Congress daily

PRECISION MEDICINE IN CANCER CARE

SATURDAY
SEPTEMBER 27 2014

DAILY EDITORIALS | SESSIONS NOT TO MISS | ORIGINAL ARTICLES | LBAs

ESMO
MADRID 2014

INSIDE...
Proffered Paper Session
BIOMARKERS AND TUMOUR HETEROGENEITY
09.00 – 10.45 Cordoba

SESSION
Proffered Paper Session
NSCLC, METASTATIC 1
16.00 – 17.45 Madrid

PICKS OF THE DAY

Welcome to ESMO 2014 in Madrid

ESMO 2014 was officially opened yesterday in front of a large crowd of delegates by ESMO President, Professor Rolf A. Stahel from University Hospital Zurich, Switzerland, who welcomed attendees to "The most important ESMO Congress yet."

This, he said, was a Congress of records. The number of delegates attending ESMO 2014 has increased by 15% compared with ESMO 2012, from 16,000 to over 18,500, confirming that the oncology community considers ESMO to be one of the most important medical congresses in the world. And it's not just European oncology professionals who choose ESMO. "The numbers of Congress participants from outside Europe support this as a global collaboration and a truly international event," he said.

Professor Stahel spoke of his vision to make ESMO a dynamic force in facilitating research in Europe.

> **"We must develop new ways to work together on a local, national and international level"**
>
> – HE TOLD DELEGATES

ESMO should be a central force in co-ordinating co-operation between researchers and national research groups. ESMO also aims to foster relationships with national cancer centres to assist with the dissemination of their expertise and experience to national and local research groups. The ESMO Congress provides a global forum in which to present cutting-edge research and share expertise on best clinical practice. **"Perhaps more importantly,"** suggested Professor Stahel, **"It offers delegates the rare opportunity for face-to-face meetings, which promote information exchange and networking. It is these types of interaction that effectively promote progress in research."**

ESMO members are particularly well placed to make the most of the Congress experience, Professor Stahel went on to explain, with benefits combining hospitality, customer service and educational and scientific updates. The advantages of membership are not lost on the oncology community, and ESMO membership has grown nearly 150% in the last 10 years, currently nearing 10,000 members. **"Particularly encouraging is the increase in the number of female oncology professional members, who now make up around 38% of the membership, something that was instrumental in the development of ESMO's Women for Oncology (W4O) initiative launched by my predecessor Professor Martine Piccart, Institute Jules Bordet, Belgium,"** he said. Professor Stahel announced the next step in this initiative, the ESMO Women for Oncology Award, which will recognise people who have significantly contributed to support the career development of women in oncology and actively who have worked to sensitise organisations to perceive the female oncology workforce as a valuable resource.

"We in ESMO are particularly proud of our excellent reputation for education and the development of educational resources," continued Professor Stahel. A number of educational efforts are aimed at a group ESMO is passionate about nurturing: the Young Oncologists, who have their own track during the Congress. **"Young oncologists are the future**

continued on page 3

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27.09.2014

For all Congress delegates

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User name: Your ESMO ID: this is the number printed on your delegate badge. All ID codes have to be 5 digits, if your badge ID is 3–4 digits please add a 0 at the start of the ID.
Password: ESMO2014

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Daily Editorial

Evandro de Azambuja,
Congress Daily Editor-in-Chief

Institut Jules Bordet,
Brussels, Belgium

Precision medicine: The two sides of the coin

Today ESMO 2014 begins in earnest. Over the course of the Congress, the Congress Daily Editorial Team – myself, Associate Editors Markus Joerger, Floriana Morgillo and Guest Associate Editor Giuseppe Curigliano – will be keeping you up to date with the latest information presented at the meeting.

Along with thousands of oncology professionals from across Europe and beyond, I cannot wait to learn about the latest advances in all areas of cancer care, but I am sure that one particular area will be in the spotlight: precision medicine.

We have been talking excitedly about pharmacogenomics, personalisation and targeting for 20 years or more. But I am glad precision medicine in cancer care is the theme this year because I believe that we are at a tipping point. Precision medicine is at last moving – and fast – from theory to practice, from bench to bedside. We are witnessing significant improvements in patient outcomes and, in some cases, in patients' quality of life.

"We are privileged to be able to serve cancer patients during this exciting time in cancer research, with the rapidly expanding diagnostic and therapeutic armamentarium available to us today allowing us to design and deliver clinical trials that are rapidly changing the standard of care," commented Professor Johann de Bono, ESMO 2014 Scientific Committee Chair.

I have been fortunate to participate in this development. I have watched how advances in high-throughput technologies, from microarrays to next generation sequencing, have paved the way for the first targeted therapeutics.[1] The pace of development in oncology is one of the fastest.

We all know the story of the renowned cancer drug imatinib, which, after initial success, stalled as have many early targeted therapeutics. But this year's congress shows that we are again making promising progress as we build on work over the last decade to characterise the genomes of thousands of patients in different cancer types.[2] Several Proffered Paper and Special Symposium Sessions are set to reveal some of the very latest tumour characterisations, highlighting new classifications, predictive biomarkers and potential new therapeutic targets. Also, we have learned that some cancers are not only one type of disease but rather many. A good example is breast cancer. In the early 2000's, breast cancer was considered only one disease; with new technologies, four subtypes have been reported. These have helped in the development of cancer therapies by enabling the selection of patients most likely to respond to a particular new type of therapy to be included in clinical trials. Nowadays, breast cancer can be divided into many more tumour subtypes.

So can we start to herald precision medicine as a revolution in cancer care? Let us not forget that most of the precision therapies that we will discuss this week are still in clinical development. However, as the costs of genome sequencing continue to drop, personalisation will become increasingly common over the next decade. It will become a straightforward matter to classify tumours against a complex array of biomarkers and to use this information to optimise therapy combinations.

With this goal in mind, one of the big pushes in research at the moment is to identify predictive biomarkers for new and existing therapies. While laboratory analyses continue to identify potential markers, clinicians are working on new trial designs, which will generate suitable data to assess their predictive and/or prognostic role.

It is always a challenge to translate laboratory results into clinical benefit, but when it comes to genomic research, the scale of the problem is so much bigger. The volume of data produced by high-throughput systems is staggering. So laboratory and clinical work must be accompanied with substantial investment in bioinformatics research; we desperately need new algorithms, data mining and powerful analysis to identify meaningful biomarkers and test their prognostic/predictive roles.[1] This will be particularly important where only a small amount of tumour tissue is available to sample.

Of course, tissue samples taken at diagnosis are just a snapshot of a tumour's genomic landscape, which typically evolves over time.[3] One cannot forget the tumour heterogeneity, which may be responsible for tumour resistance. To what extent can precision medicine overcome these dynamics? One option is to target multiple tumour pathways at once. Already we are seeing a transition from the 'single biomarker, single drug' approach to combinations of two or more therapies based on more complex pathways. Also, in some cases, targeted agents are given to patients without any chemotherapy. However, toxicity may limit the number of combination therapies available to a given patient. Therefore, oncology researchers are focusing on how to use biomarker data to optimise combinations for the best outcomes with minimal toxicity.

However, while the research landscape is full of promise, can European healthcare systems afford the luxury of personalisation? I believe the economic analysis looks favourable. For example, it is widely believed that the cost of patient genome sequencing should soon shrink below the $1000 mark. The emphasis on finding predictive biomarkers will help to make targeted therapies more affordable. Development costs for targeted therapeutics may be lower too. We are already beginning to see the design of trials with alternative endpoints to traditional drug trials and the use of adaptive trial designs, which consider information as it accumulates throughout a trial, and this should help to speed up development and reduce costs.

So much progress, yet so many questions! Even after 20 years of debate – and 20 years of research – we still do not have all the answers. Over the next few days these debates will continue, but I for one am full of hope. Precision medicine is making steady but significant progress. The lives of our oncology patients are being changed. ■

1. Servant N, et al. Front Genet 2014;5:152
2. Garraway LA, et al. J Clin Oncol 2013;31:1803–5
3. Garrway LA, et al. Cancer Discov 2012;2:214–26

Opening Ceremony continued

of our Society and our profession," Professor Stahel commented. From next year, ESMO is opening up membership to students in the hope of encouraging talented young professionals to choose medical oncology as their specialty.

Professor Stahel also announced that next year ESMO is taking the Congress to Asia and the first ESMO Asia Congress will take place in Singapore, 18–21 December 2015. With almost 20% of our current members from Australasia, ESMO is responding to this development in our membership base by working to meet the needs of members in expanding regions.

Last, but by no means least, Professor Stahel saw more good reasons to celebrate in 2015, with ESMO's 40th anniversary, for which the Society hopes to build on the accomplishments made during its first four decades.

Following on from Professor Stahel, ESMO 2014 Local Officer, Dr Ramon Colomer from Hospital Universitario de La Princesa, Madrid, Spain, chose co-operation as the focus of his address. He described the changes and advances in oncology in Spain in general and in Madrid in particular, and of the success achieved by the collaborative efforts of international societies like ESMO, national groups such as SEOM, and patient groups. More from Dr Colomer will be featured in tomorrow's edition of the Congress Daily.

ESMO Scientific Chair, Professor Johann de Bono from The Royal Marsden Hospital, Sutton, UK, then delivered his Scientific Address in which he expanded on the choice of Precision Medicine in Cancer Care as this year's Congress theme, telling

Professor Rolf A. Stahel and Dr Ramon Colomer

delegates that, **"Our vision is for better patient outcome and more efficient healthcare, faster and more cost-effective drug development and utilisation of circulating biomarkers."** Abstract submission this year increased by 24% compared with ESMO 2012, and more than one-third of the accepted abstracts involved predictive biomarkers and targeted drugs focussing on novel and established therapeutic targets.

ESMO Fellowship and Award Committee Chair, Dr Josep Tabernero from Vall d'Hebron University Hospital, Barcelona, Spain, then presented ESMO awards to three members of the European oncology community. More on each of these awards will be featured in Congress Daily today and in the following days. ■

Breakthroughs in immunotherapy

Immunotherapy of cancer

As a concept, immunotherapy seems to be an ideal option for cancer therapy: using the body's own defences to fight and destroy abnormal, cancerous cells. Now, after years of slow progress, clinical trials are finally producing some exciting results, with some of them demonstrating increased survival for patients with metastatic disease.

> **"We are seeing encouraging responses in patients"**
>
> COMMENTED DR GEORGE COUKOS FROM THE CENTRE HOSPITALIER UNIVERSITAIRE VAUDIOS, LAUSANNE, SWITZERLAND

Indeed, last year *Science* labelled immunotherapy as the science advance of the year.

"We now have a number of approved immunotherapeutics, with several more in advanced development. In my opinion, this is one of the most exciting fields to be working in," added Dr Coukos.

A major breakthrough has been the development of checkpoint inhibitors – typically monoclonal antibodies that block the activity of immunosuppressive ligands released by many cancer cells. For example, nivolumab inhibits the binding between the T cell receptor PD-1 and its ligands, thereby preventing T cell differentiation. In the phase II CheckMate-010 trial of nivolumab for renal cell carcinoma in patients receiving up to 3 prior therapies (including at least one vascular endothelial growth factor-targeting agent), 20–22% of patients responded and the median overall survival was 18.2 months.[1]

The cancer vaccine sipuleucel-T won approval from the FDA in 2010 as the first ever therapeutic vaccine for cancer.[2] The treatment harvests leukocytes from a patient and incubates them with a fusion protein made up of prostatic acid phosphatase and granulocyte-macrophage colony stimulating factor (GM-CSF). This activates the patient's immune cells, which are reinfused to trigger an immune response against cancer cells.

Learn more about TILs in today's Proffered Paper Session on the Immunotherapy of Cancer **11:00 – 12:15, Barcelona: Abstract 10480**

Another recent immunotherapeutic approach under investigation is the exploitation of tumour infiltrating lymphocytes (TILs). A process called adoptive cell therapy essentially grows quantities of TILs from a patient's tumour for reinfusion to boost the antitumour immune response.

"Immunotherapy will add to the treatment armamentarium for many cancer patients, especially in kidney and non-small-cell lung cancers and melanoma, where slow growth favours the immunological approach," said ESMO 2014 Congress President Professor Rolf Stahel from the University Hospital Zürich, Switzerland. "It is crucial that oncologists stay abreast of these advances."

In addition to precision medicine, immunotherapy is also a focus of the ESMO 2014 congress.

To help you keep up to date, talks will cover all key aspects of immuno-oncology, with a Keynote Lecture on Delivering Precision Immunotherapy today **13.00 – 13.45, Barcelona**

In 2013 ESMO held its first Immuno-Oncology Symposium. The symposium was a resounding success, with oncologists coming from across Europe learned about recent clinical advances, including trial updates on drug combinations and sequences. The event will take place again this year in Geneva, Switzerland. ■

1. Motzer RJ, et al. J Clin Oncol 2014;32(Suppl 5s): Abstract 5009
2. http://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/ucm210215.htm

ESMO Symposium on Immuno-Oncology 2014, 21–22 November, Geneva, Switzerland. Find out more and register: http://www.esmo.org/Conferences/Immuno-Oncology-2014

Helpful

Congress Information

Abstracts

Gain quick and easy access to ESMO 2014 abstracts from our scientific journal Annals of Oncology. **Abstracts will also be on a USB key; the voucher is included in the delegate bag.**

ePosters

A USB key voucher for the ePosters will be included in the delegate bag. **Eight terminals with large plasma screens for poster viewing and communicating with presenters are available in Hall 8, ePoster area.**

Madrid 3 for 2 Membership offer!

Stop by and see us at the Membership Services Desks in the registration area, at the Membership Services Centre or in the ESMO Members' Lounge to benefit from this special congress offer. **Exhibition Hall - Booth S2**

ESMO booth

For all educational products and services. **Located in the Exhibition Hall - Booth S2**

ESMO Membership Services Centre

The ESMO Team is available to answer all your membership needs. **Located in the Exhibition Hall - Booth S2**

For 2014 The ESMO Members Lounge

Our exclusive 'members only' area, **located in Hall 10,** has been designed to provide ESMO members with an exclusive area to network with other members of the ESMO community, access your email, relax in-between sessions and simply recharge your batteries.

Pathway of the day: RAS/RAF/MEK/ERK

Dr Caroline Robert,

Institut Gustave Roussy,
Paris, France

The RAS/RAF/MEK/ERK pathway (also known as the MAPK pathway; Figure) regulates key cellular functions including proliferation, survival, differentiation, angiogenesis and migration. Activation of the pathway at the cell surface is initiated by ligand binding to receptor tyrosine kinases. The resulting signal cascades sequentially via RAS, RAF, mitogen-activated protein kinase (MEK) and finally extracellular signal-regulated kinase (ERK); the latter regulates gene transcription in the cell nucleus.

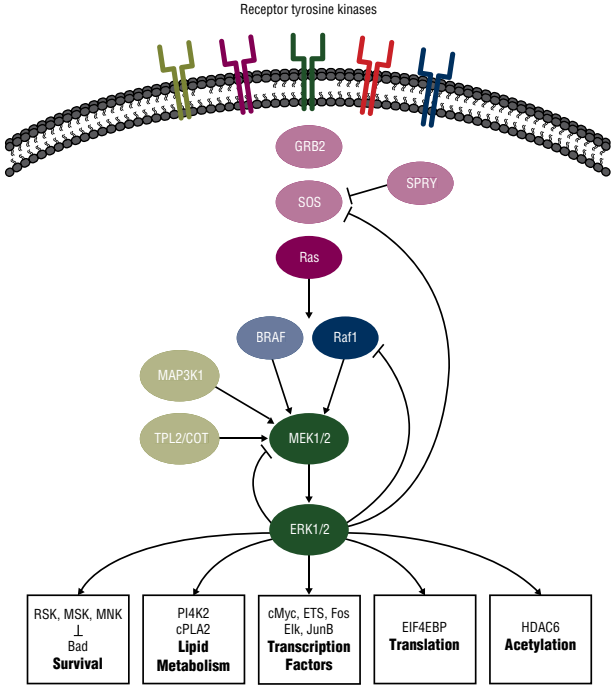
Activating point mutations of RAS genes (most often the KRAS variant) are generally acquired early in tumourigenesis and are found in approximately 30% of human cancers, such as pancreatic, colorectal and lung cancers.

Three variants of the RAF gene exist, which encode for the respective ARAF, BRAF and RAF-1 (or CRAF) proteins. Mutations in the serine threonine kinase gene, BRAF, occur frequently in a number of cancers, particularly melanoma, papillary thyroid, colon and serous ovarian cancers. The second-generation BRAF inhibitors, dabrafenib and vemurafenib, are approved for the treatment of advanced melanoma.

Although MEK gene mutations occur rarely and are associated with a small proportion of melanoma, lung and colon cancers, MEK is a key downstream protein in the RAS/RAF/MEK/ERK pathway and thus a prime target for inhibitor therapy. Sensitivity to MEK inhibitors is enhanced in tumour cells harbouring RAS pathway mutations. The MEK inhibitor, trametinib, is approved for the treatment of BRAF-mutated melanoma. Improved clinical benefit has been demonstrated with combined BRAF and MEK inhibitor therapy. For instance, dabrafenib/trametinib combination enhances response rates and progression-free survival in advanced melanoma.[1] ■

1. Flaherty KT, et al. N Engl J Med 2012;367:1694–703

Hear Dr Robert's presentation of the results of the COMBI-v phase III trial comparing combined BRAF/MEK inhibition with BRAF inhibition alone in patients with BRAF V600E/K mutation-positive cutaneous melanoma on **Monday, 16.30 – 16.45, Madrid: Abstract LBA4_PR**



Model of the ERK1/2 MAPK signaling network controlled by receptor tyrosine kinases and Ras. Clin Cancer Res 2014;20:2516–22.

ESMO Lifetime Achievement Award

Professor Rolf A. Stahel, Professor Peter Boyle and Dr Josep Tabernero

At yesterday's opening session, in front of a large crowd, internationally renowned epidemiologist Professor Peter Boyle from the University of Strathclyde, Glasgow, UK, stepped up to receive the ESMO Lifetime Achievement Award.

Chair of the ESMO Fellowship and Award Committee Dr Josep Tabernero from Vall d'Hebron University Hospital, Barcelona, Spain, presented the Award, which commends Professor Boyle's long-standing contribution to cancer epidemiology, education and prevention.

Dr Tabernero described Professor Boyle as, **"A global reference in cancer education and prevention, whose exceptional expertise is continuously called upon by policy makers, scientific societies, academies, foundations, and patient advocacy groups."**

In 2006, Professor Boyle became the first non-medical oncologist to be elected for full ESMO membership. Since then he has edited international cancer reports and led a project to co-ordinate the European Parliament's cancer research. Today, among his many roles, he works as a Professor of Global Public Health and President of the World Prevention Alliance – an initiative that he founded.

Although the award recognises a lifetime's work, Professor Boyle considers his role to be far from over. Looking to the future he wants to tackle the dramatic difference in cancer care between rich and poor countries, a goal he shares with ESMO. He explained, **"If I could use this award for just one thing, it would be to draw attention to this disparity and address it with conclusive action."**

If anyone can handle such a task, surely it will be Professor Boyle. As Dr Tabernero said, **"Peter's dedication, his ability to engage us all in ultimately reversing the many disparities that exist in access to optimal cancer treatment and care across borders, make him so particularly deserving of this award."** ■

> **"I am honoured, both for myself and for my discipline. To be recognised for my contributions to oncology motivates me to redouble my efforts."**
>
> – PROFESSOR PETER BOYLE

HEAD AND NECK CANCER ON TRIAL

Don't miss today's Proffered Paper Session on Head and Neck Cancer.

Late-breaking abstracts will give data on: the phase III LUX-Head & Neck 1 study comparing afatinib with methotrexate for the treatment of recurrent/metastatic head and neck cancer progressing on platinum-based therapy (Abstract LBA29); and an analysis of serum biomarkers and gene mutations associated with clinical outcomes in the phase III SELECT study investigating lenvatinib in thyroid cancer (Abstract LBA30)

Session Info:
Proffered Paper Session, Head and Neck Cancer

DAY/DATE:
SATURDAY 27 SEPTEMBER
09.15 – 10.45 ROOM: BILBAO

TAKE PART IN ESMO 40TH ANNIVERSARY CELEBRATIONS!

Have your photo taken at the 40th anniversary photo area
ESMO Main Booth S1

Young Oncologists: How to achieve career success

Young Oncologists Vesalius talk

Young oncologist sessions

Friday evening saw young oncologists pick the brains of three established professionals to learn the steps to career success.

ESMO's Young Oncologist session (YO) mentor Dr Christoph Zielinski spoke about how his career has developed. Dr Zielinski now heads the oncology department at the University Hospital of Vienna and is co-ordinating the Comprehensive Cancer Center of Vienna, Austria but he did not always have his sights set on oncology. Upon graduation he looked to immunology – the exciting science of the time. It was only when he took up a position at the Cancer Research Center in Boston, US that oncology became his passion, inspiring him to continue cancer research upon his return to Europe.

For Dr Zielinski, studying abroad is key to success. **"International fellowships offer the opportunity to develop translational research skills. I advise all aspiring academics to spend at least 3 years abroad to pursue a research project."**

Dr Zielinski knows first-hand how to make the most out of international opportunities. He advised, **"When selecting where to stay, do not be afraid to approach a smaller institution: while it may lack international reputation, it will give you more chances to get involved and hone your skills."**

Dr Nicholas Pavlidis from the University of Ioannina, Greece, commented on his own experiences of studying in America and London. **"I agree with Dr Zielinski that studying abroad is a brilliant opportunity. It undoubtedly helped me to develop as a professional oncologist."**

Dr Pavlidis later returned to Greece to found a medical school at the University of Ioannina. **"Of course, returning to a small country such as Greece will be trickier today in our harsh economic climate,"** he added. **"However, I do encourage you to return home to share you new skills."**

Medical oncologist Dr Angelo Di Leo also offered advice to young oncologists looking to go into research. Dr Di Leo knows how to excel in the laboratory: his early research explored personalised chemotherapy and today he works on biomarkers for breast cancer.

Together, these senior peers revealed the wealth of international opportunities open to young oncologists, offering advice on how to make the right decisions in the face of daily pressure and 'burn out'.

After the talks, delegates enjoyed a unique opportunity to ask questions and chat informally with these mentors. As ever, networking is the key to unlocking doors to career progression.

Don't worry if you missed the Vesalius talk – ESMO 2014 offers many more opportunities to network. The ESMO Members' Lounge offers the perfect place to network for career development; you also have access to workstations – why not visit ESMO's YO Corner while you are online?

For further tips on how to get ahead, remember to attend Monday's YO Forum (09.00 – 10.30, Pamplona). Professor Peter Schmid, Professor of Experimental Cancer Medicine at Imperial College London, UK, will begin the session with an overview of the YO mentoring scheme. Could a mentor make a difference to your career? If paperwork gets you down, then make sure you stay and listen to Dr Fatima Cardoso from the Champalimaud Cancer Center, Lisbon, Portugal who will offer practical advice on how to write successful grant applications.

The YO track is packed with opportunities to get practical advice, expand your contacts and kindle your motivation to achieve. Whichever sessions you pick, expect to be inspired.

Young oncologists who wish to follow the mentors' advice may be interested in the ESMO Fellowship Programme, which will be introduced during Monday's YO Special Session **11.00 – 12.30, Pamplona**.

Join us!

The reference society for medical oncologists!

Are you part of the ESMO community? Membership brings many perks not just at this Congress but throughout the year.

Chair of the ESMO Membership Committee, Dr Ravan Popescu from the Hirslanden Medical Centre, Aarau, Switzerland, says, "Being a part of the ESMO community provides members with representation, gives members a united voice and guarantees access to information."

Have you already been to the exclusive Members' Lounge (Hall 10)? Take a moment to relax, catch up with colleagues and make important new contacts.

Do not worry if you feel you are missing out – it is not too late to become an ESMO member right here in Madrid!

Just drop by the ESMO Membership Services Centre, S2 in the Exhibition, where friendly ESMO staff will guide you through the many benefits of joining the ESMO community. Whether you are looking for full access to Annals of Oncology, the Congress webcasts or want regular updates on the latest research and clinical guidance, ESMO membership has something to offer you.

As a member of our community you have unrivalled opportunities to network with peers and senior fellows. These contacts could lead to important collaborations and career progression in the future.

Exclusive offer!

New and existing members can purchase 3 years of membership for the price of 2! But hurry, this offer is only available while you are here in Madrid!

Also at the ESMO Booth, members can pick up our latest publications and learn how to access OncologyPRO, a free online portal for members packed with Congress webcasts and educational resources.

While you are at the Booth, take a stroll around the Society Village – a great opportunity to meet representatives from national oncology societies who can tell you more about local activities and support networks.

ESMO Membership Booth
Open Saturday to Monday in the Exhibition Hall

Membership Services Desks
Open every day in the Registration Hall

Membership Services Centre
Open Saturday to Monday in the Exhibition Hall

ESMO Examination – tonight

Tonight oncologists across the globe will sit the ESMO Examination (17.30–20.00, Hall 7). Here in Madrid, candidates will join international colleagues to answer 100 multiple choice questions and demonstrate their broad knowledge of medical oncology.

The ESMO Exam certificate, awarded to all candidates who score 60% or more, is valid for 5 years. ■

A record-breaking 438 oncologists have already signed up to take the exam, but it is still not too late for ESMO Members to register! **Head to the ESMO Lounge to register today (10.00 – 14.00).**

Session Info:	**ESMO Examination**
Day/Date:	**Saturday 27 September**
Room:	**Hall 7**
Session Time:	**17.30 – 20.00**

RELAX!

In our exclusive 'members only' area, located in Hall 10

DOES THE ADDITION OF BEVACIZUMAB TO CHEMOTHERAPY IMPROVE SURVIVAL IN ADVANCED CERVICAL CANCER?

Find out tomorrow in a late-breaking abstract presentation from Dr Krishnansu Tewari from Irvine Medical Center, Orange County, CA, USA, who will be discussing the final overall survival results of a phase III trial investigating this treatment approach (LBA26).

Other late-breaking abstracts in this session will discuss the results of a double-blind trial investigating the addition of cediranib to carboplatin-paclitaxel for metastatic/recurrent cervical cancer (LBA25_PR) and the investigation of second-line dovitinib in metastatic endometrial cancer according to mutations in fibroblast growth factor receptor 2 (FGFR2) (LBA27)

Session Info:
Proffered Paper Session, Gynaecological Cancers

DAY/DATE:
SUNDAY 28 SEPTEMBER
16.00 – 17.45 ROOM: BARCELONA

ESMO Clinical Practice Guidelines

The ESMO Clinical Practice Guidelines are an invaluable source of the latest research and clinical data on a wide range of tumour types. Prepared by leading experts in the field, these evidence-based guidelines provide clinicians with recommendations for the diagnosis and management of different cancers, to enable them to deliver the best standard of care for their patients.

For 2014, there are updates to the following Guidelines: Metastatic Colorectal Cancer, Follicular Lymphoma, Metastatic Non-Small-Cell Lung Cancer, Bladder Cancer, Hodgkin's Lymphoma, High-Grade Glioma and Anal Cancer. In addition, there are two brand new Guidelines on Myelodysplastic Syndromes and Bone Health in Cancer Patients. Visit the ESMO Booth at the Congress for more information or go to the website http://www.esmo.org/Guidelines-Practice/Clinical-Practice-Guidelines.

Two sessions tomorrow, will see case presentations and discussions on a variety of tumour types led by the experts involved in producing the guidelines. ■

Do not miss this opportunity to put your questions on diagnosis and treatment to some of the leading lights in cancer care!

Day/Date:	**Sunday 28 September**
Room:	**Sevilla**
Session Info:	**ESMO Clinical Practice Guidelines 1**
Featuring:	**Advanced NSCLC, gastric marginal zone lymphoma or MALT-type, high-grade glioma and HPV in head and neck cancer**
Session Time:	**10.45 – 12.45**
Session Info:	**ESMO Clinical Practice Guidelines 2**
Featuring:	**Advanced melanoma, gestational trophoblastic disease, Waldenström's macroglobulinaemia and cervical cancer**
Session Time:	**13.45 – 15.45**

Oncology across the globe: ESMO's Joint Symposia

Precision medicine – the theme of this ESMO 2014 Congress – is at the frontier of oncology. In the coming days ESMO will team up with oncology societies from as far afield as Asia, Africa and America for 10 Joint Symposium Sessions, many of which will focus on issues relevant to the evolution of personalised medicine and stratified cancer care.

Day/Date:	**Saturday 27 September**
Room:	Granada
Session Info:	ESMO-CSCO: Global collaboration in phase I cancer drug development
Session Time:	09.15 – 10.45
Room:	Cordoba
Session Info:	ESMO-ESP: Tissue markers for immuno-oncology
Session Time:	11.00 – 12.30
Room:	Alicante
Session Info:	ESMO Emerging Countries Committee (ECC) - AORTIC-SLACOM-UICC: Personalised medicine with limited resources: Myth or reality?
Session Time:	14.15 – 15.45
Day/Date:	**Sunday 28 September**
Room:	Valencia
Session Info:	ESMO-JSMO: How to integrate genome sequencing data in oncology
Session Time:	09.15 – 10.45
Room:	Bilbao
Session Info:	ESMO-EONS: Oral tumor therapy: Collaboration and coordination of healthcare professional activities to enhance patient adherence
Session Time:	14.15 – 15.45
Day/Date:	**Monday 29 September**
Room:	Granada
Session Info:	ESMO-ASCO: The evolution of the clinical trial landscape
Session Time:	11.00 – 12.30
Room:	Valencia
Session Info:	ESMO-EANM: Impact of molecular imaging on management of lymphoma
Session Time:	11.00 – 12.30
Room:	Granada
Session Info:	ESMO-SEOM Joint Symposium: Investigation driven precision oncology
Session Time:	14.15 – 15.45
Room:	Pamplona
Session Info:	ESMO-ESTRO-ESSO: Integration of local therapy with targeted agents in oligometastatic breast cancer
Session Time:	14.15 – 15.45
Room:	Alicante
Session Info:	ESMO-SIOPE Session: Long-term side effects in adolescent and young adults
Session Time:	09.15 – 10.45

Young Oncologists: Working towards success

YO Masterclass

In the YO Masterclass yesterday afternoon, which was run in collaboration with the European Association for Cancer Research, four speakers from across Europe discussed exciting areas where basic science is being integrated into clinical research. You can read a report of this session in today's Congress Daily.

Young Oncologist Track

The Masterclass marked the beginning of four packed days of sessions designed specifically for early career oncologists: the Young Oncologists track. YO sessions include educational talks, workshops and discussions, packed with practical advice guaranteed to enhance your skills for research and clinical practice.

The topics were chosen by young oncologists from across Europe, so you can be sure to find plenty of relevant support.

Don't miss the YO Breakfast sessions (08.00 – 08.45, Palma) which cover some of the more stressful and challenging situations you may face: how to address the media (Saturday), finding a good work-life balance (Sunday) and exploring the boundaries of the doctor-patient relationship (Monday).

Young Oncologist Fellowships

ESMO prides itself in the support that it offers for young oncologists. At Monday's YO Special Session (11.00 - 12.30, Pamplona) you can learn more about the fellowship program and hear from previous fellowship winners Floriana Morgillo from the Seconda Università degli Studi di Napoli, Italy, and Hatem Azim from Insitute Jules Bordet, Brussels, Belgium as they present their projects here at congress.

Floriana knows that winning the fellowship was a significant step forward for her career and that the contacts she made with international scientists were essential for collaboration as she continues with her research.

For Hatem, the fellowship was a career defining opportunity. It allowed him to combine several research projects and complete a PhD. Today he works as the associate scientific director of a breast cancer research unit in Brussels, Belgium.

Find out more – the YO Corner

YO Corner is a section of ESMO's website dedicated to early career oncologists. Here you will discover a wealth of advice and information to develop your skills and progress your research.

Plus, you will find some newly launched features:

Image of the Month challenges you to test your skills. Can you make a diagnosis from this month's image, sent in by Dr Carmen Herrero Vicent and colleagues from Instituto Valenciano de Oncología, València, Spain.

The YO Corner Journal Club can help you to keep up to date with recent research with critical reviews of the latest key papers from YO members across Europe. If you would like to write your own review, please get in touch.

We make it easy for you to stay in touch with your newly-found YO friends too. Just check out our social media channels:

- Facebook
- Twitter – start tweeting right away and tell us about your congress experience so far
- LinkedIn

ESMO prides itself on it supporting its Young Oncologists. Don't miss the chance to use the opportunities ESMO provides to get practical advice and enhance your skills to help you make the best of your research opportunities.

Find more online

http://www.esmo.org/Conferences/ESMO-2014-Congress/Young-Oncologists-Track
http://www.esmo.org/Career-Development/Young-Oncologists-Corner

KEY EDUCATIONAL SESSIONS SATURDAY 27 SEPTEMBER

Biology must guide the treatment in sarcoma
09.00 – 10.30 Pamplona

Symptoms in oncology
09.15 – 10.45 Valencia

Clinical issues in metastatic NSCLC
11.00 – 12.30 Madrid
Missed it?
Session repeated Sunday:
11.00-12.30 Pamplona

Management of breast cancer in specific populations
11.00 – 12.30 Sevilla
Missed it?
Session repeated today:
16.00 – 17.30 Valencia

Skin tumours update
11.00 – 12.30 Granada

Clinical impact of tumour biology in the management of oesophago-gastric cancer
11:00 – 12:30 Valencia

A multidisciplinary approach to locoregionally advanced rectal cancer
16.00 – 17.30 Sevilla
Missed it?
Session repeated Sunday:
11.00 – 12.30 Granada

Presidential Symposium 1

DAY/DATE:
SUNDAY 28 SEPTEMBER
16.00 – 17.30 **ROOM: MADRID**

At the first Presidential Symposium tomorrow, speakers will present the results of phase III studies with the potential to influence current treatment approaches in metastatic breast cancer and non-small-cell lung cancer (NSCLC).

Abstract: 3500_PR Final results of the phase III CLEOPATRA study, including overall survival, in which HER2-positive metastatic breast cancer patients were treated with the novel first-line treatment combination of pertuzumab, trastuzumab and docetaxel

Presenter: Dr Sandra Swain, Washington, DC, USA

Abstract: 11730 Results of the phase III MAGRIT study to assess the efficacy of the recMAGE-A3 + AS15 cancer immunotherapeutic as adjuvant treatment for patients with resected MAGE-A3-positive NSCLC

Presenter: Dr Johan Vansteenkiste, Leuven, Belgium

Abstract: LBA2_PR Results of the phase III IMPRESS study investigating whether the addition of gefitinib to chemotherapy was more effective than chemotherapy alone in treating epidermal growth factor receptor (EGFR) mutation-positive NSCLC progressing on first-line gefitinib

Presenter: Dr Tony Mok, Hong Kong, China

METASTATIC BREAST CANCER: SENSITIVITY TO ENDOCRINE THERAPY

Resistance to endocrine therapy is a serious obstacle in the battle against breast cancer. This important issue is addressed in a Patient Cases Session tomorrow.

Led by Dr Philippe Bedard from Princess Margaret Hospital, Toronto, Canada, and Dr Javier Cortes Castan from Instituto Oncologico Baselga, Barcelona, Spain, the session will discuss how to overcome resistance in oestrogen receptor-positive breast cancer and how to manage the heterogeneity of triple-negative breast cancer.

As this is such a controversial area, you should make sure to attend!

Session Info:
Patient Cases. Targeting intrinsic subtypes of metastatic breast cancer: The spectrum of sensitivity to endocrine therapy

DAY/DATE:
SUNDAY 28 SEPTEMBER
08.00 – 09.00 ROOM: GRANADA

CHALLENGE YOUR EXPERT

SATURDAY 27 AND SUNDAY 28 SEPTEMBER

Medical treatment for advanced endometrial cancer
08.00 – 09.00 Alicante

Is hormone therapy really harmless in elderly people?
08.00 – 09.00 Bilbao

Management of relapsed germ cell tumours
08.00 – 09.00 Salamanca

Larynx preservation: How should we decide the best treatment?
08.00 – 09.00 San Sebastian

MONDAY 29 AND TUESDAY 30 SEPTEMBER

Adjuvant treatment of breast cancer
08.00 – 09.00 Alicante

Current diagnosis and treatment of CUP
08.00 – 09.00 San Sebastian

SCLC: Current approaches and the role of radiotherapy (thoracic and PCI) in stage IV disease
08.00 – 09.00 Bilbao

Thromboembolic disorders in oncology: Present status and novel agents
08.00 – 09.00 Salamanca

YO Breakfast

HOW TO ADDRESS THE MEDIA: PRACTICAL ADVICE FOR YOUNG ONCOLOGISTS

DAY/DATE:
SATURDAY 27 SEPTEMBER
08.00 – 08.45 ROOM: PALMA

HOW TO FIND THE RIGHT WORK-LIFE BALANCE: TIME MANAGEMENT FOR YOUNG ONCOLOGISTS

DAY/DATE:
SUNDAY 28 SEPTEMBER
08.00 – 08.45 ROOM: PALMA

RISKS AND BOUNDARIES: THE DOCTOR / CANCER PATIENT RELATIONSHIP

DAY/DATE:
MONDAY 29 SEPTEMBER
08.00 – 08.45 ROOM: PALMA

Patient Cases

SATURDAY 27 SEPTEMBER

Therapeutic challenges in oncogene addicted lung cancers
08.00 – 09.00 Granada

Multimodal treatment approaches in bladder cancer
08.00 – 09.00 Valencia

Immunotherapy or targeted therapy for oncogene addicted melanoma
09.15 – 10.15 Salamanca

Cancer evolution: What can we learn from N=1 molecular studies?
10.30 – 11.30 Salamanca

Pregnancy, fertility and cancer
11.45 – 12.45 Salamanca

Challenging cases of oligometastatic NSCLC
14.30 – 15.30 Bilbao

Avoiding overdiagnosis and overtreatment in cancer screening: Assessing the role of personalised screening
16.00 – 17.00 Salamanca

SUNDAY 28 SEPTEMBER

Targeting intrinsic subtypes of metastatic breast cancer: The spectrum of sensitivity to endocrine therapy
8.00 – 9.00 Granada

Challenges in oligometastatic disease: Ways towards long-term survival of metastatic CRC
8.00 – 9.00 Valencia

Clinical and ethical issues in cancer genetics
9.15 – 10.15 Salamanca

How does one manage rare neuroendocrine malignancies?
10.30 – 11.30 Salamanca

Response, neurological function and other objectives in the management of patients with brain metastases
11.45 – 12.45 Salamanca

Treatment of medullary thyroid cancer (MTC)
14.30 – 15.30 Salamanca

The management of isolated lung metastases from soft tissue sarcomas (STS)
16.00 – 17.00 Valencia

MONDAY 29 SEPTEMBER

Treatment of castration-resistant prostate cancer (CRPC) in special situations
08.00 – 09.00 Granada

Primary surgery or neoadjuvant chemotherapy for ovarian cancer: How should we select the patients?
08.00 – 09.00 Valencia

Imaging decisions in haematological malignancies
09.15 – 10.15 Salamanca

Demonstrating the emergence of resistance
10.30 – 11.30 Salamanca

Integrating systemic and locoregional therapies in a patient with advanced hepatocellular carcinoma (HCC)
11.45 – 12.45 Salamanca

Immunotherapy in clinical practice
14.30 – 15.30 Valencia

Challenges in managing breast cancer in young patients
16.00 – 17.00 Salamanca

RESIDUAL BREAST CANCER AFTER NEOADJUVANT THERAPY

Neoadjuvant therapy is a well-established treatment approach for many solid tumours. A Special Symposium tomorrow, led by Dr Evandro De Azambuja from Institut Jules Bordet, Brussels, Belgium, and Dr Suzette Delaloge from Institut Gustave Roussy, Villejuif, France, will focus on this approach in the treatment of breast cancer.

Topics being discussed include: assessing the risk of relapse in specific breast cancer subtypes according to post-neoadjuvant therapy residual disease; which biomarkers can help to define patient prognosis; and whether molecular imaging can predict pathological complete response. The problem of designing clinical trials including patients after neoadjuvant treatment will also be addressed.

Session Info:
Special Symposium. Residual disease after neoadjuvant therapies

DAY/DATE:
SUNDAY 28 SEPTEMBER
09.15 – 10.45 ROOM: GRANADA

ESMO recognises new centres of excellence

At a special Award Ceremony today 15 cancer centres from around the globe will be given the prestigious recognition of 'ESMO Designated Centre of Integrated Oncology and Palliative Care' Malaga Auditorium, North Centre from 17.30.

These centres have been accredited as recognition for providing comprehensive services in supportive and palliative care as part of their routine care and for their pioneering integration of palliative care into routine cancer treatment.

The title will last for 3 years, during which time the centres will play an active role in the promotion of palliative care. ■

Attend the ESMO Designated Centre Special Session to learn about the work of these centres and to hear more from senior peers about the availability, costs and evidence for care integration **Saturday 17.30 – 19.35, Malaga Auditorium**

Twitter #ESMO14

Centre	City/Town	Country
Cairo Oncology Centre (Cairo Cure)	Cairo	Egypt
Dept. Palliative Care and Symptom Control, Dept. Internal Medicine/Oncology, Maxima Medical Centre	Veldhoven	Netherlands
Hospital Universitario Puerta De Hierro de Majadahonda (Servicio de Oncologia Médica)	Majadahonda (Madrid)	Spain
Humanitas Cancer Center	Milan	Italy
Institut de Cancérologie de l'Ouest	Pays de la Loire	France
Instituto de Oncología y Radioterapia de la Clínica Ricardo Palma	Lima	Peru
Klinik für Hämatologie und Onkologie, Palliativmedizin Klinikum Bad Hersfeld	Bad Hersfeld	Germany
Maasstadziekenhuis	Rotterdam	Netherlands
Medical Oncology Unit RAO Umberto I Hospital	Siracusa	Italy
Oncologia Medica, Azienda Ospedaliera Universitaria Integrata Verona	Verona	Italy
Oncologia Ospedale Murri & Hospice Montegranaro ASUR Marche	Fermo	Italy
Palliative Care Unit, Thoraxklinik am Universitätsklinikum Heidelberg	Heidelberg	Germany
Palliative Medicine & Home-Based Hospitalization Unit, Centro Clinico Champalimaud da Fundação Champalimaud - Centre for the Unknown	Lisboa	Portugal
Princess Margaret Cancer Centre, University Health Network	Toronto	Canada
Unit of Supportive and Palliative Care in Cancer. Medical Oncology Department. Institute of Hematologic and Oncologic Diseases. Hospital Clinic of Barcelona	Barcelona	Spain

LATEST CLINICAL FINDINGS IN NEUROENDOCRINE TUMOURS

ESMO is proud to present the results of the latest research in neuroendocrine tumours (NET) in a Proffered Paper Session today. Among the exciting data being presented, do not miss:

Abstract: 1132O The final overall survival results of the phase III RADIANT-3 trial, investigating the use of everolimus for the treatment of advanced pancreatic NET, presented by Dr James Yao from the MD Anderson Cancer Center, Houston, TX, USA

Session Info:
Proffered Paper Session, Neuroendocrine tumours

DAY/DATE:
SATURDAY 27 SEPTEMBER
11.00 – 12.20 ROOM: PAMPLONA

ESMO Masterclass: how to turn knowledge into cancer care

Yesterday the YO Track series for young oncologists set off to a successful start. At the YO Masterclass, young oncologists heard speakers from the European Association for Cancer Research discuss how to bridge the gap between basic science and clinical research.

One way to integrate scientific knowledge into trial design is to use clinical models. Dr Joan Seoane from the Vall D'Hebron Institute of Oncology, Barcelona, Spain, began the Masterclass by explaining how frustration at the lack of progress in glioblastoma treatment – **"Why are we going so slowly? Why are we not able to find new compounds against this disease?"** – has led him to develop a novel clinical model.

Established cell lines – which are used to model novel compounds – are out-dated, argued Dr Seoane. He questioned how such selected cells can represent the heterogeneous characteristics of human tumours, but believes that he has developed a superior alternative.

"Now we are developing 'patient-derived models'. These models are based on tumour samples obtained from patients during surgery or biopsy," he explained. Tissue samples are then quickly inoculated into several mice in locations that mimic the patient's original tumour and this allows researchers to test the efficacy of a variety of drugs.

"If performed in parallel with clinical trials, these models are powerful tools to assess response to particular compounds," said Dr Seoane. His work shows how knowledge of basic cellular genetics can directly link to clinical trials.

Laboratory research continues to expand our knowledge of tumour heterogeneity. But Professor Carlos Caldas from the University of Cambridge, UK, admitted that expanding our understanding of heterogeneity does not appear to make life easier for oncology clinicians.

"On the surface, this knowledge appears to be novel and so daunting that the practise of oncology will be impossible," said Dr Caldas. But beneath the surface, this knowledge is far from new.

Oncologists were aware of clonal evolution as early as 1976. **"Today, we are really re-learning what we already knew,"** said Dr Caldas. He explained that modern sequencing and laboratory techniques show the extent of tumour heterogeneity. **"If you stratify breast cancer based on genomic drivers you see that it is actually 10 different diseases and each of these diseases has completely different chromosomal rearrangements."**

But while this shift in the paradigm of knowledge is undoubtedly exciting, how will it translate to clinical trials and, ultimately, patient care?

"We cannot be doing 10 biopsies on patients every 3 months," admitted Dr Caldas. **"But we take blood samples all of the time."**

Liquid biopsies now allow clinicians to analyse circulating DNA within the blood and Dr Caldas hopes that such biopsies will – when combined with knowledge of heterogeneity – help to identify predictive biomarkers and inform the development of novel treatments.

Liquid biopsies can detect circulating tumour cells (CTCs), a biomarker for metastasis. Dr Klaus Pantel from the Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany, discussed how recent research shows that high CTC counts correlate with high tumour cell burdens and poor progression-free survival in metastatic breast cancer.

"If you want to monitor the efficacy of a breast cancer treatment, changes in CTC counts give better indications than serum factors," said Dr Pantel. But he admitted that detecting CTCs is far from straightforward, especially in the early stages of cancer where CTC numbers may be low. Even during metastasis, there are 1 million blood cells to every CTC.

But Dr Pantel has developed a novel method to detect CTCs. **"In this approach, a needle is put into a vein and this catches tumour cells while they are in circulation,"** explained Dr Pantel. He added, **"We have proof of principle data in several cancer types."**

To bring CTC detection into the clinic, Dr Pantel knows that he will need to study metastasis and try to understand how it will change the management of cancer patients. **"One of the most exciting questions is, can we identify the cells that are responsible for metastasis?"**

But another question was on the mind of Dr Timothy Yap from the Institute of Cancer Research, London, UK. He asked, "How can we personalise the development of novel combination therapies?"

Dr Yap thinks that the answer lies in a new generation of clinical trials. **"It is critical to incorporate real-time predictive biomarkers into trial designs,"** said Dr Yap. At the Institute in London, Dr Yap and colleagues are already putting this into practise.

The clinicians collect patient tumour and blood samples from patients with metastatic cancer. The samples are analysed within days and individual patients are quickly matched to suitable targeted treatments available in phase 1 trials. However, Dr Yap is first to recognise that this is by no means the perfect trial design.

"All of this is really nice, but in reality there are plenty of issues with predictive biomarkers," he explained and commented on the many improvements that remain to be made in the design of trials, especially for novel drug combinations. Improved patient selection will be key.

Session and YO Committee Chair, Dr Raffaele Califano from The Christie NHS Foundation Trust and University Hospital of South Manchester, UK, said, **"It was a great pleasure to see the session so well attended. It shows that young oncologists have great interest in linking basic research to next generation clinical trials."**

Viene de la contraportada.

tipranavir) •Anticonceptivos hormonales •Hipnóticos (p. ej. diazepam, midazolam, zolpidem) •Inmunosupresores (p. ej. ciclosporina, tacrolimus, sirolimus) •Estatinas metabolizadas por CYP3A4 (p. ej. atorvastatina, simvastatina) Es probable que el inicio de la inducción ocurra después de 3 días de tratamiento repetido con dabrafenib. Cuando se suspende el tratamiento con dabrafenib la inducción es contrarrestada de forma gradual, pueden incrementarse las concentraciones susceptibles de CYP3A4, CYP2B6, CYP2C8, CYP2C9 y CYP2C19, UDP glucuronosil transferasa (UGT) y los trasportadores de sustratos; por ello, los pacientes deben ser monitorizados en caso de toxicidad y la pauta posológica de estos medicamentos debe ser ajustada. *In vitro*, dabrafenib es un inhibidor del mecanismo de CYP3A4. Por lo tanto, durante los primeros días de tratamiento se pueden observar inhibición transitoria de CYP3A4. Efectos de dabrafenib sobre los sistemas transportadores de sustancias Dabrafenib es un inhibidor *in vitro* del polipéptido transportador de aniones orgánicos humanos (OATP1B1 y OATP1B3), por lo tanto la relevancia clínica no se puede descartar. Se recomienda precaución cuando se administren conjuntamente dabrafenib y sustratos de OATB1B1 y OATP1B3, como las estatinas. Aunque dabrafenib y sus metabolitos, hidroxi-dabrafenib, carboxi-dabrafenib y desmetil-dabrafenib, son inhibidores del transportador de aniones orgánicos humanos OAT1 y OAT3 *in vitro*, el riesgo de interacciones entre medicamentos es mínimo basándose en la exposición clínica. Dabrafenib y desmetil-dabrafenib también demostraron ser inhibidores moderados de la proteína humana de resistencia al cáncer de mama (BCRP); sin embargo, basándose en la exposición clínica, el riesgo de interacción entre medicamentos es mínimo. Efectos de los alimentos sobre dabrafenib Los pacientes deben de tomar dabrafenib al menos una hora antes o dos horas después de las comidas debido al efecto de los alimentos sobre la absorción de dabrafenib. Población pediátrica Los estudios de interacción sólo se han realizado en adultos. **Fertilidad, embarazo y lactancia** Mujeres en edad fértil /Anticoncepción en mujeres Las mujeres en edad fértil deben utilizar un método anticonceptivo eficaz durante el tratamiento y durante las 4 semanas siguientes a la suspensión del tratamiento. Dabrafenib puede disminuir la eficacia de los anticonceptivos hormonales, por lo que se debe utilizar otro método anticonceptivo alternativo. Embarazo No hay datos relativos al uso de dabrafenib en mujeres embarazadas. En estudios en animales se ha observado toxicidad en la reproducción y toxicidades en el desarrollo embriofetal, incluyendo efectos teratogénicos. No se debe administrar dabrafenib a mujeres embarazadas a no ser que los beneficios para la madre superen los posibles riesgos para el feto. Si la paciente se queda embarazada durante el tratamiento con dabrafenib, se le debe informar del posible riesgo para el feto. Lactancia Se desconoce si dabrafenib se excreta en la leche materna. Debido a que muchos medicamentos se excretan en la leche materna, no se puede descartar la existencia de riesgo para los lactantes. Se debe decidir si es necesario suspender la lactancia o suspender el tratamiento con dabrafenib, tras considerar el beneficio de la lactancia para el niño y el beneficio del tratamiento para la madre. Fertilidad No hay datos en seres humanos. En animales, se ha observado que dabrafenib puede afectar a la fertilidad de machos y hembras como un efecto adverso sobre los órganos reproductores masculinos y femeninos. Se debe informar a los pacientes masculinos del posible riesgo de deterioro de la espermatogénesis, que puede ser irreversible. **Efectos sobre la capacidad para conducir y utilizar máquinas** La influencia de dabrafenib sobre la capacidad para conducir y utilizar máquinas es pequeña. A la hora de considerar la capacidad del paciente para realizar tareas que requieran juicio, habilidades motoras o cognitivas, se deben tener en cuenta tanto el estado clínico del paciente como el perfil de reacciones adversas de dabrafenib. Los pacientes deberán ser conscientes de la posibilidad de padecer fatiga o problemas oculares que afectan a estas actividades. **Reacciones adversas** Resumen del perfil de seguridad El perfil de seguridad se basa en los datos procedentes de cinco estudios clínicos en monoterapia e incluyen 578 pacientes con melanoma. Las reacciones adversas más frecuentes (≥ 15 %) notificadas con dabrafenib fueron, hiperqueratosis, cefalea, pirexia, artralgia, fatiga, náusea, papiloma, alopecia, erupción cutánea y vómitos. Tabla de reacciones adversas Las reacciones adversas que fueron notificadas se enumeran bajo la clasificación de órganos del sistema MedDRA, por frecuencia y por nivel de gravedad. La siguiente clasificación se ha utilizada para ordenarlas por frecuencia: Muy frecuentes: ≥ 1/10. Frecuentes: ≥ 1/100 a < 1/10. Poco frecuentes: ≥ 1/1.000 a < 1/100. Raras: ≥ 1/10.000 a < 1/1.000. No conocida: (no se pueden estimar a partir de los datos disponibles).

Tabla 3: Reacciones adversas notificadas en los ensayos clínicos en melanoma

Sistema de clasificación de órganos	Frecuencia (todos los grados)	Reacciones adversas
Neoplasias benignas, malignas y no especificadas (incluyendo quistes y pólipos)	Muy frecuentes	Papiloma
	Frecuentes	Carcinoma cutáneo de células escamosas
	Frecuentes	Queratosis seborreica
	Frecuentes	Acrocordón
	Frecuentes	Carcinoma de células basales*
	Poco frecuentes	Nuevo melanoma primario
Trastornos del sistema inmunológico	Poco frecuentes	Hipersensibilidad
	Poco frecuentes	Paniculitis
Trastornos del metabolismo y de la nutrición	Muy frecuentes	Disminución del apetito
	Frecuentes	Hipofosfatemia
	Frecuentes	Hiperglucemia
Trastornos del sistema nervioso	Muy frecuentes	Cefalea
Trastornos oculares	Poco frecuentes	Uveítis
Trastornos respiratorios, torácicos y mediastínicos	Muy frecuentes	Tos
Trastornos gastrointestinales	Muy frecuentes	Náusea
	Muy frecuentes	Vómitos
	Muy frecuentes	Diarrea
	Frecuentes	Estreñimiento
	Poco frecuentes	Pancreatitis
Trastornos de la piel y del tejido subcutáneo	Muy frecuentes	Hiperqueratosis
	Muy frecuentes	Alopecia
	Muy frecuentes	Erupción cutánea
	Muy frecuentes	Síndrome de eritrodisestesia palmoplantar
	Frecuentes	Piel seca
	Frecuentes	Prurito
	Frecuentes	Queratosis actínica
	Frecuentes	Lesión en la piel
	Frecuentes	Eritema
Trastornos musculoesqueléticos y del tejido conjuntivo	Muy frecuentes	Artralgia
	Muy frecuentes	Mialgia
	Muy frecuentes	Dolor en las extremidades
Trastornos renales y urinarios	Poco frecuentes	Fallo renal, fallo renal agudo
	Poco frecuentes	Nefritis
Trastornos generales y alteraciones en el lugar de administración	Muy frecuentes	Pirexia
	Muy frecuentes	Fatiga
	Muy frecuentes	Escalofríos
	Muy frecuentes	Astenia
	Frecuentes	Enfermedad parecida a la gripe
Exploraciones complementarias	Frecuentes	Disminución de la FEVI
	Poco frecuentes	Prolongación intervalo QT

Notificación de sospechas de reacciones adversas Es importante notificar sospechas de reacciones adversas al medicamento tras su autorización. Ello permite una supervisión continuada de la relación beneficio/riesgo del medicamento. Se invita a los profesionales sanitarios a notificar las sospechas de reacciones adversas a través del Sistema Español de Farmacovigilancia de Medicamentos de Uso Humano, www.notificaRAM.es. Descripción de las reacciones adversas seleccionadas *Pirexia* En los ensayos clínicos se han notificado episodios de fiebre. El 1 % de los pacientes de los ensayos clínicos presentaron eventos febriles graves no infecciosos, identificados como fiebre acompañada de escalofríos graves, deshidratación, hipotensión y/o insuficiencia renal aguda de origen pre-renal en sujetos con una función renal basal normal. El inicio de estos eventos febriles graves no infecciosos se produjo principalmente durante el primer mes de tratamiento. Los pacientes con eventos febriles graves no infecciosos respondieron bien a las reducciones y/o interrupciones de dosis y a los cuidados complementarios. *Carcinoma cutáneo de células escamosas (CCE)* En el 9 % de los pacientes tratados con dabrafenib aparecieron casos de carcinoma cutáneo de células escamosas (incluyendo aquellos clasificados como queratoacantomas o subtipos mixtos de queratoacantomas). Aproximandamente el 70 % de los eventos se produjo durante las primeras 12 semanas de tratamiento, con una mediana del tiempo de aparición de 8 semanas. El 96 % de los pacientes que desarrollaron CCE continuaron el tratamiento sin modificaciones de la pauta posológica. *Nuevo melanoma primario* En los ensayos clínicos se han notificado casos de nuevos melanomas primarios. Estos casos fueron tratados mediante extirpación y no fueron necesarias modificaciones del tratamiento. *Neoplasia maligna no cutánea* La activación de la señalización de MAP-kinasa en células BRAF nativas que fueron expuestas a inhibidores BRAF, incluyendo aquellas con mutaciones RAS, puede conducir a un aumento de riesgo de aparición de neoplasias malignas no cutáneas. Se han visto casos de neoplasias malignas en pacientes trados con dabrafenib, provocados por mutaciones RAS. Se debe monitorizar a los pacientes en función de la clínica. *Prolongación intervalo QT* Un sujeto integrado en la población de seguridad experimentó una prolongación QTcB > 500 mseg y solamente el 3 % experimentó el peor caso de prolongación QTc de > 60 mseg. *Disminución de la FEVI* Se han notificado casos de disminución de la FEVI en el 1 % de los pacientes, siendo en la mayoría de los casos sintomática y reversible. Los pacientes con FEVI por debajo del límite inferior normal no fueron incluidos en los ensayos clínicos con dabrafenib. *Artralgia* Los casos de artralgia notificados en los ensayos clínicos han sido muy frecuentes (25 %), aunque estos fueron principalmente clasificados de gravedad Grado 1 y 2, siendo poco frecuentes los casos de Grado 3 (< 1 %), y no se notificó ningún caso de Grado 4. *Hipofosfatemia* En los ensayos clínicos con dabrafenib se han notificado muy frecuentemente casos de hipofosfatemia (7 %). Se debe tener en cuenta que aproximadamente la mitad de estos casos (4 %) presentaron una gravedad de Grado 3. *Pancreatitis* Se han notificado casos de pancreatitis en sujetos tratados con dabrafenib. Se debe investigar cuanto antes la aparición de dolor abdominal de origen desconocido y realizar un análisis de amilasa y lipasa séricas. Se debe monitorizar detenidamente a los pacientes que reinicien el tratamiento con dabrafenib tras un episodio de pancreatitis. *Fallo renal* Los casos de fallo renal debidos a pirexia asociada a azotemia prerrenal o a nefritis granulomatosa fueron poco frecuentes. Sin embargo, no se han estudiado los efectos de dabrafenib en pacientes con insuficiencia renal (definida por niveles de creatinina > 1,5 x LSN). Se debe tener precaución en estos pacientes. Poblaciones especiales *Pacientes de avanzada edad* Del número total de pacientes incluidos en los estudios de dabrafenib (N = 578), el 22 % eran mayores de 65 años, y un 6 % eran mayores de 75 años. En comparación con sujetos más jóvenes (< 65 años), hubo un mayor número de pacientes ≥ 65 años que presentaron reacciones adversas que condujeron a reducciones de dosis (22 % vs 12 %) o interrupciones (39 % vs 27 %). Además, los pacientes de mayor edad experimentaron más reacciones adversas graves en comparación con los pacientes jóvenes (41 % vs 22 %). No se encontraron diferencias globales de eficacia entre estos sujetos y los sujetos más jóvenes. **Sobredosis** No existe un tratamiento específico para tratar la sobredosis de dabrafenib. Si se produce una sobredosis, el paciente debe ser tratado con medidas complementarias y una apropiada monitorización según sea necesario. **DATOS FARMACÉUTICOS Periodo de validez** 2 años. **Precauciones especiales de conservación** Este medicamento no requiere condiciones especiales de conservación. **Naturaleza y contenido del envase** Frasco de polietileno de alta densidad (PEAD) de color blanco opaco con un tapón de rosca de polipropileno y un desecante de silica gel. Cada frasco puede contener 28 o 120 cápsulas duras. Puede que solamente estén comercializados algunos tamaños de envases. **Precauciones especiales de eliminación** La eliminación del medicamento no utilizado y de todos los materiales que hayan estado en contacto con él se realizará de acuerdo con la normativa local. **TITULAR DE LA AUTORIZACIÓN DE COMERCIALIZACIÓN** GlaxoSmithKline Trading Services Limited. Currabinny. Carrigaline. County Cork. Irlanda. **FECHA DE LA PRIMERA AUTORIZACIÓN** 26 de Agosto de 2013 **FECHA DE LA REVISIÓN DEL TEXTO** Junio 2014 **CONDICIONES DE PRESCRIPCIÓN Y DISPENSACIÓN** Medicamento sujeto a prescripción médica. Diagnóstico hospitalario. Dispensación hospitalaria sin cupón precinto. **PRESENTACIONES Y PRECIO (Notificado)** Tafinlar 50 mg, envase de 28 cápsulas PVP 1.133,91€ PVP IVA 1.179,27 € Tafinlar 75 mg, envase de 28 cápsulas PVP 1.672,91€ PVP IVA 1.739,83 € Para más información, consulte la Ficha Técnica completa del producto. La información detallada de este medicamento está disponible en la página web de la Agencia Europea de Medicamentos http://www.ema.europa.eu.

A First-Line BRAF Inhibitor

Tafinlar® (dabrafenib)

TAFINLAR is indicated in monotherapy for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation

- Before taking TAFINLAR, patients must have confirmation of tumour BRAF V600 mutation using a validated test

Treatment with TAFINLAR was proven to significantly extend progression-free survival (PFS) vs dacarbazine[1]

Efficacy in Previously Untreated Patients (BREAK-3 Trial)[1]

	TAFINLAR (n=187)	Dacarbazine (n=63)
PFS median, months (95% CI)	**6.9** (5.2, 9.0)	**2.7** (1.5, 3.2)
Hazard ratio (95% CI)	0.37 (0.24, 0.58) *P*<0.0001	

6.9 months
Median PFS with TAFINLAR

Investigator assessment, 25 Jun 2012, secondary data cutoff subsequent to primary data cutoff on 19 Dec 2011.

The safety profile is based on data from 5 clinical monotherapy studies and included 578 patients with melanoma. The most frequently occurring adverse reactions (≥15%) of any grade for TAFINLAR included hyperkeratosis, headache, pyrexia, arthralgia, fatigue, nausea, papilloma, alopecia, rash, and vomiting.[1]

TAFINLAR can also cause serious, less common side effects, including increasing the risk of developing new primary cutaneous malignancies, serious febrile drug reactions, uveitis, iritis, and embryofoetal toxicity.[1]

Prescribing Information

(Please refer to full SmPC before prescribing)
Tafinlar® (dabrafenib) 50mg and 75mg capsules. Each capsule contains dabrafenib mesilate, equivalent to 50mg and 75mg of dabrafenib, respectively. **Indication** In monotherapy for adults with unresectable or metastatic melanoma with a BRAF V600 mutation. **Dosage and administration** Before taking dabrafenib, patients must have confirmation of BRAF V600 mutation using a validated test. 150mg twice daily (b.d.) with interval of ~12hrs between doses (max. total daily dose 300mg), taken until patient no longer derives benefit or develops unacceptable toxicity. Take ≥1 hour before or ≥2 hours after a meal, at similar times every day. Swallow capsules whole with water; do not chew, crush or mix with food/liquids. If dose is missed, do not take if <6 hours until next dose. *Dose modification:* Management of ADRs may require treatment interruption, dose reduction or discontinuation. 1st reduction: 100mg b.d., 2nd reduction: 75mg b.d., 3rd reduction: 50mg b.d. (min. dose). Consider dose re-escalation following same dosing steps as de-escalation when ADR under effective management. *Renal impairment:* No dose adjustment required in mild or moderate impairment. Caution advised in severe renal impairment. *Hepatic impairment:* No dose adjustment required in mild impairment. Caution advised in moderate and severe hepatic impairment. *Elderly:* No initial dose adjustment required in patients >65 yrs. *Paediatrics:* Safety & efficacy not established in patients <18 yrs. **Contraindications** Hypersensitivity to active substance or excipients. **Special Warnings and Precautions** *Pyrexia:* Interrupt treatment if temperature ≥38.5°C and investigate for infection. Restart once fever resolves with anti-pyretics. Restart at reduced dose if fever associated with other severe signs or symptoms as clinically appropriate. *Cutaneous squamous cell carcinoma (CuSCC) and new primary melanoma:* Examine skin prior to treatment, monthly during treatment and for up to 6 months after discontinuation. Patients should inform their physician immediately if a new lesion develops. Dose modifications/interruptions not recommended. *Non-cutaneous secondary/recurrent malignancy:* Head and neck examination and chest/abdominal scan prior to treatment. Monitor as clinically appropriate and for up to 6 months after discontinuation. *Renal failure:* Monitor serum creatinine routinely while on therapy, and interrupt treatment as clinically appropriate if creatinine increases. *Uveitis:* Monitor for signs and symptoms of ophthalmological reactions while on therapy. *Pancreatitis:* Investigate unexplained abdominal pain promptly, including serum amylase & lipase measurements. Monitor closely when re-starting dabrafenib. *QT prolongation:* Treatment not recommended in patients with uncorrectable electrolyte abnormalities, long QT syndrome or those taking medicinal products known to prolong QT interval. Monitor ECG and electrolytes before treatment, one month after therapy, and after dose modification. Permanent treatment discontinuation recommended if QTc increase is both >500msec and >60msec change from baseline. **Undesirable effects** Please refer to full SmPC before prescribing. *Very common:* papilloma, decreased appetite, headache, cough, nausea, vomiting, diarrhoea, hyperkeratosis, alopecia, rash, PPE syndrome, arthralgia, myalgia, pain in extremity, pyrexia, fatigue, chills, asthenia. *Common:* cuSCC, seborrhoeic keratosis, skin tags, basal cell carcinoma, hypophosphataemia, hyperglycaemia, constipation, dry skin, pruritus, actinic keratosis, skin lesion, erythema, influenza-like illness, LVEF decrease. **Interactions** Avoid co-administration with strong inducers or inhibitors of CYP2C8 and CYP3A4, and agents that increase gastric pH, when possible. Exercise caution when co-administering with digoxin and with warfarin; consider additional INR monitoring. Dabrafenib may reduce efficacy of hormonal contraceptives; use alternative effective contraception and continue for 4 weeks post-discontinuation. **Pregnancy** Do not administer to pregnant women unless benefit to mother outweighs the risk to foetus. **Basic NHS Cost** 50mg x 28-capsule pack £933.33; 75mg x 28-capsule pack £1,400.00. **Marketing authorisation (MA) nos.** EU/1/13/865/001; EU/1/13/865/003. **MA holder** GlaxoSmithKline Trading Services Ltd., Kinsale Road, Cork. **Legal category** POM. UK/MLO/0002/14. March 2014.

Adverse events should be reported by the HCP in their country of origin according to local guidelines.
For UK attendees, reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events can also be reported to GlaxoSmithKline on +44 (0) 800 221 441 (UK Free phone number).
Spanish attendees can report suspect adverse drug reaction to the GSK Safety Unit unidad.farmacovigilancia@gsk.com. Fax: +34 918 075 910 or Mobile: +34 669 443 468.

Further information is available from Customer Contact Centre, GlaxoSmithKline, Stockley Park West, Uxbridge, Middlesex UB11 1BT; customercontactuk@gsk.com; Freephone: 0800 221 441.

Abbreviated Summary of Product Characteristics for TAFINLAR in Spanish can be found below and continues on the reverse page.

Please see full Summary of Product Characteristics for TAFINLAR available at booth #126.

Reference: 1. GlaxoSmithKline. TAFINLAR Summary of Product Characteristics.

TAFINLAR is not currently marketed in all territories and prescribers should check local marketing authorisation status before prescribing. Cost and reimbursement status may also vary.

▼Este medicamento está sujeto a seguimiento adicional, lo que agilizará la detección de nueva información sobre su seguridad. Se invita a los profesionales sanitarios a notificar las sospechas de reacciones adversas. Ver la sección 4.8, en la que se incluye información sobre cómo notificarlas. **NOMBRE DEL MEDICAMENTO** Tafinlar 50 mg cápsulas duras Tafinlar 75 mg cápsulas duras **COMPOSICIÓN CUALITATIVA Y CUANTITATIVA** Tafinlar 50 mg cápsulas duras: cada cápsula dura contiene dabrafenib mesilato equivalente a 50 mg de dabrafenib. Tafinlar 75 mg cápsulas duras: cada cápsula dura contiene dabrafenib mesilato equivalente a 75 mg de dabrafenib. Lista completa de excipientes: Contenido de la cápsula: celulosa microcristalina, estearato de magnesio, dióxido de sílice coloidal. Cubierta de la cápsula: óxido de hierro rojo (E172), dióxido de titanio (E171), hipromelosa (E464). Tinta de impresión: óxido de hierro negro (E172), shellac, propilenglicol. **FORMA FARMACÉUTICA** Cápsula dura (cápsula). Tafinlar 50 mg cápsulas duras: cápsulas opacas de color rojo oscuro, de aproximadamente 18 mm de longitud, impresas con 'GS 1EW' y '50 mg'. Tafinlar 75 mg cápsulas duras: cápsulas opacas de color rosa oscuro, de aproximadamente 19 mm de longitud, impresas con 'GS 1HF' y '75 mg'. **DATOS CLÍNICOS Indicaciones terapéuticas** Dabrafenib está indicado para el tratamiento en monoterapia de pacientes adultos con melanoma no resecable o metastásico con mutación BRAF V600. **Posología y forma de administración** El tratamiento con dabrafenib debe iniciarse y ser supervisado por un médico especializado en el uso de medicamentos anticancerígenos. Antes de comenzar el tratamiento con dabrafenib, los pacientes deben tener un diagnóstico de mutación BRAF V600 positiva en el tumor, confirmado por un test validado. No se ha establecido la eficacia y seguridad de dabrafenib en pacientes con melanoma BRAF de tipo nativo por lo tanto dabrafenib no se debe utilizar en pacientes con melanoma BRAF de tipo nativo. Posología La dosis recomendada de dabrafenib es de 150 mg (dos cápsulas de 75 mg) dos veces al día (equivalente a una dosis diaria total de 300 mg). Dabrafenib se debe de tomar al menos una hora antes o dos horas después de las comidas, dejando un intervalo de aproximadamente 12 horas entre ambas tomas. Dabrafenib se debe tomar a las mismas horas todos los días para favorecer el cumplimiento del tratamiento por parte del paciente. *Duración del tratamiento* El tratamiento debe de continuar hasta que el paciente no obtenga beneficio clínico del tratamiento o cuando desarrolle una toxicidad intolerable (ver Tabla 2). *Dosis olvidadas* Si olvida tomar una dosis, no debe volver a tomar el medicamento si quedan menos de 6 horas hasta la próxima toma. *Modificaciones de dosis* Se dispone de dos tipos de cápsulas con concentraciones de dabrafenib de 50 mg y 75 mg para poder ajustar de manera efectiva las modificaciones de dosis necesarias. El manejo de las reacciones adversas puede requerir la interrupción del tratamiento, la reducción de dosis o la suspensión del tratamiento (ver Tablas 1 y 2). No se recomienda realizar modificaciones o interrupciones del tratamiento por reacciones adversas de Carcinoma Cutáneo de Células Escamosas (CCE) o nuevo melanoma primario. El tratamiento se debe interrumpir si la temperatura del paciente es ≥ 38,5°C. Se debe examinar a los pacientes en busca de signos y síntomas de infección. Las reducciones de dosis recomendadas y las recomendaciones de modificación de dosis recomendadas, se presentan en la Tabla 1 y Tabla 2 respectivamente. No se recomiendan ajustes posológicos de dosis menores de 50 mg dos veces al día.

Tabla 1: Reducciones de dosis recomendadas para dabrafenib

Nivel de dosis	Pauta posológica
Dosis completa	150 mg dos veces al día
Primera reducción	100 mg dos veces al día
Segunda reducción	75 mg dos veces al día
Tercera reducción	50 mg dos veces al día

Tabla 2: Esquema de modificaciones de dosis de dabrafenib en función de los Acontecimientos Adversos (AA) de cualquier grado

Grado (CTC-AA)*	Modificaciones de dosis recomendadas
Grado 1 o Grado 2 (Tolerable)	Continuar el tratamiento y monitorizar a los pacientes en función de la clínica.
Grado 2 (Intolerable) o Grado 3	Interrumpir el tratamiento hasta que la toxicidad sea de grado 0-1 y reducir la dosis un nivel cuando se reinicie el tratamiento.
Grado 4	Suspender o interrumpir el tratamiento hasta que la toxicidad sea de grado 0-1 y reducir un nivel la dosis cuando se reinicie el tratamiento.

*Grado de intensidad de acontecimientos adversos clínicos según los criterios de Common Terminology Criteria for Adverse Events (CTC-AE) v4.0

Cuando una reacción adversa individual se maneja de manera efectiva, se puede considerar realizar un re-escalado de dosis, siguiendo las mismas pautas posológicas empleadas para las reducciones de dosis. La pauta posológica no debe exceder de 150 mg dos veces al día. *Pacientes No Caucásicos* No se ha establecido la eficacia y seguridad de dabrafenib en pacientes no caucásicos. No se dispone de datos. *Pacientes de edad avanzada* No se requieren ajustes de la dosis inicial en pacientes > 65 años de edad. *Insuficiencia renal* No se requieren ajustes de dosis en pacientes con insuficiencia renal leve o moderada. No existen datos clínicos en sujetos con insuficiencia renal grave y no se ha podido determinar la posible necesidad de ajuste de dosis. Dabrafenib se debe utilizar con precaución en pacientes con insuficiencia renal grave. *Insuficiencia hepática* No se requieren ajustes de dosis en pacientes con insuficiencia hepática leve. No existen datos clínicos en sujetos con insuficiencia hepática de moderada a grave y no se ha podido determinar la posible necesidad de ajuste de dosis. El metabolismo hepático y la secreción biliar son las principales rutas de eliminación de dabrafenib y sus metabolitos, por lo que los pacientes con insuficiencia hepática de moderada a grave pueden presentar un aumento de la exposición. Dabrafenib se debe utilizar con precaución en pacientes con insuficiencia hepática moderada o grave. *Población pediátrica* No se ha establecido todavía la seguridad y eficacia de dabrafenib en niños y adolescentes (< 18 años de edad). No se dispone de datos clínicos. En los estudios de dabrafenib en animales jóvenes aparecieron efectos adversos, los cuales no fueron observados en animales adultos. Forma de administración Las cápsulas se deben tragar enteras con agua. No se deben masticar o machacar y no se deben mezclar con alimentos o líquidos, debido a la inestabilidad química de dabrafenib. **Contraindicaciones** Hipersensibilidad al principio activo o a alguno de los excipientes. **Advertencias y precauciones especiales de empleo** No se ha establecido la eficacia y seguridad de dabrafenib en pacientes con melanoma BRAF de tipo nativo y por lo tanto, dabrafenib no se debe utilizar en pacientes con melanoma BRAF de tipo nativo. Pirexia En los ensayos clínicos se han notificado episodios de fiebre. El 1 % de los pacientes de los ensayos clínicos presentaron eventos febriles graves no infecciosos, definidos como fiebre acompañada de escalofríos graves, deshidratación, hipotensión y/o insuficiencia renal aguda de origen pre-renal en sujetos con una función renal normal. El inicio de estos eventos febriles graves no infecciosos se produjo principalmente durante el primer mes de tratamiento. Los pacientes con eventos febriles graves no infecciosos respondieron bien a las reducciones y/o interrupciones de dosis y a los cuidados complementarios. El tratamiento con dabrafenib se debe interrumpir si la temperatura del pacientes es ≥ 38,5°C. Se debe examinar a los pacientes en busca de signos y síntomas de infección. El tratamiento con dabrafenib se puede reiniciar cuando la fiebre remita mediante el uso profiláctico adecuado de antiinflamatorios no esteroideos o paracetamol. Si la fiebre se asocia con otros signos o síntomas graves, se debe reiniciar el tratamiento con dabrafenib a una dosis reducida una vez que la fiebre remita y según la clínica del paciente. Carcinoma cutáneo de células escamosas (CCE) Se han notificado casos de CCE (incluyendo aquellos clasificados como queratoacantomas o subtipos mixtos de queratoacantomas) en pacientes tratados con dabrafenib. Antes de empezar el tratamiento con dabrafenib, se recomienda realizar exámenes cutáneos para detectar CCE. Durante todo el tratamiento y durante los 6 meses posteriores a la finalización del tratamiento las revisiones se realizaran mensualmente. Se debe monitorizar a los pacientes durante un periodo de 6 mes tras la suspensión del tratamiento con dabrafenib o hasta la iniciación de otra terapia antineoplásica. Los casos de CCE se deben tratar mediante extirpación dermatológica y el tratamiento con dabrafenib se debe continuar sin ajustes de dosis. Se debe indicar a los pacientes que informen inmediatamente a su médico si desarrollan nuevas lesiones. Nuevo melanoma primario En los ensayos clínicos se han notificado casos de nuevos melanomas primarios. Estos casos fueron identificados durante los primeros 5 meses de tratamiento, y se trataron mediante extirpación sin la necesidad de realizar modificaciones en el tratamiento. Se deben monitorizar las lesiones cutáneas tal y como se ha descrito anteriormente para casos de CCE. Carcinoma maligno no cutáneo secundario/recurrente Los experimentos *in vitro* han demostrado señales de activación paradójica de la proteína quinasa activada por mitogenos (MAP-kinasa) en células BRAF nativas con mutaciones RAS, cuando fueron expuestas a inhibidores BRAF. Esto puede provocar un aumento del riesgo de aparición de neoplasias malignas no cutáneas relacionadas con la exposición a dabrafenib cuando existen mutaciones en RAS. Se han notificado casos de neoplasias malignas asociadas a mutaciones RAS con otro inhibidor de BRAF (leucemia mielomonocítica crónica y carcinoma no cutáneo de células escamosas en cabeza y cuello), y con dabrafenib cuando se administró en combinación un inhibidor de MEK, trametinib (cáncer colorectal, cáncer de páncreas). Antes de iniciar el tratamiento, los pacientes se deben someter a exploraciones de cabeza y cuello, con inspección visual de la mucosa oral y palpación de los nódulos linfáticos, así como realizar un escaner por Tomografía Computerizada (TC) de tórax y abdomen. Durante el tratamiento, se debe monitorizar a los pacientes según se indique clínicamente, incluyendo exploraciones de cabeza y cuello cada 3 meses y TC de tórax y abdomen cada 6 meses. Se recomienda realizar exploraciones anales y pélvicas (en mujeres) antes y al final del tratamiento o cuando se considere clínicamente necesario. Se debe realizar un recuento completo de células sanguíneas cuando esté indicado clínicamente. Tras la suspensión del tratamiento con dabrafenib, se debe continuar la monitorización de neoplasias no cutáneas secundarias/recurrentes durante 6 meses o hasta el inicio de otro tratamiento antineoplásico. Cualquier resultado anómalo debe ser tratado de acuerdo a la práctica clínica. Insuficiencia renal Se han identificado casos de insuficiencia renal en < 1 % de los pacientes tratados con dabrafenib. Los casos observados estuvieron asociados generalmente a pirexia y deshidratación, y respondieron bien a interrupciones de dosis y medidas generales complementarias. Se ha notificado nefritis granulomatosa. Se debe monitorizar periódicamente los niveles de creatinina en suero de los pacientes mientras estén recibiendo tratamiento. Si se producen aumentos de los niveles de creatinina, podría ser necesario interrumpir el tratamiento con dabrafenib cuando sea apropiado clínicamente. No se ha estudiado el uso de dabrafenib en pacientes con insuficiencia renal (definida por niveles de creatinina > 1,5 x LSN), por lo tanto, se debe utilizar con precaución en este grupo de pacientes. Uveitis Se han notificado reacciones oftalmológicas, incluyendo uveitis e iritis. Se debe monitorizar a los pacientes de manera rutinaria durante el tratamiento, para detectar signos y síntomas oculares (del tipo, cambios en la visión, fotofobia y dolor ocular). Pancreatitis Se han notificado casos de pancreatitis en < 1 % de los sujetos tratados con dabrafenib. Uno de los eventos ocurrió en el primer día de tratamiento y volvió a aparecer tras administrar una dosis reducida. Se debe investigar cuanto antes la aparición de dolor abdominal inexplicable y realizar un análisis de amilasa y lipasa en suero. Se debe monitorizar detenidamente a los pacientes que reinicien el tratamiento con dabrafenib tras un episodio de pancreatitis. Prolongación del intervalo QT El peor caso de prolongación del intervalo QTc fue de > 60 milisegundos (mseg), que fue observado en el 3 % de los sujetos tratados con dabrafenib (Un caso > 500 mseg integrado en la población de seguridad). No se recomienda el tratamiento con dabrafenib en pacientes con anomalías electrolíticas no corregibles (incluyendo magnesio), síndrome de QT largo, o que esten tomando medicamentos que prolongan el intervalo QT. Se debe monitorizar el electrocardiograma (ECG) y los electrolitos de todos los pacientes, antes del tratamiento con dabrafenib, tras un mes de tratamiento y después de realizar modificaciones de la pauta posológica. Se recomienda, especialmente en pacientes con insuficiencia hepática de moderada a grave, llevar a cabo una monitorización del ECG y los electrolitos una vez al mes durante los 3 primeros meses de tratamiento, y a partir de entonces con una frecuencia de 3 meses o con mayor frecuencia, según se requiera clínicamente. No se recomienda iniciar el tratamiento con dabrafenib en pacientes con QTc > 500 mseg. Si durante el tratamiento con dabrafenib el intervalo QTc sobrepasa los 500 mseg, se debe interrumpir temporalmente el tratamiento, corregir las alteraciones electrolíticas (incluyendo magnesio) y controlar los factores de riesgo cardiaco que prolongan el intervalo QT (por ejemplo, insuficiencia cardiaca congestiva, bradiarritmias). El tratamiento se debe reiniciar cuando el intervalo QT descienda por debajo de 500 mseg y a dosis inferiores a las descritas en la Tabla 2. Se recomienda suspender permanentemente el tratamiento con dabrafenib si el intervalo QTc aumenta hasta alcanzar valores > 500 mseg y si se modifica en > 60 mseg con respecto a los valores previos al tratamiento. Efectos de otros medicamentos sobre dabrafenib Dabrafenib es un sustrato de CYP2C8 y CYP3A4. Siempre que sea posible, se debe evitar el uso concomitante con inductores potentes de estas enzimas, ya que estos agentes pueden disminuir la eficacia de dabrafenib. Siempre que sea posible, se debe evitar el uso concomitante con agentes que aumentan el pH gástrico, ya que pueden disminuir la biodisponibilidad de dabrafenib. Efectos de dabrafenib sobre otras sustancias Dabrafenib es un inductor del metabolismo enzimático que puede provocar la pérdida de eficacia de muchos medicamentos que se utilizan de forma habitual. Es importante realizar una revisión de la utilización de medicamentos que usa el paciente cuando se inicia el tratamiento con dabrafenib. Se debe evitar el uso concomitante de dabrafenib con medicamentos que son sustratos sensibles a ciertas enzimas metabolizadoras o transportadoras, si no puede realizarse una monitorización de la eficacia y de los ajustes de la dosis. La administración concomitante de dabrafenib con warfarina puede provocar una disminuación de la exposición a warfarina. Se debe tener precaución y se recomienda un mayor control del INR (International Normalized Ratio) cuando se utilice dabrafenib de forma concomitante con warfarina y cuando se suspenda el tratamiento de dabrafenib. La administración concomitante de dabrafenib con digoxina puede provocar una disminuación de la exposición a digoxina. Se debe tener precaución y se recomienda una mayor monitorización cuando digoxina (un transportador de sustrato) se use simultaneamente con dabrafenib y cuando se suspenda el tratamiento de dabrafenib. **Interacción con otros medicamentos y otras formas de interacción** Efectos de otros medicamentos sobre dabrafenib Dabrafenib es un sustrato de las enzimas metabólicas CYP2C8 y CYP3A4, mientras que los metabolitos activos, hidróxi-dabrafenib y desmetil-dabrafenib son sustratos de CYP3A4. Los medicamentos que actúan como inhibidores o inductores potentes de CYP2C8 o CYP3A4, tienden a aumentar o disminuir las concentraciones de dabrafenib, respectivamente. Por ello, y si es posible, durante el tratamiento con dabrafenib se debe considerar la administración de agentes alternativos. Se debe tener precaución cuando se administren inhibidores potentes (por ejemplo, ketoconazol, nefazodona, claritromicina, ritonavir, saquinavir, telitromicina, itraconazol, voriconazol, posaconazol, atazanavir) con dabrafenib. Se debe evitar la coadministración de dabrafenib con inductores potentes de CYP2C8 o CYP3A4 (por ejemplo, rifampicinia, fenitoina, carbamazepina, fenobarbital, o Hierba de San Juan (*Hypericum perforatum*)) con dabrafenib. Los datos farmacocinéticos mostraron un aumento de la C_{max} (26 %) y el AUC (57 %) a dosis repetidas de dabrafenib con ketoconazol (un inhibidor de CYP3A4), e incrementos del AUC (48 % y 61 %, respectivamente) de los metabolitos hidróxi-dabrafenib y desmetil-dabrafenib. Se identificó un descenso del 33 % en el AUC para carboxi-dabrafenib. La solubilidad de dabrafenib es pH dependiente con disminuciones de la solubilidad cuando mayor sea el pH. Los medicamentos como los inhibidores de la bomba de protones, que inhiben la secrección gástrica elevando el pH gástrico, pueden disminuir la solubilidad de dabrafenib y reducir su biodisponibilidad. No se ha llevado a cabo ningún ensayo clínico para evaluar el efecto del pH en la farmacocinética de dabrafenib. Debido al riesgo teórico de que los agentes que elevan el pH puedan disminuir la biodisponibilidad oral y la exposición a dabrafenib, se debe evitar en la medida de lo posible el uso de medicamentos que aumenten el pH gástrico durante el tratamiento con dabrafenib. Efectos de dabrafenib sobre otros medicamentos Dabrafenib es un inductor enzimático que incrementa la síntesis de enzimas que metabolizan medicamentos entre las que se incluyen CYP3A4, CYP2C9 y CYP2B6. También puede incrementar la síntesis de transportadores. Este efecto provoca una reducción de los niveles plasmáticos de medicamentos metabolizados por estas enzimas, y puede afectar a algunos medicamentos transportados. La reducción de las concentraciones plasmáticas puede provocar una pérdida o una reducción del efecto clínico de estos medicamentos. Existe también el riesgo de un aumento en la formación de metabolitos activos de estos medicamentos. Entre las enzimas que pueden ser inducidas se incluyen CYP3A presente en el hígado e intestino, CYP2B6, CYP2C8, CYP2C9, CYP2C19 y UGTs (enzimas glucurónido conjugadas). El transportador de proteína Pgp puede también ser inducido al igual que otros transportadores, por ejemplo MRP-2, BCRP y OATP1B1/1B3. *In vitro*, dabrafenib produce incrementos en CYP2B6 y CYP3A4 de manera dosis dependiente. En un estudio de interacción de fármacos, la C_{max} y el AUC de midazolam administrado por vía oral (un sustrato de CYP3A4) disminuyó un 61 % y un 74 %, respectivamente, al administrarlo junto con dosis repetidas de dabrafenib, usando una formulación con menor biodisponibilidad que la formulación de dabrafenib. Es de esperar que existan interacciones con muchos medicamentos que se eliminen a través del metabolismo o por transporte activo. Estos medicamentos se deben evitar o se deben utilizar con precaución, si su efecto terapéutico es de gran importancia para el paciente y si los ajustes de dosis no se pueden realizar con facilidad en función de la eficacia o las concentraciones plasmáticas. Se sospecha que el riesgo de daño hepático tras la administración de paracetamol es mayor en pacientes tratados de forma concomitante con inductores enzimáticos. Es de esperar que el número de medicamentos afectados sea grande, aunque la magnitud de la interación puede variar. Entre el grupo de medicamentos que pueden verse afectados se incluyen los siguientes, pero no están limitados sólo a estos: •Analgésicos (p. ej. fentanilo, metadona) •Antibióticos (p. ej. claritromicina, doxiciclina) •Medicamentos anticancerígenos (p. ej. cabazitaxel) •Anticoagulantes (p. ej. acenocumarol, warfarina) •Antiepilépticos (p. ej. carbamazepina, fenitoina, primidona, ácido valproico) •Antipsicóticos (p. ej. haloperidol) •Bloqueantes de canales de calcio (p. ej. diltiazem, felodipino, nicardipino, nidefipino, verapamilo) •Glucosidos cardiacos (p. ej. digoxina) •Corticosteroides (p. ej. dexametasona, metilprednisolona) •Antivirales para el VIH (p. ej. amprenavir, atazanavir, darunavir, delavirdina, efavirenz, fosamprenavir, indinavir, lopinavir, saquinavir,

Continúa al dorso.