First-line immunotherapy for advanced NSCLC: A chink in nivolumab’s armour? Greater patient selection needed!

Nivolumab is approved in Europe and the USA in previously treated advanced non-small-cell lung cancer (NSCLC) having demonstrated a survival benefit versus docetaxel in CheckMate-017 and -067. Furthermore, patients with advanced NSCLC with PD-L1-positive tumours experienced durable responses with first-line nivolumab monotherapy in the phase I CheckMate-012 study. Yesterday Dr Mark Socinski of the UPMC Cancer Center, Pittsburgh, Philadelphia, USA, presented late-breaking results from CheckMate-026, one of the first studies in chemotherapy-naïve patients with stage IV or recurrent NSCLC to compare immunotherapy with a platinum-based regimen (Abstract LBA7_PR). A total of 541 patients received nivolumab 3 mg/kg every 2 weeks or investigator’s choice (IC) of platinum-based doublet chemotherapy every 3 weeks for up to 6 cycles. Despite an enriched population with PD-L1-positive tumours (threshold defined as ≥1%; n= 423), nivolumab did not show superior median progression-free survival compared with IC (4.2 months versus 5.9 months; hazard ratio 1.15, p=0.25).

The low threshold of PD-L1 expression used for patient selection in CheckMate-026 may have accounted for the lack of observed improvement in progression-free survival with nivolumab compared with chemotherapy.

While the threshold of PD-L1 positivity in CheckMate-026 was ≥1%, a similar study comparing first-line pembrolizumab with platinum-doublet chemotherapy in advanced NSCLC, KEYNOTE-024, used a much higher threshold of ≥50% (Abstract LBA8) and showed significant clinical benefit for the anti-PD-1 therapy. Let’s see whether the combination of nivolumab and ipilimumab, as in CheckMate-227, will trump chemotherapy in treatment-naïve, low PD-L1 expressors with NSCLC.

Controversy of the Day: Biosimilars and bioequivalents. A wise choice in a demanding treatment landscape?

It is evident that there are a number of discrepancies between countries in relation to the care received by cancer patients. Among the key differences identified in the workforce, including the number of people with the skills needed to meet the demands of a looming cancer epidemic.

The aim of the project is to gather data that identify future gaps and needs in the oncology workforce so they can be incorporated in national cancer plans.

Breast cancer was chosen as the first disease to survey because of its high frequency and the need for multidisciplinary management, which will highlight the broad requirements of the oncology workforce and the skills needed to meet the demands of a looming cancer epidemic.

The pilot study will begin in early 2017 with results expected to be available at the ESMO 2017 Congress. It is anticipated that the study will be rolled out in other European countries a number of discrepancies in relation to the care received by cancer patients.

Two studies of trastuzumab biosimilars for the treatment of patients with HER2-positive metastatic breast cancer were presented yesterday, Dr Hope Rugo (UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, California, USA; Abstract LBA16) described how the biosimilar, Myl-1401O, was associated with an equivalent overall response rate (ORR) to trastuzumab at 24 weeks (primary endpoint; 69.6% vs 64.0% trastuzumab). Other endpoints from this phase III study in 458 randomised patients, such as progression-free and overall survival, also showed no significant difference between the agents. Importantly, safety, pharmacokinetic and immunogenicity findings appeared similar.

A second study presented by Dr Cristina Saura based on a poster by Dr Maria Shustova (USC “BIOCAD”, St Petersburg, Russian Federation; Abstract 224PD) reported how the biosimilar BCD-022 was statistically equivalent in terms of ORR (53.6% versus 53.7%, respectively), with BCD-022 showing non-inferiority to trastuzumab. Other efficacy parameters (complete and partial responses, stable disease and disease progression) were equivalent between the agents, too. Both medications were associated with comparable safety and immunogenicity findings.

While biosimilars have been available in Europe for more than a decade, they have not been universally accepted and their use varies greatly by product and country. In the Netherlands, for example, adoption of biosimilars has been good and estimated at 40%. However, concerns have been raised over the post-marketing quality and long-term safety of biosimilars. Particular concerns relate to extrapolation of indication. If the reference product is licensed to treat multiple therapeutic indications, extrapolation of the biosimilar for use in these same indications may be possible without the need for comparative clinical trials, but this must be scientifically justified.

The European Medicines Agency (EMA) has created guidelines for obtaining marketing authorisation of biosimilars. Regulatory approval requires that a biosimilar is characterised analytically and clinically; efficacy and safety (including immunogenicity) should be assessed in the most sensitive patient populations with endpoints that can detect any clinically meaningful differences between the proposed biosimilar and the reference product. This enables manufacturers to develop biological therapies that are broadly accessible within a tailored development programme.

2. Siegel JF, Fischer A. www.biologicsblog.com/blog/ten-years-of-biosimilars-in-europe/

WHO-ESMO workforce survey

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Breast cancer was chosen as the first disease to survey because of its high frequency and the need for multidisciplinary management, which will highlight the broad requirements of the oncology workforce and the skills needed to meet the demands of a looming cancer epidemic.

The pilot study will begin in early 2017 with results expected to be available at the ESMO 2017 Congress. It is anticipated that the study will be rolled out in other European countries later next year. A strategic goal from the study’s findings is to promote universal healthcare coverage in accordance with the WHO principles.
Female oncologists: Still paying the price for being a woman

ESMO Women for Oncology initiative began in 2013 and was borne from the realisation that female oncologists are under-represented in leadership positions. In an online survey this year, ESMO explored the gender-related challenges faced by oncology professionals. The survey results gave a valuable and unique insight into the perceptions of those working in oncology today.

At the Women for Oncology Session yesterday, Professor Solange Peters from the University of Lausanne, Switzerland, presented key results from the survey. Of the 482 male and female participants, the majority (77%) were female and were medical oncologists (66%). Most respondents (60%) worked in a team in which there were more women than men although the responsible person in the team was male in 64% of cases.

In terms of obstacles that respondents had encountered during their career progression, finding a balance between work and family featured prominently (65% of respondents), although the belief that men were perceived as natural leaders and women were team members and supporters was also common (40% of respondents). When questioned about their thoughts on the main barriers that prevented gender equality in the workplace, regardless of gender, respondents said that a lack of work–life balance was a key factor (52% of respondents), and that social pressures were also prominent (31% of respondents).

After the session, Professor Peters commented that some of the additional survey results not presented in yesterday’s talk were rather surprising and made for uncomfortable reading. Astonishingly, 41% of surveyed female respondents said that they had encountered unwanted sexual comments, attention or advances by a superior colleague, with 69% of these encountering generalised sexist remarks and behaviours in the workplace.

How can the gender gap in oncology be closed? Half of survey respondents believed that the best approach for the oncology community to take would be to promote work–life balance. Other suggestions considered important were the development and provision of leadership training for women (response: 28.7% of males, 44.2% of females) and the offer and support of flexible working hours (response: 35.1% of males, 41.6% of females).

Full results from the survey will be available from the ESMO website.

More than one-quarter (27%) of female respondents believed that their gender significantly impacted their career, compared with 14% of male respondents.

In commenting after the session, Professor Edith Perez, Vice President and Head of US Medical Affairs, Genentech/Roche BioOncology, and Professor of Medicine, Mayo Clinic, USA, said that gender inequality is an important global issue and one that is currently receiving much attention in science. She said she is pleased to see a good balance of male and female presenters at the ESMO Congress.
Achieving a good depth of response, addressing symptoms and increasing overall survival are the main treatment goals for incurable diseases, such as multiple myeloma. Rational therapeutic approaches consider individual pathology, transplant eligibility, disease stage, comorbidities, patient age and wider health, quality of life and minimisation of toxicity. Because of these complexities, the optimal sequence of therapies for relapsing refractory multiple myeloma (RRMM) has yet to be established. An enhanced understanding of multiple myeloma disease mechanisms has led to more targeted therapies, and there is now a plethora of treatments available for this disease (Figure) leading to the use of multi-combination treatments becoming common practice.

Combination of the proteasome inhibitor bortezomib with dexamethasone is a standard regimen for RRMM treatment. Adding an immunotherapy with a novel mechanism of action to this approach is an intriguing proposition and was the subject of a proffered paper on the daratumumab CASTOR study presented yesterday by Dr Katja Weisel of Tübingen University, Germany (Abstract 906O).

Daratumumab is a human monoclonal antibody that targets CD38, an antigen located on the surface of myeloma cells. Daratumumab monotherapy recently became the first anti-CD38 to be approved by the EMA for pre-treated patients with RRMM, after open-label studies showed impressive improvements in progression-free survival (PFS) and durable responses. Addition of daratumumab significantly improved median PFS (median not reached versus 7.2 months; 61% risk reduction; hazard ratio 0.39; 95% confidence interval 0.28—0.53; p<0.0001), and overall response rates (83% versus 63%, respectively; p<0.0001) compared with bortezomib plus dexamethasone alone in this highly refractory population. The daratumumab combination had a manageable safety profile that was consistent with the known profiles of the single agents. In light of these findings, Dr Weisel concluded that this triple combination could potentially be considered a new standard of care for patients with RRMM currently receiving the double combination only.

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Second-generation ALK inhibitor improves outcome in NSCLC progressing on crizotinib

Crizotinib changed the face of treatment for ALK-positive non-small-cell lung cancer (NSCLC) but resistance develops almost inevitably within the first year of treatment. Promising phase I/II efficacy findings for the second-generation ALK inhibitor, ceritinib, in NSCLC progressing on crizotinib-based treatment were confirmed by the results of the open-label, phase III ASCEND-5 study, presented in a Proffered Paper Session yesterday by Professor Giorgio Scagliotti from the University of Turin, Italy (Abstract LBA42_PR).

Among 231 patients previously treated with chemotherapy and crizotinib, ceritinib significantly improved progression-free survival (PFS) (median 5.4 months versus 1.6 months, p<0.001) and increased response rate (39.1% versus 6.9%) compared with chemotherapy (docetaxel or pemetrexed). The median treatment exposure was 30.3 weeks for ceritinib and 6.3 weeks for chemotherapy. No difference was found between the study arms in relation to overall survival, with most patients crossing over to chemotherapy after progressing. Gastrointestinal adverse events were more common with ceritinib, and fatigue, alopecia and neutropenia were seen more frequently with chemotherapy. Significant improvements in lung cancer-specific symptoms and overall health status were also seen with ceritinib versus chemotherapy (p<0.05).

Ceritinib significantly prolonged PFS by nearly 4 months and improved quality of life.

The field of ALK-positive lung cancer is evolving very rapidly, with a wealth of new agents in development. The use of better ALK inhibitors upfront, as demonstrated by the J-ALEX data, is certain to further improve outcomes in crizotinib-naive patients. In addition, although resistance inevitably develops, their differential activity across ALK-resistance mutations should provide clinicians with new options at progression. Last but not least, the role of immunotherapy in this disease setting has to be defined, and ALK inhibitor-based combinations with PD-L1 inhibitors are already underway in the clinic.
Precision medicine: Evolving trial design for targeted treatment

Physicians can now analyse tumours for the presence of multiple genes and proteins, but there are currently no guidelines to determine which molecular assays are suitable for metastatic cancers.

Last year, the first Molecular Analyses for Personalized (MAP) Medicine conference explored the use of genomics to help improve therapy selection in this setting. New technologies, including next-generation sequencing of tumours, have been validated but the conference concluded that precision medicine trials should be stratified according to the level of evidence available for the identified genomic alterations.

A number of oncology trials have begun to address the complexities of tumour pathology by identifying drugs that may be highly effective in patients with particular mutations, regardless of their cancer type. Umbrella trials allow testing of multiple treatments targeted to specific tumour pathways in patients grouped according to an identified molecular alteration.

Umbrella trials therefore eliminate the need for numerous regulatory and ethical approvals and give drug sponsors access to an existing network of study centres and a central pool of patients screened for specific mutations.

Like umbrella trials, basket trials treat by causative mutation, rather than tumour histology. Patients with identified tumour alterations, regardless of cancer type, are matched to a medication targeting that specific mutation or pathway, allowing investigation of multiple, often rare, tumour pathologies (Figure). Although basket trials have resulted in notable successes, including vemurafenib in BRAF V600E-mutated lung cancer, effectively blocking an identified mutation does not necessarily ensure clinical tumour response, and success in one cancer cannot be assumed across other tumour types, as illustrated by a lack of response to vemurafenib in BRAF V600E-mutated colorectal cancer.

Combination treatment is a rational approach in precision medicine as tumours may exploit alternative biological pathways for survival, although in the aforementioned vemurafenib study, addition of the anti-EGFR antibody cetuximab did not improve outcomes in patients with colon cancer.

The uncertainties of precision medicine were starkly emphasised in a presentation concerning olaparib in advanced gastric cancer given on Saturday by Dr Yung-Jue Bang of the Seoul National University Hospital, South Korea (Abstract LBA25). Originally, a basket trial of olaparib in patients with recurrent solid tumours who all had BRCA1/2 mutations showed encouraging results in ovarian cancer. This finding allowed more targeted investigation, and olaparib maintenance treatment was recently approved for patients with BRCA1/2-mutated ovarian cancer after responding to platinum-based second-line chemotherapy. A phase II trial of olaparib plus paclitaxel in metastatic/recurrent gastric cancer yielded a promising increase in overall survival versus paclitaxel alone, particularly in patients with low levels of ataxia-telangiectasia mutation (ATM), a key activator of DNA damage response, suggesting that precision medicine with olaparib may also be a possibility in gastric cancer. Despite these early signals, the phase III GOLD trial failed to show a significant increase in OS for patients with advanced gastric cancer treated with olaparib plus paclitaxel in either the total population or in ATM-negative patients. Pooling resources and patients using novel approaches, like umbrella trials, are vital in identifying new and effective anti-cancer drugs.

Combined targeted therapy shows promise for BRAF V600E-mutated metastatic CRC

Combined targeted treatment appears to have therapeutic potential in BRAF V600E-mutated colorectal cancer (BRAFm mCRC) according to latest data from an ongoing study presented yesterday by Dr Ryan Corcoran from Massachusetts General Hospital, Boston, USA (Abstract 455O). These are important findings given that BRAFm mCRC is notoriously difficult to treat and is associated with poor prognosis; targeted therapies (BRAF and MEK inhibitors) have previously had minimal activity, although preclinical data have provided a rationale for investigating combined inhibition.1

This study of 134 patients with BRAFm mCRC assessed the BRAF inhibitor dabrafenib (D), the MEK inhibitor trametinib (T), and the anti-EGFR antibody panitumumab (P) across three treatment arms (DP, TP and DTP) and reported clinical responses (Table) and evidence of downstream target inhibition. DTP had an acceptable tolerability profile with the most common adverse events being rash, diarrhoea, fatigue and nausea.

Serial circulating tumour DNA (ctDNA) analysis revealed >70% reduction in BRAF V600E mutant fraction (MF) in 12 out of 14 (86%) DP-treated patients by week 4, with six of the 12 patients achieving partial response by week 6. RAF mutations that were not detectable at baseline were detected in ctDNA at progression in seven of 12 (58%) patients who achieved complete/partial response or stable disease, indicating a potential resistance mechanism. “These data suggest that ctDNA analysis may have value in monitoring disease response and progression in BRAFm mCRC,” noted Dr Corcoran.

“…ctDNA analysis may have value in monitoring disease response and progression in BRAFm mCRC.”

Despite clinically relevant data emerging from this study, consideration should be given to the potential toxicities arising from combination therapies targeting multiple pathways. 1. Corcoran RB, et al. Cancer Discov 2012;2:227–35

**ENDPOINT** | **COMBINATION** |
--- | --- | ---
 | DP (N=20) | TP (N=31) | DTP (N=83) |
Complete/partial response, % patients | 10 | 0 | 18 |
Stable disease, % patients | 80 | 53 | 67 |
Median progression-free survival, months | 3.4 | 2.8 | NYM |

NYM, not yet mature

Encouraging results for nivolumab in advanced hepatocellular carcinoma

Therapeutic options for patients with advanced hepatocellular carcinoma (aHCC) failing first-line sorafenib are limited and best supportive care is associated with a survival time of only around 7–8 months. Immunotherapy with the anti-PD-1 monoclonal antibody nivolumab is a potential new approach to improve patient outcomes.

In a Proffered Paper Session yesterday, Dr Ignacio Melero from Universidad de Navarra, Pamplona, Spain, presented results from an interim analysis of the phase I/II CheckMate 040 study (Abstract 615O). Patients with aHCC were treated with nivolumab 0.1–10 mg/kg in three dose escalation cohorts: hepatitis B virus (HBV)-infected; hepatitis C virus (HCV)-infected; and uninfected. This was followed by nivolumab 3 mg/kg in an expansion phase comprising four cohorts: uninfected sorafenib-naïve/intolerant; uninfected sorafenib progressors; HBV-infected; and HCV-infected.

The 9-month overall survival rate in this interim analysis was 71%.

Serial circulating tumour DNA (ctDNA) analysis revealed >70% reduction in BRAF V600E mutant fraction (MF) in 12 out of 14 (86%) DTP-treated patients by week 4, with six of the 12 patients achieving partial response by week 6. RAF mutations that were not detectable at baseline were detected in ctDNA at progression in seven of 12 (58%) patients who achieved complete/partial response or stable disease, indicating a potential resistance mechanism. “These data suggest that ctDNA analysis may have value in monitoring disease response and progression in BRAFm mCRC,” noted Dr Corcoran.

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The 9-month overall survival rate in this interim analysis was 71%.
A renaissance in the treatment and management of ovarian cancer?

High-grade ovarian cancer currently has a poor prognosis; however, a number of tumour subtypes have been recognised that could lead to targeted treatments and perhaps, better outcomes. A number of presentations at ESMO 2016 highlight important developments in ovarian cancer.

Poly ADP ribose polymerase (PARP) family proteins are involved in DNA repair. BRCA1/2 genes code for PARP-independent DNA repair enzymes, meaning that BRCA mutation-positive tumours are particularly susceptible to PARP inhibition. On the basis of improvements in progression-free survival (PFS) in phase II trials,² the PARP inhibitor olaparib received accelerated US FDA and EMA approval in 2014 (Abstract LBA33_PR). Maintenance therapy with niraparib significantly improved PFS compared with placebo in patients with gBRCAm ovarian cancer (21.0 months versus 5.5 months, respectively; p<0.0001) and in gBRCAm-negative patients who were later identified as homologous recombination (HR) DNA-repair (12.9 months versus 3.8 months, respectively; p<0.0001). HR DNA-repair deficiency is an important target in ovarian cancer and is present in <30% of patients. Intriguingly, niraparib also significantly improved PFS in patients who did not harbour BRCA mutations or HR DNA-repair deficiency (8.3 months versus 3.9 months with placebo; p=0.0001). Patient-reported outcomes were similar for niraparib and placebo. The mechanism responsible for the effect of niraparib in patients negative for BRCA mutation and HR DNA-repair deficiency is currently unknown. These exciting results were further bolstered by data from a pooled analysis of two phase II studies of the PARP inhibitor rucaparib in patients with high-grade ovarian carcinoma and gBRCAm or somatic BRCAm previously treated with ≥2 lines of chemotherapy (Abstract B560). Rucaparib has a breakthrough therapy designation in the USA in this indication and Dr Rebecca Kristeleit of the University College London, Cancer Institute, UK, reported that the median confirmed response duration with rucaparib was 9.2 months in these two trials. Phase III trials are ongoing.

Not only do these data confirm the positive results achieved with PARP inhibition for patients with relapsing gBRCAm ovarian cancer, but they also give new hope for all ovarian cancer patients. A major challenge, however, is the identification of patients who may benefit from PARP-inhibitor therapy, but who lack BRCA mutations. Although adopting different identification methods, the above studies detected patients lacking BRCA mutations or HR DNA-repair deficiency. The intriguing data for niraparib showing a benefit in these patients may reflect the fact that the methods used are not definitive and that some patients harbour a DNA-repair deficiency not detectable with current tests.

Androgens may also have a role in the aetiology of epithelial ovarian cancer and androgen receptors are frequently expressed in this tumour type. Abiraterone inhibits androgen biosynthesis and is commonly used for the treatment of prostate cancer. On Friday, Dr Susana Banerjee of The Royal Marsden NHS Foundation Trust, London, UK, reported the results of the phase II abiraterone CORAL study in 42 patients with hormone therapy-naïve epithelial ovarian cancer (Abstract LBA33_PR). Sustained efficacy was seen in a patient with low-grade serous disease but not in a patient with low-grade serous disease but who lacked BRCA mutations. The intriguing data for niraparib and rucaparib may reflect the fact that the methods used are not definitive and that some patients harbour a DNA-repair deficiency not detectable with current tests.

While these results allow us to make positive projections for better outcomes in the treatment of ovarian cancer, it is important that patient management and support evolve alongside molecular medicine. On Saturday, I reported interim results from ENGAGE, an oncologist-led model of gBRCAm testing and genetic counselling for patients with ovarian cancer being enrolled across 26 centres internationally (Abstract LBA34). Routine BRCA testing in ovarian cancer patients is advocated by several scientific societies and is part of current clinical guideline recommendations. However, the classical model of genetic counselling may not enable the systematic testing of all ovarian cancer patients and could lead to substantial delays in testing turnaround time. This new model proposed in the ENGAGE study could help overcome these barriers and lead to efficient resource use, while providing the opportunity to test most patients. Moreover, the use of effective prevention procedures in at-risk unaffected family members has the potential to greatly impact the incidence and mortality of this deadly disease.

It appears that treatment and management of ovarian cancer are currently going through a renaissance and future advancements are eagerly anticipated.

Intensive follow-up of patients with curatively treated colorectal cancer (CRC) for 5 years using carcinoembryonic antigen (CEA) and/or computed tomography (CT) analysis increases the detection of treatable recurrence, but only in colon cancer. Furthermore, a survival advantage is only observed in patients with recurrence from a left-sided colon cancer. These were the conclusions of a mature overall survival (OS) analysis from the FACS trial (a randomised clinical trial conducted in 39 UK hospitals) presented yesterday by Dr Siân Pugh from the University of Southampton, UK (Abstract 453O).

In the study, 1,202 patients who received curative-intent treatment for primary stage I–III CRC were followed up with intensive (either CEA alone, CT scan alone or both modalities) or minimum (symptomatic ± single CT scan) strategies. At 12-years’ follow-up, intensive monitoring by CEA and/or CT scan significantly increased the detection of surgically treatable recurrence compared with minimum monitoring (7.0% versus 2.7%, respectively; p=0.003). Treatable colon, but not rectal, tumour recurrences were more commonly detected by intensive follow-up, although this translated into a survival advantage only in those with recurrence from a left-sided colon cancer (median OS: 4.4 years versus 3.1 years, respectively; p=0.03).

This small but positive signal for improved OS with increased detection of recurrence (at least in a subpopulation) in the FACS follow-up study contrasts with the findings of a recent meta-analysis. This evaluated trials of CEA and/or CT monitoring for early detection of asymptomatic metastatic disease after potentially curative resection of primary CRC and included 16 randomised comparisons, 11 with published survival data. More intensive monitoring brought forward the diagnosis of recurrence by a median of 10 (interquartile range 5–24) months. In 10 of 11 studies, the authors reported no demonstrable difference in OS. Seven randomised, controlled trials, published from 1996 to 2016, assigned 3,325 patients to a monitoring protocol intensified by the introduction of new methods or increasing the frequency of existing follow-up protocols compared with less invasive monitoring. More intensive monitoring protocols were not associated with a detectable difference in OS (hazard ratio 0.98; 95% confidence interval 0.87–1.11).

While intensive follow-up after surgery for CRC is common practice, it is based on limited evidence, and there is no general guidance regarding surveillance across Europe. Given the large patient population and extended follow-up of the FACS trial, these important data may be used to inform clinical practice and guide future monitoring of CRC patients.

Commenting on the results of the analysis, Professor Dirk Arnold from CUF Hospitals in Lisbon, Portugal, cautions that they must be viewed in the context of the treatment options available, which may differ for earlier or later detection of relapse. At the time most of these analyses were conducted, including the FACS follow-up, treatment options were often very limited and life expectancy/OS was poor. Today’s treatment landscape includes (potentially) curative approaches for oligometastatic disease and localised metastasis, making the detection of early relapse crucial. This is an essential part of the ESMO Clinical Practice Guidelines and is in agreement with most national treatment recommendations, which advocate the use of follow-up with CT scans/ultrasound and CEA evaluations to detect early relapsing disease.1

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The first approved treatment in over 2 decades to deliver a survival advance beyond the benefit of chemotherapy.1,2

Portrazza, a human mAb targeting EGFR, demonstrated a positive benefit/risk profile in this hard-to-treat patient population.2

95% of patients in SQUIRE expressed EGFR1

The large majority of patients (95.2% of evaluable patients; n=935) had detectable for EGFR protein expression 1

17% improvement in median OS1,3

In the EGFR-expressing population, median OS for the Portrazza arm was 11.5 months vs 9.9 months in the GC arm (HR=0.79 [0.69, 0.92]; P=0.002)1,3

51% of patients continued with single-agent Portrazza1

Patients who continued with necitumumab after the end of chemotherapy received a median of 4 additional cycles of treatment1

The safety profile of the ITT population was generally manageable, with well-known EGFR mAb-related adverse events1

• As expected with EGFR inhibition, rash and hypomagnesaemia (grade 3) were more common with Portrazza plus GC1

• The most common serious adverse reactions (grade 3) observed in Portrazza-treated patients were skin reactions (6.3%) and venous thromboembolic events (4.3%)4

Adverse Events/((Product Characteristics

Portrazza BLEED:

Arm (HR=0.79 [0.69, 0.92]; P=0.002)4: the Portrazza arm (11.5 months vs 9.9 months in the GC arm; HR=0.96; 95% CI: 0.84 [0.74, 0.99]) demonstrated a positive benefit/risk profile in this hard-to-treat patient population.1,3

Special warnings and precautions for use:

Special warnings and precautions for use: This may lead to severe hypomagnesaemia. The patients' concentration of serum electrolytes should be monitored for signs of infusion-related reactions (see section 4.4 of the Summary of Product Characteristics). Progressively decreasing serum concentration of magnesium frequently occurs. Hypomagnesaemia is treated by oral or intravenous replacement with magnesium chloride. In patients with hypomagnesaemia, magnesium should be given as intravenous infusion. Progressively decreasing serum concentration of magnesium frequently occurs. Hypomagnesaemia is treated by oral or intravenous replacement with magnesium chloride. In patients with hypomagnesaemia, magnesium should be given as intravenous infusion. Progressively decreasing serum concentration of magnesium frequently occurs. Hypomagnesaemia is treated by oral or intravenous replacement with magnesium chloride. In patients with hypomagnesaemia, magnesium should be given as intravenous infusion.

Special precautions for disposal and other handling: Portrazza is an active pharmaceutical ingredient that can be hazardous if inhaled or swallowed. Therefore, it should not be inhaled or swallowed. Therefore, it should not be inhaled or swallowed. Therefore, it should not be inhaled or swallowed.

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Chemotherapy. 2,3

Portrazza, a human mAb targeting EGFR, demonstrated a positive benefit/risk profile in this hard-to-treat patient population.2

1. The largest majority of patients (95.2% of evaluable patients; n=935) had detectable for EGFR protein expression 1

2. The most common serious adverse reactions (grade 3) observed in Portrazza-treated patients were skin reactions (6.3%) and venous thromboembolic events (4.3%)4

3. In the EGFR-expressing population, median OS for the Portrazza arm was 11.5 months vs 9.9 months in the GC arm (HR=0.79 [0.69, 0.92]; P=0.002)1,3

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This Summary of Product Characteristics has been rewritten and shortened compared to the original Summary of Product Characteristics. These changes were introduced to make the Summary of Product Characteristics more concise and easier to read. The integrity of information contained in the Summary of Product Characteristics has not been compromised. The Summary of Product Characteristics conforms to the guidelines of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH).
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VARGATEF nintedanib

IT’S ABOUT TIME

VARGATEF is a trade-named European Prescribing Information. Please refer to local prescribing information as it may vary between countries. Different brands are used in some countries. Presentation: Soft gelatin capsules, each containing 100 mg or 150 mg nintedanib (see table). Indications: VARGATEF is indicated in combination with docetaxel for the treatment of adult patients with locally advanced, metastatic or locally recurrent non-small cell lung cancer (NSCLC) of adenocarcinoma histology after first-line chemotherapy. Posology and method of administration: 300 mg once daily administered approximately 30 hours apart, on days 1 to 11 of a standard 21 day dosing cycle. VARGATEF must be taken on the same day of docetaxel. Adverse reactions may be managed by temporary treatment interruption, dose reductions or permanent treatment discontinuation. Contraindications: Pregnancy (to nintedanib, ascites or lung), or any of the components. Special warnings and precautions: Patients should be closely monitored for gastrointestinal disorders, hypothyroidism, and a combination of both. Gastrointestinal disorders: Nausea, vomiting, and diarrhea. Hypothyroidism: Thyroid dysfunction. VARGATEF is not recommended in patients with pre-existing liver disease and its use in patients with moderate liver impairment is recommended. There are no data on the potential effect of VARGATEF on female fertility. Women of child-bearing potential should be advised to avoid becoming pregnant and to use adequate contraceptive during and at least 3 months after the last dose of VARGATEF. There is no information on the use of VARGATEF in pregnant women. Breast-feeding should be discontinued during treatment with VARGATEF. Effects on ability to drive and use machines: Minor influence. Interactions: VARGATEF may increase the concentration and half-life of other medicines. Key common interactions include: mixed function monooxygenase inhibitors (e.g., ketoconazole, corticosteroids, endocannabinoids, antiepileptic drugs, antipsychotics, antibiotics, antifungals, anti-HIV, anti-HBV, anti-HCV, anti-HIV/anti-HCV, anti-HIV/anti-HBV), thiazides, pyrimethamine, quinolones, and rifampicin. An increased risk of severe liver injury may occur with concomitant use of clarithromycin. VARGATEF is contraindicated in patients with severe liver impairment (Child-Pugh Class C). The effect of VARGATEF on the QT interval has not been shown to be clinically significant. VARGATEF may cause QT interval prolongation. Overall, increased liver enzymes and gastrointestinal symptoms. Marketing Authorization Numbers (Europe): EUTA/11/003/0001 to EUTA/11/003/0006. Marketing Authorization Holder: Boehringer Ingelheim International GmbH, Binger Straße 1-3, 56499 Rheinberg, Germany. Date of product information preparation: April 2015. SAC = aldehyde synthetase/aldolase A1 = aspartate aminotransferase/ALT. * Indications and usage: Nintedanib is approved in the European Union (EU) under the zone name VARGATEF for use in combination with docetaxel in adult patients with locally advanced, metastatic or locally recurrent NSCLC of adenocarcinoma histology after first-line chemotherapy. Registration conditions and full information, please refer to local prescribing information. VARGATEF is not approved in other countries. The company’s product information is fully available at the booth.