MUNICH 2018 ESMO

DAILY REPORTER

SECURING ACCESS TO OPTIMAL CANCER CARE

FRIDAY
19 OCTOBER 2018

Today's Top Picks

Welcome to the ESMO 2018 Congress

Josep Tabernero
ESMO President

I am delighted and proud to welcome you to ESMO 2018. This year, we expect an attendance of over 26,000 oncology professionals from all over the world, spanning a range of disciplines, fields and stakeholder groups. In addition to the presentation of latest ground-breaking results and practice-changing data, our Congress represents an essential platform for collective discussions on how best to secure optimal care for every patient with cancer.

ESMO advocates for access by all patients, wherever they live and whenever they need it, to the right clinical expertise and medicines. The latest advances should be available to all and crucial to this is ESMO's portfolio of specialised education for oncologists.

Sharing data, different experiences, perspectives and best practices will trigger the ideas that will ultimately translate into optimal care.

The ESMO 2018 Congress programme achieves the perfect balance and blend of a comprehensive educational programme and a platform for the delivery and debate of the very latest international oncology research.

Among the myriad must-attend sessions are 'Big data in cancer management: Genomics and disease stratification', 'Technologies of the future' and 'Emerging opportunities in cancer immunotherapy', and Keynote Lectures 'Beyond resistance in immune-oncology' and 'How do we manipulate the tumour microenvironment for immunotherapy'. For our junior colleagues, I strongly recommend attending the Young Oncologists track, which builds on previous years' successes. Importantly, in view of the widely documented issue of burnout among younger oncologists, this year's Vesalius Talk will tackle 'Work/life balance at early stages of a young oncologist's career'.

To aid policy-informing discussions regarding affordable, accessible and sustainable models of cancer care, the ESMO–DGHO (German Society of Haematology and Medical Oncology) Joint Symposium 'Access to anti-cancer drugs' will present current strategies used in Germany to manage access, shortages and pricing of innovative medicines.

This year we have collaborated with the European Oncology Nursing Society (EONS) to offer a dedicated 3-day nursing track, which highlights the central role of nurses in our multidisciplinary teams, as well as the critical need to further strengthen collaboration between nurses and medical oncologists in our shared ambition of offering access to optimal care to all patients. Additionally, the ESMO Patient Advocacy track emphasises the key part patients play in this endeavour.

I encourage you to engage with colleagues from other disciplines, lend your voice to the stimulating conversations that will follow, and seize on the many great educational, scientific and multidisciplinary networking opportunities on offer. I look forward to spending the next few days with you all and hope that you also enjoy wonderful Munich as the host city of our 2018 Congress!

Markus Joerger
Editor-in-Chief of the ESMO 2018 Daily Reporter, Cantonal Hospital, St. Gallen, Switzerland

Introducing the *Daily Reporter* editorial team

Welcome to Munich and the ESMO 2018 Congress! As always, the Editorial Team at the *Daily Reporter*—the official Congress newspaper—will be at hand to help you navigate the jam-packed scientific and educational programmes to ensure you don't miss a thing!

Bringing you a wide variety of articles across five editions, the newspaper reflects the broad content of ESMO 2018 and will feature hot topics in medical oncology, including important new data relating to specific organ sites. Expert commentaries will also offer a clinical perspective to help you better understand and apply key research findings in your daily oncology practices. Excitingly, this year we welcome five new members to the Editorial Team and look forward to sharing some fresh ideas and expertise, particularly in our daily editorials that should help you put latest data into context. On behalf of the *Daily Reporter* Associate Editors—Anna Maria Frezza, Carmen Criscitiello, Alessandra Curioni, Matteo Lambertini, Rodrigo Dienstmann and Jon Zugazagoitia—I hope we can assist you in making ESMO 2018 a truly memorable experience!

Don't forget to collect your copy of the *Daily Reporter* each morning from one of the stands around the Congress centre!

Look out for ESMO 2018 Congress TV

Available onsite and on the ESMO YouTube channel

YouTube

Challenge Your Expert: Metabolic targets in cancer

Understanding how cancer cells metabolically transform to allow rapid tumour growth is key to developing new, targeted therapeutic approaches. In this Challenge Your Expert Session, you will have the opportunity to speak to a leading expert in cell biology and metabolomics: Professor Eyal Gottlieb from the Israel Institute of Technology, Haifa. Do you want to ask about the role of the tumour microenvironment? Pathways of nutrient utilisation and metabolism that are essential for cancer cells? The interaction between metabolism and epigenetics in cancer? How can knowledge about cancer cell biology contribute to the development of anticancer therapies?

Don't miss tomorrow's Challenge Your Expert Session, 'Metabolic targets in cancer', Saturday, 20 October 08.00 – 09.00, Hall B3, Room 22.

Heated discussions in ovarian cancer

Hyperthermic intraperitoneal chemotherapy (HIPEC) is currently being investigated as a potential new treatment approach for ovarian cancer. This is a particularly lethal gynaecological malignancy; at diagnosis most patients have evidence of disease spread beyond the ovaries to the peritoneal surface. Intraperitoneal delivery of chemotherapy following primary cytoreductive surgery has shown survival benefits when combined with intravenous chemotherapy, but uptake has been hindered by gastrointestinal/renal side effects, catheter-related problems and inconvenient administration.[1] Delivery of intraperitoneal chemotherapy during surgery under hyperthermic conditions (i.e. heated chemotherapy) is believed to increase chemotherapy penetration and the sensitivity of cancer to treatment. Recurrence-free and overall survival benefits, without increased toxicity or reduced quality of life, were reported recently following the addition of HIPEC to interval cytoreductive surgery in a phase III study of patients with stage III epithelial ovarian cancer.[1]

1. van Driel WJ, et al. N Engl J Med 2018;378:230–40

Hear more from the experts and cast your vote on the feasibility of this hyperthermic treatment approach in the Controversy Session tomorrow, 'HIPEC – is there a role in ovarian cancer?'

Saturday, 20 October 08.00 – 09.00, Hall A1 – Room 15.

ESMO 2018 Wi-Fi access

Wi-Fi access is free to the ESMO Congress delegates.

Connection information:
Network name (SSID): ESMO2018
No authentication is needed once selected

EONS welcomes oncology professionals

Lena Sharp
EONS President. Regional Cancer Centre, Stockholm-Gotland and Karolinska Institute, Stockholm, Sweden

In an exciting collaboration aimed at fostering educational exchange and teamwork, the 11th European Oncology Nursing Society (EONS11) Congress is taking place alongside ESMO 2018.

Lena Sharp, EONS President, commented, "We are delighted to collaborate with ESMO this year to offer cancer nurses a unique opportunity to benefit from sessions at the ESMO Congress. In addition, we at EONS are very proud of the dedicated 3-day cancer nursing track we have developed that is designed to be of interest and benefit to physicians as well as nurses."

Participants are strongly encouraged to attend sessions from both programmes, allowing cancer nurses and oncologists to understand the challenges faced by each other and share optimal practices in their own healthcare teams.

Today, nurses play an active role in person-centred care, often managing the side effects of therapy and offering patients and their families support and guidance. Through mutual understanding and collaboration, physicians and nurses can work in teams to provide the best care for their patients.

Dr Sharp highlights some of the insights oncologists can gain from EONS11, "The programme includes major themes of cancer nursing leadership and cancer nurse roles, amongst others. There are sessions covering how nurses can successfully lead cancer services—for example, cancer nurse-led services have proven to provide safe, high-quality cancer care—and sessions on managing complex symptom burden related to multimodal cancer treatment."

Cancer care has become more complex with the introduction of precision therapies and diagnostic tools, alongside restricted healthcare budgets and new healthcare policies, which must be balanced against the psychosocial and educational needs of patients and caregivers. Optimal nurse–physician collaboration is essential. It is hoped that oncologists attending EONS11 will benefit from the valuable perspectives and insights that nurses can bring to the team.

An EONS Press Conference will take place on Friday, 19 October at 16.00 in the Press Conference Room, Press West Entrance, Second Floor. All journalists are welcome to attend and find out more about EONS and EONS11.

EGFR mutations: Optimising targeted therapy for NSCLC

Rodrigo Dienstmann
Associate Editor of the ESMO 2018 Daily Reporter, Vall d'Hebron Institute of Oncology, Barcelona, Spain

Somatic mutations of the *EGFR* gene are detected in a subgroup of patients with non-small-cell lung cancer (NSCLC)[1] and recent advances have proved that the EGFR-dependent signalling pathway plays an important role in the development and progression of NSCLC. Targeted therapeutic agents, such as the *EGFR* targeting tyrosine kinase inhibitors (TKIs) gefitinib, erlotinib, afatinib and osimertinib, have transformed the management of patients with NSCLC and *EGFR* mutations, and represent one of the most significant advances in lung cancer treatment in decades.

These drugs have demonstrated significant improvements in objective response rates and progression-free survival following treatment with EGFR-TKIs when compared to platinum-based chemotherapy in patients with advanced NSCLC and *EGFR* mutations. However, disease progression eventually occurs, and novel therapeutic strategies are therefore needed.[2] Mechanisms of acquired resistance to these first- and second-generation EGFR-TKIs have been identified. The most common is the presence of a mutation in the ATP-binding pocket of the *EGFR* gene, namely T790M. Based on this, a third-generation EGFR-TKI has been developed: osimertinib. This agent appears to overcome resistance to first-generation EGFR-TKI but has also demonstrated superior progression-free survival compared with first-generation EGFR-TKIs in the first-line setting.[3]

It is important to understand further mechanisms of resistance, including additional mutations in *EGFR*, activation of alternative signalling pathways, and phenotypic or histologic transformations. As multiple resistant mechanisms may be involved, combination and multitargeted therapeutics may be promising strategies to overcome acquired resistance to EGFR-targeting TKIs.[4] Furthermore, as our understanding of *EGFR* mutations and mechanisms of treatment resistance grows, determining the best therapeutic approach for such patients is crucial.

1. Lynch TJ, et al. New Engl J Med 2004;350:2129–39
2. Soo RA, et al. Lung Cancer 2018;115:12–20
3. Economopoulou P, Mountzios G. Ann Transl Med 2018;6:138
4. Xu J, et al. Oncotarget 2017;8:90557–78

Don't miss tomorrow's Special Symposium
'New aspects of targeted therapy of NSCLC'

Saturday, 20 October 11.00 – 12.30 Hall A1 – Room 17.

Are NCCPs the route to sustainable, affordable and accessible care?

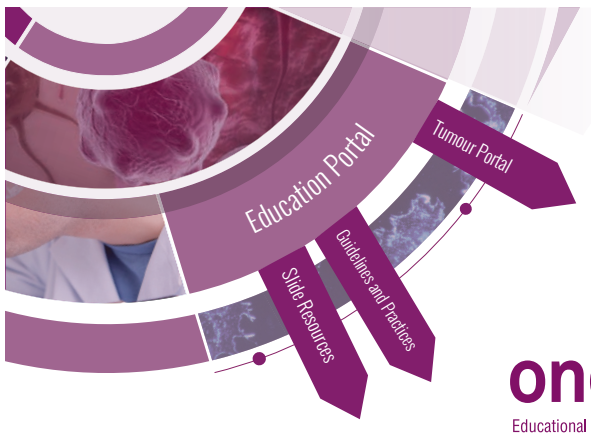
National Cancer Control Plans (NCCPs)—public health programmes based on systematic, equitable and evidence-based strategies that are implemented at a country level—can conceivably reduce cancer burden and improve services for cancer patients and their families.[1] Planning and implementation are key to the success of NCCPs.

In a Special Session to be held tomorrow, an esteemed panel will discuss ways to ensure sustainable, accessible and affordable cancer care within NCCPs. Co-Chair and Deputy Director of Planning and Operations at the US National Cancer Institute (NCI), Dr Lisa Stevens will introduce the concept of NCCPs. Following this, Dr Alexandru Eniu, ESMO Global Policy Committee Chair (Cancer Institute "Ion Chiricuta", Cluj-Napoca, Romania), will discuss whether, and how, a country should develop an NCCP. The session will continue with examples of NCCPs from various countries in Central and Eastern Europe, including updates on their progress and the impact they have made on cancer burden and services. The session will conclude with an interactive Q&A, moderated by Co-Chair Professor Giuseppe Curigliano (European Institute of Oncology, Milan, Italy).

1. www.who.int/cancer/nccp/en/

Find out more about NCCPs and their role in improving cancer services in a Special Session: tomorrow, 'The way to assure sustainable, accessible and affordable cancer care within National Cancer Control Plans (NCCP)',

Saturday, 20 October
14.45 – 16.15, ICM – Room 14a.



oncology//PRO®
Educational Portal for Oncologists

The ESMO site for all your oncology resource needs

Are you struggling to keep abreast of the latest developments in oncology? Help is at hand with OncologyPRO, the ESMO educational portal for oncologists that provides a single gateway to multiple valuable oncology resources. All content is free to access with your ESMO membership and ranges from the latest oncology news to E-learning modules, oncology meeting resources (abstracts, webcasts and slides), and publications, including ESMO Clinical Practice Guidelines. Tumour-specific educational resources can be quickly identified through the Tumour Sites, and search results can be refined by topic and date. Why not sign up to the OncologyPRO alert today to ensure you don't miss any of the new content?

The OncologyPRO website is compatible with all devices, including smartphones, so can easily be viewed while you're on the move.

Access the OncologyPRO portal today at: www.oncologypro.org

The importance of recognising T-cell therapy toxicities

John Haanen
Netherlands Cancer Institute, Amsterdam

Adoptive cell therapies (ACT) involve the administration of immune cells with direct anticancer activity, which can be either genetically engineered host T-cells or naturally occurring autologous tumour-infiltrating lymphocytes (TILs). Chimeric antigen receptor (CAR) T-cell therapies using gene-modified T-cells derived from individual patients to specifically recognise native tumour-associated antigens in a non-major histocompatibility complex-restricted manner have demonstrated striking and durable clinical benefit, resulting in US FDA and EMA approval. Other T-cell therapies include gene-modified T-cell receptors (TCRs), which recognise tumour-specific (mutated) peptide fragments presented by HLA molecules, and TILs derived from within a patient's tumour and then manipulated *in vitro* with IL-2 for the expansion of tumour-reactive clones to instigate an antitumour immune response when reinfused back into the patient. These therapies provide a means of precisely targeting defined cancer antigens and therefore avoiding the toxicity associated with donor lymphocyte infusion.[1] However, these agents are not without their own toxicities, which may be quite different from those we are used to encountering.

T-cell therapies may instigate a range of toxicities, from the transient to the serious or life threatening. Specific toxicities tend to occur with specific T-cell therapy and tumour type. For example cytokine release syndrome—common with CAR T-cell therapy—is a consequence of massive polyclonal activation of T-cells, resulting in very high cytokine levels, which results in hypotension and fever. Also, severe neurological changes, or potentially sudden death have occurred in patients infused with CAR T-cells. Other side effects are related to the non-restricted expression of the antigen in the tumour. Toxicities that manifest as dermatological events occur frequently with T-cell therapies. For instance, vitiligo is common with TILs for melanoma, owing to T-cell recognition of tissue-specific antigens in normal melanocytes. Infusion of TCR gene-modified T-cells targeting melanocyte antigens can induce skin toxicity (rash), uveitis and hearing loss, due to the presence of melanocytes in the skin, the eye and inner ear. Also, a skin rash can be an early sign of cytokine release syndrome with CAR T-cell therapy. It's therefore important to detect any potential skin reactions early.

The immense potential value of T-cell therapies for a range of tumours cannot be ignored. In order to maximise this potential, we must have strategies in place to reduce the incidence of toxicities, including closely monitoring patients so that adverse events can be detected quickly and appropriate management undertaken rapidly.

1. Morris EM, Stauss HJ. Blood 2016;127:3305–11

Don't miss the Special Symposium
'Toxicities from specific agents'

Today, 16.00 – 17.30 in ICM – Room 14b.

Join the conversation

@myESMO
#ESMO18

ESMO-MCBS in perspective

A recent study concluded that the rising cost of novel anticancer drugs was not accompanied by a proportional improvement in clinical benefit.[1] The ESMO Magnitude of Clinical Benefit Scale (MCBS) uses a rational, structured and consistent approach to provide a relative ranking of the magnitude of clinically meaningful benefit that can be expected from a new anticancer therapy. Access to anticancer medicines is an essential component of high-quality cancer care and the MCBS can help to deliver cost-effective and affordable care in the face of limited public and personal resources.

Learn more about the practical uses of the scale in the Special Session 'ESMO-MCBS in perspective' today, 14.00 – 15.30, ICM – Room 14c.

Presentations include the application of the ESMO-MCBS in haematological diseases and a report from the World Health Organization that will shed light on the value of the scale in helping countries to prioritise systemic cancer therapies.

1. Saluja R, et al. J Oncol Pract 2018;14:e280–94

Don't miss the ESMO Examination tomorrow!

Don't forget that the main session of the 2018 ESMO Examination will be held tomorrow, either at the Congress centre (Hall B3, Room 21), or a 5-minute walk from the Congress centre at Wappenhalle (Konrad-Zuse-Platz 7, 81829 Munich). Check your confirmation letter to find out your designated venue.

Be sure to arrive on time to ensure you are granted access to the examination room: enrolment starts at 16.00 and the ESMO Examination starts at 17.30 on Saturday, 20 October.

If you haven't yet registered for the 2018 ESMO Examination, you may still do so at the ESMO Member Lounge from 09.00 to 13.00 on Saturday. Any remaining seats will be offered on a first come, first served basis. Find out more at: www.esmo.org/Career-Development/ESMO-Examination.

WOMEN FOR ONCOLOGY

An ESMO Initiative

'Sharing the power' with ESMO Women for Oncology

Keynote speakers will outline their personal experiences and thoughts on the concept of sharing power between men and women to create a more inclusive professional work environment and bring about gender balance. Representatives from national women's initiatives will also talk about their activities and experiences at a country level, and delegates will have an opportunity to discuss possible approaches to implement the sharing concept in practice.

WOMEN FOR ONCOLOGY

Be sure to attend the ESMO Women for Oncology Forum on 'Sharing the power'

Today, 13.30 – 15.30, Hall B4 – Room 24.

A huge thank you to the Scientific Committee

ESMO President Josep Tabernero, ESMO 2018 Scientific Chair Solange Peters and ESMO Educational Chair Andrés Cervantes extend their profound gratitude to the ESMO 2018 Scientific Committee for developing this year's scientific and educational programme. Through considerable effort and extensive collaboration, they have achieved an international and multidisciplinary event that informs and challenges the oncology community to work towards securing access to optimal care for every patient with cancer.

"With its international reach, the calibre of its faculty and presenters and its high-quality content, the annual ESMO Congress is the best place in Europe to become informed on new research and to develop the networks and collaborations needed to improve patient care. Oncology professionals coming to ESMO 2018 will have a fantastic opportunity to absorb and discuss the very latest findings in the hottest areas of oncology, including immunotherapies, precision oncology and the technologies of the future," commented Professor Peters.

Josep Tabernero
ESMO President

Solange Peters
ESMO 2018 Scientific Chair

Andrés Cervantes
ESMO Educational Chair

Basic science: Richard Marais, Manchester, UK; ***Breast cancer, early stage:*** Carlos Caldas, Cambridge, UK; ***Breast Cancer, metastatic:*** Fatima Cardoso, Lisbon, Portugal; ***CNS tumours:*** Matthias Preusser, Vienna, Austria; ***Developmental therapeutics:*** Alex A. Adjei, Rochester, MN, USA; ***Gastrointestinal tumours, colorectal:*** Dirk Arnold, Hamburg, Germany; ***Gastrointestinal tumours, non-colorectal:*** Yoon-Koo Kang, Seoul, Republic of Korea; ***Genitourinary tumours, non-prostate:*** Karim Fizazi, Villejuif, France; ***Genitourinary tumours, prostate:*** Silke Gillessen, Manchester, UK; ***Gynaecological cancers:*** Susana Banerjee, London, UK; ***Haematological malignancies:*** Marco Ladetto, Alessandria, Italy; ***Head and neck cancer:*** Amanda Psyrri, Athens, Greece; ***Immunotherapy of cancer:*** George Coukos, Lausanne, Switzerland; ***Melanoma and other skin tumours:*** Caroline Robert, Villejuif, France; ***NETs and endocrine tumours:*** Marianne Pavel, Berlin, Germany; ***Non-metastatic NSCLC and other thoracic malignancies:*** Enriqueta Felip, Barcelona, Spain; ***NSCLC, metastatic:*** Martin Reck, Grosshansdorf, Germany; ***Public health and health economics:*** Carin Uyl-de Groot, Rotterdam, Netherlands; ***Sarcoma:*** George Demetri, Boston, MA, USA; ***Supportive and palliative care:*** Karin Jordan, Halle, Germany; ***Translational research:*** Caroline Dive, Manchester, UK, Fabrice André, Villejuif, France

Treating lung cancer with immunotherapy: What's new?

With the success of immunotherapy in metastatic non-small-cell lung cancer (NSCLC) and with data from preclinical investigations and human lung cancer samples suggesting the presence of an immunosuppressive microenvironment in early-stage disease, checkpoint inhibitors are being increasingly studied in non-metastatic NSCLC.[1] Many trials of checkpoint inhibitors have recently completed or are ongoing in early-stage resectable NSCLC in different settings (neoadjuvant, adjuvant, combined neoadjuvant then adjuvant therapy) and in various combinations with traditional modalities. Promising results have been observed in the PACIFIC trial, where progression-free survival was significantly longer with durvalumab versus placebo after chemoradiotherapy in stage III NSCLC,[2] which has recently led to US FDA approval.

Unlike advanced NSCLC, there has been less progress made in the treatment of extensive-stage small-cell lung cancer (SCLC). However, in the phase I/II CheckMate-032 trial, nivolumab alone or combined with ipilimumab showed good activity in previously treated SCLC,[3] the effects being enhanced in patients with a high tumour mutational burden.[4] Based on this trial, in August this year nivolumab was granted accelerated approval by the US FDA for the third-line treatment of metastatic SCLC.[5] Promising early phase III data suggest atezolizumab with chemotherapy may improve survival in the initial treatment of extensive-stage SCLC.[6]

Optimising treatment combinations and patient selection may be the key to expanding the use of immunotherapy across the spectrum of lung cancer.

1. Puri S, et al. Curr Treat Options Oncol 2018;19:39
2. Antonia SJ, et al. N Engl J Med 2017;377:1919–29
3. Antonia SJ, et al. Lancet Oncol 2016;17:883–95
4. Hellmann MD, et al. Cancer Cell 2018;33:853–61
5. www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm617370.htm
6. www.roche.com/media/releases/medcor-2018-06-25.htm

Don't miss the sessions on Saturday, 20 October

'Immunotherapy and targeted therapy in the landscape of non-metastatic NSCLC'
09.15 – 10.45, Hall A2 – Room 18.

'Novel therapies for small cell lung cancer'
14.45 – 16.30, Hall A1 – Room 17.

ESMO YOUNG ONCOLOGISTS

Achieving the right balance between work and life

Teresa Amaral

The recognition that oncologists have a poor work/life balance is not new. An ESMO online survey of 595 young oncologists (≤40 years of age) in 2013–2014 revealed that only 37% thought they had a good work/life balance, with 60% feeling that they had insufficient time to spend on vacation.[1] These aspects were significantly associated with burnout.

Commenting on the subject, Dr Teresa Amaral, an ESMO Young Oncologist Committee member said, "It seems impossible to find a work/life balance nowadays. We are permanently 'electronically connected' and it is difficult to unplug ourselves. The right work/life balance differs from person to person and also differs for the same person at different stages of their life. At the start of your career you may want to dedicate more time to your work, whereas if you have just become a parent you will probably want to spend more time with your family. Nevertheless, a balance needs to exist, and achieving that balance should be our focus. Dr Amaral went on to explain that her personal life suffered because of work commitments. "I didn't notice at the time," she said, "but it was my friends who drew my attention to the problem. Unfortunately, I am also aware of many examples of work/life imbalance from colleagues, particularly from recent mothers who feel like they are under-performing both at home and at work. My understanding is that currently, too few institutions are providing the psychological support that is needed. However, awareness of the problem is increasing among both peers and senior colleagues and this needs to be expressed. Personally, my advice to colleagues would be: organise your time; relinquish perfectionism; reduce time-wasting activities, start small and enjoy your successes; and be sure to recognise your achievements."

1. Banerjee S, et al. Ann Oncol 2017;28:1590–6

Don't miss the YO Session

'YO Vesalius Talk: Work/life balance at early stages of young oncologists' career'

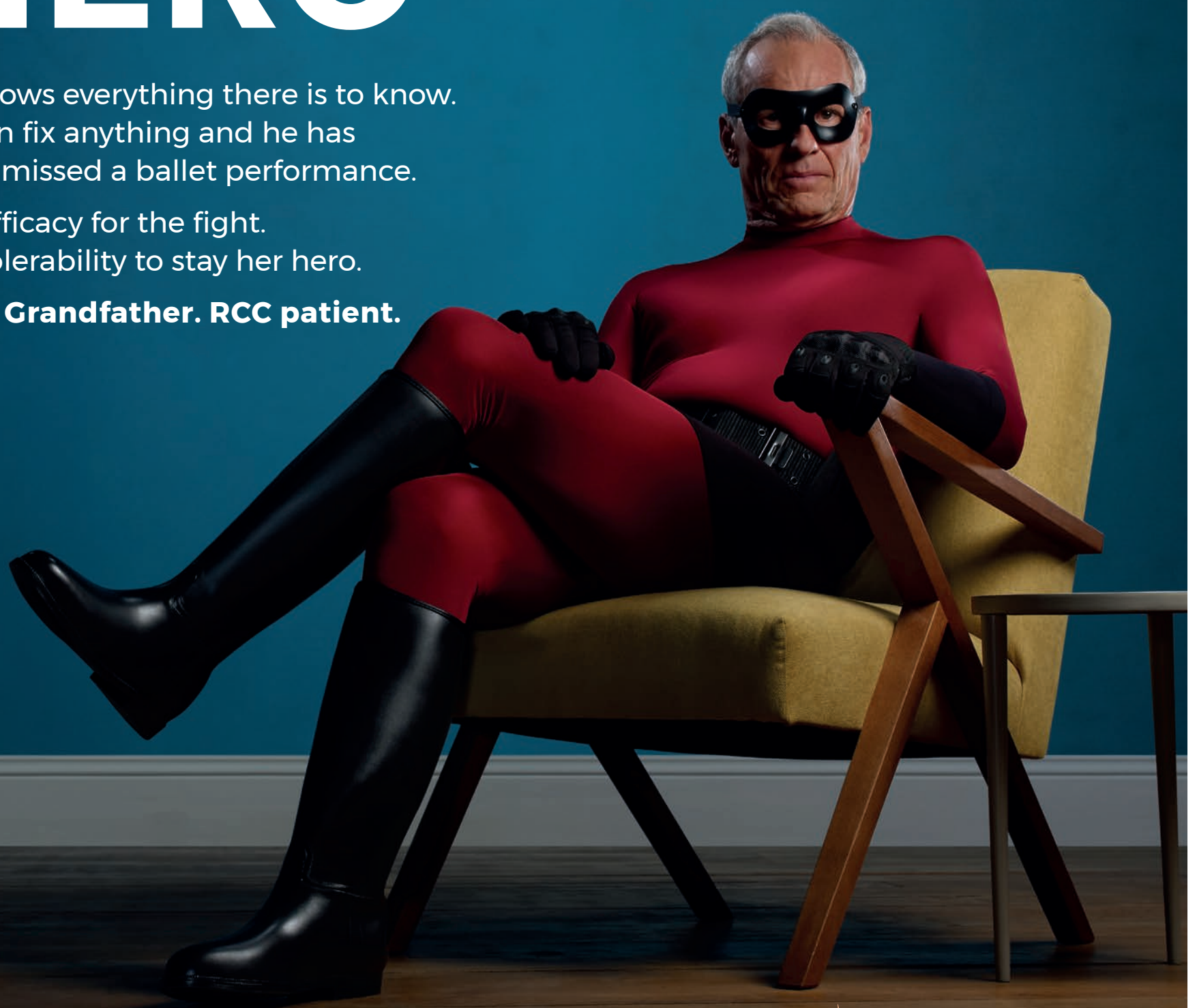
Today, 17.30 – 19.15, ICM – Foyer.

STILL MY HERO

He knows everything there is to know.
He can fix anything and he has
never missed a ballet performance.

The efficacy for the fight.
The tolerability to stay her hero.

Hero. Grandfather. RCC patient.



EUSAPharma

FOTIVDA▼
(tivozanib)

For first-line aRCC

Fotivda is indicated for the first line treatment of adult patients with advanced renal cell carcinoma (RCC) and for adult patients who are VEGFR and mTOR pathway inhibitor-naïve following disease progression after one prior treatment with cytokine therapy for advanced RCC.[1]

ABBREVIATED PRESCRIBING INFORMATION – Fotivda ▼ (tivozanib).

Before prescribing Fotivda please refer to full Summary of Product Characteristics.

Presentation: Hard capsules containing 890 or 1340 microgram tivozanib. **Indication:** First line treatment of adult patients with advanced renal cell carcinoma (RCC) and for adult patients who are VEGFR and mTOR pathway inhibitor-naïve following disease progression after one prior treatment with cytokine therapy for advanced RCC. **Dosage & Administration:** Recommended dose is 1340 microgram once daily for 21 days, followed by a 7 day rest period to comprise one complete treatment cycle of 4 weeks. This treatment schedule should be continued until disease progression or unacceptable toxicity. No more than one dose of Fotivda must be taken per day. ***Paediatric population:*** no data are available. ***Elderly patients:*** no dose adjustment is required. ***Renal impairment:*** mild or moderate renal impairment - no dose adjustment is required, severe renal impairment – caution is advised due to limited experience, patients undergoing dialysis - no experience of tivozanib in this patient population. ***Hepatic impairment:*** Before starting and during treatment evaluate ALT, AST, bilirubin and AP to determine hepatic function before starting and during treatment with close monitoring of tolerability. Severe hepatic impairment - not recommended, moderate impairment reduce to one 1340 microgram capsule every other day due to increased risk of adverse reactions, mild impairment - no dose adjustment. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. Co administration with herbal preparations containing St. John's wort (Hypericum perforatum). **Special warnings and precautions for use:** ***Hypertension*** - blood pressure should be well controlled prior to initiating tivozanib. During treatment patients should be monitored for hypertension. ***Arterial thromboembolic events*** - must be used with caution in patients who are at risk for, or who have a history of these events (such as myocardial infarction, stroke). ***Venous thromboembolic events*** - tivozanib has not been studied in patients who had a VTE within the preceding 6 months of clinical study initiation. Treatment decision, especially in patients who are at risk for VTEs, should be based on individual patient benefit/risk assessment. ***Cardiac failure*** - signs or symptoms of cardiac failure should be periodically monitored throughout treatment. ***Haemorrhage*** - use with caution in patients who are at risk for, or who have a history of bleeding. ***Proteinuria*** - monitoring for proteinuria before initiation of, and periodically throughout treatment is recommended. Risk factors for proteinuria include high blood pressure. ***Hepatotoxicity*** - AST, ALT, bilirubin, and AP should be monitored before initiation of and periodically throughout treatment with tivozanib because of the potential risk of hepatotoxicity. Severe hepatic impairment - not recommended, moderate impairment reduce to one 1340 microgram capsule every other day due to increased risk of adverse reactions, mild impairment - no dose adjustment. ***Posterior reversible encephalopathy syndrome (PRES)*** - Tivozanib must be discontinued in patients developing signs or symptoms of PRES. ***Hand foot skin reaction*** - management of patients experiencing HFSR may include topical therapies for symptomatic relief with consideration of temporary interruption and/or reduction in treatment dose or, in severe or persistent cases, permanent discontinuation of treatment. ***QT interval prolongation*** - use with caution in patients with a history of QT interval prolongation or other relevant pre existing cardiac disease and those receiving other medications known to increase the QT interval with baseline and periodic monitoring of electrocardiograms and maintenance of electrolytes (e.g. calcium, magnesium, potassium) within the normal range recommended. ***Gastrointestinal perforation/fistula*** – use with caution in patients at risk for GI perforation or fistula and recommended to periodically monitor symptoms of gastrointestinal perforation or fistula throughout treatment. ***Wound healing complications*** - for precautionary reasons, temporary interruption of tivozanib therapy is recommended in patients undergoing major surgical procedures. ***Hypothyroidism*** - thyroid function should be monitored before initiation of, and periodically throughout treatment. ***Elderly patients*** - may be at increased risk of adverse reactions. ***Interactions: St. John's wort (Hypericum perforatum)*** – contraindicated. ***CYP3A4 inducers*** – effects not studied but recommend that concomitant administration of tivozanib with strong CYP3A4 inducers should be undertaken with caution. Moderate CYP3A4 inducers are not expected to have a clinically relevant effect on tivozanib exposure. ***CYP3A4 inhibitors*** - no influence on tivozanib serum concentrations. ***Medicinal products for which intestinal absorption is restricted by BCRP*** - tivozanib inhibits the transporter protein BCRP in vitro, but the clinical relevance of this finding is unknown. Caution should be exercised if tivozanib is co-administered with rosuvastatin. Ensure that a suitable time window (e.g. 2 hours) is applied between administration of tivozanib and the BCRP substrate. ***Contraceptives*** - no data available therefore women using hormonal contraceptives should add a barrier method. **Women of childbearing potential/contraception in males and females:** Women of childbearing potential and female partners of male patients taking tivozanib should avoid becoming pregnant while on tivozanib. Effective methods of contraception should be used by male and female patients and their partners during therapy, and for at least one month after completing therapy. Women using hormonal contraceptives should add a barrier method. ***Pregnancy*** - tivozanib should not be used during pregnancy. ***Breast-feeding*** - women should not breast-feed while taking tivozanib. ***Fertility*** - animal studies indicate that male and female fertility may be affected by treatment with tivozanib. **Effects on ability to drive and use machines:** Tivozanib may have a minor influence and patients should be advised to be cautious when driving or using machines if they experience asthenia, fatigue, and/or dizziness during treatment. ***Side effects: Very common (≥ 1/10)*** - Decreased appetite, Headache, Hypertension, Dyspnoea, Dysphonia, Cough. ***Common (≥ 1/100 to < 1/10)*** - Skin exfoliation, Erythema, Pruritus, Alopecia, Rash, Acne, Dry skin, Arthralgia, Myalgia, Musculoskeletal chest pain, Proteinuria, Blood creatinine increased, Chest pain, Chills, Pyrexia, Peripheral oedema, Amylase increased, Lipase increased, Blood thyroid stimulating hormone increased. ***Uncommon (≥ 1/1,000 to < 1/100)*** - Fungal infection, Pustular rash, Thrombocytopenia, Haemoglobin increased, Hyperthyroidism, Goitre, Transient ischaemic attack, Memory impairment, Increased lacrimation, Ear congestion, Pulmonary oedema, Coronary artery insufficiency, Electrocardiogram QT prolonged, Duodenal ulcer, Urticaria, Dermatitis, Hyperhidrosis, Xeroderma, Muscular weakness, Mucosal inflammation. ***Rare (≥ 1/10,000 to < 1/1,000)*** - Posterior reversible encephalopathy syndrome (PRES). **Packaging, quantity and price:** 890 mcg bottle, 21 capsules, €4,537.86; 1340 mcg bottle, 21 capsules €4,537.86. Prices stated reflect those in Germany. Prices may vary between other countries. **Storage requirements:** Shelf life is 5 years. Keep the bottle tightly closed in order to protect from moisture. **Legal Category:** POM. **Marketing Authorisation Number(s):** Fotivda 890 µg: EU/1/17/1215/001, Fotivda 1340 µg: EU/1/17/1215/002. Full prescribing information, including the SmPC, is available from the Marketing Authorisation Holder: EUSA Pharma (UK) Ltd, Breakspear Park, Breakspear Way, Hemel Hempstead HP2 4TZ. **Date of preparation:** November 2017 (P/GLB/TIV/2017.30.01)

Adverse events should be reported as per local regulatory authorities requirements. Adverse events should also be reported to
E: safety@eusapharma.com F: Fax: +44 (0) 3305001167

Abbreviations:
AE, adverse event; aRCC, advanced renal cell carcinoma; CI, confidence interval; HR, hazard ratio; mTOR, mechanistic target of rapamycin; PFS, progression-free survival; VEGFR, vascular endothelial growth factor receptor; VEGFR-TKI, vascular endothelial growth factor receptor tyrosine kinase inhibitor.

Reference:
1. Fotivda Summary of Product Characteristics. February 2018.

Date of preparation: June 2018

P/GLB/TIV/2018.14.01