell death induced by radiotherapy may enhance immune checkpoint activity.

Precision medicine in NETs is the topic of a Special Symposium 'Precision medicine in NETs: Myth or reality?' chaired by Dr Rocio Garcia-Carbonero (Madrid, Spain) and Professor Kjell Öberg (Uppsala, Sweden) today (16.30 – 18.00, Oslo).

Tomorrow. in a Proffered Paper Session **'Endocrine and neuroendocrine tumours' (16.30 – 18.30, Rome; Abstract 4190)**, Dr Ivana Sullivan from Institut Gustave Roussy, Villejuif, France will describe how the use of whole-exome sequencing (WES) may provide new insights into the genetic landscape of pulmonary NETs and therefore provide much needed opportunities for precision medicine in this setting.

WES identified many somatic variants, while two variants (*TP53* and *RB1*) were observed exclusively in specimens collected from patients with large-cell neuroendocrine carcinoma.

Today, it is very common that so-called genomic profiling is provided for various malignant diseases to determine which treatments are relevant. This is particularly important for patients who have already received first- or second-line treatment for their disease. Therefore, data from genomic profiling of pulmonary NETs should inform about its molecular landscape. It might indicate areas (genetic mutations) that are druggable.

The NETTER-1 study is the first randomised, controlled study with radioactive targeted treatment that has clearly demonstrated a significant benefit for ^{177}Lu-DOTATATE compared with cold octreotide in patients with NETs. Previously, a large number of patients with NETs have been treated with this compound but not in a randomised fashion. Therefore, data have not been very robust or suitable to satisfy regulatory bodies. It is quite clear that there is a significant benefit in terms of PFS with the radioactive treatment compared with (even high-dose) cold octreotide. Importantly, quality of life is also significantly improved. Therefore, this type of treatment will be a worldwide standard of care in the near future for patients with small intestinal NETs. Similar data are anticipated soon for pancreatic NETs.

1. Strosberg J, et al. Eur J Cancer 2015;51(Suppl 3):S710. Abstract LBA6

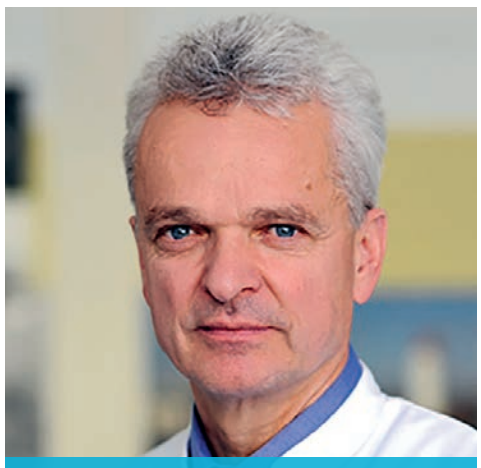
ESMO Focus Talks

Sunday 9 October, 10.45
Professor Rossana Berardi (Italy) and Professor Ulrik Lassen (Denmark)
Setting standards in medical oncology training: the 2016 edition of the ESMO/ASCO Global Curriculum

Monday 10 October, 12.30
Dr Erika Martinelli (Italy) and Antonio D'Alessio (Italy)
Your career in oncology, with ESMO by your side

All sessions will take place at the ESMO Booth in the Society Village.

Addition of ipilimumab to cetuximab and radiotherapy **appears well tolerated in previously untreated head and neck cancer**



Professor Ulrich Keilholz: *Charité Comprehensive Cancer Center, Berlin, Germany*

The combination of cetuximab, radiotherapy and immune checkpoint inhibitors represent a potentially powerful new treatment paradigm. However, the risk of development of autoimmune adverse events with 'afferent' inhibitors, such as the anti-CTLA-4 agents, necessitates careful execution of clinical studies.

Data from a phase I dose-escalation study in previously untreated locally advanced squamous cell carcinoma of head and neck (SCCHN) suggest that standard cetuximab and intensity modulated radiotherapy (C-IMRT) may be safely combined with ipilimumab (1 mg/kg) in patients with intermediate- or high-risk disease, according to a Late-Breaking Abstract poster yesterday by Dr Julie Bauman from UPMC Hillman Cancer Center, Pittsburgh, Philadelphia, USA (Abstract LBA36). However, dermatological immune-related adverse events (irAEs) unique to this combination and likely reflective of autoimmune effects were observed at ipilimumab 3 mg/kg and were dose-limiting. Among 12 patients receiving ipilimumab 1 mg/kg, there were no dose-limiting toxicities in the first 6 patients and one anaphylactic reaction to cetuximab in the expanded cohort. Grade 3–4 irAEs of special interest occurring with both doses were rash (28%), diarrhoea (6%) and colitis (6%).

The recommended phase II dose for ipilimumab in combination with standard C-IMRT is 1 mg/kg.

The observation that immunosuppressive regulatory T-cells found in the circulation of patients with SCCHN expressing CTLA-4 are negatively correlated with clinical outcomes[1,2] has led to the innovative use of checkpoint inhibitors in SCCHN but, until now, development has been overwhelmingly in the recurrent or metastatic setting.

Combinations of standard treatment with the 'efferent' checkpoint inhibitors, PD-1 and PD-L1, are now required to establish if they have a preferred safety profile in this setting.

1. Trivedi S, et al. Ann Oncol 2015;26:40–7
2. Strauss L, et al. Clin Cancer Res 2007;13:6301–11

A changing landscape in the treatment of metastatic melanoma

The introduction of the kinase inhibitors vemurafenib, dabrafenib and trametinib, and the immune checkpoint inhibitor ipilimumab, has had a hugely favourable impact on the prognosis of patients with metastatic melanoma. Several trials are investigating these and other novel therapies to determine optimal regimens for specific melanomas.

Positive late-breaking data from a phase III trial of combination therapy for melanoma were reported yesterday by Dr Caroline Robert from Gustave Roussy Comprehensive Cancer Center, Villejuif, France (Abstract LBA40). In the COMBI-v study of 704 patients with *BRAF V600E/K*-mutant melanoma, results of an updated 3-year analysis revealed an increased rate of overall survival with first-line dabrafenib plus trametinib compared with vemurafenib (45% versus 32%, respectively) with no apparent increase in toxicities.

Tomorrow, Dr Axel Hauschild will present promising data from a poster by Dr Jason Chesney (Brown Cancer Center University of Louisville, Kentucky, USA; Abstract 1108PD) reporting a phase II study of combined immunotherapy with herpes simplex virus 1-based oncolytic talimogene laherparepvec and ipilimumab compared with ipilimumab alone in 173 patients with unresected stage IIIB IV melanoma. In an interim analysis (median follow-up 61.2 weeks) of 82 patients, the confirmed objective response rate was higher with the combination (35.7%) than with ipilimumab alone (17.5%). Adverse events were comparable across the treatment arms.

The 3-year overall survival results support the long-term use of dabrafenib in combination with trametinib for the first-line treatment of *BRAF*-mutant melanoma.

In the same session, Dr Christian Blank will present a poster by Dr John Park (Crown Princess Mary Cancer Centre, Westmead Hospital, Sydney, Australia; Abstract 1114PD). This retrospective analysis (median follow-up 7.0 months) of 66 patients with brain metastases from melanoma and poor prognoses who were treated with anti-PD-1 therapy suggests that immune checkpoint inhibitors may have a role in this setting. The intracranial response rate was 20%, while the disease control rate was 56%. If confirmed, these could be important data for patients who are frequently excluded from immunotherapy trials.

Both abstracts will be presented tomorrow at the Poster Discussion Session **'Melanoma and other skin tumours' (11.00 – 12.00, Rome).**

Remember to attend the Educational Session 'Melanoma: Does the run of success continue?' today at 14.45 – 16.15, Stockholm

Targetable *BRAF* genomic alterations: Identified in breast cancer

Evandro de Azambuja: *Associate Editor of the ESMO 2016 Daily Reporter. Jules Bordet Institute, Brussels, Belgium*

BRAF genetic alterations (GA) have not been considered therapeutically relevant in patients with breast cancer so far, in contrast to other solid tumours such as advanced melanoma, non-small-cell lung cancer and colorectal cancer where its role in targeting therapies is well defined.

While uncommon, *BRAF* GA do occur in breast cancer and might be potentially targetable. This is the conclusion of a comprehensive genomic profiling analysis of 7,850 tumours that identified *BRAF*-altered breast cancer in 83 (1.1%) cases, including primary (35%) and metastatic (65%) sites. GA identified following profiling of >300 cancer-related genes included base substitutions, small insertions and deletions, copy number alterations and fusions/rearrangements. Targetable genes more commonly altered in the presence of *BRAF* GA compared with *BRAF* wild type breast cancer were *CDK6* (p=0.001), *HGF* (p<0.001) and *MET* (p<0.001), while there were significantly fewer *ERBB2* mutations in tumours with *BRAF* amplification or substitution (p=0.011). Notably, *BRAF* GA appeared to occur most commonly in HER2-negative and triple-negative metastatic breast cancers. Of the 83 cases with *BRAF* GA, 15.7% were *V600E* substitutions that have been shown to predict response to BRAF inhibitors or the combination of BRAF and MEK inhibitors in melanoma and non-small-cell lung cancer. It remains unclear whether *BRAF V600E* GA may also predict response to these oral anticancer drugs in breast cancer.

While uncommon, *BRAF* genomic alterations do occur in breast cancer and might be potentially targetable.

BRAF has been well studied as a potential treatment target in several tumour types, but the genomic landscape of breast cancer is complex and the role of *BRAF* remains to be fully elucidated.

These hypothesis-generating data will be discussed today by Dr Luis Costa based on a poster by Dr Joan Albanell from Institut Hospital del Mar d'Investigacions Mèdiques, Barcelona, Spain, during the Poster Discussion Session **'Breast cancer, metastatic' (16.30 – 17.30, Brussels; Abstract 228PD).**

Faces in the crowd

Delegate **voices**

“I am a young oncologist and this is the first meeting I have attended. I have to say ‘Wow!’”

Magdelena Derus, Medical Oncologist, Opole, Poland

“My main reasons for coming to ESMO are to find out about clinical trials and hot topics. The programme so far is good.”

Rubina Ahmed, Cancer Research UK, London

“I have come to ESMO for networking opportunities, for the brilliant minds here and for a peek into future trends.”

Adeola Ayoola, Medical Oncologist, Bedford Park, Australia

“This is the biggest event I’ve ever attended and my first impressions are that it is very well organised. I’m particularly interested in the Young Oncologist Track.”

Kamil Zalewski, Swietohrzyskie, Kielce, Poland

“I’m looking forward to hearing about latest news on immunotherapy in gastrointestinal tumours.”

Mohammed Harb, Chief of the Division of Medical Oncology, Moncton Hospital, Canada

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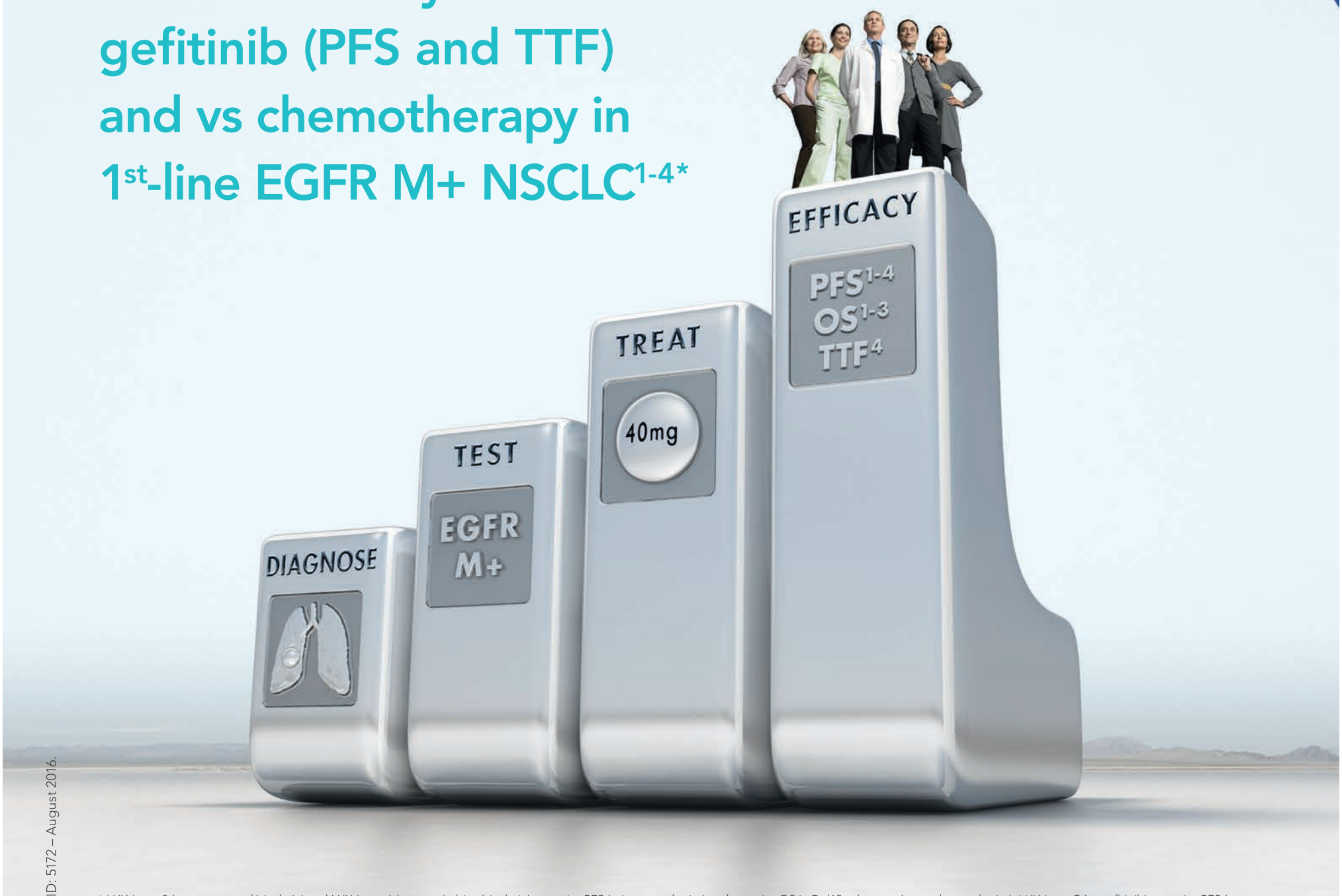

* LUX-Lung 3 (vs pemetrexed/cisplatin) and LUX-Lung 6 (vs gemcitabine/cisplatin): superior PFS (primary endpoint) and superior OS in Del19 subgroup (secondary endpoint); LUX-Lung 7 (vs gefitinib): superior PFS (co-primary endpoint).

GIOTRIF® Abbreviated European Prescribing Information. Please refer to local prescribing information as it may vary between countries. Different brand names are used in some countries. Presentations: Film-coated tablets each containing 20 mg, 30 mg, 40 mg or 50 mg afatinib (as dimaleate). Indication: GIOTRIF® as monotherapy is indicated for the treatment of Epidermal Growth Factor Receptor (EGFR) TKI-naïve adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating EGFR mutation(s); locally advanced or metastatic NSCLC of squamous histology progressing on or after platinum-based chemotherapy. Posology and method of administration: EGFR mutation status should be established prior to initiation of GIOTRIF®. Recommended dose is 40 mg oral once daily to be taken without food. Dose escalation to a maximum of 50 mg/day may be considered in patients who tolerate 40 mg/ day. Symptomatic adverse reactions may be successfully managed by treatment interruption and dose reductions or treatment discontinuation. No starting dose adjustment necessary in patients with mild or moderate renal or hepatic impairment. Not recommended in patients with severely impaired renal function (< 30 mL/min creatinine clearance), severe hepatic impairment, children or adolescents. Contraindications: Hypersensitivity to afatinib or to any of its excipients. Special warnings and precautions for use: Diarrhoea, including severe diarrhoea, and rash/acne may require interruption and dose reduction or discontinuation of therapy. Higher exposure to afatinib has been observed in female patients, patients with lower body weight and those with underlying renal impairment. Interstitial Lung Disease (ILD) or ILD-like adverse reactions, including fatalities, have been reported in patients receiving GIOTRIF®. If ILD is diagnosed, permanently discontinue GIOTRIF®. Discontinue GIOTRIF® in patients who develop severe hepatic impairment. If keratitis is diagnosed, the benefits and risks of continuing treatment should be carefully considered. Cardiac monitoring, including an LVEF assessment, should be considered in patients with cardiac risk factors and patients who develop relevant cardiac signs/symptoms during treatment. GIOTRIF® contains lactose. Interactions: P-gp inhibitors should be administered using staggered dosing, preferably 6 hours or 12 hours apart from GIOTRIF®. Strong inducers of P-gp may decrease exposure to afatinib. It is unlikely that GIOTRIF® changes the plasma concentrations of other P-gp substrates. GIOTRIF® may increase the bioavailability of orally administered breast cancer resistance protein (BCRP) substrates. Fertility, pregnancy and lactation: Women of childbearing potential should be advised to avoid becoming pregnant. No or limited amount of data are available from use in pregnant women. The risk for humans is thus unknown. Advise against breast-feeding while receiving GIOTRIF®. An adverse effect on fertility cannot be excluded. Effects on ability to drive and use machines: Minor influence. Undesirable effects: Very common: diarrhoea, rash, dermatitis acneiform, pruritus, dry skin, epistaxis, decreased appetite, paronychia. Common: cystitis, dehydration, hypokalaemia, dysgeusia, conjunctivitis, dry eye, rhinorrhoea, dyspepsia, cheilitis, alanine aminotransferase increased, aspartate aminotransferase increased, palmarplantar erythrodysaesthesia syndrome, muscle spasms, renal impairment/renal failure, pyrexia, weight decreased. Uncommon: keratitis, interstitial lung disease. Liver function test abnormalities including elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were observed. Overdose: dermatological (rash/ acne) and gastrointestinal events (especially diarrhoea). Marketing Authorisation Number(s): EU/1/13/879/001 to EU/1/13/879/012. Marketing Authorisation Holder: Boehringer Ingelheim International GmbH, Binger Strasse 173, D-55216 Ingelheim am Rhein, Germany. Date of last revision of prescribing information: 24/05/2016.

Afatinib is approved in a number of markets, including the EU, Japan, Taiwan and Canada under the brand name GIOTRIF® and in the US under the brand name GIOTRIF®. In Europe it is approved for: 1) the treatment of epidermal Growth Factor Receptor (EGFR) TKI-naïve adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating EGFR mutation(s); 2) locally advanced or metastatic NSCLC of squamous histology progressing on or after platinum-based chemotherapy. Registration conditions differ internationally, please refer to locally approved prescribing information. Afatinib is under regulatory review by health authorities in other countries worldwide. Afatinib is not approved in other indications. The compulsory product information is freely available at the booth.

EGFR M+=epidermal growth factor receptor mutation positive; NSCLC=non-small cell lung cancer; PFS=progression-free survival; OS=overall survival; TTF=time to treatment failure.

1. Yang JC et al. Lancet Oncol. 2015;16(2):141-51.
2. Sequist LV et al. J Clin Oncol. 2013;31(27):3327-3334.
3. Wu YL et al. Lancet Oncol. 2014;15(2):213-22.
4. Park K et al. Lancet Oncol. 2016;17(5):577-89.

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GIOTRIF® (afatinib) tablets
RAISING EXPECTATIONS