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DAILY REPORTER

SECURING ACCESS TO OPTIMAL CANCER CARE

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Today's Top Picks

New practices for managing prostate cancer?

Retrospective data suggest a role for local treatment—radical surgery or radiotherapy—in improving survival outcomes in metastatic prostate cancer.[1] Now, the role of radiotherapy for patients with newly-diagnosed metastatic disease has been elucidated by the ground-breaking multi-arm, multi-stage, randomised controlled STAMPEDE trial, in results presented by Dr Chris Parker from The Royal Marsden NHS Foundation Trust, Sutton, UK (Abstract LBA5_PR). The researchers reported on the impact of localised radiotherapy plus standard care (lifelong androgen deprivation therapy) versus standard care alone in 2,061 patients. Localised radiotherapy improved failure-free survival regardless of extent of metastases (hazard ratio [HR] 0.76; 95% confidence interval [CI] 0.68–0.84). Overall survival, the primary endpoint of the trial, improved in patients with oligometastatic disease (HR 0.68; 95% CI 0.52–0.90), but not in those with higher metastatic burden (HR 1.07; 95% CI 0.90–1.28).

STAMPEDE supports a role for localised radiotherapy in newly-diagnosed oligometastatic prostate cancer.

Further potentially practice-changing data have emerged for the management of high-risk localised prostate cancer (Abstract 7910). Professor Karim Fizazi (Institut Gustave Roussy, Villejuif, France) presented updated results from the GETUG-12 phase III trial, after a median follow-up of 12 years, showing that adding docetaxel plus estramustine to standard goserelin therapy significantly reduced the risk of clinical relapse events in men with high-risk localised disease (HR 0.75; p=0.0491). Clinical relapse events included local relapse, metastases and deaths.

Docetaxel-based therapy improves clinical relapse-free survival in high-risk localised prostate cancer.

Furthermore, 12-year cancer-specific survival rates were higher with the combination of docetaxel, estramustine and goserelin than with goserelin alone (88.2% versus 83.9%, respectively; HR 0.70; 95% CI 0.40–1.22).

1. Parikh RR, et al. Prostate 2017;77:559–72

To read about other presentations from yesterday's Presidential Symposium, turn to pages 3 and 8.

Is it time to change drug registration criteria in oncology?

Alongside the advances made in the development of cancer treatments in recent decades, there is the ever-present challenge of providing a true and fair assessment of new drugs. In an era of well-defined drug targets, the value of a new drug may not necessarily be in achieving an improved outcome in all patients, but rather in a subset of patients. Tools such as the ESMO Magnitude of Clinical Benefit Scale could be used to standardise the drug approval process, regardless of the therapy and its mode of action.

So where should the bar be set in the regulatory approval process? This topic is the focus of a Special Session today. Dr Ian Tannock (Princess Margaret Cancer Centre, Toronto, Canada) will discuss why standards should not be lowered for new drug registrations, while Professor Hans-Georg Eichler, Senior Medical Officer for the European Medicines Agency, will present the case for accelerated/conditional approvals as a new regular way of drug registration. Professor Bettina Ryll, Chair of the ESMO Patient Advocates Working Group, will discuss the patients' perspective and expectations. This session promises to be lively, interesting and informative—don't miss it!

Hear the discussions in the Special Session
'The changing scenario of drug registration'

Today, 11.00 – 12.30, Hall B3 – Room 21.

Calling all ESMO members: Don't forget to attend the ESMO General Assembly

The ESMO General Assembly will be held today at 18.30 (doors open from 17.30 to view the ESMO Annual Financial Statement and Auditor's Report) and is open to all ESMO members in good standing (membership fees paid). You must be identified as a member to gain access to the room; if you do not have 'Member' printed on your congress badge or your badge lacks a member ribbon, please stop by the Member Services desks prior to the General Assembly. ESMO student members are also welcome to attend the General Assembly, but they do not have the right to vote.

ESMO members will be asked to vote on a general revision of the bylaws. Important changes are being proposed that will give members a greater say in the running of the Society.

The agenda is as follows:

1. Approval of the President's Annual Report
2. Overview of the Annual Financial Statements and the Auditor's Report
3. Approval of the Audited Annual Financial Statements

Changes ahead in the management of HPV-positive head and neck cancers?

Lisa Licitra
Fondazione IRCCS Istituto Nazionale dei Tumori, Milan and University of Milan, Italy

Ezra Cohen
University of California at San Diego, La Jolla, CA, USA

The latest (8th) edition of the Head and Neck Section of the American Joint Committee on Cancer (AJCC) Staging Manual was published last year and, for the first time, includes separate recommendations specifically for human papillomavirus (HPV)-positive and HPV-negative head and neck cancers.[1] This significant update incorporates a separate staging algorithm for HPV-associated oropharyngeal cancer, which will provide much greater accuracy for predicting survival in newly diagnosed patients.[2]

This major change reflects advances in the understanding of head and neck cancers, including the realisation that HPV positivity is a risk factor for an oropharyngeal cancer subtype that affects relatively young, healthy individuals who have had little or no tobacco exposure. The incidence of this 'novel disease' has risen rapidly over the last few decades (5% per year in the USA and elsewhere)[2] and is associated with an improved prognosis compared with HPV-negative oropharyngeal cancer. Importantly, the updated AJCC staging enables HPV-associated disease to be differentiated from oropharyngeal cancer arising from other causes.[2]

HPV positivity as a differentiating factor in the management of patients with oropharyngeal cancer is the topic of a Multidisciplinary Interactive Session, 'Different approaches and advances in the management of HPV+ patients', today at 11.15 – 12.15, Hall A1 – Room 15.

1. Amin MB, et al, eds. AJCC Cancer Staging Manual. 8th ed. New York: Springer; 2017
2. Lydiatt WM, et al. CA Cancer J Clin 2017;67:122–37

Ablation techniques in colorectal cancer patients with oligometastatic disease

Ulrich Güller
Cantonal Hospital, St. Gallen, Switzerland

For colorectal cancer patients with oligometastatic disease (OMD) non-amenable to curative resection, systemic therapy is the standard of care and should be considered as the initial treatment strategy.[1] However, due to technical improvements, metastases-directed local ablative therapies (LATs) have become an option as an adjunct to systemic treatments.

For patients with OMD confined to a single organ, or a few organs (e.g. liver and lung), surgery—in addition to systemic treatment—is now often part of the standard approach and long-term survival or even cure may be attained in selected patients.[1] However, for patients with more extensive OMD involving several sites or lesions not amenable to curative intent, the surgical approach is highly controversial. LAT in addition to systemic therapy may be considered with the aim of achieving long-term disease control, even though cure is unlikely. The most appropriate LAT should be selected from a 'toolbox' of procedures according to size and localisation of the metastases, anticipated rates of local control, invasiveness of the procedure, non-tumour-related prognostic considerations, patient preferences and local expertise. The LAT toolbox includes radiofrequency ablation, irreversible electroporation, microwave ablation, stereotactic ablative body radiation therapy, radioembolisation with yttrium-90 microspheres and (chemo-)embolisation.

The integration of ablative therapies into the treatment of OMD not amenable to curative intent is rapidly evolving and support is growing; however, further prospective data from well-designed trials or well-conducted cohort studies are urgently needed to investigate which patients benefit most from which toolbox option and how this can best fit into the overall treatment strategy. Most importantly, it is key that the rapidly improving understanding of the immense tumour heterogeneity among patients with metastatic colorectal cancer is integrated into the decision-making process.

1. Van Cutsem E, et al. Ann Oncol 2016;27:1386–422

Don't miss the Multidisciplinary Interactive Session
'The paradigm of oligometastatic disease and ablative treatment'

Today, 11.15 – 12.15, ICM – Room 1.

Neoadjuvant erlotinib for stage III NSCLC:
A new standard?

In a Late-Breaking Abstract presentation yesterday, Dr Wen-Zhao Zhong from Guangdong Lung Cancer Institute, Guangzhou, China, reported that neoadjuvant treatment with the tyrosine kinase inhibitor, erlotinib, improved outcomes compared with gemcitabine plus cisplatin (GC) in 72 patients with stage IIIA N2 *EGFR*-mutant non-small-cell lung cancer (NSCLC; Abstract LBA48_PR). The first randomised trial to compare erlotinib with chemotherapy in the neoadjuvant setting for this population, the study reported a numerically higher objective response rate with erlotinib compared with GC (54.1% versus 34.3%) and a statistically significantly longer median progression-free survival (21.5 months versus 11.9 months; hazard ratio 0.42; p=0.003). Overall survival data are immature. There were no grade 3–4 toxicities with erlotinib, compared with 29.4% of patients with GC.

"Given that the prognosis for patients with stage III NSCLC continues to be extremely poor, ongoing research into combined modality treatments, including alternative neoadjuvant regimens, is vital," said Dr Rafael Rosell from the Catalan Institute of Oncology, Germans Trias i Pujol Research Institute and Hospital, Badalona, Barcelona, Spain. "With continued increase in our understanding of tumour biology, we can expect to optimise and personalise neoadjuvant therapy through the use of targeted agents, such as erlotinib."

Neoadjuvant erlotinib represents a new treatment option for patients with stage III NSCLC.

Earlier use of olaparib may be beneficial in ovarian cancer

The first phase III study of a PARP inhibitor as maintenance therapy after first-line chemotherapy for ovarian cancer has reported positive findings. In the SOLO1 trial of olaparib in patients with *BRCA*-mutated (*BRCA*m) advanced ovarian cancer, the primary endpoint—investigator-assessed progression-free survival (PFS)—was met, with a statistically significant and clinically meaningful improvement in PFS compared with placebo.

Olaparib is currently approved for maintenance of platinum-sensitive relapsed ovarian cancer in patients responding to platinum rechallenge, regardless of *BRCA*m status, and for *BRCA*m advanced ovarian cancer treated with ≥3 prior lines of chemotherapy. First data from SOLO1, conducted in 391 patients with newly-diagnosed, stage III–IV ovarian cancer, were presented in a Late-Breaking Abstract presentation yesterday (Abstract LBA7_PR) in the Presidential Symposium.

At a median follow-up of 41 months, maintenance olaparib reduced the risk of progression or death by 70% compared with placebo (primary PFS analysis). These unprecedented findings are supported by further significant improvements in median time to second progression (not reported with olaparib versus 41.9 months for placebo; hazard ratio [HR] 0.50), and median time to first subsequent therapy or death (51.8 months versus 15.1 months, respectively; HR 0.30). Adverse events were mostly low grade, and health-related quality of life scores did not change from baseline following treatment with olaparib.

These exciting new olaparib data suggest PARP inhibitors may have a role earlier in therapy for ovarian cancer and underline the importance of determining *BRCA*m status at diagnosis.

A phase III trial (PAOLA-1) is currently evaluating olaparib in combination with bevacizumab as a first-line maintenance treatment in patients with newly-diagnosed advanced ovarian cancer, regardless of *BRCA*m status. Results are expected in 2019.

Mixed results for probiotic in preventing chemotherapy-induced diarrhoea

Diarrhoea is a common side effect of chemotherapy, ranging from a short-lived, uncomplicated event to a persistent, challenging problem warranting chemotherapy modification.[1]

Since chemotherapy induces a change in the gut microbiome, it is thought that probiotics could help rebalance the altered microbiome and reduce the severity of diarrhoea.

Studies of variable quality suggest probiotics may reduce the incidence of severe chemotherapy-induced diarrhoea, although no consensus recommendation exists on a probiotic strain for this indication.[2]

Yesterday, results were presented of a randomised, double-blind, single-centre study of 291 patients in India who received probiotic or placebo from 2 weeks before starting chemotherapy to 2 weeks after cycle 3 (Abstract 1682O_PR). Probiotic had an insignificant impact on the incidence of severe chemotherapy-induced diarrhoea; however, there was a significant reduction in the incidence of diarrhoea overall.

"As cancer nurses, patients often ask us which foods and supplements they should take to reduce the impact of chemotherapy toxicity. Given the myriad chemotherapy options available today, the added complexity resulting from combination regimens and individual patient risk factors, careful consideration is warranted before recommending any foods/supplements, including probiotics," said Anita Margulies, a clinical oncology nurse.

She added, "Diarrhoea has become a complex symptom and caution must be exercised in managing it, particularly with immunotherapy-related diarrhoea. Taking all data into account, too many variables still exist and, currently, probiotic use cannot be considered standard prophylactic care. It would therefore be inappropriate for nurses to recommend probiotics until further well-designed studies, including quality of life evaluations, prove otherwise."

1. McQuade RM, et al. Front Pharmacol 2016;7:414
2. Ciorba MA, et al. Curr Opin Support Palliat Care 2015;9:157–62

The oncologist of the future: Automated systems as an aid to improve cancer risk and survival predictions

Automated systems can translate the complexity of big data into information that enables improved understanding and treatment of cancer. Two presentations yesterday reported on the use of automated programmes on large datasets to predict cancer risk and survival.

The authors of a Chinese study described the use of a tool to help predict an individual's risk of colorectal cancer (CRC; Abstract 12P). Data from 18,406 CRC patients and 701,776 healthy individuals were used to build the model. The automated analysis included a variety of demographic, clinical and laboratory variables (including complete blood cell count, comprehensive metabolic panel, lipid profiles and urinalysis), and provided an easy, cost-effective method to tailor appropriate interventional strategies.

The model predicted CRC with an accuracy of >95% using routine blood and urine analysis.

In a study from the USA, data from 12,588 patients treated for metastatic cancer were analysed using a fully automated model that included 4,126 predictor variables. The model was trained and tested to predict a cancer patient's prognosis, with the aim of helping clinicians guide treatment decisions (Abstract 1512O). The model's concordance (*C*)-index for overall survival (OS) in the test set was 0.79, indicating a relatively accurate measure of survival prediction. For patients receiving palliative radiotherapy, the model's *C*-index for OS was significantly better than that of an existing predictive model (0.75 versus 0.64, respectively; p<0.001).

The model showed high predictive performance, suggesting it could be useful in guiding patient care.

Commenting on the findings, Dr Alessandra Curioni-Fontecedro, Associate Editor of the ESMO 2018 *Daily Reporter* (Comprehensive Cancer Center, University Hospital Zurich, Switzerland), said, "These two studies underline the importance of automated systems in becoming part of clinical practice in the future. A fundamental aspect is the quality and variety of data used to train and test such tools. With growing knowledge of patient features (radiological, clinical, molecular, etc.) only artificial intelligence will have the capacity to trawl the complexity of big data to support the oncologist in patient care."

Get ahead in your career: ESMO Fellowship opportunities for young oncologists

Are you a young oncologist who aspires to further your career, participate in high-quality research and expand your professional network? Then don't miss today's Young Oncologist Fellowship Session 'Fellowships in Europe: Educational opportunities for young oncologists' (14.15 – 15.45, ICM – Room 14a).

Co-chaired by Dr Evandro de Azambuja (Institut Jules Bordet, Brussels, Belgium) and Dr Guillem Argilés (Vall d'Hebron University Hospital, Barcelona, Spain), the session will provide key information about the ESMO Fellowship Programme, its aims and the educational opportunities on offer. These include short-term educational visits lasting a few days, clinical programmes from 6 weeks to 1 year, and translational research projects lasting up to 2 years.

You will also receive invaluable insights and practical tips from a former fellow, before hearing presentations on the best paper derived from an ESMO Fellowship and the best ESMO Fellowship project for 2018. Can you really afford to miss it?

Timing of immunotherapy in locally advanced unresectable NSCLC

Progression-free survival (PFS) and overall survival (OS) are improved with consolidation durvalumab, an immune checkpoint inhibitor, in patients with locally advanced unresectable non-small-cell lung cancer (NSCLC) who have not progressed post-chemoradiation.[1,2] But how soon should durvalumab be started? According to a subgroup analysis of the PACIFIC phase III trial, presented yesterday by Professor Corinne Faivre-Finn (University of Manchester and The Christie NHS Foundation Trust, UK), durvalumab provided clinical benefit compared with placebo regardless of time (< or ≥14 days) from radiotherapy to randomisation, but the benefit was more pronounced in patients who started durvalumab earlier, within 14 days of completion of chemoradiotherapy (Abstract 1363O). Moreover, the toxicity profile was similar in patients with earlier or later start.

Earlier timing of durvalumab versus placebo resulted in a more robust PFS and OS benefit.

"More studies are needed to clarify the optimal timing and duration of durvalumab treatment, although these exploratory data suggest that the interaction between radiotherapy and immunotherapy matters for these patients, and that an earlier start results in better outcome," commented Professor Johan Vansteenkiste from University Hospitals Leuven, Belgium. "Moreover, administering durvalumab sooner rather than later does not appear to result in a worse safety profile," he said.

1. Antonia SJ, et al. N Engl J Med 2017;377:1919–29
2. Antonia SJ, et al. N Engl J Med 2018. Sep 25. Epub ahead of print

Emerging biomarkers for immunotherapy response

Carmen Criscitiello

Associate Editor of the ESMO 2018 Daily Reporter, European Institute of Oncology, Milan, Italy

Investigations to select patients more likely to respond to immune checkpoint inhibitors have identified PD-L1 protein expression as a predictive biomarker; however, several challenges exist with this strategy, including the use of different testing platforms, utilisation of different antibodies, varying definitions of PD-L1 positivity and tumour heterogeneity.

Additional plasma- and tissue-based enrichment strategies are being evaluated to identify patients more likely to benefit from immune checkpoint inhibitors. Serum/blood-based biomarkers are attractive due to their convenience and accessibility, and emerging candidate markers include eosinophil, lymphocyte and neutrophil counts, peripheral blood cytokines and peripheral T-cells.[1]

Of recent interest is tumour mutational burden: the total number of non-synonymous mutations per coding region, which has been evaluated as a potential biomarker in melanoma and lung and bladder cancer. Moreover, microsatellite instability owing to deficiency in DNA mismatch repair linked to hypermutation rates has now been incorporated into the US FDA approval for pembrolizumab. Tissue-based strategies under investigation as predictive biomarkers include the presence of tumour infiltrating lymphocytes, T-cell receptor clonality, a composite biomarker of four T-cell-related features ('immunoscore'), multiplex immunohistochemistry assessing the expression of multiple proteins of interest, and expression of multiple immune-related genes incorporated into an 'immune gene signature'.[1]

Larger prospective studies are needed to validate promising biomarkers to enable immunotherapy to be more selectively prescribed to those patients likely to benefit.

1. Voong KR, et al. Ann Transl Med 2017;5:376

Don't miss the Educational Session
'The force awakens: Immunotherapy in thoracic malignancies'

Today, 14.45 – 16.15 in Hall A2 – Room 18.

Join the conversation

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Growing evidence supports induction checkpoint blockade in early-stage NSCLC

Immunotherapy is now a pillar of therapy for selected patients with advanced non-small-cell lung cancer (NSCLC). There is increasing interest in whether peri-operative immunotherapy in early-stage disease confers survival benefit; a pertinent question given that 30–60% of patients with stage I–III NSCLC ultimately develop post-resection metastases.[1,2]

Growing evidence raising hope of a practice-changing role for neoadjuvant checkpoint inhibition in early NSCLC includes data from a pilot study first presented in 2016.[3] The study suggested that the PD-1 inhibitor nivolumab is well tolerated and shows promising antitumour activity (major pathological response of 45%) in the neoadjuvant setting in stage I–IIIA NSCLC.[3,4]

Now, exciting preliminary phase II data from the NEOSTAR trial have emerged. Patients with stage I–IIIA (single N2) NSCLC receiving neoadjuvant therapy with nivolumab or nivolumab plus ipilimumab, a checkpoint anti-CTLA-4, achieved an overall major pathological response rate of 26% (Abstract LBA49). In this interim analysis involving 32 evaluable patients, the overall response rate was 22%, including 1 complete response and 6 partial responses.

Neoadjuvant checkpoint blockade induces higher proliferation and activation of tumour-infiltrating lymphocytes versus untreated resected tumours (p<0.001).

The results also indicate that distinct antitumour immune responses may be elicited depending on the neoadjuvant checkpoint inhibitor regimen: patients receiving neoadjuvant nivolumab plus ipilimumab showed significantly higher proliferation of certain T-cell subsets than those receiving nivolumab alone. Both regimens were generally well tolerated. The data were presented by Dr Tina Cascone from The University of Texas MD Anderson Cancer Center, Houston, TX, USA.

Other studies of neoadjuvant checkpoint blockade in early NSCLC are ongoing and their data are eagerly awaited to supplement these encouraging results.

1. Deslypere G, et al. Ther Adv Med Oncol 2018;10:1–11
2. Yeh J, et al. J Thorac Dis 2018;10:S451–59
3. www.esmo.org/Conferences/Past-Conferences/ESMO-2016-Congress/Press-Media/Neoadjuvant-Immunotherapy-Prior-to-Surgery-is-Safe-and-Feasible-in-Early-Lung-Cancer
4. Forde PM, et al. N Engl J Med 2018;378:1976–86

Treating *ALK/ROS1/NTRK* fusion-positive NSCLC: What more do we know?

Anaplastic lymphoma kinase (*ALK*), c-ros oncogene 1 (*ROS1*) and neurotropic tropomyosin receptor kinase (*NTRK*) gene fusions are oncogenic drivers in a number of solid tumours, including non-small-cell lung cancer (NSCLC). Although targeted agents to these gene fusion rearrangements are available and initially effective, their use is limited by subsequent disease progression, most commonly to the central nervous system (CNS); nearly half of patients with *ALK*-positive NSCLC receiving the first-generation ALK inhibitor (ALKi), crizotinib, develop CNS metastases.[1] This shortcoming has been mitigated by the high CNS activity of newer-generation inhibitors. Data from studies presented at this year's ESMO Congress provide hope for improved outcomes in patients with *ALK/ROS-1/NTRK* fusion-positive NSCLC.

Professor Ben Solomon (Peter McCallum Cancer Centre, Victoria, Australia) presented phase I/II data showing that lorlatinib, a third-generation, brain-penetrant, ALK/ROS1 inhibitor, exhibited some antitumour activity in ROS tyrosine kinase inhibitor (TKI)-naïve patients but also, albeit to a lesser extent, in ROS TKI-pretreated patients and in those with difficult-to-treat mutations (Abstract 1380PD).

In a Late-Breaking Abstract presentation, Dr Enriqueta Felip (Vall d'Hebron Institute of Oncology, Barcelona, Spain) revealed final survival results from the phase II ASCEND-3 trial of ceritinib, a second-generation ALKi (Abstract LBA57). Ceritinib demonstrated prolonged overall survival (OS; 51.3 months) and progression-free survival (PFS; 16.6 months) in 124 chemotherapy pretreated (≤3 lines) patients with *ALK*-positive NSCLC.

In another Late-Breaking Abstract presentation, Dr Sanjay Popat (Royal Marsden Hospital NHS Foundation Trust, London, UK) discussed results showing improved intracranial efficacy with brigatinib, a second-generation ALKi, versus crizotinib in the first interim analysis of the phase III, open-label, randomised ALTA-1L trial in 275 ALKi-naïve patients with *ALK*-positive NSCLC (Abstract LBA58). Intracranial PFS was significantly improved with brigatinib versus crizotinib (hazard ratio [HR] 0.42; 95% confidence interval [CI] 0.24–0.70; p=0.0006) and time to intracranial progression without prior systemic progression was prolonged (HR 0.30; 95% CI 0.15–0.60; p<0.001).

Second-generation ALK-inhibitors show promising findings in *ALK*-positive metastatic NSCLC.

Yesterday, Professor George Demetri (Dana-Farber Cancer Institute, Boston, MA, USA) described Late-Breaking Abstract results of a pooled analysis of three phase I and II studies (ALKA-372-001, STARTRK-1 and STARTRK-2) where the CNS-active TRK/ROS1 inhibitor, entrectinib, was used to treat patients with *NTRK* fusion-positive advanced tumours, including NSCLC (Abstract LBA17). In 54 patients in the efficacy evaluable population, median PFS was 11.2 months (95% CI 8.0–14.9) and median OS was 20.9 months (95% CI 14.9–not reached). In the 355 patients who received entrectinib across the trials, entrectinib was well tolerated; most treatment-related adverse events were grade 1–2 and were managed with dose reduction, and discontinuation due to adverse events occured in only 3.9% of patients.

Commenting on these results, Dr Stefan Zimmermann (Lausanne University Hospital, Switzerland) said, "The future addition of entrectinib and possibly lorlatinib to the therapeutic armamentarium for *ROS1*-rearranged NSCLC will provide patients with a highly active treatment option, especially in the presence of CNS metastases. With the multiplication of agents for *ALK/ROS1/NTRK*-gene-fused lung cancer, discussion and education about sequencing strategies becomes a priority."

1. Weickhardt AJ, et al. J Thorac Oncol 2012;7:1807–14

How feasible is precision medicine in clinical practice?

Precision medicine based on tumour molecular profiling has become the holy grail of cancer treatment. However, the true clinical benefit in the real-world setting is not as clear-cut as might be expected. Presentations over the last 2 days revealed some interesting insights into this area.

In terms of the rate of molecular alterations, the Hellenic Cooperative Oncology Group reported archival samples with pathogenic mutations in 57% of patients with a range of tumour types (n=3,084; Abstract 1876P). Among prospectively performed analyses, the first nationwide Spanish molecular screening programme for advanced breast cancer reported ≥1 alteration in 63% of the patients (n=260; Abstract 2840)—a matched drug being available for 71% of patients with a detected genomic aberration—and a large US community practice cancer programme identified alterations in 94% of 6,496 tumour samples from patients with advanced disease, with 47% being considered clinically relevant (Abstract 18910_PR). Nearly one-quarter (23%) of a subset of 4,490 patients received genomically matched treatment.

However, a retrospective tissue analysis cautioned that the number of genomically profiled patients benefiting from matched treatment in the phase I START clinical trial programme was small (Abstract 1833PD), in line with prior evidence from the literature.[1] Among 1,196 patients screened, 35.6% of the 968 with a valid tissue sample had molecular alterations and 174 alterations were potentially actionable. Only 90 patients with positive tests entered a matched clinical trial, with an overall clinical benefit rate of just 3.67%.

Of 1,196 patients screened, the overall clinical benefit rate with targeted therapy was less than 4%.

Prolonged delays for trial entry, additional selection criteria and a lack of clinical trial places were all reasons for non-enrolment of patients with alteration-positive tumours into matched-agent trials.

Professor Fabrice André (Institut Gustave Roussy, Villejuif, France) commented, "All these studies emphasise that sequencing tumours leads to confusing results because each genomic alteration has a different level of evidence to be actionable. In order to address this issue, ESMO have released the first scale (ESMO Scale for Clinical Actionability of molecular Targets; ESCAT)[2] to rank and prioritise genomic alterations, which should improve the interpretation of sequencing results and the interpretation of clinical trials in the field. In addition, yesterday, the ESMO Precision Medicine Working Group released recommendations for daily practice related to sequencing, including detection of *TRK* fusions, microsatellite instability and how to handle genetic variants detected by next generation sequencing."

1. André F, et al. Lancet Oncol 2014;15:267–74
2. Mateo J, et al. Ann Oncol 2018;29:1895–902

Cancer survival: Striving for equity across Europe

In 2017, the WHO's landmark resolution on cancer prevention and control was adopted by WHO Member States across the globe, resulting in renewed promise of efforts to reduce the burden of cancer and provide healthcare for all.[1] Cancer care is a key health policy issue at the global level, intended to reduce the estimated 30–50% of preventable cancers and the annual 8.8 million cancer deaths.[2] Arguably, the greatest impact of cancer from human and financial perspectives is felt in low- and middle-income countries, where a mere 5% of global resources for cancer prevention and control are spent.[3]

In line with the WHO Cancer Resolution, the ESMO Leaders Generation Programme and the ESMO Global Policy Committee have identified cancer prevention, timely access to treatment and care, palliative and survivorship care as well as the collection of comprehensive data through cancer registries as key topics for recommendations that may help to achieve the goals of reducing cancer burden worldwide.[1] Additionally, in its Vision 2020, ESMO advocates for sustainability in relation to quality treatments and cancer prevention so that there is equal access to screening programmes and optimal care, regardless of the limited budget of healthcare systems in some countries.[4]

Now is the time to implement policies and programmes for achieving the goals set out in the WHO Cancer Resolution.

1. Prager GW, et al. ESMO Open 2018;3:e000285
2. www.who.int/cancer/en/
3. http://apps.who.int/gb/ebwha/pdf_files/WHA70/A70_32-en.pdf
4. www.esmo.org/About-Us/ESMO-2020-Vision

Don't miss the Special Symposium

'Global surveillance of cancer survival: Impact on cancer control'

Today, 11.00 – 12.30 in Hall B3 – Room 20.

Challenging new frontiers in renal and bladder cancer

Cytoreductive nephrectomy has been the standard of care in metastatic renal-cell carcinoma (mRCC) for many years; however, treatment options have expanded rapidly to include targeted therapies and many interesting strategies have been tested recently. In a recent study defining the benefit of initial nephrectomy in the era of targeted therapies, sunitinib alone was found not to be inferior to nephrectomy followed by sunitinib in patients with intermediate- or poor-risk mRCC.[1] To add further complexity, two recent trials showed the superiority of a c-MET inhibitor (cabozantinib)[2] and a checkpoint inhibitor combination (nivolumab plus ipilimumab)[3] over sunitinib in patients with intermediate- or poor-risk disease.

The treatment of urothelial carcinoma has also been transformed in recent years. Pembrolizumab, nivolumab and atezolizumab have been approved in Europe for locally advanced or metastatic urothelial carcinoma following prior platinum-containing chemotherapy. Pembrolizumab and atezolizumab are also approved as front-line therapy in patients who are ineligible for cisplatin. However, preliminary data from two ongoing trials has led the EMA to restrict the front-line use of pembrolizumab and atezolizumab to patients with tumours expressing high PD-L1 levels.[4]

The treatment of both renal and bladder cancer is rapidly evolving. Results from recently completed trials and ongoing studies have increased the complexity of the treatment landscape and emphasised the need for an individualised approach.

1. Méjean A, et al. N Engl J Med 2018;379:417–27
2. Choueiri TK, et al. J Clin Oncol 2017;35:591–7
3. Motzer RJ, et al. N Engl J Med 2018;378:1277–90
4. www.esmo.org/Oncology-News/EMA-Restricts-Use-of-Pembrolizumab-and-Atezolizumab-in-Bladder-Cancer

Androgen deprivation therapy: Awareness of adverse events

Androgen deprivation therapy (ADT) is a mainstay of prostate cancer treatment. Although effective, ADT is associated with multiple harmful effects that can result in significant morbidity and a substantial detrimental impact on quality of life.[1] Such toxicities include bone loss, sexual dysfunction, hot flushes, gynaecomastia, anaemia, fatigue and cognitive changes.[1] Metabolic changes have also been observed, such as weight gain, insulin resistance and, in some studies, increased risk of diabetes. Several observational studies suggest a higher risk of cardiovascular events, although most studies do not report increased cardiovascular mortality.[1]

Patients on long-term ADT should be monitored for adverse events, which in some cases can be managed, for example, by treating bone loss with bisphosphonates or denosumab and encouraging regular exercise to reduce unfavourable metabolic effects and fatigue. However, there are no evidence-based strategies to mitigate several other serious effects. Given these toxicities, it is important to avoid using ADT in certain situations where it is not warranted, such as standard initial monotherapy of localised disease, and to use ADT only when recommended.

1. Nguyen PL, et al. Eur Urol 2015;67:825–36

Don't miss the Multidisciplinary Interactive Session

'The challenges of toxicities from endocrine treatment in men with prostate cancer'

Today, 15.00 – 16.00
in Hall B3 – Room 23.

Significant PFS benefit with first-line axitinib–avelumab in advanced RCC

The advent of immunotherapy is creating a paradigm shift in the first-line treatment of advanced renal cell carcinoma (RCC), which has traditionally involved single-agent tyrosine kinase inhibitors (TKIs), such as sunitinib. Following the phase III CheckMate-214 trial, combined nivolumab and ipilimumab is to become a recommended treatment option in previously untreated patients with intermediate/poor-risk metastatic RCC.[1]

There is also increasing interest in the potential benefit of combining targeted agents and immunotherapy, with a phase Ib trial showing encouraging antitumour activity with axitinib, a VEGF TKI, and avelumab, a PD-L1 inhibitor, in treatment-naïve patients with advanced RCC.[2] These data support the rationale for combining these agents. Additionally, new-generation VEGF TKIs are well-tolerated and can attenuate tumour-induced immunosuppression, potentially allowing tumours to become more responsive to immunotherapy.

Combined axitinib and avelumab could represent a new first-line standard of care for advanced RCC.

Reinforcing the phase I findings, exciting, late-breaking data from the randomised, controlled, phase III JAVELIN Renal 101 trial were presented in yesterday's Presidential Symposium (Abstract LBA6_PR). Involving over 880 patients with advanced RCC—most (around 62%) with intermediate-risk disease—the trial reports a significantly longer median progression-free survival (13.8 months versus 8.4 months; p=0.0001) and higher confirmed objective response rate (51% versus 26%) with first-line axitinib plus avelumab versus sunitinib, irrespective of tumour PD-L1 status. Overall survival data are currently immature.

1. Powles T, et al. Eur Urol 2017. Dec 7. Epub ahead of print
2. Choueiri TK, et al. Lancet Oncology 2018;19:451–60

New key survival data from KEYNOTE-010

Pembrolizumab's prolongation of overall survival (OS) in the pivotal KEYNOTE-010 trial was the basis for its approval in patients with previously treated, PD-L1-positive, advanced non-small-cell lung cancer (NSCLC).[1] In KEYNOTE-010, 1,034 patients with previously treated NSCLC and PD-L1 expression on ≥1% of tumour cells were randomised to pembrolizumab 2 mg/kg or 10 mg/kg or docetaxel 75 mg/m² every 3 weeks.[1]

Yesterday, in a Late-Breaking Abstract presentation, Professor Roy Herbst (Yale School of Medicine, New Haven, CT, USA) provided updated survival data after an additional 30 months' follow-up (median 42.6 months; Abstract LBA63). Among all patients, 23% who received pembrolizumab (pooled doses) were alive after 3 years compared with 11% on docetaxel. Among 79 patients who completed 35 cycles of pembrolizumab, the 3-year OS rate was 99%, with 95% having partial or complete response as their best response. Twenty-five of the 79 patients had progressive disease after stopping 35 cycles and 14 of these patients were then able to start a second pembrolizumab course (although one was then found to be ineligible). The best overall response among the 14 patients was partial response in 43% and stable disease in 36%.

Overall, long-term safety was similar to that seen in the primary analysis: fewer patients had grade 3–5 treatment-related adverse events (AEs) with pembrolizumab (16%) than docetaxel (36%), although more patients had immune-mediated AEs and infusion reactions with pembrolizumab.

Long-term treatment with pembrolizumab continued to prolong OS versus docetaxel with manageable safety.

1. Herbst RS, et al. Lancet 2016;387:1540–50

Snapshots of new data in pancreatic and biliary tract cancers

Adding chemoradiotherapy (CRT) to adjuvant gemcitabine chemotherapy does not improve outcomes in patients with curatively resected pancreatic ductal adenocarcinoma (PDAC), according to the results of a phase III trial in 147 patients presented by Dr Hui-Ju Chang from the National Institute of Cancer Research, Miaoli, Taiwan (Abstract 626PD). The median follow-up was 54.5 months. There was no significant difference when gemcitabine was given alone or when combined with gemcitabine-based CRT in recurrence-free survival (12.1 months versus 13.3 months; p=0.80) or overall survival (OS; 23.5 months versus 21.5 months; p=0.73).

Adjuvant systemic chemotherapy should remain the standard of care for PDAC after curative surgery.

Dr Angela Lamarca from The Christie NHS Foundation Trust, Manchester, UK, commented, "These results provide us with another piece of the jigsaw for the adjuvant treatment of resected PDAC and indicate that our current efforts should focus on improving systemic therapy approaches for these patients."

In a Proffered Paper Session yesterday, Professor Daisuke Sakai from Osaka University, Japan, reported results from a phase III randomised study comparing first-line gemcitabine/cisplatin plus S-1 (GCS) versus gemcitabine/cisplatin (GC) in patients diagnosed with advanced biliary tract cancer (Abstract 6150). Median OS was 13.5 months and 12.6 months in the GCS and GC arms, respectively (hazard ratio 0.79; 95% confidence interval 0.63–0.99; p=0.046). There was an increased response rate in the GCS arm (41.5%) compared with the GC arm (15.0%). The study results were discussed by Professor Juan W Valle (The Christie NHS Foundation Trust/ University of Manchester, Manchester, UK) during the session, who concluded that GCS may be a new treatment option for performance status 0–1 patients and that, based on the increased response rate but modest impact on OS, "Patient selection may depend on intent of therapy (i.e. surgery if good response)."

ESMO YOUNG ONCOLOGISTS

ESMO Young Oncologists network the night away!

Over 200 young oncologists gathered on Saturday evening in a relaxed and informal environment. The young delegates connected and shared experiences–there was no doubting their enthusiasm and drive towards their shared cause of making a difference in cancer care together.

The growing burden of cancer costs

The healthcare burden associated with cancer is huge and rising globally due to an increase in absolute numbers of patients with cancer and the growth in expenditure on cancer drugs. The ESMO Leaders Generation Programme has proposed a strategic framework that is in line with the 2017 WHO Cancer Resolution to achieve effective cancer care for all on the background of this growing burden.[1] A key priority is the efficient use of national resources that assures equity in cancer care that is sustainable, affordable and available to everyone. Expanding the availability of essential cancer treatment packages has been shown to produce significant health and economic benefits. In lower-resource settings, national cancer control plans should prioritise high-impact packages of services that are cost-effective and essential.

New innovative medicines can further contribute by increasing cure rates, but health planners need to determine the clinical value of new treatments. Tools such as the ESMO Magnitude of Clinical Benefit Scale provide a resource to prioritise the reimbursement of newly licensed medicines based on their incremental clinical benefit to patients.[2] The use of modern, effective, yet costly

anticancer treatments must be considered alongside the current gaps in access to high-quality cancer care and the high proportion of patients unable to access basic health services.

1. Prager GW, et al. ESMO Open 2018;3:e000285
2. Cherny NI, et al. Ann Oncol 2015;26:1547–73

Don't miss the Educational Session
'Affordability and sustainability of new cancer drugs'

Today, 16.30 – 18.00 in Hall B3 – Room 22.

Celebrating the growing community of ESMO Designated Centres of Integrated Oncology and Palliative Care

Institutes newly accredited as an ESMO Designated Centre of Integrated Oncology and Palliative Care in 2018 were acknowledged in an award ceremony that took place yesterday afternoon during the Session 'Improving research, education and clinical practice in oncology and palliative care'. The accreditation recognises cancer centres that are achieving a high standard of comprehensive medical oncology supportive and palliative care. These include:

All India Institute of Medical Sciences, Dr B. R. A. IRCH, Dept of Palliative Medicine
(New Delhi, Delhi, India)

Asklepios Klinik Altona
(Hamburg, Germany)

Chiba Cancer Center
(Chiba, Japan)

Comprehensive Cancer Centre
(Alexandria, Egypt)

CUF Porto Hospital – Oncology and Palliative Care Unit
(Porto, Portugal)

Department of Clinical Oncology and Palliative Medicine, Mitsubishi Kyoto Hospital
(Kyoto, Japan)

Department of Hematology and Oncology - "Anna Meyer" Children's University Hospital
(Florence, Italy)

King Faisal Specialist Hospital and Research Centre, Oncology Centre
(Riyadh, Saudi Arabia)

Millennium Healthcare
(Cairo, Egypt)

National Cancer Center Hospital East
(Chiba, Japan)

National Center for Cancer Care & Research
(Doha, Qatar)

North Estonia Medical Centre
(Tallinn, Estonia)

Northwest Oncological Center
(Alkmaar, Netherlands)

Oslo University Hospital
(Oslo, Norway)

Santa Maria Goretti Hospital, Oncology Unit
(Latina, Italy)

St. Josefs-Krankenhaus Potsdam-Sanssouci
(Potsdam, Germany)

Sunway Medical Centre
(Sunway City, Malaysia)

Sygehus Lillebælt
(Vejle/Kolding, Denmark)

Unidade de Oncologia e Equipa de Cuidados Paliativos – Hospital Prof Dr Fernando Fonseca
(Amadora, Portugal)

University Hospital Fundación Jiménez Díaz
(Madrid, Spain)

Find out more about applying for ESMO Designated Centre accreditation at www.esmo.org/Patients/Apply-to-Become-an-ESMO-Designated-Centre

Liquid biopsy in metastatic lung cancer—ready for prime time?

Benjamin Besse

Gustave Roussy Cancer Campus, Villejuif, France

With the advent of targeted therapies, molecular profiling is needed to guide therapeutic decisions for patients with metastatic lung cancer, both at diagnosis and following the development of resistance. This can result in multiple biopsies during the disease course.

The gold standard method for mutation analysis involves examining DNA extracted from a tissue biopsy; however, drawbacks include a lack of feasibility in some cases, invasiveness, the possible acquisition of insufficient tissue or suboptimal tissue quality for gene sequencing.[1] There has been much interest in using less-invasive liquid biopsy approaches analysing circulating tumour DNA (ctDNA) released into plasma from cancer cells during apoptosis/necrosis. Gene sequencing technologies have become faster, cheaper and more accurate; however, ctDNA tests are used primarily for patients in whom tissue is not available, or to guide targeted therapy in some specific situations. In the near future, we might envisage liquid biopsy approaches eventually becoming reasonable alternatives to tissue biopsies, particularly when consecutive sampling is indicated for advanced disease. Additional applications to detect minimal residual disease in early stages are being actively explored.

1. Bernabé R, et al. Eur J Cancer 2017;81:66–73

Don't miss the Challenge Your Expert session

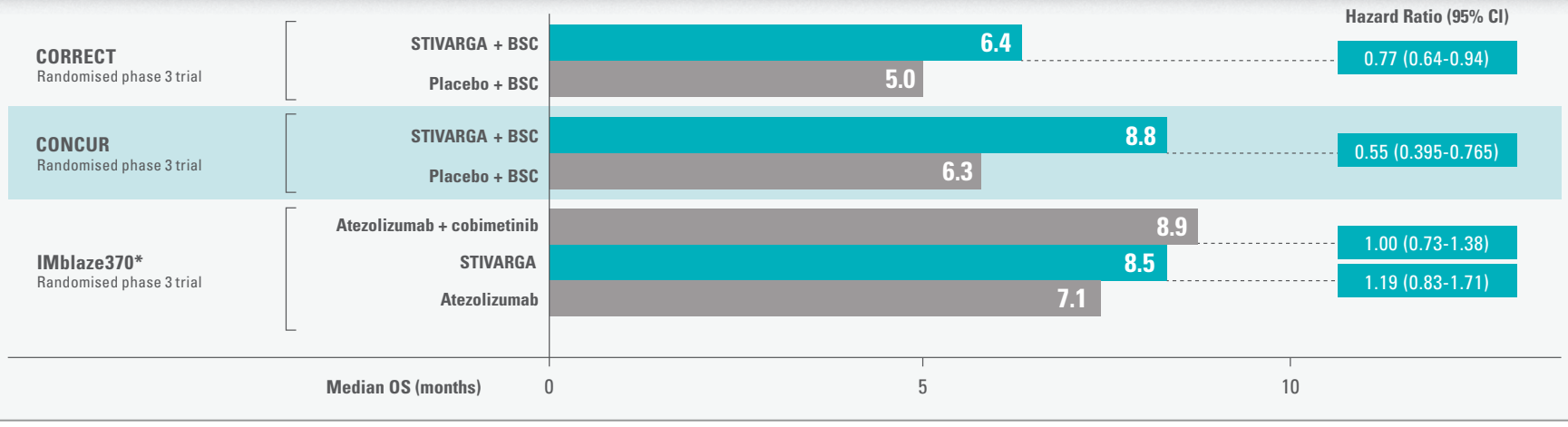
'Clinical application of liquid biopsy in metastatic lung cancer'

Today, 08.00 – 09.00 in Hall B3 – Room 23.

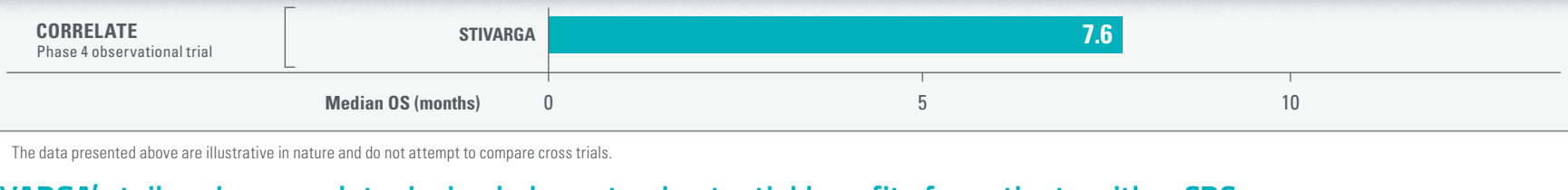
Consider STIVARGA® (regorafenib) to extend overall survival (OS) for your 3L patients with mCRC

Robust median OS improvements with STIVARGA demonstrated across a range of studies

Median OS results across phase 3 clinical trials[1-3]



Median OS results from phase 4 CORRELATE study[4]



The data presented above are illustrative in nature and do not attempt to compare cross trials.

STIVARGA's tailored approach to dosing helps extend potential benefits for patients with mCRC

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) recommend the following dose escalation schedule[5,6]

STIVARGA dose escalation approach based on ReDOS[5-7†]

	Cycle 1				Cycle 2
Week	1	2	3	4	1
Once-daily dose	80 mg	120 mg	160 mg	Dosing-free interval	Last dose from Cycle 1

Regorafenib dose optimization study[7]

- ReDOS is a randomized phase 2 study of a planned dose escalation with STIVARGA (starting from a lower dose) compared to the standard dose in patients with refractory mCRC[‡§]
- Median OS was 9.0 months with the STIVARGA escalating dose vs 5.9 months with the STIVARGA standard dose (*P*=0.0943)

- The recommended dosage of regorafenib is 160 mg (4 tablets of 40 mg) taken once daily for 3 weeks, followed by 1 week off therapy. This 4-week period is considered a treatment cycle. Dosage interruptions and/or dose reductions may be required based on individual safety and tolerability. Dosage modifications are to be applied in 40-mg (1 tablet) steps. The lowest recommended daily dose is 80 mg. The maximum daily dose is 160 mg

3L, third-line; BSC, best supportive care; CORRECT, COloRectal cancer treated with REgorafenib or plaCebo after failure of standard Therapy; CORRELATE, Safety and Effectiveness of Regorafenib in Routine Clinical Practice Settings; ReDOS, REgorafenib Dose Optimization Study.

*This study was designed to evaluate the primary endpoint of OS in 3 study arms: atezolizumab + cobimetinib, atezolizumab monotherapy, and regorafenib. The combination regimen of atezolizumab + cobimetinib failed to meet its primary endpoint of superior OS relative to regorafenib. The OS difference between the combination arm and the regorafenib arm was not statistically significant (*P*=0.9871).

†The study supporting the dose escalation schedule has not been reviewed by the FDA. The study was a randomised, phase 2, US-based trial, through the ACCRU (Academic and Community Cancer Research United) research network, that looked at the proportion of patients who completed 2 cycles of STIVARGA and initiated a third cycle (N=116).[3] The efficacy of the alternative dosing schedule cannot be compared to the efficacy of other trials.[7]

‡Escalating dose regimen was 80 mg orally, once daily on days 1 through 7; 120 mg orally, once daily on days 8 through 14; 160 mg orally, once daily on days 15 through 21; followed by 7 days off therapy. Cycle 2 started at the last level dosed during Cycle 1.

§Standard dosing regimen was regorafenib 160 mg orally, once daily for 21 days, followed by 7 days off therapy.

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Stivarga 40 mg film-coated tablets (Refer to full SmPC before prescribing.)
Composition: *Active ingredient*: 40 mg regorafenib. *Excipients:* Cellulose microcrystalline, croscarmellose sodium, magnesium stearate, povidone (K-25), silica (colloidal anhydrous), iron oxide red (E172), iron oxide yellow (E172), lecithin (derived from soya), macrogol 3350, polyvinyl alcohol (partly hydrolysed), talc, titanium dioxide (E171). **Indication:** As monotherapy for the treatment of adult patients with: 1. metastatic colorectal cancer (CRC) who have been previously treated with, or are not considered candidates for, available therapies. These include fluoropyrimidine based chemotherapy, an anti-VEGF therapy and an anti-EGFR therapy; 2. unresectable or metastatic gastrointestinal stromal tumors (GIST) who progressed on or are intolerant to prior treatment with imatinib and sunitinib; 3. hepatocellular carcinoma (HCC) who have been previously treated with sorafenib. **Contraindications:** Hypersensitivity to the active substance or any of the excipients. **Warnings and Precautions:** It is recommended to perform liver function tests before initiation of treatment and monitor closely (at least every 2 weeks) during the first 2 months of treatment. Thereafter, periodic monitoring should be continued at least monthly and as clinically indicated. Mild, indirect (unconjugated) hyperbilirubinaemia may occur in patients with Gilbert's syndrome. Close monitoring of the overall safety is recommended in patients with mild or moderate hepatic impairment. Stivarga is not recommended for use in patients with severe hepatic impairment (Child-Pugh C). In cases of worsening infection events, interruption of Stivarga treatment should be considered. Blood counts and coagulation parameters should be monitored in patients with conditions predisposing to bleeding, and in those treated with anticoagulants or other concomitant medicinal products that increase the risk of bleeding. Patients with oesophageal varices should be evaluated and treated as per SOC/guidelines before starting treatment with Stivarga. Permanent discontinuation should be considered in the event of severe bleeding. Discontinuation of Stivarga is recommended in patients developing gastrointestinal perforation or fistulae. Patients with a history of ischaemic heart disease should be monitored for clinical signs and symptoms of myocardial ischaemia. In patients who develop cardiac ischaemia and/or infarction, interruption of Stivarga is recommended until resolution. The decision to restart Stivarga therapy should be based on careful consideration of the potential benefits/risks of the individual patient. Stivarga should be permanently discontinued if there is no resolution. In patients developing posterior reversible encephalopathy syndrome (PRES), discontinuation of Stivarga, along with control of hypertension and supportive medical management of other symptoms is recommended. Blood pressure should be controlled prior to initiation and during treatment and it is recommended to treat hypertension. In cases of severe or persistent hypertension despite adequate medical management, treatment should be temporarily interrupted and/or the dose reduced. In case of hypertensive crisis, Stivarga should be discontinued. For patients undergoing major surgical procedures it is recommended to interrupt treatment temporary for precautionary reasons, and to resume treatment based on clinical judgment of adequate wound healing. Management of hand-foot skin reaction (HFSR) may include the use of keratolytic creams and moisturizing creams for symptomatic relief. Dose reduction and/or temporary interruption, or, in severe or persistent cases, permanent discontinuation of Stivarga should be considered. It is recommended to monitor biochemical and metabolic parameters during treatment and to institute replacement therapy if required. Dose interruptions or reduction, or permanent discontinuation should be considered in case of persistent or recurrent significant abnormalities. In clinical trials, a higher incidence of HFSR, severe liver function test abnormalities and hepatic dysfunction was observed in Asian (in particular Japanese) patients treated with Stivarga compared with Caucasians. This medicinal product contains 55.8 mg sodium per daily dose of 160 mg, equivalent to 3% of the WHO recommended maximum daily intake of 2 g sodium for an adult. Each daily dose of 160 mg contains 1.68 mg of lecithin (derived from soya). There is insufficient data on patients who discontinued sorafenib therapy due to sorafenib-related toxicity or only tolerated a low dose (< 400 mg daily) of sorafenib. **Undesirable effects:** *Very common:* infection,‖ thrombocytopenia, anaemia, decreased appetite and food intake, haemorrhage,‖ hypertension, dysphonia, diarrhoea, stomatitis, vomiting, nausea, hyperbilirubinaemia, increase in transaminases, HFSR, rash, asthenia/fatigue, pain, fever, mucosal inflammation, weight loss. *Common:* leucopenia, hypothyroidism, hypokalaemia, hypophosphataemia, hypocalcaemia, hyponatraemia, hypomagnesaemia, hyperuricaemia, dehydration, headache, tremor, peripheral neuropathy, taste disorders, dry mouth, gastro-oesophageal reflux, gastroenteritis, alopecia, dry skin, exfoliative rash, muscle spasms, proteinuria, increase in amylase, increase in lipase, abnormal International normalized ratio. *Uncommon:* hypersensitivity reaction, myocardial infarction, myocardial ischaemia, hypertensive crisis, gastrointestinal perforation,‖ gastrointestinal fistula, pancreatitis, severe liver injury,‖ nail disorder, erythema multiforme. *Rare:* keratoacanthoma/squamous cell carcinoma of the skin, PRES, Stevens-Johnson syndrome, toxic epidermal necrolysis.
‖Fatal cases have been reported.
Classification for supply: Medicinal product subject to restricted medical prescription.
Marketing Authorisation Holder: Bayer AG, D-51368 Leverkusen, Germany
Date of the underlying Prescribing Information: June 2018

REFERENCES: 1. Grothey A, Van Cutsem E, Sobrero A, et al; for the CORRECT Study Group. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet.* 2013;381(9863):303-312. **2.** Li J, Qin S, Xu R, et al; on behalf of the CONCUR Investigators. Regorafenib plus best supportive care versus placebo plus best supportive care in Asian patients with previously treated metastatic colorectal cancer (CONCUR): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol.* 2015;16(6):619-629. **3.** Bendell J, Ciardiello F, Tabernero J, et al. Efficacy and safety results from IMblaze370, a randomised phase III study comparing atezolizumab+cobimetinib and atezolizumab monotherapy vs regorafenib in chemotherapy-refractory metastatic colorectal cancer. *Ann Oncol.* 2018;29(suppl 5). doi:10.1093/annonc/mdy208.003. Abstract LBA-004. **4.** Ducreux M, Petersen LN, Öhler L, et al; CORRELATE Investigators. Safety and effectiveness of regorafenib in patients with metastatic colorectal cancer in routine clinical practice: final analysis from the prospective, observational CORRELATE study. Poster presented at: European Society for Medical Oncology (ESMO) 20th World Congress on Gastrointestinal Cancer; June 20-23, 2018; Barcelona, Spain. **5.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Rectal Cancer V.2.2018. © National Comprehensive Cancer Network, Inc. 2018. All rights reserved. Accessed July 13, 2018. To view the most recent and complete version of the guideline, go online to NCCN.org. **6.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Colon Cancer. V.2.2018. © National Comprehensive Cancer Network, Inc. 2018. All rights reserved. Accessed July 13, 2018. To view the most recent and complete version of the guideline, go online to NCCN.org. **7.** Bekaii-Saab TS, Ou F-S, Anderson DM, et al. Regorafenib dose optimization study (ReDOS): a randomized phase II trial to evaluate dosing strategies for regorafenib in refractory metastatic colorectal cancer (mCRC)—an ACCRU Network study. Poster presented at: American Society of Clinical Oncology (ASCO) 2018 Gastrointestinal Cancers Symposium; January 18-20, 2018; San Francisco, CA.

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