Horizon Scanning in Oncology

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Health Technology Assessment

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1 Drug description

Generic/Brand name/ATC code:

Nivolumab/Nivolumab BMS (for non-small cell lung cancer),
Opdivo® (for melanoma)/L01XC17

Developer/Company:

Nivolumab was developed as a collaboration between Ono Pharmaceutical and Medarex. Medarex was acquired by Bristol-Meyers Squibb (BMS) in 2009. Ono Pharmaceutical and BMS have a strategic collaboration agreement to jointly develop and commercialise all collaboration products [1].

Description:

immunotherapy with nivolumab, a monoclonal antibody targeting PD-1

The programmed cell death receptor-1 (PD-1) is expressed on a number of cell types, including activated T-cells, activated B-cells and natural killer cells. The PD-1 receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. Its main endogenous ligands PD-L1 and PD-L2 are expressed in activated immune cells and in many tumour cells in response to inflammatory stimuli. Tumours have been shown to escape immune surveillance by expressing PD-L1 and PD-L2, thereby suppressing tumour-infiltrating lymphocytes via PD-1/PD-L1, 2 interactions and preventing immune-mediated rejection of the tumour. Nivolumab is a fully human IgG4 monoclonal antibody that blocks binding of PD-1 to PD-L1. Inhibition of these interactions has been demonstrated to enhance T-cell response and cell-mediated immune response against tumour cells [2-4].

administered intravenously every two weeks

Nivolumab is administered as an intravenous infusion over 60 minutes at a dose of 3 mg per kilogram of body weight every two weeks [4, 5].

2 Indication

for the second-line therapy of metastatic squamous NSCLC

Nivolumab is indicated for the second-line therapy of metastatic squamous non-small cell lung cancer (NSCLC).

3 Current regulatory status

EMA: licensed for squamous NSCLC in July 2015

In Europe, nivolumab received marketing authorisation:

- for the treatment of locally advanced or metastatic squamous NSCLC after prior chemotherapy in adults under the brand name Nivolumab BMS® on 20 July 2015 [6].
- as monotherapy for the treatment of advanced (unresectable or metastatic) melanoma in adults under the brand name Opdivo® on the 19 June 2015 [4].

In the U.S., nivolumab is licensed for:

- metastatic squamous NSCLC with progression on or after platinum-based chemotherapy since March 2015.
- unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, as a BRAF inhibitor. This indication was approved under accelerated approval in December 2014 [5].

4 Burden of disease

4,371 new lung cancer cases in Austria and 52,717 in Germany each year

Primary lung cancer is the leading cause of cancer death worldwide. While the mortality of lung cancer is declining in men, increasing rates in women have been observed in Europe [7]. In Austria, 4,371 patients were newly diagnosed with lung cancer in 2011 equalling an incidence rate of 65.4 cases per 100,000 persons. 3,619 patients died from lung cancer in 2011 [8]. In Germany, 52,717 patients were newly diagnosed with lung cancer in 2011 resulting in an incidence rate of 65.4 cases per 100,000 persons. 43,944 died in 2011 [9]. Age-standardised rates show that incidence and mortality are about twice as high in men than in women, however, incidence is slowly decreasing in men but increasing in women.

most common type of lung cancer is non-small cell lung cancer

The most common type of lung cancer is NSCLC which accounts for about 85%–90% of all lung cancers. Two major types of NSCLC can be distinguished: non-squamous and squamous cell (epidermoid) carcinoma. Of all NSCLC, histologically about 22% are squamous cell carcinomas [10] which are characterised as presence of keratin production by tumour cells and/or intercellular desmosomes ("intercellular bridges") [11].

main risk factor: smoking

The main risk factor for NSCLC is smoking. However, radiation therapy and environmental toxins such as second-hand smoke, asbestos or radon, and metals may also cause this type of cancer [7]. Patients with lung cancer are usually diagnosed at a late stage since symptoms do not manifest until they are locally advanced or there is metastatic disease. Cough, haemoptysis, chest pain, dyspnoea or hoarseness may be indicative of lung cancer.

for diagnosis: x-ray, CT, laboratory testing, cytology, IHC

EGFR, ALK testing for squamous-cell NSCLC not recommended

For diagnosis, it is recommended to take a first-imaging chest x-ray followed by a CT scan, a clinical history, a physical exam and to conduct laboratory tests. To further characterise the tumour's pathology, small biopsy samples should be taken and cytology should be performed; immune-histochemical staining (IHC) serves to differentiate the cancer histologically. Since the presence of specific genetic mutations – i.e. mutations in the epithelial growth factor receptor (EGFR) and rearrangements of the anaplastic lymphoma kinase (ALK) genes – enables administration of targeted therapies, patients with non-squamous NSCLC should be tested for EGFR mutations and ALK rearrangements before the initiation of first-line treatment. Due to the low incidence of these mutations in patients with squamous-cell NSCLC, testing of these mutations is not recommended in Europe. The only exception being people who never smoked or people who are former light smokers [7, 12].

TNM system for prognosis and therapeutic decisions

life expectancy of stage IV disease is 4 months

After this initial evaluation, staging of the cancer according to the Tumor Node Metastasis (TNM) system is done to determine the appropriate therapy as well as for deriving a prognosis. The TNM system groups lung cancer into 4 stages, based on the size of the tumour and presence or absence of nodal and distant metastases. Besides the extent of the disease, prognostic factors include European Cooperative Oncology Group (ECOG) Performance Status, gender and weight loss [12]. Even though survival rates have been increasing constantly with the year of diagnosis, still only 18% of all patients with lung cancer are alive 5 years after diagnosis [8]. Patients at early stages survive for a median of 59 months, whereas patients with advanced stage IV disease have a life expectancy of about 4 months. In Austria, of newly diagnosed lung cancer patients, 34% of tumours were disseminated.

5 Current treatment

first-line therapy: platinum-based chemotherapy

second-line therapy: docetaxel

For the first-line therapy of patients with NSCLC without mutations and a good performance status (ECOG 0–2), a platinum-based doublet chemotherapy is recommended [7]. Patients with a performance status (PS) of 0–2 who are progressing on first-line therapy should be offered second-line chemotherapy. Single-agent therapy is preferred, since combination regimens have not shown superior results. For patients with squamous histology, docetaxel is indicated according to recent guidelines [7, 13]. For patients not eligible for chemotherapy, erlotinib is currently recommended for all NSCLC histological subtypes.

6 Evidence

search in 4 databases

424 references in total

1 phase III and 1 phase II study included

A literature search was conducted on 19 June 2015 in four databases (Medline, Embase, CRD Database and The Cochrane Library). Search terms used were "Nivolumab", "bms 936558", "mdx 1106", "ono 4538", "Opdivo", "PD-1 inhibitor*", "PD-L1 inhibitor*", " PD-1 receptor*", "PD-L1 receptor*", "Programmed Cell Death 1 Receptor", "Carcinoma, Non-Small-Cell Lung", "non-small cell lung", "nonsmall cell lung", "NSCLC*". 424 references were identified.

The manufacturer submitted 2 full-text publications, both already identified by the systematic search, and 3 presentations of which one provided additional information to the phase III study and was therefore included [14].

6.1 Efficacy and safety – phase III studies

Table 1: Summary of efficacy

Study title Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer [15, 16]		
Study identifier	CheckMate 017; ClinicalTrials.gov number NCT01642004; Protocol number CA209017; IND number 100052; EUDRACT number 2011-004792-36	
Design	randomised, open-label, international phase III trial	
	Duration	*Enrolment:* October 2012–December 2013 *Median follow-up*: minimum follow-up app. 11 months *Cut-off dates for interim analysis*: database lock 15 December 2014 On 10 January 2015, early termination of the study was recommended on the basis of a pre-specified interim analysis showing that overall survival among patients receiving nivolumab was superior to that among patients receiving docetaxel.
Hypothesis	Superiority Initially, confirmed objective response rate was also a primary end point, but on the basis of mature data regarding the objective response rate in an expanded cohort of patients with NSCLC who had been treated in the phase 1b study MDX-1106-03 (ClinicalTrials.gov number NCT00730639), the ongoing trial was amended before the planned interim analysis to make overall survival the sole primary end point. The boundary for declaring superiority for overall survival at the interim analysis was a P value of less than 0.03, which was based on an O'Brien-Fleming alpha-spending function. If the P value for overall survival indicated statistical significance, then the key secondary end points of response rate and progression-free survival were tested hierarchically at the 5% alpha level.	
Funding	Bristol-Myers Squibb	
Treatment groups	Overall study population: 272	
	I(ntervention) (n=135)	nivolumab intravenously (IV), at a dose of 3 mg per kilogram of body weight every 2 weeks until disease progression or discontinuation of treatment owing to toxic effects or for other reasons; dose reductions were not permitted; after initial disease progression treatment was permitted at the investigator's discretion
	C(ontrol) (n=137)	docetaxel intravenously, at a dose of 75 mg/m² of body-surface area every 3 weeks until disease progression or discontinuation of treatment owing to toxic effects or for other reasons

Endpoints and definitions	Overall survival (primary outcome)	OS	time from randomisation to the date of death		
	Objective response rate	ORR	number of subjects with a BOR (= best response designation, as determined by the investigators, recorded between the date of randomisation and the date of objectively documented progression per RECIST 1.1 or the date of subsequent anti-cancer therapy, whichever occurs first) of CR or PR divided by the number of randomised subjects		
	Progression-free survival	PFS	time from randomisation to the date of the first documented event of tumour progression, death, or last tumour assessment that could be evaluated		
	Patient-reported outcomes	QoL	disease-related symptoms and health status were assessed with the use of the Lung Cancer Symptom Scale and the European Quality of Life-5 Dimensions questionnaire. Outcome measures included the proportion of patients who had clinically meaningful improvement in the average Lung Cancer Symptom Scale score by week 12		
	Duration of response	DOR	defined as the time between the date of first confirmed response to the date of the first documented tumour progression (per RECIST 1.1), or death due to any cause, whichever occurs first		
Results and analysis					
Analysis description	OS and PFS were analysed via a two-sided log-rank test stratified by prior use of paclitaxel, and region. The HR and the corresponding confidence intervals (CI) have been estimated using a stratified Cox proportional hazards model. Survival curves for each randomised arm have been estimated using the Kaplan-Meier (KM) method.				
Analysis population	Inclusion	❁ stage IIIB or IV squamous-cell NSCLC who had disease recurrence after one prior platinum-containing regimen ❁ ECOG PS score ≤1 ❁ patients with stable brain metastases were eligible ❁ submission of a pre-treatment tumour-tissue specimen for biomarker analyses ❁ prior maintenance therapy, including an epidermal growth factor ❁ receptor tyrosine kinase inhibitor, was allowed			
	Exclusion	❁ autoimmune disease, symptomatic interstitial lung disease, systemic immunosuppression, prior therapy with T-cell co-stimulation or checkpoint-targeted agents, or prior docetaxel therapy ❁ more than one prior systemic therapy for metastatic disease			
	Characteristics		I	C	
		Median age (range), yrs	62 (39–85)	64 (42–84)	
		Males/Females, %	82/18	71/29	
		Disease stage IIIB/IV, %	21/78	18/82	
		Smoking status: current smoker or former smoker/never smoked, %	90/7	94/5	
		Other previous systemic therapy, % Gemcitabine Paclitaxel Vinorelbine Etoposide Pemetrexed Bevacizumab Fluorouracil Cetuximab	 44 34 15 13 1 1 0	 52 34 8 2 1 0 1	
		Time from completion of most recent prior regimen, % <3 months 3–6 months >6 months	 47 26 26	 43 29 27	

Descriptive statistics and estimated variability	Treatment group	I	C
	Number of subjects	N=135	N=137
	Median OS months, (95%CI)	9.2 (7.3–13.3)	6.0 (5.1–7.3)
	OS at 1 year %, (95%CI)	42 (34–50)	24 (17–31)
	ORR %, (95%CI)	20 (14–28)	9 (5–15)
	Best overall response Complete response Partial response Stable disease Progressive disease Could not be determined	 1 (1) 26 (19) 39 (29) 56 (41) 13 (10)	 0 12 (9) 47 (34) 48 (35) 30 (22)
	PFS months, (95%CI)	3.5 (2.1–4.9)	2.8 (2.1–3.5)
	Median DOR months, (range)	NR (2.9–20.5*)	8.4 (1.4*–15.2*)
	QoL	NA	NA
Effect estimate per comparison	Comparison groups		I vs C
	OS	HR	0.59
		95%CI	0.44–0.79
		P value	<0.001
	ORR	Odds ratio	2.6
		95%CI	1.3–5.5
		P value	0.008
	PFS	HR	0.62
		95%CI	0.47–0.81
		P value	<0.001

Abbreviations: CI = confidence interval; CR = complete response; ECOG = Eastern Cooperative Oncology Group; HR = hazard ration; NA = not available; NR = not reached; n = number; PR = partial response; PS = performance status

* This is a censored value. The value of 1.4 was censored owing to the start of subsequent therapy in one patient, and the other values were censored because the response was ongoing at the time of analysis.

Table 2: Treatment-related adverse events of any grade reported in ≥ 20% of patients in either group and of grade 3 or 4 in ≥ 3%

Grade (according to CTC version 4.0)	**Outcome**, n (%)	**I** (n=131)	**C** (n=129)
Any Grade	Any event	76 (58)	111 (86)
	Fatigue	21 (16)	42 (33)
	Decreased appetite	14 (11)	25 (19)
	Nausea	12 (9)	30 (23)
	Diarrhoea	10 (8)	26 (20)
	Anaemia	2 (2)	28 (22)
	Neutropenia	1 (1)	42 (33)
	Alopecia	0	29 (22)
Grade 3 or 4	Any event	9 (7)	71 (55)
	Fatigue	1 (1)	10 (8)
	Asthenia	0	5 (4)
	Anaemia	0	4 (3)
	Leukopenia	1 (1)	5 (4)
	Neutropenia	0	38 (30)
	Febrile neutropenia	0	13 (10)
Grade 5	Any serious event	0	3 (2)
	Treatment-related deaths	0	3 (2)

The CheckMate 017 trial, an open-label phase III study, compared nivolumab with docetaxel in a total of 272 patients with squamous-cell NSCLC who had previously been treated with one platinum-containing regimen [15]. Patients had a median age of 63 years, the majority were men (76%) and 56% were younger than 65 years. Patients had advanced/metastatic disease and an ECOG of ≤ 1. 6% had never smoked, whereas 92% were either current or former smokers. Besides cisplatin or carboplatin other previous therapies included gemcitabine (48%), paclitaxel (34%), and vinorelbine (16%) as well as other agents such as etoposide and monoclonal antibodies. After a median of 8 doses nivolumab and 3 doses docetaxel, 36% in the nivolumab group and 30% in the docetaxel group received further systemic therapy. 24% in the nivolumab group subsequently received docetaxel and 2% in the docetaxel group received further immunotherapy.

CheckMate 017 trial compared nivolumab with docetaxel in 272 previously treated patients with squamous-cell NSCLC

In January 2015, the study was terminated early due to the results of an interim analysis, showing that overall survival was superior for nivolumab. In this interim analysis, median OS, the primary outcome, was improved by 3.2 months in patients treated with nivolumab, resulting in a hazard ratio of 0.59 ($p<0.001$) compared to docetaxel. The OS rate at 1 year was 42% with nivolumab compared to 24% with docetaxel. Consistent results were also shown in most subgroup analyses, according to previous chemotherapy, gender and smoking status [16]. Only in the small subgroups of patients aged ≥ 75 years (29 patients) and for the 31 individuals from the rest-of-the-world geographic region outcomes indicated improvements for docetaxel.

early termination

median OS + 3.2 months for nivolumab group

OS rate at 1 year 42% vs 24%

An objective response, as assessed by investigators and RECIST criteria v 1.1, was achieved in statistically significantly more patients in the nivolumab group (20%) than in the docetaxel group (9%). Only 1% showed a complete response with nivolumab and none with chemotherapy. Partial responses were observed in 19% in the intervention group (I) and in 9% in the comparison (C) group. 29% versus 34% had stable and 41% versus 35% had progressive disease respectively. In the remaining cases, best overall response could not be determined with a substantial difference between the nivolumab group and the docetaxel group (10% vs 22%). Time to response was similar in both groups, however, at the interim analysis duration of response had not been reached with nivolumab therapy but was 8.4 months with docetaxel. Median progression-free survival (PFS) was extended by 0.7 months for patients treated with nivolumab.

statistically significant improvements in response rate mainly due to partial response

duration of response not yet reached in nivolumab group and 8.4 months in the docetaxel group

PD-L1 expression was evaluated retrospectively as a secondary endpoint in 225 of the 272 patients using a validated automated IHC assay. Outcomes were analysed for different expression levels (1%, 5% and 10%). No differences were found between PD-L1-positive and -negative tumours. PD-L1 expression was therefore neither predictive nor prognostic for any outcome.

no difference in outcomes according to PD-L1 expression

In terms of treatment-related adverse events (AEs), more patients in the docetaxel group experienced AEs of any grade (I 58% vs C 86%) and of grade 3 or 4 (I 7% vs C 55%). No grade 5 AEs were observed with nivolumab but 2% with docetaxel, and treatment discontinuation due to treatment-related AEs was also less frequent in the nivolumab group (3%) than in the docetaxel group (10%). Serious AEs of at least grade 3 (I 2% vs C 21%) were pneumonitis in the nivolumab group and (febrile) neutropenia and dehydration in the docetaxel group. Higher rates of treatment-related serious AEs in the docetaxel group were mainly caused by haematologic toxic events and infections. Treatment-related select AEs, potentially due to immunologic aetiology, of at least grade 3 comprised colitis, pneumonitis and tubulointerstitial nephri-

AEs 58% vs 86%, serious AEs 2% with nivolumab and 21% with docetaxel

tis (I 1% vs C 0% each) [14]. Immune-modulating medication, most often glucocorticoids, was administered in 18%–100% of patients, depending on the grade of the observed AEs [16].

6.2 Efficacy and safety – further studies

phase II study in 117 patients with ≥ 2 prior therapies

The CheckMate 063 trial was a single-arm phase II trial assessing nivolumab in 117 squamous-cell NSCLC patients who had received two or more prior therapies [17, 18]. Patients had to have disease progression or recurrence after both a platinum doublet-based chemotherapy and at least one additional systemic therapy. Included patients were on average 65 years old, had an ECOG of ≤ 1 and had received 2 (35%), 3 (44%) or ≥ 4 (21%) previous therapies. Since best response to the last therapy was progressive disease in 61% of cases, the majority of patients can be considered refractory.

0% complete responses, 15% partial responses

better outcomes for PD-L1-positive tumours

Objective response assessed by an independent radiology review committee was the primary outcome. 0% of patients achieved a complete response, 15% a partial response, 26% had stable disease and 44% progressive disease. Median PFS was 1.9 months, median OS 8.2 months, and the OS at 1 year was 40.8%. PD-L1 expression was measured (cut-off 5%) in 88% of participants, of which 33% had PD-L1-positive tumours. More favourable objective responses and reductions in target tumour lesion burden were observed for patients with PD-L1-positive tumours.

AEs in 74%, grade ≥ 3 in 17%

In terms of safety outcomes, treatment-related AEs of any grade were observed in 74% and of grade 3 or 4 in 17%. Most common AEs of any grade were fatigue (33%), decreased appetite (19%) and nausea (15%) whereas fatigue (4%), pneumonitis (3%) and diarrhoea (3%) were the most frequent grade 3 or 4 AEs. Two deaths were considered to be treatment-related; one case of hypoxic pneumonia and one ischaemic stroke.

After a median treatment duration of 2.3 months, nivolumab therapy was ended in most instances due to disease progression. 24% of patients subsequently received further therapy.

7 Estimated costs

no costs for Austria or Germany available

estimates: € 20,000/case

No costs for nivolumab are available yet either for Austria or for Germany. However, in Germany treatment costs comparable to those of ipilimumab or vermurafenib are expected, which would be about € 20,000 per case [19]. According to UK Medicines Information, Opdivo® was launched in Japan at an annual cost of $ 143,000 per patient and analysts expect an annual cost of at least $ 110,000 in the US [20].

8 Ongoing research

3 phase III studies ongoing for NSCLC

Two ongoing phase III studies were found on www.clinicaltrials.gov and on www.clinicaltrialsregister.eu assessing nivolumab therapy in NSCLC, including both squamous as well as non-squamous cancers.

- NCT02041533 (CheckMate 026): Evaluating nivolumab versus investigator's choice chemotherapy as first-line therapy in subjects with strongly stage IV or recurrent PD-L1-positive NSCLC. Estimated study completion date: January 2018.
- NCT02477826 (CheckMate 227): Comparing nivolumab, or nivolumab plus ipilimumab with platinum-doublet chemotherapy in subjects with chemotherapy-naïve stage IV or recurrent NSCLC. Estimated study completion date: December 2020.

under investigation for further tumour types

Nivolumab is also under investigation in phase III for non-squamous NSCLC (CheckMate 057, NCT01673867, estimated completion date May 2016), glioblastoma, head and neck carcinoma, renal cell carcinoma and gastric cancer. Current phase II studies of the drug are on chronic lymphocytic leukaemia, multiple myeloma, cervical cancer and colon cancer.

9 Commentary

market authorisation in Europe in July 2015 and in March 2015 in the U.S.

The EMA granted marketing authorisation of nivolumab for the treatment of locally advanced or metastatic squamous-cell NSCLC after prior chemotherapy in adults in July 2015 [6]. Similarly, the drug was licensed in March 2015 by the FDA for the same indication but specifying previous therapy as platinum-based chemotherapy.

first immunotherapy showing prolonged OS: + 3.2 months

risk of progression or death reduced by 38%

response rates also improved with nivolumab, but data missing in 22% of patients in docetaxel group

Based on the findings of the CheckMate 017 trial it was decided to license nivolumab for squamous-cell NSCLC, making it the first immunotherapy medicine licensed in the European Union for this cancer and the first to demonstrate improvements in OS [21]. Median OS, the primary outcome of this phase III trial, was increased by 3.2 months in the nivolumab group in comparison to the docetaxel group, resulting in a reduction of risk of death by 41%. With 38%, the risk of progression or death was also statistically lower, leading to a gain in median PFS by 0.7 months. Duration of response was not yet reached in the nivolumab group and was 8.4 months in the docetaxel group. Response rates also favoured the PD-L1 inhibitor (20% vs 9%), with the majority being partial responses (19% vs 9%). However, response rate could not be determined in a substantial number of patients particularly in the docetaxel group (I 10% vs C 22%). The extent to which this difference may impact on the rates observed is as yet unknown.

fewer any-grade and serious AEs with nivolumab

In terms of safety outcomes, treatment-related AEs were less frequent in the nivolumab group than in the chemotherapy group. Any-grade AEs occurred in 58% in the nivolumab group in comparison to 86% in the docetaxel group, and grade 3 or 4 AEs in 7% and 55% respectively.

influence of molecular mutations on treatment decision of squamous-cell NSCLC not established yet

With the development of targeted therapies such as EGFR tyrosine-kinase inhibitors (TKI) (e.g. gefitinib, erlotinib), new treatment options have become available for lung cancer. However, the influence of molecular mutations on predicting response of squamous-cell NSCLC to targeted therapies has not been properly investigated yet, since EGFR mutations are present in less than 5% and ALK mutations are even rarer in this type of lung cancer [22, 23]. European Guidelines therefore do not recommend routine EGFR testing in confirmed squamous-cell carcinoma before initiation of therapy. Thus, first-line therapy with a platinum-containing regimen followed by docetaxel after disease progression is currently recommended for squamous-cell NSCLC [7, 23].

few treatment options for squamous-cell NSCLC, OS gains

different response criteria?

biomarkers for patient selection?

Due to few treatment options with unsatisfactory results, several new therapeutic options are under investigation for squamous-cell NSCLC. Immunotherapy, including PD-L1 inhibitors, has therefore been discussed with great interest in the clinical community. The gains in median OS and a doubling of 1-year survival rates achieved by nivolumab are considered as clinically relevant. However, these results stem from an interim analysis and long-term follow-up data will only become available later, but subsequent therapies may distort OS outcomes. In terms of PFS, improvements were small, but tumour response has been measured using the RECIST criteria. Since immunotherapy may lead to an initial lymphocyte infiltration and, accordingly, to a preliminary volume gain, tumours may be falsely labelled as progressive. Thus, immune-related response criteria have been suggested to avoid early termination of therapy and to capture late responders [24]. However, no consensus exists on the duration of therapy in the light of ongoing radiographic progression or for patients who are not progressing. Also, prolonged responses have been observed after only few treatment cycles [25].

contradictory evidence for PD-L1 as predictor of response

potentially due to lack of standardised assay?

Selection strategies for the identification of patients with the highest potential to benefit from this costly therapy are also under investigation. One potential biomarker for patient selection is PD-L1 [26]. Not only its prognostic but also its predictive value for response to immune-checkpoint inhibitors is under investigation [27] even though nivolumab was licensed regardless of PD-L1 positivity or negativity. However, the currently available data is inconsistent [28]. In the CheckMate 017 trial, no association of PD-L1 negativity or positivity with clinical outcomes was observed. In contrast, other studies have shown a correlation between PD-L1 expression and tumour response [26, 27]. This difference may be caused by the lack of standardised assays for determining PD-L1 expression, methods of sample preservation and definition of a cut-off value for PD-L1 positivity (currently ranging from 1% of 10% of stained tumour cells) [27, 29]. Thus, studies are needed that compare outcomes for patients assessed as PD-L1-negative compared to those assessed as PD-L1-positive based on a standardised definition using a validated assay [27, 28]. Furthermore, since PD-L1 expression is influenced by the tumour micro-environment, repeated assessment may be indicated but also difficult to implement in clinical practice [25, 26].

immunotherapy in combination with CTLA-4 inhibitors may improve depth and duration of response?

also for overcoming resistance to targeted therapies?

Combinations of PD-L1 inhibitors with CTLA-4 inhibitiors such as ipilimumab, and combinations with other immune checkpoint modulators are under investigation, as they are expected to increase immune response by increasing T-cell activity, and thus to improve the depth and duration of responses (CheckMate 227) [26, 30, 31]. Another advantage of combining agents with different modes of action may be overcoming resistance to targeted therapies. On the other hand, as the spectrum of AEs is similar with respect to immune-related AEs such as colitis, hepatitis, pancreatitis or pneumonitis [32], there is concern that the frequency of these AEs could increase in com-

bination therapies. This has been shown in other indications [33], therefore the safety of combined but also sequential administration of immune-therapies in NSCLC should be assessed.

nivolumab under investigation in earlier lines of therapy, for non-squamous NSCLC

Nivolumab is currently under investigation as second-line therapy for *non*-squamous-cell NSCLC with first results showing also an increase in OS (CheckMate 057 trial [34]), in the first-line setting for NSCLC, and for other types of cancer. As a result, further extensions of indication can be expected. In terms of lung-cancer and with an expected extension to the more frequent non-squamous types, efficacy of nivolumab in tumours with EGFR and ALK mutations is of interest. Accordingly, the impact of previous targeted therapies or immunotherapy on the efficacy and safety of nivolumab needs to be investigated [31]. Moreover, with the prospect of nivolumab therapy being moved to earlier lines of therapy for potentially many more tumours, duration of therapy and re-treatment as well as long-term consequences of modifying the immune-system need to be evaluated [26].

efficacy after previous therapy with targeted agents, duration of response and long-term consequences need to be determined

improved outcomes and fewer AEs in phase III study

Overall, improved outcomes in all assessed endpoints were demonstrated in the CheckMate 017 trial, with fewer AEs in comparison to standard second-line chemotherapy. It is likely that the drug will become the new standard for the treatment of non-squamous NSCLC. Nonetheless, high costs are incurred, data for patient-reported outcomes have not been published yet and long-term adverse effects of immune therapies are unknown.

QoL data missing, high costs, long-term AEs unknown

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