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ASCO DIRECT™ AM2017 | Live

CONGRESS REPORT

ASCO DIRECT™ Live Belgium: 2017 Annual Meeting

6 & 7 June 2017

- Prostate
- Gynaecology
- Gastroenterology
- Breast
- Melanoma
- Innovative therapy
- Lung and Thoracic cancers

CONTENT

Text: Vox Medica, Noorden
Design: NDOC, Buren
Photography: ruben eshuis photography
Editing: Sheridan Henness, PhD, of Springer Healthcare Communications

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Walmolen 1 | P.O. Box 246
3990 GA Houten
http://springerhealthcare.nl/

FOREWORD

ASCO DIRECT™ Live Belgium: 2017 Annual Meeting

Take home messages presented near home

This year, for the first time, a live, local and interactive event took place in Belgium simultaneously with the ASCO® Annual Meeting in Chicago. During this two-day meeting, Belgian oncologists were informed about the most important and interesting developments in oncology presented at the ASCO Annual Meeting.

Some unique aspects of the ASCO DIRECT™ meeting, which took place in Dolce la Hulpe, Brussels, were:

- Live connection each day with Chicago;
- Broadcast of selected videos from lectures in Chicago;
- Clinical relevance discussions, initiated and moderated by Belgian experts; and
- The opportunity to learn about the latest research without jetlag and without delay.

The first day was devoted to prostate, gynaecological, gastrointestinal and breast cancer. During the second day, the highlights in the field of melanoma, innovative therapies and lung/thoracic cancers were presented.
This local meeting provided a suitable, informal and freely accessible alternative to a time-consuming transatlantic journey to the ASCO Annual Meeting. The question is: to be or not to be at the ASCO Annual Meeting? The answer after this two-day event is the ASCO DIRECT™ meeting is a great alternative!

Pre-registration:
www.mednet.healthcare/ascodirect2018
or send an email to: nascholing@springer.com

Save the date

ASCO DIRECT™ Live

ASCO DIRECT™ Live Belgium: 2018 Annual Meeting

Date: Tuesday 5 and Wednesday 6 June 2018
Location: Brussels

ASCO DIRECT™ Live Belgium: 2018 Annual Meeting is a live, local and interactive event for HCPs. During one or two days Belgian oncologists will be informed about the most important and interesting developments in oncology, presented at the ASCO® Annual Meeting.

Most important features of ASCO DIRECT Live:

- Official ASCO-branded event
- Simultaneous with ASCO Annual Meeting in Chicago
- Live connection each day with Chicago
- Broadcast of selected Annual Meeting videos
- Clinical relevance discussions, initiated and moderated by Belgian experts
- Program built by local program committee
- Peer-to-peer interaction (locally and with experts in Chicago), cross-disciplinary discussions
- Learn about the latest research without jetlag and without delay

In June 2017 the first ASCO DIRECT Live Belgium took place in Brussels. The meeting was very successful and well reviewed by the participants with a rating of 7.9 out of 10!

The plans and the program for 2018 are in development.
Register interest early as places are limited.

Pre-registration:
www.mednet.healthcare/ascodirect2018 or send an email to: nascholing@springer.com

Target Audience:
ASCO DIRECT Live Belgium: 2018 Annual Meeting is recommended for medical oncologists, gastroenterologists and pulmonologists.

Symptom monitoring

Symptoms are common in advanced cancer and are often severe and debilitating. They interfere with daily activities and frequently lead to emergency room (ER) and hospital visits. Therefore, symptom management is a cornerstone of high-quality oncology practice. In current practice, there are multiple hurdles, like limited time and competing priorities.

Furthermore, patients are often reluctant to report symptoms, until they become severe. 'These communication hurdles inhibit the ability of clinicians to detect and react to symptoms, before they worsen', Dr. Ethan Basch (North Carolina, US) says about this reactive approach. 'An alternative is to systematically monitor symptoms.'
In a randomized trial, presented during the ASCO meeting, it was found that systematic symptom monitoring with patient self-reporting improved outcomes, including quality of life (QoL) and overall survival (OS). The QoL data were published last year. Compared with standard care, 31% more patients in the self-reporting arm experienced a QoL benefit ($p<0.001$)[1]. This analysis showed that median OS was 5 months longer among patients in the self-reporting arm versus those receiving standard care (31.2 vs. 26.0 months, $p=0.03$). Based on these results, Dr. Basch concludes that this approach should be considered for inclusion in standard symptom management[2]. Simultaneously with this presentation, the results were published online in JAMA[3].
Dr. Peter Vuylsteke (CHU UCL, Belgium) reports that this was a great presentation and great news, and sums up the main results: 'You lower the ER visits, there is a 5-month survival benefit and a better QoL'. He continues, 'So we could implement this monitoring system quite easily and cheaply in Belgium.' One of the attendees asks who is responsible in case of a call during the weekend or at night. 'Will the nurse be first contact? Or are oncologists continuously in contact with their patients?' There is a back-up system, in which nurses can be the first responders, Dr. Vuylsteke answers. 'This is no reason for not implementing this system.'

Dr. Peter Vuylsteke:
'This is a great presentation and great news'

'We could implement this monitoring system quite easily and cheaply in Belgium'

ADT with abiraterone

The incidence of metastatic hormone-naïve prostate cancer (mCNPC) among patients with prostate cancer is 3% in the US, 6% across Europe, 4-10% in Latin America and 60% in Asia Pacific. Historically, androgen deprivation therapy (ADT) has been the standard of care. Initially, that strategy is effective in almost all patients, because androgen receptor (AR) signalling is a strong oncogenic driver in this disease. However, after a median duration of 1 year, most men progress to metastatic castration-resist-

ant prostate cancer (mCRPC), largely driven by reactivation of AR signalling.
Since 2015, ADT plus docetaxel is a new standard of care for men with mCNPC and high metastatic burden. In the phase II LATITUDE trial, addition of abiraterone plus prednisone to ADT led to a significantly improved OS with a 38% reduction in the risk of death and a significant 53% reduction of radiographic progression-free survival (rPFS). The overall safety profile of ADT plus abiraterone and prednisone is consistent with prior studies in patients with mCRPC[4;5]. According to Dr. Karim Fizazi (Paris, France), these findings indicate that the addition of abiraterone and prednisone to ADT can potentially be considered a new standard of care for patients with high-risk, newly diagnosed mCNPC.

Hormone therapy has been the mainstay of treatment for prostate cancer since the 1940s. Two main changes are the addition of radiotherapy to high-risk node-negative (N0M0) disease, which improves outcomes, and the addition of docetaxel, which became part of the standard of care in 2014-2015.

Dr. Peter Vuylsteke:
‘STAMPEDE provides a potential cure for patients with high-risk disease, which might avoid the treatment with chemotherapy’

Recruitment in the STAMPEDE trial was completed prior to this change in the treatment paradigm, so there were no docetaxel-exposed patients in this cohort. In patients with hormone-naïve prostate cancer, abiraterone plus prednisone resulted in a highly significant improvement in OS by 37% (hazard ratio [HR] 0.63), failure-free survival (FFS) by 71% (HR 0.29) and symptomatic skeletal events by 55% (HR 0.45). The treatment was well tolerated[6;7]. Based on these findings, Dr. Nicholas James (Birmingham, UK) thinks that abiraterone plus prednisone should be part of the standard of care for men starting long-term ADT.
In his response to the presented data of the LATITUDE and STAMPEDE trials, Dr. Vuylsteke adds that these are quite impressive data. ‘STAMPEDE provides a potential cure for patients with high-risk disease, which might avoid treatment with chemotherapy.’
An attendee points out that the participants of the STAMPEDE trial are high-risk patients, but without metastases. ‘You expose them for a long time to prednisone. Are there comparable trials with enzalutamide, where you avoid the addition of prednisone?’ Dr. Vuylsteke replies that those data are not available. ‘Prednisone is intended to reduce the side effects instead of providing additional benefit. The treatment of side effects should not give extra side effects.’

Enzalutamide vs. abiraterone

Abiraterone plus prednisone and enzalutamide are both indicated as first-line therapy for patients with mCRPC. However, they have not been directly compared. Although these agents are frequently used in clinical practice, the optimal treatment sequence has not been evaluated prospectively. Finally, there is a continuing need for the development of predictive biomarkers, particularly for selecting patients with the poorest outcomes.
Dr. Kim Chi (Vancouver, Canada) presented the results of a randomized phase II crossover study of abiraterone plus prednisone versus enzalutamide in that patient population. He found a higher prostate-specific antigen (PSA) response with enzalutamide compared with abiraterone plus prednisone, but no difference in time to progression or time to PSA progression. Furthermore, detection of circulating tumour DNA (ctDNA) was feasible and informative; it was associated with measures of tumour burden and poor outcomes. Genomic alterations in BRCA2/ATM, TP53, the PI3K pathway, RB1, and AR were all associated with earlier progression and primary resistance. In multivariate analyses including clinical factors and the presence of ctDNA, these alterations remained significantly associated with shorter time to progression (TTP). Finally, AR genomic structural rearrangements encoding for truncated AR are detectable in ctDNA from treatment-naïve mCRPC and may identify primary resistant disease[8]. In Brussels, Dr. Vuylsteke says that these treatment strategies look similarly effective in first line. ///

Surgery, a previous randomized trial

Upfront surgery aiming at macroscopic complete resection is the standard treatment in patients with primary advanced ovarian cancer. A previous randomized trial showed a significant advantage in PFS, but not in OS for systematic pelvic and para-aortic lymphadenectomy (LNE) in patients with no or small residual disease of 0-10 mm.

A retrospective analysis of prospective AGO phase III trials suggested a potential OS benefit for removing clinically negative pelvic and para-aortic lymph nodes in patients with otherwise macroscopic complete resection.
A prospective randomized AGO study, presented by Dr. Philipp Harter (Essen, Germany), showed that patients with complete resection during upfront surgery who are treated in quality assured centres have an excellent prognosis. Systematic pelvic and para-aortic LNE in patients with advanced ovarian cancer with both intra-abdominal complete resection and clinically negative lymph nodes improves neither OS nor PFS, despite detecting and removing sub-clinical retroperitoneal lymph node metastases in more than half (56%) of patients. According to Dr. Harter, these data indicate that systematic LNE of clinically negative lymph nodes in patients with advanced ovarian cancer and complete resection should be omitted[9]. Dr. Caroline Duhem (Centre Hospitalier de Luxembourg) finds this a practice-changing trial.

Dr. Caroline Duhem:
'Patients with complete resection during upfront surgery and treated in quality assured centres have an excellent prognosis'

Adjuvant chemo- and radiation therapy
Dr. Stephanie de Boer (Leiden, the Netherlands) presented the final results of the international randomized PORTEC-3 trial of adjuvant chemotherapy and radiation therapy (RT) versus RT alone for women with high-risk endometrial cancer. The rationale for this trial was that 15% of endometrial cancers have high-risk features. These patients have an increased risk of distant metastases and endometrial cancer-related death. Several trials of chemotherapy alone versus RT alone found no differences in PFS or OS. However, the RTOG phase II trial showed that a combination of RT and chemotherapy is promising. In addition, the NSGO/EORTC phase III trial suggested a PFS benefit with sequential RT and chemotherapy.

The primary endpoints of the PORTEC-3 trial were 5-year OS and FFS, i.e. occurrence of relapse or endometrial cancer-related death. The 5-year OS was 82% for combination therapy versus 77% for RT (HR 0.79; p=0.18). The 5-year FFS was 76 and 69%, respectively (HR 0.77; p=0.078). The greatest benefit of RT plus chemotherapy in 5-year FFS was found in the subgroup with stage III endometrial cancer (69% for combination therapy vs. 58% for RT; HR 0.66; p=0.032)[10].
In conclusion, RT plus chemotherapy showed a trend towards an improved 5-year FFS in patients with high-risk endometrial cancer (risk reduction of 7% in FFS and 5% in OS). In contrast, there was a significant 11% FFS benefit with RT plus chemotherapy for stage III disease. The Dutch investigators found significantly more toxicity with combination therapy during the first 12 months after randomization. 'Tingling and numbness had the largest negative impact on QoL', Dr. De Boer said. In response, Dr. Duhem says that overall this was a negative study, with the exception of a positive trend in a subgroup of patients.

Dr. Caroline Duhem:
'Overall this was a negative study, with the exception of a positive trend in a subgroup'

Immunotherapy
Recurrent or metastatic cervical, vaginal, and vulvar cancers have a poor prognosis. Second-line treatment options for patients with recurrent or metastatic cervical cancer result in a median PFS of approximately 2-4 months and objective response rates (ORRs) of 0-14%. So there is an unmet need for these patients.
The role of immunotherapy is evolving in different tumour types, including gynaecologic malignancies. During the ASCO meeting, the results of the CheckMate 358 trial, which had a high Belgian involvement, were presented. Before the presentation, Dr. Duhem says that it 'covers the current hype on immunotherapy'.
The programmed cell death (PD)-1 inhibitor nivolumab has demonstrated antitumour activity in several tumour types. In the Checkmate 358 trial, nivolumab demonstrated encouraging clinical activity in patients with recurrent or metastatic cervical, vaginal, and vulvar cancer. The ORR was 20.8%; the responses were observed in the tumours across PD ligand 1 (PD-L1) expression profiles. The disease control rate was 70.8%. The median OS was not reached; the 6-month OS rate was 87.1%. The observed safety profile was manageable and consistent with previous results seen with nivolumab monotherapy in other tumour types[11]. Dr. Antoine Hollebecque (Villejuif, France) thinks that these data support further evaluation of nivolumab in these patients, including in combination with other therapies. ///

Dr. Caroline Duhem:
'The CheckMate 358 trial had a high Belgian involvement'

Gastric or gastroesophageal junction carcinoma

Since the publication of the MAGIC trial in NEJM in 2006[12], chemotherapy with epirubicin, cisplatin, and 5-fluorouracil (ECF) has been standard of care for esophagogastric adenocarcinoma. However, the outcomes of these patients remained unsatisfactory, with median and 5-year survival being 25 months and 36% respectively.

In phase II studies, the research group of Dr. Salah-Eddin Al-Batran (Frankfurt, Germany) demonstrated that triplet chemotherapy with docetaxel, oxaliplatin, and 5-fluorouracil/leucovorin (FLOT) was tolerable and was associated with encouraging rates of response in patients with gastric and gastroesophageal (G/GEJ) adenocarcinoma.
The presented data of the FLOT4-AIO study showed that docetaxel-based chemotherapy with FLOT increased rates of curative surgery and prolonged PFS and OS in comparison with ECF or epirubicin, cisplatin and capecitabine (ECX) [median OS of 35 months with ECX/ECF vs. 50 months with FLOT; HR 0.77; p=0.012]. The relative effect of FLOT was consistent across subgroups and sensitivity analyses. Furthermore, there was no increase in surgical morbidity and mortality, re-surgeries, and hospitalization times[13]. Dr. Al-Batran concluded that FLOT is a new standard of care in perioperative treatment of patients with G/GEJ adenocarcinoma.
In a response from Brussels, Dr. Donatienne Taylor (Namur, Belgium) says that this is a quite straightforward trial. 'The increase of 15 months in OS is really impressive. The surgical procedures did not increase morbidity, even in elderly patients. So that is interesting.' An attendee asks about the reimbursement of docetaxel in this setting. Dr. Taylor replies that it is not reimbursed in Belgium.

Dr. Al-Batran:
'FLOT is a new standard of care in perioperative treatment of patients with G/GEJ adenocarcinoma'

Dr. Taylor introduces the next selected lecture, which is about immunotherapy in the treatment of advanced disease. PD-1 and its ligands PD-L1 and PD-L2 have been shown to be overexpressed in gastric cancers. Pembrolizumab is a selective antibody that blocks the interaction between PD-1 and its ligands. In a previous phase 1b trial, pembrolizumab demonstrated promising antitumour activity in advanced G/GEJ cancer with an ORR of 22% and excellent tolerability.
Dr. Charles Fuchs (New Haven, USA) reported that pembrolizumab monotherapy resulted in promising antitumour activity and durable responses in patients with advanced G/GEJ adenocarcinoma, who had progressed after ≥2 prior lines of therapy. Furthermore, in this analysis of the KEYNOTE-059 trial, the ORR was higher in patients with a PD-L1-positive tumour, although partial and complete responses were also observed in patients with a PD-L1-negative tumour. Treatment appeared to be well tolerated and consistent with the results of other large trials with pembrolizumab[14]. Dr. Fuchs believes that these results suggest that pembrolizumab is a potential treatment option for patients with G/GEJ adenocarcinoma, who progressed after ≥2 prior lines of therapy. 'Ongoing trials are assessing pembrolizumab in earlier lines of therapy and in combination with chemotherapy', he adds.
In response, Dr. Taylor states that during the same session the results of another form of immunotherapy in the same patient category were presented, namely the CheckMate 032 study with nivolumab with or without ipilimumab[15]. 'The response rates were pretty similar, although there was little advantage for the combination therapy.'
An attendee comments that PD-L1 expression status is not a suitable biomarker in this setting. A possible explanation is that this status was determined prior to the previous treatment lines, so the expression could change from negative to positive during the treatment period. Dr. Taylor says that microsatellite instability (MSI) should be included in future analyses.

Colon cancer
The current standard of care for patients with stage III colon cancer consists of 6 months of oxaliplatin-based treatment, in which there is a choice between FOLFOX and CAPOX. However, long-term treatment increases the risk of toxicity. For example, oxaliplatin is associated with cumulative dose-dependent neurotoxicity, namely 12.5% grade 3 neuropathy after a treatment period of 6 months[16]. Shorter duration of treatment without loss of efficacy would be of benefit to patients and health care resources.
IDEA (International Duration Evaluation of Adjuvant chemotherapy) is an academic collaboration from six randomized phase III trials, performed in 12 countries, where the Mayo Clinic served as an independent statistical centre. Dr. Qian Shi (Rochester, USA) showed that 3 versus 6 months of treatment resulted in a higher compliance and substantially lower (grade ≥2) neurotoxicity (17% vs. 48% with FOLFOX and 15% vs. 45% with CAPOX). The non-inferiority of 3 months oxaliplatin-based adjuvant therapy in terms of disease-free survival (DFS) was not established in overall stage III colon cancer. However, results comparing DFS between 3 and 6 months of treatment depended on risk groups and regimen[17].
Dr. Taylor asks if in daily practice the treatment duration will be changed. This will depend on the tolerability of the treatment. 'The difference in outcomes between the two strategies was very small. Although the difference was not statistically significant, it was clinically relevant, so we cannot deny this study. Furthermore, IDEA was not designed to compare the FOLFOX and CAPOX regimens, which were the choice of the investigators. There were huge differences between the trials. In the French trial, there was only 10% CAPOX-treated patients, while in the trial from England 60% of patients were treated with CAPOX. In low-risk patients, it seems reasonable to choose a treatment duration of 3 months. The general conclusion is that in high-risk patients, one should stick to a treatment duration of 6 months.' ///

Dr. Taylor:
'In high-risk patients, one should stick to a treatment duration of 6 months'

PARP inhibition

Members of the poly ADP ribose polymerase (PARP) family of proteins, particularly PARP1 and 2, are involved in cellular response to single-strand DNA breaks. Inhibition of PARP activity results in 'trapping' of the protein on DNA, inhibition of replication fork progression and increased double-strand DNA (dsDNA) breaks. Resolution of lesions caused by PARP inhibition is dependent on functioning homologous recombination. BRCA1 and BRCA2 are important components of the homologous recombination pathway. In vitro, cells lacking BRCA1/2 are sensitive to PARP inhibition, so-called 'synthetic lethality'.

Dr. Mark Robson (New York, USA) presented the results of the phase III OlympiAD trial, in which olaparib monotherapy was compared with the physician's choice of standard-of-care chemotherapy in patients with HER2-negative metastatic breast cancer and a germline BRCA mutation. The median PFS was 7.0 months with olaparib and 4.2 months with chemotherapy (HR 0.58; p=0.0009). Since these results were significantly different, a planned interim analysis on the OS was conducted. However, that analysis showed no significant difference (median OS 19.3 months with olaparib and 19.6 months with chemotherapy; HR 0.90; p=0.5665).

Olaparib was generally well tolerated, with <5% of patients discontinuing treatment for toxicity and a lower rate of grade ≥3 adverse events (AEs) compared with chemotherapy. OlympiAD is the first phase III study in metastatic breast cancer patients, demonstrating benefit for a PARP inhibitor over an active comparator[18;19]. According to Dr. Vuylsteke, these are very interesting data. 'It's not chemotherapy, so it is well tolerated. As BRCA-mutated breast cancers are often triple negative, these patients could benefit from pembrolizumab in the metastatic setting.'

Dr. Mark Robson:
'The results of OlympiAD are one of the major findings of this meeting.'

During a live connection with Chicago, Prof. Michael Wells (Leeds, UK) adds that a non-cytotoxic drug resulted in a survival benefit, which was found in a randomized trial. 'That is one of the major findings of this meeting.' He thinks that the trial design is intriguing, because the control arm was a treatment of the physician's choice. So there was no artificial comparator chosen, because a real-world setting lacks a single standard treatment. The downside of that strategy is that you can't compare the results with a specific agent. The data doesn't provide a comparison with platinum-based chemotherapy or answer whether we should be looking at an earlier line of treatment.

HER2 blockade

Afterwards, 'the long awaited results of the APHINITY trial', as Dr. Vuylsteke states, were presented by Prof. Gunter Von Minckwitz (Neu-Isenburg, Germany).

Although pertuzumab and trastuzumab both inhibit HER2, these drugs have complementary mechanisms of action. In patients with HER2-positive metastatic breast cancer, pertuzumab added to trastuzumab and docetaxel significantly improved not only PFS, but also OS. In the neoadjuvant setting, the addition of pertuzumab to trastuzumab plus docetaxel significantly improved and almost doubled the pathological complete response rate. However, in a significant proportion of patients' recurrence of HER2-positive early breast cancer occurs in the long term.

Dr. Peter Vuylsteke:
'During the ASCO meeting, the long awaited results of the APHINITY trial were presented'

The APHINITY trial met its primary objective, because pertuzumab reduced the risk of invasive DFS (IDFS) events, a slightly modified endpoint, by 19% compared with placebo at a median follow-up of 45.4 months (stratified HR 0.81; p=0.045). The treatment effect was homogenous throughout all subgroups. However, the node-positive and HR-negative cohorts appeared to derive most benefit at that point in time; this might change during a longer follow-up period. Cardiac toxicity was low and not different between the two arms. Diarrhoea had a higher incidence in the pertuzumab arm and occurred predominantly during the 18-24 weeks of chemotherapy, mainly associated with the TCH regimen (docetaxel, carboplatin, trastuzumab). Continued follow-up for up to 10 years is, according to Dr. Von Minckwitz, crucial for this study. The next analyses will be time-driven in 2.5 years[20]. Directly after this presentation the results were released in an online publication in NEJM[21].

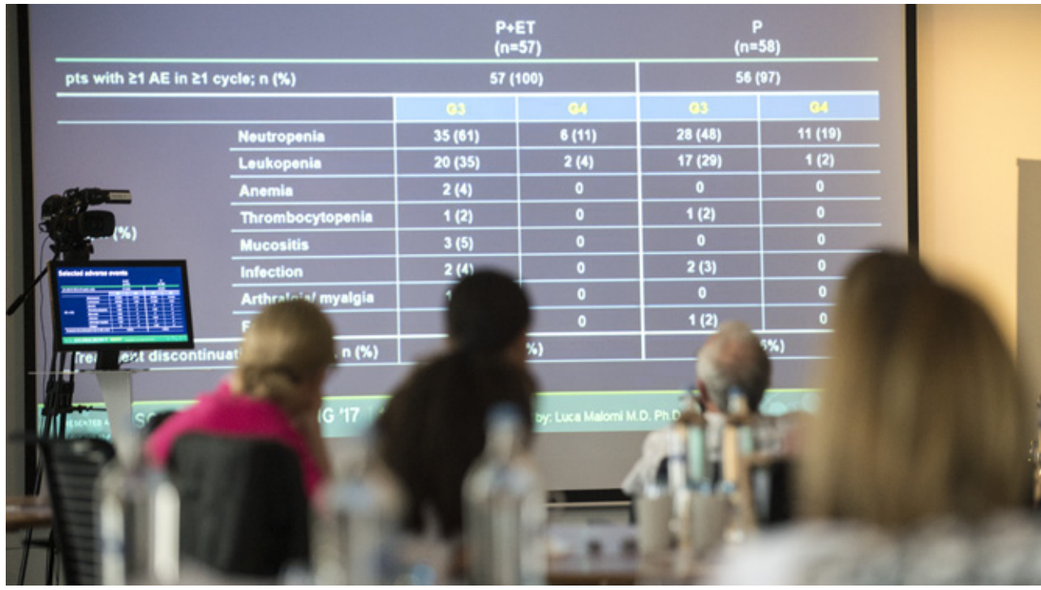
Dr. Vuylsteke finds the absolute benefit of this trial small, especially due to the results in the trastuzumab arm. These patients already have a very good DFS, he explains. However, there is no reimbursement in Belgium. During the live connection, Prof. Jean-Pierre Armand (Paris, France) adds that the drug is also not reimbursed in France in the adjuvant setting, because there are no data on survival. The question is whether to use it only in node-positive patients.

CDK4/6 inhibition

Palbociclib is a potent, selective, orally available inhibitor of cyclin-dependent kinases 4 and 6 (CDK4/6). It is preferentially active in luminal breast cancer in preclinical models and has a synergistic effect in combination with endocrine therapy. The results of the PALOMA trials have led to the approval of palbociclib in combination with endocrine therapy for the treatment of patients with HR+/HER2- metastatic breast cancer. Clinical data of palbociclib as a single agent in patients with HR+/HER2- metastatic breast cancer are limited to heavily pre-treated patients. Additional pre-clinical evidence suggests that adding palbociclib to endocrine therapy may partially reverse acquired resistance to that particular endocrine therapy.

The TREnd study, presented by Dr. Luca Malorni (Prato, Italy), reached the pre-specified threshold for activity in both arms, i.e. clinical benefit rate (CBR), a composite of complete response, partial response and stable disease for >6 months, of ≥40%. Palbociclib has clinical activity as a single agent in moderately pre-treated patients with ER+/HER2- metastatic breast cancer, with a CBR of 60%, which is clinically meaningful in this patient population. Although no difference in CBR was observed between the two study arms, the duration of clinical benefit, PFS and the related subgroup analyses by duration of prior endocrine therapy suggest that palbociclib could reverse acquired resistance to the same endocrine agent used in the prior line of endocrine therapy. The safety results were in line with previous data. Translational studies investigating the resistance mechanisms are ongoing[22].

The question, which was raised by the TREnd trial, is whether to restart the same hormonal therapy on which the patient had previously progressed. Dr. Vuylsteke thinks that palbociclib could reverse the hormonal resistance. ///



Targeted therapy

Combination therapy with the BRAF inhibitor dabrafenib and the MEK inhibitor trametinib is associated with rapid clinical responses and has improved clinical outcomes in patients with BRAFV600-mutant metastatic melanoma (MM). However, long-term (>3 year) clinical efficacy and safety data are limited.

Dr. Vibeke Kruse:
'This trial provides the most mature phase III data analysing anti-PD-1 to date'

Prof. Georgina Long (Sydney, Australia) presented the updated 5-year follow-up data on the efficacy and safety of this doublet therapy in MM. The 4- and 5-year OS rates were 30% and 28%, respectively, demonstrating a stabilization of the OS curve. The PFS curve also remained stable (13% after both 4 and 5 years). This longest follow-up to date of the combination therapy of a BRAF and a MEK inhibitor in patients with BRAFV600-mutant MM revealed stable OS and PFS. This was associated with consistent tolerability. These results demonstrate that some patients with MM can achieve durable benefit with this combination therapy[23]. 'There are very few contraindications to giving a MEK inhibitor', Dr. Kruse adds.

Immunotherapy

In a previous analysis of the phase III KEYNOTE-006 study, pembrolizumab demonstrated superior PFS and OS in comparison with ipilimumab in ipilimumab-naïve patients with advanced melanoma. Dr. Caroline Robert (Villejuif, France) presented data showing the long-term outcomes for all patients who completed the treatment with pembrolizumab. After a follow-up period of 33 months, OS rates were 50% in the pooled pembrolizumab arms and 39% in the ipilimumab arm (PFS rates were 31% and 14% and the ORRs were 42% and 16%, respectively). So, pembrolizumab provided durable efficacy after stopping the protocol-specified duration of treatment in patients with ipilimumab-naïve advanced melanoma. The risk for progression or death nearly 10 months after completing pembrolizumab was 9% and did not appear to differ by best response to pembrolizumab[24].

According to Dr. Kruse, this trial provides the most mature phase III data analysing anti-PD-1 to date. 'It's important, because it is the first trial to analyse what happens if we stop treatment after 2 years. After discontinuation after 2 years, most patients have a good prognosis. After a follow-up period of 10 months, 91% of patients remain progression free. This is a quite short period, so I am very curious what happens with those patients after 2 or 3 years. As expected, patients with a complete response do better than those in a partial response or with stable disease. So it is not necessary to keep on treating patients for 4 to 5 years or even during a longer period. Because of financial reasons and toxicity, it might be defendable to stop after a certain time. However, we need the confirmation that we can re-introduce treatment after the patients developed disease progression.'
Afterwards, Dr. Kruse mentions some other learning points from the ASCO meeting about the systemic treatment of melanoma. She thinks it is possible to stop treatment with anti-PD-1, but not with a MAPK inhibitor. Almost the reverse is true with respect to re-treatment: possible for a MAPK inhibitor, but unknown for anti-PD-1. Finally, she thinks that it's possible to resume anti-PD-1 after an immune-related AE on anti-PD-1 plus anti-CTLA-4, but one should be aware of toxicity. ///

Prof. Georgina Long:
'This longest follow-up to date revealed stable OS and PFS.'

TRK inhibition

The tropomyosin receptor kinase (TRK) is uncommonly expressed in normal tissues or cancer. Fusion drives abnormally high expression and activation of the TRK kinase domain. Dr. David Michael Hyman (New York, USA) presented data on the selective TRK inhibitor larotrectinib (LOXO-101) in adult and paediatric patients with a TRK fusion cancer.

He and his co-investigators found that larotrectinib had a consistent and durable antitumour activity in TRK fusions cancers, regardless of tumour type and age. The ORR was 76%. Furthermore, 91% of patients remained progression-free after 6 months. The patients had minimal side effects; the treatment was well tolerated for a long period of time[25]. According to Dr. Hyman, larotrectinib may offer a potential new standard of care for patients with TRK fusion cancer. Routine pan-cancer screening will be important to identify these patients, as well as those with other tumour-agnostic biomarkers (MSI-H). Although these data are very promising, before implementing them in daily practice, according to Dr. Hyman, we need a broader tumour profiling. Prof. Ahmad Awada (Brussels, Belgium) agrees that this is clearly a very effective drug. 'Possibly we should screen more patients for the presence of TRK fusion.'

Molecular screening

The second abstract reported the results of one of the largest trials assessing high-throughput genomic analyses for a large variety of cancer patients. This study also assessed the implications for clinical practice. That is the reason why this abstract was selected, Prof. Awada adds.

ProfiLER is a French prospective molecular profiling trial exploring cancer cell genomic alterations to guide targeted treatment. It was found that routine genomic testing is feasible in a local and regional setting. More than half of tumours had molecular alterations that are potentially actionable. However, screening heavily-pre-treated patients with advanced cancer limits the number of patients who can actually receive molecular targeted agents (MTA). Patients who could receive the recommended MTA have a better OS than those who did not[26].

Prof. Awada says that two other studies, which were presented in the same session, reported the same results. One out of ten patients receives MTA and that is according to him a major problem. 'An important message of these trials is to screen early in the evolution of these diseases. Otherwise patients who could have benefited from MTA will pass away.'

IDO1 inhibition

Inhibition of indoleamine-2,3-dioxygenase 1 (IDO1) may promote normal effector T-cell activity, an immunogenic state and complement targeting of PD-L1 with atezolizumab. Navoximod is a small molecule inhibitor of IDO1.

Combination therapy with navoximod and atezolizumab was generally well-tolerated. Treatment-related grade ≥3 AEs and treatment discontinuation due to AEs were within the range of atezolizumab monotherapy. Clinical activity was observed during dose escalation in a heterogeneous patient population of IDO1 in tumour cells. 'Interestingly, the combination was not more toxic than the single agent', Prof. Awada says of these results, which were presented by Dr. Howard Burris (Nashville, USA)[27]. ///

Dr. David Michael Hyman:
'Larotrectinib may offer a potential new standard of care for patients with TRK fusion cancer'

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

NAME OF THE MEDICINAL PRODUCT OPDIVO 10 mg/mL concentrate for solution for infusion. **QUALITATIVE AND QUANTITATIVE COMPOSITION** Each mL of concentrate contains 10 mg of nivolumab. One vial of 4 mL contains 40 mg of nivolumab. One vial of 10 mL contains 100 mg of nivolumab. Nivolumab is produced in Chinese hamster ovary cells by recombinant DNA technology. Excipient with known effect Each mL of concentrate contains 0.1 mmol (or 2.5 mg) sodium. For the full list of excipients, see section 6.1. **PHARMACEUTICAL FORM** Concentrate for solution for infusion (sterile concentrate). Clear to opalescent, colourless to pale yellow liquid that may contain few light particles. The solution has a pH of approximately 6.0 and an osmolality of approximately 340 mOsm/kg. **CLINICAL PARTICULARS Therapeutic indications** Melanoma OPDIVO as monotherapy or in combination with ipilimumab is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults. Relative to nivolumab monotherapy, an increase in progression-free survival (PFS) for the combination of nivolumab with ipilimumab is established only in patients with low tumour PD-L1 expression (see sections 4.4 and 5.1). Non-Small Cell Lung Cancer (NSCLC) OPDIVO as monotherapy is indicated for the treatment of locally advanced or metastatic non-small cell lung cancer after prior chemotherapy in adults. Renal Cell Carcinoma (RCC) OPDIVO as monotherapy is indicated for the treatment of advanced renal cell carcinoma after prior therapy in adults. Classical Hodgkin lymphoma (cHL) OPDIVO as monotherapy is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin. Squamous Cell Cancer of the Head and Neck (SCCHN) OPDIVO as monotherapy is indicated for the treatment of squamous cell cancer of the head and neck in adults progressing on or after platinum-based therapy (see section 5.1). Urothelial Carcinoma OPDIVO as monotherapy is indicated for the treatment of locally advanced unresectable or metastatic urothelial carcinoma in adults after failure of prior platinum-containing therapy. **Posology and method of administration** Treatment must be initiated and supervised by physicians experienced in the treatment of cancer. Posology *OPDIVO as monotherapy* The recommended dose of OPDIVO is 3 mg/kg nivolumab administered intravenously over 60 minutes every 2 weeks. *OPDIVO in combination with ipilimumab* The recommended dose is 1 mg/kg nivolumab administered as an intravenous infusion over 60 minutes every 3 weeks for the first 4 doses in combination with 3 mg/kg ipilimumab administered intravenously over 90 minutes. This is then followed by a second phase in which 3 mg/kg nivolumab is administered as an intravenous infusion over 60 minutes every 2 weeks. Treatment with OPDIVO, either as a monotherapy or in combination with ipilimumab, should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient. Atypical responses (i.e., an initial transient increase in tumour size or small new lesions within the first few months followed by tumour shrinkage) have been observed. It is recommended to continue treatment with nivolumab for clinically stable patients with initial evidence of disease progression until disease progression is confirmed. Dose escalation or reduction is not recommended. Dosing delay or discontinuation may be required based on individual safety and tolerability. Guidelines for permanent discontinuation or withholding of doses are described in Table 1. Detailed guidelines for the management of immune-related adverse reactions are described in section 4.4.

Table 1: Recommended treatment modifications for OPDIVO or OPDIVO in combination with ipilimumab

Immune-related adverse reaction	Severity	Treatment modification
Immune-related pneumonitis	Grade 2 pneumonitis	Withhold dose(s) until symptoms resolve, radiographic abnormalities improve, and management with corticosteroids is complete
	Grade 3 or 4 pneumonitis	Permanently discontinue treatment
Immune-related colitis	Grade 2 diarrhoea or colitis	Withhold dose(s) until symptoms resolve and management with corticosteroids, if needed, is complete
	Grade 3 diarrhoea or colitis	
	-OPDIVO monotherapy	Withhold dose(s) until symptoms resolve and management with corticosteroids is complete
	-OPDIVO+ipilimumab	Permanently discontinue treatment
	Grade 4 diarrhoea or colitis	Permanently discontinue treatment
Immune-related hepatitis	Grade 2 elevation in aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin	Withhold dose(s) until laboratory values return to baseline and management with corticosteroids, if needed, is complete
	Grade 3 or 4 elevation in AST, ALT, or total bilirubin	Permanently discontinue treatment
Immune-related nephritis and renal dysfunction	Grade 2 or 3 creatinine elevation	Withhold dose(s) until creatinine returns to baseline and management with corticosteroids is complete
	Grade 4 creatinine elevation	Permanently discontinue treatment
Immune-related endocrinopathies	Symptomatic Grade 2 or 3 hypothyroidism, hyperthyroidism, hypophysitis,	Withhold dose(s) until symptoms resolve and management with corticosteroids (if needed for symptoms of acute inflammation) is complete. Treatment should be continued in the presence of hormone replacement therapy[a] as long as no symptoms are present
	Grade 2 adrenal insufficiency	Permanently discontinue treatment
	Grade 3 diabetes	
	Grade 4 hypothyroidism	
	Grade 4 hyperthyroidism	
	Grade 4 hypophysitis	
	Grade 3 or 4 adrenal insufficiency	
	Grade 4 diabetes	
Immune-related skin adverse reactions	Grade 3 rash	Withhold dose(s) until symptoms resolve and management with corticosteroids is complete
	Grade 4 rash	Permanently discontinue treatment
	Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Permanently discontinue treatment (see section 4.4)
Other immune-related adverse reactions	Grade 3 (first occurrence)	Withhold dose(s)
	Grade 3 myocarditis	Permanently discontinue treatment
	Grade 4 or recurrent Grade 3; persistent Grade 2 or 3 despite treatment modification; inability to reduce corticosteroid dose to 10 mg prednisone or equivalent per day	Permanently discontinue treatment

Note: Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (NCI-CTCAE v4).Recommendation for the use of hormone replacement therapy is provided in section 4.4.

OPDIVO or OPDIVO in combination with ipilimumab should be permanently discontinued for: Grade 4 or recurrent Grade 3 adverse reactions; Patients treated with OPDIVO must be given the patient alert card and be informed about the risks of OPDIVO (see also package leaflet). When OPDIVO is administered in combination with ipilimumab, if either agent is withheld, the other agent should also be withheld. If dosing is resumed after a delay, either the combination treatment or OPDIVO monotherapy could be resumed based on the evaluation of the individual patient. *Special populations Paediatric population* The safety and efficacy of OPDIVO in children below 18 years of age have not been established. No data are available. *Elderly* No dose adjustment is required for elderly patients (≥ 65 years) (see sections 5.1 and 5.2). Data from NSCLC and SCCHN patients 75 years of age or older are too limited to draw conclusions on this population. *Renal impairment* Based on the population pharmacokinetic (PK) results, no dose adjustment is required in patients with mild or moderate renal impairment (see section 5.2). Data from patients with severe renal impairment are too limited to draw conclusions on this population. *Hepatic impairment* Based on the population PK results, no dose adjustment is required in patients with mild hepatic impairment (see section 5.2). Data from patients with moderate or severe hepatic impairment are too limited to draw conclusions on these populations. OPDIVO must be administered with caution in patients with moderate (total bilirubin > 1.5 × to 3 × the upper limit of normal [ULN] and any AST) or severe (total bilirubin > 3 × ULN and any AST) hepatic impairment. Method of administration OPDIVO is for intravenous use only. It is to be administered as an intravenous infusion over a period of 60 minutes. The infusion must be administered through a sterile, non-pyrogenic, low protein binding in-line filter with a pore size of 0.2-1.2 µm. OPDIVO must not be administered as an intravenous push or bolus injection. The total dose of OPDIVO required can be used directly as a 10 mg/mL solution or can be diluted to as low as 1 mg/mL with sodium chloride 9 mg/mL (0.9%) solution for injection or glucose 50 mg/mL (5%) solution for injection. When administered in combination with ipilimumab, OPDIVO should be given first followed by ipilimumab on the same day. Use separate infusion bags and filters for each infusion. For instructions on the handling of the medicinal product before administration, see section 6.6. **Contraindications** Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. **Undesirable effects** Summary of the safety profile In the pooled dataset of nivolumab 3 mg/kg as monotherapy across tumour types (n = 2227), the most frequent adverse reactions (≥ 10%) were fatigue (30%), rash (17%), pruritus (12%), diarrhoea (12%), and nausea (12%). The majority of adverse reactions were mild to moderate (Grade 1 or 2). With a minimum of 24 months followup in NSCLC, no new safety signals were identified. In the pooled dataset of nivolumab in combination with ipilimumab in melanoma (n = 448), the most frequent adverse reactions (≥ 10%) were rash (51%), fatigue (43%), diarrhoea (42%), pruritus (35%), nausea (25%), pyrexia (19%), decreased appetite (15%), hypothyroidism (15%), vomiting (14%), colitis (14%), abdominal pain (13%), arthralgia (11%), and headache (11%). The majority of adverse reactions were mild to moderate (Grade 1 or 2). Among the patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in CA209067, 151/313 (48%) had the first onset of Grade 3 or 4 adverse reactions during the initial combination phase. Among the 147 patients in this group who continued treatment in the single-agent phase, 37 (25%) experienced at least one Grade 3 or 4 adverse reaction during the single-agent phase. Tabulated summary of adverse reactions Adverse reactions reported in the pooled dataset for patients treated with nivolumab monotherapy (n = 2227) and for patients treated with nivolumab in combination with ipilimumab (n = 448) are presented in Table 2. These reactions are presented by system organ class and by frequency. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); not known (cannot be estimated from available post-marketing data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

	Nivolumab monotherapy	Nivolumab in combination with ipilimumab
Infections and infestations		
Common	upper respiratory tract infection	pneumonia[a], upper respiratory tract infection
Uncommon	pneumonia[a], bronchitis	bronchitis
Neoplasms benign, malignant and unspecified (including cysts and polyps)		
Rare	histiocytic necrotising lymphadenitis (Kikuchi lymphadenitis)	
Blood and lymphatic system disorders		
Very common	neutropaenia[a,b]	
Common		eosinophilia
Uncommon	eosinophilia	
Immune system disorders		
Common	infusion related reaction[c], hypersensitivity[c]	infusion related reaction[c], hypersensitivity
Uncommon		sarcoidosis
Rare	anaphylactic reaction[c]	
Not known	solid organ transplant rejection	solid organ transplant rejection
Endocrine disorders		
Very common		hypothyroidism
Common	hypothyroidism, hyperthyroidism, hyperglycaemia[a]	adrenal insufficiency, hypopituitarism, hypophysitis, hyperthyroidism, thyroiditis, hyperglycaemia[a]
Uncommon	adrenal insufficiency, hypopituitarism, hypophysitis, thyroiditis	diabetic ketoacidosis, diabetes mellitus
Rare	diabetes mellitus, diabetic ketoacidosis	
Metabolism and nutrition disorders		
Very common		decreased appetite
Common	decreased appetite	dehydration
Uncommon	dehydration, metabolic acidosis	
Hepatobiliary disorders		
Common		hepatitis[c]
Uncommon	hepatitis[c]	
Rare	cholestasis	
Nervous system disorders		
Very common		headache
Common	peripheral neuropathy, headache, dizziness	peripheral neuropathy, dizziness
Uncommon	polyneuropathy	Guillain-Barré syndrome, polyneuropathy, neuritis, peroneal nerve palsy, autoimmune neuropathy (including facial and abducens nerve paresis), encephalitis[c]
Rare	Guillain-Barré syndrome, demyelination, myasthenic syndrome, autoimmune neuropathy (including facial and abducens nerve paresis), encephalitis[c]	
Eye disorders		
Common		uveitis, blurred vision
Uncommon	uveitis, blurred vision, dry eye	
Cardiac disorders		
Common		tachycardia
Uncommon	tachycardia	arrhythmia (including ventricular arrhythmia)[d], atrial fibrillation, myocarditis[c,d]
Rare	arrhythmia (including ventricular arrhythmia)[d], atrial fibrillation, myocarditis[c,d]	
Vascular disorders		
Common	hypertension	hypertension
Rare	vasculitis	
Respiratory, thoracic and mediastinal disorders		
Common	pneumonitis[c,e], dyspnoea[a], cough	pneumonitis[c,e], pulmonary embolism[a], dyspnoea, cough
Uncommon	pleural effusion	pleural effusion
Rare	lung infiltration	
Gastrointestinal disorders		
Very common	diarrhoea, nausea	colitis, diarrhoea, vomiting, nausea, abdominal pain
Common	stomatitis, vomiting, abdominal pain, constipation, dry mouth	stomatitis, gastritis, constipation, dry mouth
Uncommon	colitis, pancreatitis	pancreatitis, intestinal perforation, duodenitis
Rare	gastritis, duodenal ulcer	
Skin and subcutaneous tissue disorders		
Very common	rash[a], pruritus	rash[a], pruritus
Common	vitiligo, dry skin, erythema, alopecia	vitiligo, dry skin, erythema, alopecia, urticaria
Uncommon	erythema multiforme, psoriasis, rosacea, urticaria	psoriasis
Rare	toxic epidermal necrolysis[c,f], Stevens- Johnson syndrome[c,f]	toxic epidermal necrolysis[c,f], Stevens- Johnson syndrome[c]
Musculoskeletal and connective tissue disorders		
Very common		arthralgia
Common	musculoskeletal pain[a], arthralgia	musculoskeletal pain[a]
Uncommon	polymyalgia rheumatica, arthritis	spondyloarthropathy, Sjogren's syndrome, arthritis, myopathy, myositis[c,e], rhabdomyolysis[c]
Rare	myopathy, myositis[c,f], rhabdomyolysis[c,f]	
Renal and urinary disorders		
Common		renal failure[a,c]
Uncommon	tubulointerstitial nephritis, renal failure[a,c]	tubulointerstitial nephritis
General disorders and administration site conditions		
Very common	fatigue	fatigue, pyrexia
Common	pyrexia, oedema (including peripheral oedema)	oedema (including peripheral oedema), pain
Uncommon	pain, chest pain	chest pain
Investigations[b]		
Very common	increased AST, increased ALT, increased alkaline phosphatase, increased lipase, increased amylase, hypocalcaemia, increased creatinine, lymphopaenia, leucopoenia, thrombocytopaenia, anaemia, hypercalcaemia, hyperkalaemia, hypokalaemia, hypomagnesaemia, hyponatraemia, weight decreased	increased AST, increased ALT, increased total bilirubin, increased alkaline phosphatase, increased lipase, increased amylase, increased creatinine, lymphopaenia, leucopoenia, neutropaenia, thrombocytopaenia, anaemia, hypocalcaemia, hyperkalaemia, hypokalaemia, hypomagnesaemia, hyponatraemia
Common	increased total bilirubin, hypermagnesaemia, hypernatraemia, weight decreased	hypercalcaemia, hypermagnesaemia, hypernatraemia, weight decreased

[a] Fatal cases have been reported in completed or ongoing clinical studies. [b] Frequencies of laboratory terms reflect the proportion of patients who experienced a worsening from baseline in laboratory measurements. See "Description of selected adverse reactions: laboratory abnormalities" below. [c] Life-threatening cases have been reported in completed or ongoing clinical studies.[d] The frequency of adverse events in the cardiac disorders system organ class regardless of causality was higher in the nivolumab group than in the chemotherapy group in post-CTLA4/BRAF inhibitor metastatic melanoma population. Incidence rates per 100 person-years of exposure were 9.3 vs. 0; serious cardiac events were reported by 4.9% patients in the nivolumab group vs. 0 in the investigator's choice group. The frequency of cardiac adverse events was lower in the nivolumab group than in the dacarbazine group in the metastatic melanoma without prior treatment population. All were considered not related to nivolumab by investigators except arrhythmia (atrial fibrillation, tachycardia and ventricular arrhythmia). [e] Rash is a composite term which includes maculopapular rash, rash erythematous, rash pruritic, rash follicular, rash macular, rash morbilliform, rash papular, rash pustular, rash papulosquamous, rash vesicular, rash generalised, exfoliative rash, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis atopic, dermatitis bullous, dermatitis exfoliative, dermatitis psoriasiform, drug eruption and pemphigoid. [f] Reported in studies outside the pooled dataset. The frequency is based on the program-wide exposure. [g] Musculoskeletal pain is a composite term which includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, pain in extremity, and spinal pain.

The overall safety profile of nivolumab 3 mg/kg in urothelial carcinoma patients (n = 348) was consistent with that established across tumour types for nivolumab monotherapy.

Description of selected adverse reactions Nivolumab or nivolumab in combination with ipilimumab is associated with immune-related adverse reactions. With appropriate medical therapy, immune-related adverse reactions resolved in most cases. Permanent discontinuation of treatment was required in a greater proportion of patients receiving nivolumab in combination with ipilimumab than in those receiving nivolumab monotherapy for immune-related colitis (16% and 0.7%, respectively), immune-related hepatitis (9% and 1.1%), and immune-related endocrinopathies (2.5% and 0.1%). Among patients who experienced an event, high-dose corticosteroids (at least 40 mg prednisone equivalents) were required in a greater proportion of patients receiving the combination regimen than in patients receiving nivolumab monotherapy for the management of immune-related colitis (47% and 13%, respectively) and immune-related hepatitis (46% and 19%).The management guidelines for these adverse reactions are described in section 4.4. *Immune-related pneumonitis* In patients treated with nivolumab monotherapy, the incidence of pneumonitis, including interstitial lung disease and lung infiltration, was 3.0% (67/2227). The majority of cases were Grade 1 or 2 in severity reported in 0.7% (16/2227) and 1.5% (34/2227) of patients respectively. Grade 3 and 4 cases were reported in 0.7% (16/2227) and <0.1% (1/2227) of patients respectively. No Grade 5 cases were reported in these studies. Median time to onset was 3.3 months (range: 0.0-19.6). Resolution occurred in 52 patients (78%) with a median time to resolution of 5.6 weeks (range: 0.1+-53.1)+; + denotes a censored observation. In urothelial carcinoma studies, 2 Grade 5 cases of pneumonitis were reported in patients treated with nivolumab monotherapy. In patients treated with nivolumab in combination with ipilimumab, the incidence of pneumonitis including interstitial lung disease, was 7.4% (33/448). Grade 2, Grade 3, and Grade 4 cases were reported in 4.5% (20/448), 1.1% (5/448), and 0.2% (1/448) of patients, respectively. One of the Grade 3 pneumonitis worsened over 11 days with a fatal outcome. Median time to onset was 2.3 months (range: 0.7-6.7). Resolution occurred in 29 patients (87.9%) with a median time to resolution of 6.1 weeks (range: 0.3-46.9+). *Immune-related colitis* In patients treated with nivolumab monotherapy, the incidence of diarrhoea, colitis, or frequent bowel movements was 12.6% (280/2227). The majority of cases were Grade 1 or 2 in severity reported in 8.6% (191/2227) and 2.7% 61/2227) of patients respectively. Grade 3 cases were reported in 1.3% (28/2227) of patients. No Grade 4 or 5 cases were reported in these studies. Median time to onset was 1.4 months (range: 0.0-20.9). Resolution occurred in 247 patients (89%) with a median time to resolution of 1.9 weeks (range: 0.1+8.3+). In patients treated with nivolumab in combination with ipilimumab, the incidence of diarrhoea or colitis was 45.5% (204/448). Grade 2, Grade 3, and Grade 4 cases were reported in 13.2% (59/448), 15.4% (69/448), and 0.4% (2/448) of patients, respectively. No Grade 5 cases were reported. Median time to onset was 1.1 months (range: 0.0-10.4). Resolution occurred in 184 patients (90.6%) with a median time to resolution of 3.0 weeks (range: 0.1-78.7+). *Immune-related hepatitis* In patients treated with nivolumab monotherapy, the incidence of liver function test abnormalities was 6.4% (142/2227). The majority of cases were Grade 1 or 2 in severity reported in 3.5% (77/2227) and 1.2% (26/2227) of patients respectively. Grade 3 and 4 cases were reported in 1.4% (31/2227) and 0.4% (8/2227) of patients, respectively. No Grade 5 cases were reported in these studies. Median time to onset was 1.9 months (range: 0.1-18.7). Resolution occurred in 106 patients (75%) with a median time to resolution of 5.1 weeks (range: 0.1-82.6+). In patients treated with nivolumab in combination with ipilimumab, the incidence of liver function test abnormalities was 27.9% (125/448). Grade 2, Grade 3, and Grade 4 cases were reported in 6.3% (28/448), 15.0% (67/448), and 1.8% (8/448) of patients, respectively. No Grade 5 cases were reported. Median time to onset was 1.4 months (range: 0.0-11.0). Resolution occurred in 116 patients (92.8%) with a median time to resolution of 5.0 weeks (range: 0.1-53.1). *Immune-related nephritis and renal dysfunction* In patients treated with nivolumab monotherapy, the incidence of nephritis or renal dysfunction was 2.7% (60/2227). The majority of cases were Grade 1 or 2 in severity reported in 1.5% (34/2227) and 0.7% (16/2227) of patients respectively. Grade 3 and 4 cases were reported in 0.4% (9/2227) and <0.1% (1/2227) of patients, respectively. No Grade 5 nephritis or renal dysfunction was reported in these studies. Median time to onset was 2.3 months (range: 0.0-18.2). Resolution occurred in 35 patients (60%) with a median time to resolution of 12.1 weeks (range: 0.1+-77.1+). In patients treated with nivolumab in combination with ipilimumab, the incidence of nephritis and renal dysfunction was 4.2% (19/448). Grade 2, Grade 3, and Grade 4 cases were reported in 1.1% (5/448), 0.9% (4/448), and 0.7% (3/448) of patients, respectively. No Grade 5 cases were reported. Median time to onset was 2.6 months (range: 0.5-14.7). Resolution occurred in 17 patients (89.5%) with a median time to resolution of 1.9 weeks (range: 0.4-42.6+). *Immune-related endocrinopathies* In patients treated with nivolumab monotherapy, the incidence of thyroid disorders, including hypothyroidism or hyperthyroidism, was 8.5% (190/2227). The majority of cases were Grade 1 or 2 in severity reported in 3.8% (84/2227) and 4.7% (104/2227) of patients respectively. Grade 3 thyroid disorders were reported in <0.1% (2/2227) of patients. Hypophysitis (1 Grade 1, 1 Grade 2, 3 Grade 3, and 1 Grade 4), hypopituitarism (4 Grade 2 and 1 Grade 3), adrenal insufficiency (1 Grade 1, 5 Grade 2, and 5 Grade 3), diabetes mellitus (1 Grade 2), and diabetic ketoacidosis (2 Grade 3) were reported. No Grade 5 cases were reported in these studies. Median time to onset of these endocrinopathies was 2.8 months (range: 0.0-14.0). Resolution occurred in 96 patients (46%) with a median time to resolution of 42.1 weeks (0.4-96.1+). In patients treated with nivolumab in combination with ipilimumab, the incidence of thyroid disorders was 23.7% (106/448). Grade 2 and Grade 3 thyroid disorders were reported in 13.4% (60/448) and 1.6% (7/448) of patients, respectively. Grade 2 and Grade 3 hypophysitis occurred in 6.0% (27/448) and 1.8% (8/448) of patients, respectively. Grade 2 and Grade 3 adrenal insufficiency each occurred in 1.1% (5/448), and Grade 4 adrenal insufficiency occurred in 0.2% (1/448) of patients. Grade 1 and Grade 2 diabetes mellitus and Grade 4 diabetic ketoacidosis were each reported in 0.2% (1/448) of patients. No Grade 5 endocrinopathy was reported. Median time to onset of these endocrinopathies was 1.5 months (range: 0.0-10.1). Resolution occurred in 59 patients (45.0%). Time to resolution ranged from 0.4 to 74.4+ weeks. *Immune-related skin adverse reactions* In patients treated with nivolumab monotherapy, the incidence of rash was 25.6% (569/2227). The majority of cases were Grade 1 in severity reported in 19.9% (444/2227) of patients. Grade 2 and Grade 3 cases were reported in 4.7% (105/2227) and 0.9% (20/2227) of patients respectively. No Grade 4 or 5 cases were reported in these studies. Median time to onset was 1.4 months (range: 0.0117.2). Resolution occurred in 349 patients (62%) with a median time to resolution of 16.1 weeks (0.1-113.7+). In patients treated with nivolumab in combination with ipilimumab, the incidence of rash was 63.4% (284/448). Grade 2 and Grade 3 cases were reported in 19.2% (86/448) and 7.4% (33/448) of patients, respectively. No Grade 4 or 5 cases were reported. Median time to onset was 0.5 months (range: 0.0-9.7). Resolution occurred in 192 patients (67.6%) with a median time to resolution of 10.4 weeks (range: 0.1-74.0+). Rare cases of SJS and TEN some of them with fatal outcome have been observed (see sections 4.2 and 4.4). *Infusion reactions* In patients treated with nivolumab monotherapy, the incidence of hypersensitivity/infusion reactions was 5.0% (111/2227), including 5 Grade 3 and 2 Grade 4 cases. In patients treated with nivolumab in combination with ipilimumab, the incidence of hypersensitivity/infusion reactions was 3.8% (17/448); all were Grade 1 or 2 in severity. Grade 2 cases were reported in 2.2% (10/448) of patients. No Grade 3-5 cases were reported. *Complications of allogeneic HSCT in classical Hodgkin Lymphoma* In 40 evaluated patients from two cHL studies who underwent allogeneic HSCT after discontinuing nivolumab monotherapy, Grade 3 or 4 acute GVHD was reported in 7/40 patients (17.5%). Hyperacute GVHD, defined as acute GVHD occurring within 14 days after stem cell infusion, was reported in two patients (5%). A steroid-requiring febrile syndrome, without an identified infectious cause, was reported in six patients (15%) within the first 6 weeks post-transplantation, with five patients responding to steroids. Hepatic veno-occlusive disease occurred in one patient, who died of GVHD and multi-organ failure. Six of 40 patients (15%) died from complications of allogeneic HSCT after nivolumab. The 40 patients had a median follow-up from subsequent allogeneic HSCT of 2.9 months (range: 022 months). *Laboratory abnormalities* In patients treated with nivolumab monotherapy, the proportion of patients who experienced a shift from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 4.7% for anaemia (all Grade 3), 0.6% for thrombocytopaenia, 9.5% for lymphopaenia, 0.9% for neutropaenia, 1.7% for increased alkaline phosphatase, 2.6% for increased AST, 2.2% for increased ALT, 0.9% for increased total bilirubin, 0.6% for increased creatinine, 2.3% for increased amylase, 6.5% for increased lipase, 5.8% for hyponatraemia, 1.8% for hyperkalaemia, 1.4% for hypokalaemia, 1.3% for hypercalcaemia, 0.7% for hypermagnesaemia, 0.5% for hypomagnesaemia, 0.6% for hypocalcaemia, 1.0% for leucopoenia, and 0.1% for hypernatraemia. In patients treated with nivolumab in combination with ipilimumab, the proportion of patients who experienced a worsening from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 2.8% for anaemia (all Grade 3), 1.2% for thrombocytopaenia, 0.5% for leucopoenia, 6.4% for lymphopaenia, 0.7% for neutropaenia, 4.1% for increased alkaline phosphatase, 11.9% for increased AST, 14.6% for increased ALT, 0.9% for increased total bilirubin, 2.4% for increased creatinine, 8.5% for increased amylase, 18.2% for increased lipase, 1.3% for hypocalcaemia, 0.3% each for hypercalcaemia, hyperkalaemia, hypermagnesaemia, and hypernatraemia, 4.5% for hypokalaemia, and 9.2% for hyponatraemia. *Immunogenicity* Of the 2022 patients who were treated with nivolumab monotherapy 3 mg/kg every 2 weeks and evaluable for the presence of anti-product-antibodies, 231 patients (11.4%) tested positive for treatment-emergent anti-product-antibodies with fifteen patients (0.7 %) testing positive for neutralising antibodies. Of 394 patients who were treated with nivolumab in combination with ipilimumab and evaluable for the presence of anti-nivolumab antibodies, 149 patients (37.8%) tested positive for treatment-emergent anti-nivolumab antibodies with 18 patients (4.6%) testing positive for neutralising antibodies. Although the clearance of nivolumab was increased by 25% when anti-nivolumab-antibodies were present, there was no evidence of loss of efficacy or altered toxicity profile in the presence of nivolumab antibodies based on the pharmacokinetic and exposure-response analyses for both monotherapy and combination. Elderly No overall differences in safety were reported between elderly (≥ 65 years) and younger patients (< 65 years). Data from NSCLC and SCCHN patients 75 years of age or older are too limited to draw conclusions on this population (see section 5.1). Data from cHL patients 65 years of age or older are too limited to draw conclusions on this population (see section 5.1). Hepatic or renal impairment In the non-squamous NSCLC study (CA209057), the safety profile in patients with baseline renal or hepatic impairment was comparable to that in the overall population. These results should be interpreted with caution due to the small sample size within the subgroups. Reporting of suspected adverse reactions Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

MARKETING AUTHORISATION HOLDER Bristol-Myers Squibb Pharma EEIG Uxbridge Business Park Sanderson Road Uxbridge UB8 1DH United Kingdom **MARKETING AUTHORISATION NUMBER(S)** EU/1/15/1014/001-002 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION** Date of first authorisation: 19 June 2015 **DATE OF REVISION OF THE TEXT** Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

15068E1179ROS245-01- date of preparation 06-2017

LUNG AND THORACIC CANCERS

ASCO DIRECT™ LIVE BELGIUM: 2017 ANNUAL MEETING

NSCLC immunotherapy

A 'very important finding' according to Prof. Johan Vansteenkiste (UZ Leuven, Belgium), which was published in November 2016 in NEJM, concerns the phase III results of the KEYNOTE-024 trial with pembrolizumab versus investigator's choice of platinum-based chemotherapy as first-line treatment of patients with metastatic PD-L1-positive non-small-cell lung cancer (NSCLC)[28].

'The findings are not yet implemented in the ESMO guidelines, but it is not a discussion anymore that it will be implemented in the next guidelines. For patients with high PD-L1 expression, pembrolizumab is becoming a preferred option.'

Dr. Julie Brahmer:
'KEYNOTE-024 supports the role of pembrolizumab as first-line treatment of patients with NSCLC and high PD-L1 expression'

During the ASCO meeting, Dr. Julie Brahmer (Baltimore, USA) presented the longer follow-up data of this trial. Pembrolizumab continued to show OS benefit over chemotherapy as first-line therapy for advanced NSCLC with PD-L1 expression of ≥50%. After a median follow-up period of 19 months, median OS for pembrolizumab was not reached. Despite an effective crossover rate of 60%, there remained a high degree of separation of the OS curves.

Progression after the next line of therapy (PFS2) was substantially improved for pembrolizumab- versus chemotherapy-treated patients. Patients whose tumours had a PD-L1 expression of ≥50%, had better survival if they started with pembrolizumab rather than chemotherapy. Along with a favourable safety profile, Dr. Brahmer thinks that these data support pembroli-

zumab as a standard of care for first-line treatment of patients with NSCLC with a PD-L1 expression of ≥50%[29].
In a live connection with Chicago, Prof. Egbert Smit (Amsterdam, the Netherlands) gave a critical analysis of the presented trials. 'The number of patients that actually received crossover treatment, was approximately 60%. Even in those patients who have a lower level of toxicity, you still lose four in ten patients in case of progression. The same applies to chemotherapy. We used to think that residual toxicity of (chemo)therapy prohibited patients from receiving second-line treatment. We have to rethink about that assumption. Although the PFS benefit was quite comparable between treatment with immunotherapy and second-line chemotherapy afterwards as compared with the reverse sequence, there still remains a difference after 18 months.'

Prof. Johan Vansteenkiste:
'In case of tumour resistance, we give new drugs. The question is whether we could start these drugs as first-line therapy.'

NSCLC targeted therapy

The next topic was about targeted agents in the metastatic setting. ALK rearrangement defines a distinct subset of patients with NSCLC, for whom small molecule tyrosine kinase inhibitors (TKIs) of ALK are highly effective. Patients with newly diagnosed, advanced ALK-positive NSCLC receive the first-generation ALK inhibitor crizotinib, Prof. Vansteenkiste says about the current practice. 'In case of tumour resistance, we give new drugs. The question is whether we could start these drugs as first-line therapy.'
Dr. Alice Shaw (Boston, USA) presented new data from ALEX, the first global randomized phase III study which compared next- and first-generation ALK inhibitors in patients with previously untreated, advanced ALK-positive NSCLC. Alectinib significantly prolonged PFS compared with crizotinib (HR 0.47; p<0.0001), significantly delayed time to central nervous system (CNS) progression, significantly improved intracranial ORR and duration of response, and had a more favourable AE profile.
The prolonged PFS seen with alectinib is consistent with other studies of alectinib in Japanese patients (e.g., J-ALEX study). According to Dr. Shaw, the large magnitude of benefit suggests that first-line alectinib may be superior to sequential treatment with crizotinib and alectinib. Overall, she thinks that these results, which were simultaneously published online in NEJM, establish alectinib as the new standard of care for patients with previously untreated, advanced ALK-positive NSCLC[30;31].
'The ALEX study was a confirmation of the J-ALEX study', Prof. Smit says. 'Alectinib has better efficacy and less toxicity than crizotinib. However, the OS curves were comparable. So, we need longer follow-up data to make a definitive conclusion about the respective roles of these drugs.'

Small cell lung cancer

Patients with recurrent small cell lung cancer (SCLC) have limited treatment options and poor survival. In the ESMO guidelines, topotecan is recommended for patients with refractory SCLC[32]. Prof. Vansteenkiste introduces the presented data of the Checkmate 032 study: 'In this setting, where there has been very little progress since the introduction of topotecan, the next abstract is on immunotherapy'.
CheckMate 032 is a phase I/II trial, evaluating nivolumab with or without ipilimumab in patients with recurrent SCLC or other tumour types. Initial results showed durable responses and encouraging survival. A randomized extension cohort was added to further evaluate nivolumab with or without ipilimumab in patients with SCLC whose disease progressed after platinum-based therapy. Dr. Matthew Hellmann (New York, USA) presented the results. After a longer follow-up period, responses remained durable and survival promising (2-year OS 26% with nivolumab plus ipilimumab and 14% with nivolumab). Responses were observed regardless of platinum sensitivity, line of therapy or PD-L1 status. Grade 3/4 treatment-emergent AEs and deaths were more common with nivolumab plus ipilimumab than with nivolumab monotherapy[33].
Approximately 20% of SCLC patients are sensitive to immunotherapy, Prof. Smit adds during the live broadcast. 'That has been shown quite consistently across these studies. It is less clear if the addition of ipilimumab to nivolumab benefits these patients. The follow-up was too short to make any sensible comment. In an aggressive disease, like SCLC, response usually translates to a better survival, but that comes with the expense of a lot of toxicity in a patient population with usually a low performance status, high symptomatic burden and a number of comorbidities. So, before implementing the combination therapies, we should have further evidence from ongoing randomized trials.' ///

Prof. Egbert Smit:
'Better survival comes with the expense of a lot of toxicity in a patient population with usually a low performance status and high symptomatic burden'

CONCLUDING REMARKS

Finally, Prof. Vansteenkiste says that the ASCO DIRECT™ meeting was a very nice experience. 'You had the opportunity to see some of the most relevant videos, including comments to put the findings into practice. I hope you enjoyed this meeting.'

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R. E.: Dr. Chr. Lenaerts - BE/ONCO/1216/0059 - 23/12/2016

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