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1 Drug description

Generic/Brand name/ATC code:

Nivolumab/Opdivo®/none

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:

nivolumab is a monoclonal antibody against PD-1

The programmed cell death receptor-1 protein (PD-1) is expressed on a number of cell types, including activated T-cells, activated B-cells and natural killer cells. It acts as part of an immune checkpoint inhibition. 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 shown to escape immune surveillance by expressing PD-L1 and PD-L2, whereby 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. The inhibition of these interactions has demonstrated to enhance T-cell response and cell-mediated immune response against tumour cells [2–6].

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 [7].

2 Indication

first-line for unresectable or metastatic melanoma

Nivolumab is intended to be used as single-agent first-line therapy for the treatment of unresectable or metastatic melanoma.

3 Current regulatory status

under accelerated evaluation by EMA

In Europe, nivolumab is under evaluation for a centralised marketing authorisation by the European Medicines Agency (EMA) [8]. Its request for an accelerated assessment has been accepted for first- and second-line treatment of advanced (unresectable or metastatic) melanoma [9]. In addition, an application was submitted for non-small cell lung cancer [1].

approved by FDA in December 2014 for advanced melanoma following ipilimumab

Nivolumab, under the trade name Opdivo®, was approved under accelerated approval by the FDA in December 2014 for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation-positive, a BRAF inhibitor [7].

In 2013, the FDA granted fast track designation for Opdivo® not only in melanoma, but also in non-small cell lung cancer (NSCLC) and renal cell carcinoma (RCC). In May 2014, breakthrough therapy designation for Opdivo® was granted for the treatment of patients with Hodgkin lymphoma after failure of autologous stem cell transplant and brentuximab [1].

4 Burden of disease

melanoma causes the majority of skin cancer-related death

Melanoma is a malignant tumour that begins in the melanocytes. It represents less than 2% of all skin cancers, but causes the majority of skin cancer-related deaths [10; 11]. According to the WHO, 132,000 melanoma skin cancers occur globally each year, and the global incidence of melanoma continues to increase [12]. In Germany, approx. 19,200 and in Austria nearly 1,500 new cases of melanoma skin cancer were diagnosed in the year 2010. In both countries, men and women were equally affected [13; 14].

in western countries its incidence has risen markedly

Since the 1980s, age-adjusted incidence rates have risen markedly in western industrialised countries. By 2010, two years after introduction of a skin cancer screening program, there were 9,580/9,640 new cases in 2010 in German women and men, amounting to 23.0/24.0 new cases per 100,000 persons. The age-adjusted incidence rate was 17.8 for German women and 18.0 for German men (per 100,000, age-adjusted to the former European population). In Austria there were 723/785 new cases in Austrian women and men in 2010, equalling 16.9/19.3 new cases per 100,000 persons (own calculations). The average age of cancer onset was 58 years in German women and 66 years in men. Over the preceding decade, age-adjusted mortality rates were nearly constant in Germany, ranging at 2.8 in men and 1.6 in women in 2010. That same year the rate was 3.0 in Austrian men and 2.0 in Austrian women [13–15]. Whereas melanoma is one of the most common types of cancer in young adults, melanoma is most frequently diagnosed amongst people aged 55–64 years [10; 16].

most frequently diagnosed in those 55-64 years

risk factors: sun exposure, pigmentary characteristics, family history …

Risk factors for melanoma include genetic and environmental factors, such as sun exposure, pigmentary characteristics, multiple nevi, family and personal history of melanoma, immunosuppression and environmental exposures [10].

symptoms include change in appearance of a mole, itching …

Signs and symptoms of melanoma include a change in the appearance of a mole or a pigmented area, a mole that itches, bleeds or is ulcerated, and the occurrence of satellite moles [10].

staging by TNM and AJCC system

According to the 2010 TNM staging system, patients are grouped into prognostic categories based on the primary tumour (T) and the presence of regional lymphatic (N) and distant metastases (M): Stage I is limited to low-risk primary melanomas without evidence of regional or distant metastases (T1a-T2a). Stage II includes melanomas at higher risk of recurrence without regional or distant metastases (T2b-T4b). Stage III includes melanomas with involvement of lymph nodes or the presence of in-transit or satellite metastases (N1-N3). Stage IV is defined by the presence of distant metastases (M). According to the AJCC staging system, localised disease include stages I-II, regional diseases stage III and distant metastatic disease stage IV [17].

Other prognostic factors include age, gender, pathologic factors (such as the involvement of the sentinel lymph node, growth pattern, lymphatic invasion), serum s-100 protein and gene expression profiling and proteomics [18].

outcome depends on stage at diagnosis

The outcome of melanoma of the skin depends on the stage at diagnosis. It is estimated that 82–85% of patients present with localised disease, 10–13% with regional and 2–5% with distant metastatic disease. Five-year survival rates are high at an early stage, but range from 20–70% in stage III to less than 10% in stage IV [17].

5 Current treatment

For patients with advanced (unresectable or metastatic) melanoma, treatment options include surgical metastasectomy, immunotherapy, targeted inhibition of the mitogen-activated protein kinase (MAPK) pathway, radiation therapy and chemotherapy. Treatment depends on whether the disease is limited and resectable or disseminated and unresectable. If feasible, resection is recommended for limited metastatic disease, and can delay the need for systemic treatment [17; 18].

cytotoxic chemo-therapy no longer standard of care

With the approval of novel treatments, the choice and sequencing of systemic therapy has changed. Prior to the authorisation of ipilimumab and vemurafenib in the EU in the 2011 and 2012 respectively [19; 20], cytotoxic chemotherapy (e.g., dacarbazine) was widely used, despite not having proven to improve overall survival in patients with advanced melanoma [21].

To date, the choice of first-line systemic therapy depends on factors such as mutations in the MAPK pathway, the tempo of disease and the presence of cancer-related symptoms [17].

immunotherapy with CTLA4 therapy, IL-2 or anti-PD-1

Immunotherapy plays an important role in the treatment of advanced melanoma and has the potential for long-term disease control. Regimens include checkpoint inhibition with a monoclonal antibody against the negative regulatory molecule cytotoxic T-lymphocyte protein 4 (CTLA4) and monoclonal antibodies against PD-1 and its ligands, as well as high-dose interleukin-2 (IL-2). The anti-CTLA4 antibody ipilimumab is approved for previously treated and untreated patients with advanced melanoma and is the first drug that has shown to improve overall survival in metastatic melanoma. It comes with an only modest chance of response, but with the possibility for some patients to remain alive over a longer period of time. There are no biomarkers that help to select patients most likely to respond to treatment and the onset of response might be delayed. Furthermore, significant immune-related adverse events (irAEs) need to be taken into consideration. High-dose IL-2 is associated with an overall response rate of about 16% and long-term disease-free survival in a small share of treated patients. Due to its toxicity, however, it is only an option for patients with good organ function. It is not authorised for melanoma in the EU. At the end of 2014, the anti-PD-1 antibodies nivolumab and pembrolizumab were approved in the US for patients that have progressed on ipilimumab and (if BRAF V600 mutation was present) a BRAF inhibitor [3; 17; 18; 21–24].

ipilimumab improves OS but patients have only modest chance of response and risk of irAEs

IL-2 an option limited to relatively healthy patients

vemurafenib and other kinase inhibitors for BRAF-mutant melanoma

OS and response rates improved but most tumours become resistant

combination of BRAF and MEK inhibitors

Approximately one-half of the patients with advanced melanoma have a BRAF V600 mutation that activates the MAP kinase (MAPK) pathway. In patients with metastatic melanoma and BRAF V600 mutation, the BRAF inhibitor vemurafenib increases overall survival, with high overall response rates of approx. 50%, while treatment is mostly well-tolerated. Other MAPK inhibitors include the BRAF inhibitor dabrafenib and the MEK1 and MEK2 inhibitor trametinib. MEK are downstreams of BRAF in the MAPK signal transduction pathway. With BRAF inhibitors, however, the treatment to maintain response is necessary and most tumours become resistant after a median of six months. To address resistance, clinical trials of the combination of BRAF and MEK inhibitors have been conducted, showing that the combinations of dabrafenib plus trametinib and of vemurafenib plus cobimetinib yielded longer PFS and OS than treatment with a single BRAF inhibitor. The combination of BRAF and MEK inhibitors will thus very likely be the new standard therapy for patients with BRAF mutations [4; 17; 18; 21; 24–28].

Radiation therapy to symptomatic sites of metastases may achieve good palliation. Stereotactic radiosurgery may be particularly important in the management of brain metastases [18].

6 Evidence

phase III trial as first-line treatment in advanced melanoma without BRAF mutation

In addition to a free text search, a systematic literature search was conducted in Embase, Ovid Medline, CRD Database and the Cochrane Library. In total, 267 references were identified. The manufacturer provided one further publication which had already been identified by the systematic literature search. Regarding the reviewed indication – the first-line treatment for unresectable or metastatic melanoma – one phase III trial was identified [29].

6.1 Efficacy and safety – Phase III studies

Table 1: Summary of efficacy

Study title Nivolumab in previously untreated melanoma without BRAF mutation [29]		
Study identifier	Study ID Number: CA209-066 ClinicalTrials.gov Identifier: NCT01721772 (CheckMate 066) EudraCT No.: 2012-003718-16	
Design	Phase III, randomised (1:1), double-blind, active comparator, parallel assignment, multi-centre	
	Duration	*Enrolment:* January 2013 – February 2014 *Median follow-up for OS:* 8.9 months (NI), 6.8 months (DA) *Cut-off dates for analyses:* Clinical data cut-off was performed on June 24, 2014 after an unplanned interim database lock that showed a significant benefit in OS for nivolumab. This was followed by unblinding and amendment to allow patients enrolled in the dacarbazine group to receive nivolumab.

Hypothesis	Superiority		
Funding	Bristol-Myers Squibb International Corporation		
Treatment groups	Intervention (n=210)	Nivolumab 3mg per kilogram of body weight, solution for i.v. infusion every two weeks plus placebo every three weeks	
	Control (n=208)	Dacarbazine 1000 mg per square meter body-surface area, solution for i.v. infusion every three weeks plus placebo every two weeks	
Endpoints and definitions	Overall survival (primary outcome)	OS	Time from randomisation to death from any cause
	Progression-free survival	PFS	Time from randomisation to first documented progression per RECIST 1.1, as determined by the investigator, or death due to any cause
	Objective response rate	ORR	Number of subjects with complete or partial response, per RECIST 1.1, divided by the number of randomised subjects assessed by investigators
	Overall survival based on PD-L1 expression	OS by PD-L1	PD-L1 expression as predictive biomarker, measured by the endpoint OS based on PD-L1 expression level using an immunohistochemistry (IHC) assay
	Health-related quality of life	HRQoL	HRQoL as measured by mean changes from baseline in the EORTC-QLQ-C30 questionnaire V3 global health status/QoL composite scale and in the remaining EORTC QLQ-C30 scales
Results and analysis			
Analysis description	Efficacy analysis was performed in the population of patients who underwent randomisation (intention-to-treat population). OS and PFS were compared between treatment groups with two-sided log-rank test stratified according to PD-L1 status and metastasis stage. Hazard ratios were estimated using a stratified Cox proportional hazard model. Survival curves were estimated with Kaplan-Meier product-limit method. ORR was compared between treatment groups with two-sided Cochran-Mantel-Haenszel test.		
Analysis population	Key Inclusion	Untreated, histologically confirmed unresectable Stage III or Stage IV melanoma (prior adjuvant or neoadjuvant melanoma therapy was permitted if completed six weeks prior to randomisation) Known BRAF wild-type as per regionally acceptable V600 mutational status testing ECOG Performance Status of 0 or 1	
	Key Exclusion	Active brain or leptomeningeal metastases Ocular melanoma Active, serious autoimmune disease Serious or uncontrolled medical disorder	
	Characteristics	*Median age (range):* DA 66 years (26-87), NI 64 years (18-86) *Gender:* Females: DA 40%, NI 42% *Metastasis stage:* M0/M1a/M1b: DA 39%, NI 39%; M1c: DA 61%, NI 61% *Prior systemic therapy:* Adjuvant: DA 17%, NI 15%; Neoadjuvant DA 0.5%, NI 0.5% *PD-L1 status:* Positive: DA 36%, NI 35%; negative or indeterminate: DA 64%, NI 65%	

Descriptive statistics and estimated variability	Treatment group	*Control* (DA)	*Intervention* (NI)
	Number of subjects	N=208	N=210
	OS Median (months) 95% CI	 10.8 9.3-12.1	 not reached
	OS rate at one year % 95% CI	 42.1 33.0-50.9	 72.9 65.5-78.9
	PFS Median (months) 95% CI	 2.2 2.1-2.4	 5.1 3.5-10.8
	ORR % 95% CI Complete response (%) Partial response (%) Stable disease (%) Progressive disease (%) Not determined (%) Duration of response (months)	 13.9 9.5-19.4 1.0 13.0 22.1 48.6 15.4 6.0	 40.0 33.3-47.0 7.6 32.4 16.7 32.9 10.5 not reached
	OS by PD-L1 status PD-L1 pos., Median (months) 95% CI PD-L1 negative/indeterminate Median (months) 95% CI	 12.4 9.2-N.A. 10.2 7.6-11.8	 not reached not reached
	Health-related quality of life	NA	NA
Effect estimate per comparison	*Comparison groups*		*Intervention vs. Control*
	OS	Hazard ratio for death	0.42
		99.79% CI	0.25-0.73
		P value	<0.001
	PFS	Hazard ratio for death or disease progression	0.43
		95% CI	0.34-0.56
		P value	<0.001
	ORR	Odds ratio	4.06
		95% CI	2.52-6.54
		P value	<0.001
	OS, PD-L1 positive	Hazard ratio for death	0.30
		95% CI	0.15-0.60
		P value	NA
	OS, PD-L1 negative/ indeterminate	Hazard ratio for death	0.48
		95% CI	0.32-0.71
		P value	NA

Abbreviations: NA = not available; EORTC = European Organization for Research and Treatment of Cancer; QLQ-C30 questionnaire version 3 = Quality of Life Questionnaire-Core 30; PD-L1 = Programmed death-ligand 1

Table 2: TRAEs according to grade, SAEs, AEs leading to discontinuation

CA209-066 trial			
Grade (according to CTC version 4.0)	**Outcome** (%)	**Nivolumab** (n=206)	**Dacarbazine** (n=205)
Any grade	Any AE	93.2	94.6
Any grade treatment-related AEs occurring at least in ≥10% in either treatment arm	Any AE	74.3	75.6
	Fatigue	19.9	14.6
	Pruritus	17.0	5.4
	Nausea	16.5	41.5
	Diarrhoea	16.0	15.6
	Rash	15.0	2.9
	Vitiligo	10.7	0.5
	Constipation	10.7	12.2
	Asthenia	10.2	12.2
	Vomiting	6.3	21.0
	Neutropenia	0	11.2
	Thrombocytopenia	0	10.2
Grade 3 or 4 treatment-related AEs occurring at least in ≥2% in either treatment arm	Any AE	11.7	17.6
	Neutropenia	0	4.4
	Thrombocytopenia	0	4.9
	WBC count decreased	0	2.0
	Neutrophil count decreased	0	2.4
Others	Any grade SAE	31.1	38.0
	Grade 3 or 4 SAE	20.9	26.3
	Any grade treatment-related SAEs*	9.2	8.8
	Grade 3 or 4 treatment-related SAE	5.8	5.9
	Any grade AEs leading to discontinuation	6.8	11.7

*Abbreviations: TRAE = treatment related adverse event; SAE = serious adverse event; AE = adverse event; WBC = white blood cell; * the listed treatment-related SAEs were reported in at least 2% of patients.*

nivolumab vs. dacarbazine

In the **CheckMate 066 phase III trial** (CA209-066, [29]), nivolumab 3mg/kg i.v. every two weeks in combination with a placebo every three weeks was compared to dacarbazine 100mg/m^2 i.v. every three weeks in combination with a placebo every two weeks in patients with unresectable, previously untreated stage III or IV melanoma without a BRAF mutation. Patients were required to have either no or only mild symptoms as assessed by ECOG performance status. Further, tumour tissue had to be available for PD-L1 biomarker analysis. Exclusion criteria included brain metastasis, ocular melanoma, serious or uncontrolled medical disorder and active autoimmune disease. Patients with conditions not expected to recur in the absence of an external trigger were permitted.

418 adults were randomly assigned and stratified according to PD-L1 status and metastasis stage. Treatment continued until disease progression or unacceptable toxicity occurred. Tumour response was assessed by the investigator according to RECIST 1.1 at nine weeks and then every 12 weeks.

subsequently mostly ipilimumab

Treatment continuation was allowed after disease progression for those who had a clinical benefit and no substantial AEs. At the end of the treatment period, 46.1% of nivolumab-treated patients, but only 6.3% those treated with dacarbazine continued the study drug. 30.0% in the nivolumab and 54.8% in the dacarbazine group received subsequent systemic therapy, mostly with ipilimumab.

OS at 1 yr was 73% vs. 42%

median PFS 5.1 vs. 2.2 months

ORR 40% vs. 13.9%

At the time of database lock, the median follow-up for OS was 8.9 months with nivolumab and 6.8 months with dacarbazine. The primary endpoint, median OS, was not reached in patients with nivolumab and was 10.8 months with dacarbazine. At one year, the OS rate was significantly higher in the nivolumab (73%) versus the dacarbazine group (42%; HR: 0.42; 99.79% CI: 0.25–0.73; $p<0.001$). Moreover, median PFS was significantly longer with nivolumab (5.1 months) than with dacarbazine (2.2 months; HR: 0.4; 95% CI: 0.34–0.56; $p<0.001$). The ORR was also higher (40.0% vs. 13.9%; HR: 4.06; 95% CI: 2.52–6.54; $p<0.001$). An improved ORR was due to higher rates of partial (32.4% vs. 13.0%), as well as complete responses (7.6% vs. 1.0%). As the median duration of response was not reached with nivolumab, a more durable response might be present, but the median follow-up time was short. A subgroup analysis showed that nivolumab had improved OS compared to dacarbazine in both PD-L1 subgroups; its prognostic role thus remains to be determined. Data on health-related quality of life has not been published yet.

most common TAEs fatigue, pruritus, nausea

Any grade adverse events and serious adverse events occurred in 93% and 31% of patients treated with nivolumab in comparison to 95% and 38% in the dacarbazine group. Overall, treatment-related AEs (TRAEs) of any grade were observed in 74% and in 76%, of which 12% and 18% were grade 3 or 4. TRAEs leading to discontinuation were reported in 6.8% of the patients with nivolumab and 11.7% of those with dacarbazine. Treatment-related serious SAEs occurred in 9.2% and 8.8% respectively. There were no deaths attributed to the study drugs. The most frequently occurring TRAEs were fatigue, pruritus and nausea in the nivolumab group, and nausea, vomiting and diarrhoea with dacarbazine. The most frequently occurring TRAEs with a potential immunological etiology in the nivolumab group were diarrhoea (16.0%), pruritus (17.0%), rash (15.0%), vitiligo (10.7%) hypo-(4.4%) and hyperthyroidism (3.4%) and pneumonitis (1.5%). TRAEs with a potential immunological aetiology of grade 3 or 4 occurring at least in ≥1% of patients with nivolumab were limited to increased ALT (1%) and diarrhoea (1%), all of them showing a resolution of the event.

6.2 Efficacy and safety – further studies

no further studies in reviewed indication

No further study results on nivolumab from phase II/III trials in the reviewed indication (first-line treatment in advanced melanoma) are available yet.

nivolumab after progression with CTLA-4 therapy
ORR with nivolumab 31.7%

For the indication of a **subsequent line of treatment**, the FDA relied on a **phase III, randomised, open label study** that compared nivolumab 3mg/kg every two weeks to the investigator's choice of either dacarbazine or carboplatin and paclitaxel (CheckMate 037, CA209037, NCT01721746 [23]). The study was conducted in advanced melanoma patients who had progressed following ipilimumab therapy and a BRAF inhibitor, if they were BRAF V600 mutation-positive. An interim analysis was conducted after the 120 patients randomised to nivolumab had completed six months of follow-up or had progressed. In the non-comparative analysis, the ORR with nivolumab was 31.7%, mainly due to partial responses (34/38). The durability of the response was uncertain, as 33/38 responding patients had ongoing responses ranging from 2.6+ to 10+ months. Adverse reactions after a median exposure of 5.3 months included autoimmune-mediated organ toxicity, most often resulting in hypothyroidism (8%), hyperthyroidism (3%) or involving the lungs (3.4%). Grades 3 and 4 adverse reactions occurred in 42% of patients treated with nivolumab. The most common grade 3 or 4 adverse reactions occurring in 20% of nivolumab-treated patients were abdominal pain, hyponatraemia, increased aspartate aminotransferase and lipase.

AEs with irAEs incl. hypo- and hyperthyroidism

7 Estimated costs

no cost estimates for Austria or Germany

No cost estimates for nivolumab are available yet, neither for Austria nor for Germany. No cost estimates for nivolumab are available yet, neither for Austria nor for Germany. However, in Germany treatment costs comparable to those of ipilimumab or vermurafenib are expected, which would be about €20,000 per case [30]. 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 [31].

8 Ongoing research

one phase III trial of nivolumab in mono- and combination-therapy in untreated advanced melanoma

According to ClinicalTrial.gov there is one ongoing phase III trial of nivolumab in patients with previously untreated, unresectable or metastatic melanoma:

- *NCT01844505* (CheckMate 067, CA209-067; EudraCT 2012-005371-13) is a currently ongoing randomised, double-blind, multi-centre trial. It investigates nivolumab monotherapy in comparison with ipilimumab monotherapy and with a combination of nivolumab and ipilimumab. The primary endpoints are OS and PFS. The estimated primary completion date is September 2016.

Other ongoing phase III trials investigate nivolumab in combination with ipilimumab in advanced melanoma patients with a BRAF mutation with or without prior systemic therapy. In these trials, nivolumab plus ipilimumab were either followed or preceded by dabrafenib and trametinib (NCT02224781), or were administered with or without sargramostim (NCT02339571).

phase III trials in range of other indications

Further ongoing phase III trials include previously treated or first-line advanced or metastatic non-small cell lung cancer (NCT01642004, NCT01673867, NCT02041533, NCT02066636), recurrent glioblastoma (NCT02017717), recurrent or metastatic head and neck carcinoma (NCT02105636), previously untreated or pre-treated advanced or metastatic renal cell carcinoma (NCT02231749, NCT01668784), and advanced or recurrent gastric cancer (NCT02267343).

Nivolumab is also under investigation in phase II trials for advanced melanoma either as a subsequent line or in combination therapy and for further indications such as sarcomas, nasopharyngeal cancers, lymphoma, acute myeloid leukaemia, cervical cancer, pancreatic cancer, anal canal cancer, colorectal cancer and ovarian cancer.

9 Commentary

limited treatment options for advanced melanoma without BRAF mutation

For many years, the first-line therapy for patients with metastatic melanoma was restricted to cytotoxic therapy with dacarbazine, even despite the absence of a proven survival advantage [32]. With an increased characterisation of the molecular features of melanoma, new therapeutic options such as immunotherapy or targeted agents have become available. In most instances, newly approved drugs focused on melanoma harbouring BRAF mutations, e.g., vemurafenib or dabrafenib. Amongst recently approved drugs, only ipilimumab is indicated for previously treated and untreated patients regardless of their BRAF status [33].

At the end of 2014, two further agents, that is, nivolumab and pembrolizumab were approved by the FDA for patients who have progressed on ipilimumab and (if BRAF mutation-positive) a BRAF inhibitor. Accelerated approval by the FDA concerning nivolumab was based on the CheckMate 037 trial, comparing nivolumab to chemotherapy in advanced melanoma. Results on the ORR and the duration of response were based on the data of a single-arm, non-comparative, planned interim analysis; data on OS are not available yet.

In addition to the second-line setting, a phase III trial assessing nivolumab as a first-line treatment in patients with advanced melanoma without a BRAF mutation was conducted. In an interim analysis of data from CheckMate 066, nivolumab has shown a survival benefit compared to dacarbazine. Median PFS was extended by 2.9 months with nivolumab in comparison to dacarbazine, and the OS rate after one year was 73% vs. 42%. At the interim analysis, median OS and the duration of response with nivolumab had not been reached yet, as response was durable over the (short) follow-up period.

nivolumab intended to be used first-line

it has shown a survival benefit

As health-related quality of life data has not been published with the result of the CheckMate 066 trial yet, it remains unknown whether the improvement in survival will be achieved without a negative effect on the quality of life.

no quality of life data

Checkpoint inhibition is associated with a unique spectrum of irAEs that typically are transient, but can occasionally be severe or fatal. Generally, irAEs include dermatologic, gastrointestinal, hepatic and endocrine inflammatory events [34]. The most frequent TRAEs with potential immunological etiology occurring in the nivolumab arm of trial 066 were diarrhoea (16.0%), pruritus (17.0%), rash (15.0%), vitiligo (10.7%) hypo- (4.4%) and hyperthyroidism (3.4%) and pneumonitis (1.5%) [29]. TRAEs with potential immunological etiology of grade 3 or 4 occurring at least in ≥1% of patients in trial 066 were limited to increased ALT and diarrhoea. All of them were showing a resolution, but the data set was limited. Grade 3 or 4 TRAEs were with 18% more frequent in the dacarbazine group than in patients treated with nivolumab (12%), whereas serious grade 3 or 4 TRAEs were observed in 6% of patients in each group. Fewer patients with nivolumab discontinued therapy due to AEs (nivolumab 7% vs. dacarbazine 12%). In terms of AEs, any grade AEs were comparable between the two groups (93% vs. 95%). The most common TRAEs were fatigue, pruritus and nausea.

irAEs rare but data limited

Even though nivolumab was investigated only in patients without BRAF mutations in the CheckMate 066 trial, there is no biologic rationale to restrict the use to patients with BRAF wild-type. Therefore, administration to all patients with melanoma in the first-line setting can be expected, once licensed.

tested only in BRAF negative patients, but extended use expected

Despite these initial results demonstrating the improved efficacy of nivolumab over dacarbazine, several questions remain. Firstly, dacarbazine was the standard first-line therapy of melanoma at the initiation of the CheckMate 066 trial. However, ipilimumab, which is also manufactured by BMS, had not been licensed at the initiation of the trial, but has replaced dacarbazine as the preferred treatment in this setting. The comparative efficacy and safety of ipilimumab and nivolumab are thus not known yet.

dacarbazine not standard of care for first-line therapy anymore

Another related question concerns whether the sequential or combined use of nivolumab with other drugs approved for advanced melanoma, foremost ipilimumab, will yield improved outcomes over single-agent therapy as investigated in the current phase III trial. Published results from a non-randomised, open-label phase Ib study (NCT01024231), investigating either concurrent or sequenced treatment with nivolumab and ipilimumab in advanced melanoma patients, suggest that a combined administration achieves a higher level of efficacy than either of these agents alone [35; 36]. Since some authors consider high-dose IL-2 followed by ipilimumab or a PD-1 or PD-L1 antibody also as a viable option for first-line therapy, further uncertainties concerning first-line therapy arise [37].

comparative efficacy, sequential or combined use?

efficacy and safety compared to/ combined with ipilimumab?

Since the time to response to ipilimumab is rather long, and the median time to response to nivolumab was only 2.1 months in the CheckMate 066 trial, there are discussions whether combination therapy can induce more rapid and durable responses than monotherapy [21; 38]. A currently ongoing phase III trial will help answer some of these questions. The CheckMate 067 trial compares nivolumab monotherapy to ipilimumab monotherapy and to a combination of both agents in previously untreated patients. As the anti-PD-1 antibody nivolumab and the anti-CTLA4 antibody ipilimumab are associated with immune-related toxicity, the possibly increased efficacy of the combination regimen would have to be weighed against the increased toxicity [4; 34; 35; 39].

immunotherapy first-line for most patients with advanced melanoma

For patients with BRAF mutations, additional therapeutic options such as BRAF inhibitors (e.g., vemurafenib) exist. Even though immunotherapy is also the first-line therapy preferred by most authors, at least for patients with good performance status [22; 28; 37], trials assessing the combination of immunotherapy with targeted agents are underway. One phase I study assesses the combination of nivolumab and dabrafenib, of nivolumab and trametinib, and of a triple therapy of nivolumab, dabrafenib and trametinib in patients with BRAF- or NRAS-mutated metastatic melanoma (NCT02357732). Thus, further comparative trials are needed to help better characterise the optimal placement of nivolumab for patients with melanoma [5; 40].

Against this background and since the drug has also been submitted to the FDA for far more frequent types of cancer and many ongoing trials are evaluating nivolumab for a variety of cancers (e.g., NSCLC), the initial price set for the drug is of utmost importance for the overall costs. No price estimates are currently available for Austria or Germany, but annual treatment costs comparable to ipilimumab can be expected. Since combination regimens of ipilimumab and nivolumab are likely in the near future, the costs for melanoma therapy would thus increase considerably. As nivolumab is currently under investigation for several other indications, its potential for off-label use is high.

high potential for off-label use

Due to the potential high price and the expected broad use of nivolumab, biomarkers for predicting response to anti-PD1 antibodies would prove helpful in selecting patients profiting the most from these therapies. However, as assessed in the CheckMate 066 trial, no difference in outcomes was observed with regards to PD-L1 expression in the tumour.

The comparative efficacy and safety in head-to-head trials, as well as the best treatment sequence and combination of the drugs available for the treatment of advanced melanoma, have yet to be determined. This holds true for patients with and without a BRAF mutation [21; 24; 40].

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