Ludwig Boltzmann Institut
Health Technology Assessment

Horizon Scanning in Oncology
36th Prioritization – 3rd quarter 2018

General Information, efficacy and safety data

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Please note:

Within this document you find general information about the drug of interest and the indication it is intended to be used for. Further we have included full text publications of phase III trials, assessing the safety and efficacy of the drugs of interest.

Introduction

As part of the project „Horizon Scanning in Oncology“ (further information can be found here: http://hta.lbg.ac.at/page/horizon-scanning-in-der-onkologie), 9 information sources are scanned frequently to identify emerging anticancer drugs.

Every 3 months, these anticancer therapies are filtered (i.e. in most cases defined as availability of phase III results; for orphan drugs also phase II) to identify drugs at/around the same time as the accompanying drug licensing decisions of the EMA.

An expert panel consisting of oncologists and pharmacists then applies 5 prioritisation criteria to elicit those anti-cancer therapies which might be associated with either a considerable impact on financial resources or a substantial health benefit.

For the 36th prioritisation (May 2018), 12 drugs were filtered out of 404 identified and were sent to prioritisation. Of these, 7 drugs were ranked as ‘highly relevant’ by the expert panel, 5 as ‘relevant’ and none as ‘not relevant’. For ‘highly relevant’ drugs, further information including, for example, abstracts of phase III studies and licensing status is contained in this document.

The summary judgements of the expert panel for all prioritised drugs are provided in the following table.

No	Filtered Drugs – 36th prioritisation 3rd quarter 2018	Overall category
1.	Apalutamide (Erleada®) treatment and metastasis-free survival in prostate cancer	Highly relevant
2.	Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (NSCLC)	Relevant
3.	Nivolumab (Opdivo®) plus ipilimumab in lung cancer with a high tumor mutational burden	Highly relevant
4.	Pembrolizumab (Keytruda®) plus chemotherapy in metastatic NSCLC	Highly relevant
5.	Dual human epidermal growth factor receptor 2 (HER2) blockade with lapatinib (Tyverb®) plus trastuzumab in combination with an aromatase inhibitor in postmenopausal women with HER2-positive, hormone receptor-positive metastatic breast cancer	Relevant
6.	Addition of the PARP inhibitor veliparib plus carboplatin or carboplatin alone to standard neoadjuvant chemotherapy in triple-negative breast cancer	Relevant
7.	Blinatumomab (Blincyto®) for minimal residual disease (MRD) in adults with B-cell precursor acute lymphoblastic leukaemia (ALL)	Highly relevant
8.	Venetoclax (Venclyxto®, Venclexta®) plus rituximab in relapsed or refractory chronic lymphocytic leukemia (CLL)	Highly relevant
9.	Encorafenib (LGX818) plus binimetinib versus vemurafenib or encorafenib in patients with BRAF-mutant melanoma	Relevant
10.	Adjuvant pembrolizumab (Keytruda®) versus placebo in resected stage III melanoma	Highly relevant
11.	Nivolumab (Opdivo®) plus ipilimumab versus sunitinib in advanced renal cell carcinoma (RCC)	Highly relevant
12.	S-1 (Teysuno®) and irinotecan plus bevacizumab versus mFOLFOX6 or CapeOX plus bevacizumab as first-line treatment in patients with metastatic colorectal cancer (mCRC)	Relevant

1 Prostate Cancer

1.1 Apalutamide (Erleada®) treatment and metastasis-free survival in prostate cancer

Overview

Drug Description		a competitive inhibitor of the androgen receptor
Patient Indication		patients with nonmetastatic castration-resistant prostate cancer who are at high risk for the development of metastasis
Incidence in Austria		4,854 newly diagnosed per year (2015), 130.6/100,000 men/year (European Standard Population, 2013)
Ongoing Phase III		NCT01946204 (SPARTAN) ongoing until August 2019 NCT02489318 until July 2022 NCT02257736 until August 2021
Approval status for this indication	**EMA**	-
	FDA	02/2018: the FDA approved apalutamide for patients with non-metastatic castration-resistant prostate cancer
Approval status for other indications	**EMA**	-
	FDA	-
Costs		-

Phase III results

NEJM; available online February 8, 2018 (Smith et al.): *"Apalutamide treatment and metastasis-free survival in prostate cancer"*

Background
Apalutamide, a competitive inhibitor of the androgen receptor, is under development for the treatment of prostate cancer. We evaluated the efficacy of apalutamide in men with nonmetastatic castration-resistant prostate cancer who were at high risk for the development of metastasis.

Methods
We conducted a double-blind, placebo-controlled, phase 3 trial involving men with nonmetastatic castration-resistant prostate cancer and a prostate-specific antigen doubling time of 10 months or less. Patients were randomly assigned, in a 2:1 ratio, to receive apalutamide (240 mg per day) or placebo. All the patients continued to receive androgen-deprivation therapy. The primary end point was metastasis-free survival, which was defined as the time from randomization to the first detection of distant metastasis on imaging or death.

Results

A total of 1207 men underwent randomization (806 to the apalutamide group and 401 to the placebo group). In the planned primary analysis, which was performed after 378 events had occurred, median metastasis-free survival was 40.5 months in the apalutamide group as compared with 16.2 months in the placebo group (hazard ratio for metastasis or death, 0.28; 95% confidence interval [CI], 0.23 to 0.35; P<0.001). Time to symptomatic progression was significantly longer with apalutamide than with placebo (hazard ratio, 0.45; 95% CI, 0.32 to 0.63; P<0.001). The rate of adverse events leading to discontinuation of the trial regimen was 10.6% in the apalutamide group and 7.0% in the placebo group. The following adverse events occurred at a higher rate with apalutamide than with placebo: rash (23.8% vs. 5.5%), hypothyroidism (8.1% vs. 2.0%), and fracture (11.7% vs. 6.5%).

Conclusion

Among men with nonmetastatic castration-resistant prostate cancer, metastasis-free survival and time to symptomatic progression were significantly longer with apalutamide than with placebo. (Funded by Janssen Research and Development; SPARTAN ClinicalTrials.gov number, NCT01946204.)

2 Lung Cancer

2.1 Nivolumab (Opdivo®) plus ipilimumab in lung cancer with a high tumor mutational burden

Overview

Drug Description		nivolumab is a programmed death 1 (PD-1) immune checkpoint inhibitor antibody
Patient Indication		patients with squamous or nonsquamous stage IV or recurrent NSCLC who had received no previous systemic anticancer therapy as primary therapy for advanced or metastatic disease
Incidence in Austria		4,860 newly diagnosed per year (2015), 57.9/100,000 persons/year (European Standard Population, 2013), including lung, trachea and bronchial tumours
Ongoing Phase III		NCT02477826 (CheckMate 227) ongoing until 12/2020 NCT03469960 until 04/2023 NCT02998528 until 11/2028 NCT02864251 until 12/2023
Approval status for this indication	**EMA**	-
	FDA	-
Approval status for other indications	**EMA**	approved indications (product information, updated 05/2018): - as monotherapy or in combination with ipilimumab for the treatment of advanced (unresectable or metastatic) melanoma in adults - as monotherapy for the treatment of locally advanced or metastatic non-small cell lung cancer after prior chemotherapy in adults - as monotherapy for the treatment of advanced RCC after prior therapy in adults - as monotherapy for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin - as monotherapy for the treatment of squamous cell cancer of the head and neck in adults progressing on or after platinum-based therapy - as monotherapy for the treatment of locally advanced unresectable or metastatic urothelial carcinoma in adults after failure of prior platinum-containing therapy.
	FDA	approved indications (label information 04/2018) for the treatment of: - patients with BRAF V600 wild-type unresectable or metastatic melanoma, as a single agent - patients with BRAF V600 mutation-positive unresectable or metastatic melanoma, as a single agent (accelerated approval) - patients with unresectable or metastatic melanoma, in

		combination with ipilimumab (accelerated approval) - patients with melanoma with lymph node involvement or metastatic disease who have undergone complete resection, in the adjuvant setting. - patients with metastatic non-small cell lung cancer and progres sion on or after platinum-based chemotherapy; patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving nivolumab - patients with advanced renal cell carcinoma who have received prior anti-angiogenic therapy in patients with intermediate or poor risk, previously untreated advanced renal cell carcinoma, in combination with ipilimumab - adult patients with classical Hodgkin lymphoma that has relapsed or progressed after (accelerated approval) autologous hematopoietic stem cell transplantation (HSCT) and brentuximab vedotin, or 3 or more lines of systemic therapy that includes autologous HSCT - patients with recurrent or metastatic squamous cell carcinoma of the head and neck with disease progression on or after platinum-based therapy - patients with locally advanced or metastatic urothelial carcinoma who (accelerated approval) have disease progression during or following platinum-containing chemotherapy or have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy - adult and pediatric (12 years and older) patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan (accelerated approval) - patients with hepatocellular carcinoma who have been previously treated with sorafenib (accelerated approval).
Costs		One vial of 4 mL contains 40 mg of nivolumab = € 572.00 one vial of 10 mL contains 100 mg of nivolumab = € 1,430.00 (ex-factory prices) CheckMate 224 patients received either chemotherapy, nivolumab 3 mg/kg of body weight every 2 weeks = 240 mg* = € 3,432.00/dose) + ipilimumab or nivolumab monotherapy (240 mg every 2 weeks). Trial patients received a median number of 9 nivolumab doses (combination therapy with ipilimumab) -> € 30,888.00 *assuming a body weight of 80 kg

Phase III results

NEJM; available online April 16, 2018 (Hellmann et al.): *"Nivolumab plus ipilimumab in lung cancer with a high tumor mutational burden"*

Background

Nivolumab plus ipilimumab showed promising efficacy for the treatment of non‐small-cell lung cancer (NSCLC) in a phase 1 trial, and tumor mutational burden has emerged as a potential biomarker of benefit. In this part of an open-label, multipart, phase 3 trial, we examined progression-free survival with nivolumab plus ipilimumab versus chemotherapy among patients with a high tumor mutational burden (≥10 mutations per megabase).

Methods
We enrolled patients with stage IV or recurrent NSCLC that was not previously treated with chemotherapy. Those with a level of tumor programmed death ligand 1 (PD-L1) expression of at least 1% were randomly assigned, in a 1:1:1 ratio, to receive nivolumab plus ipilimumab, nivolumab monotherapy, or chemotherapy; those with a tumor PD-L1 expression level of less than 1% were randomly assigned, in a 1:1:1 ratio, to receive nivolumab plus ipilimumab, nivolumab plus chemotherapy, or chemotherapy. Tumor mutational burden was determined by the FoundationOne CDx assay.

Findings
Progression-free survival among patients with a high tumor mutational burden was significantly longer with nivolumab plus ipilimumab than with chemotherapy. The 1-year progression-free survival rate was 42.6% with nivolumab plus ipilimumab versus 13.2% with chemotherapy, and the median progression-free survival was 7.2 months (95% confidence interval [CI], 5.5 to 13.2) versus 5.5 months (95% CI, 4.4 to 5.8) (hazard ratio for disease progression or death, 0.58; 97.5% CI, 0.41 to 0.81; P<0.001). The objective response rate was 45.3% with nivolumab plus ipilimumab and 26.9% with chemotherapy. The benefit of nivolumab plus ipilimumab over chemotherapy was broadly consistent within subgroups, including patients with a PD-L1 expression level of at least 1% and those with a level of less than 1%. The rate of grade 3 or 4 treatment-related adverse events was 31.2% with nivolumab plus ipilimumab and 36.1% with chemotherapy.

Interpretation
Progression-free survival was significantly longer with first-line nivolumab plus ipilimumab than with chemotherapy among patients with NSCLC and a high tumor mutational burden, irrespective of PD-L1 expression level. The results validate the benefit of nivolumab plus ipilimumab in NSCLC and the role of tumor mutational burden as a biomarker for patient selection. (Funded by Bristol-Myers Squibb and Ono Pharmaceutical; CheckMate 227 ClinicalTrials.gov number, NCT02477826.)

2.2 Pembrolizumab (Keytruda®) plus chemotherapy in metastatic NSCLC

Overview

Drug Description		a programmed death 1 (PD-1) inhibitor
Patient Indication		Patients with metastatic nonsquamous NSCLC without sensitizing EGFR or ALK mutations who had received no previous systemic therapy for metastatic disease
Incidence in Austria		4,860 newly diagnosed per year (2015), 57.9/100,000 persons/year (European Standard Population, 2013), including lung, trachea and bronchial tumours
Ongoing Phase III		NCT02578680 (KEYNOTE-189) ongoing until 01/2020 NCT02142738 until 05/2019 NCT02220894 until 01/2020 NCT03322566 until 12/2022
Approval status for this indication	**EMA**	-
	FDA	-

Approval status for other indications	**EMA**	according to product information (updated 04/2018), pembrolizumab is indicated: - as monotherapy for the treatment of advanced (unresectable or metastatic) melanoma in adults - as monotherapy for the first-line treatment of metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express PD-L1 with a ≥ 50% tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations - as monotherapy for the treatment of locally advanced or metastatic NSCLC in adults whose tumours express PD-L1 with a ≥ 1% TPS and who have received at least one prior chemotherapy regimen; patients with EGFR or ALK positive tumour mutations should also have received targeted therapy before receiving pembrolizumab - as monotherapy for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL) who have failed autologous stem cell transplant (ASCT) and brentuximab vedotin (BV), or who are transplant -ineligible and have failed BV - as monotherapy for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum -containing chemotherapy - as monotherapy for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin -containing chemotherapy. -
	FDA	According to label information (11/2017), pembrolizumab is indicated: - for the treatment of patients with unresectable or metastatic melanoma - as a single agent for the first-line treatment of patients with metastatic NSCLC whose tumors have high PD -L1 expression [(Tumor Proportion Score (TPS) ≥50%)] as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations - as a single agent for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥1%) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy; patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA -approved therapy for these aberrations prior to receiving pembrolizumab - in combination with pemetrexed and carboplatin, as first-line treatment of patients with metastatic nonsquamous NSCLC (accelerated approval) - for the treatment of patients with recurrent or metastatic head and neck squamous cell cancer (HNSCC) with disease progression on or after platinum-containing chemotherapy (accelerated approval) - for the treatment of adult and pediatric patients with refractory classical Hodgkin lymphoma (cHL), or who have relapsed after 3 or more prior lines of therapy (accelerated approval) - for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy (accelerated approval) - for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy - for the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch

		repair deficient solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options, or colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan (accelerated approval). Limitation of Use: The safety and effectiveness of pembrolizumab in pediatric patients with MSI-H central nervous system cancers have not been established - for the treatment of patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by an FDA-approved test, with disease progression on or after two or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2/neu-targeted therapy (accelerated approval).
Costs		Keytruda® 50 mg powder for concentrate for solution for infusion = € 1,714.00 (ex-factory price). KEYNOTE – 189 – patients received pemetrexed and a platinum-based drug plus either 200 mg (€ 6,856.00 per dose) of pembrolizumab (or placebo every 3 weeks for 4 cycles, followed by pembrolizumab or placebo for up to a total of 35 cycles plus pemetrexed maintenance therapy.

Phase III results

NEJM; available online 16 April, 2018 (Gandhi et al.): *"Pembrolizumab plus chemotherapy in metastatic non‐small-cell lung cancer"*

Background
First-line therapy for advanced non‐small-cell lung cancer (NSCLC) that lacks targetable mutations is platinum-based chemotherapy. Among patients with a tumor proportion score for programmed death ligand 1 (PD-L1) of 50% or greater, pembrolizumab has replaced cytotoxic chemotherapy as the first-line treatment of choice. The addition of pembrolizumab to chemotherapy resulted in significantly higher rates of response and longer progression-free survival than chemotherapy alone in a phase 2 trial.

Methods
In this double-blind, phase 3 trial, we randomly assigned (in a 2:1 ratio) 616 patients with metastatic nonsquamous NSCLC without sensitizing EGFR or ALK mutations who had received no previous treatment for metastatic disease to receive pemetrexed and a platinum-based drug plus either 200 mg of pembrolizumab or placebo every 3 weeks for 4 cycles, followed by pembrolizumab or placebo for up to a total of 35 cycles plus pemetrexed maintenance therapy. Crossover to pembrolizumab monotherapy was permitted among the patients in the placebo-combination group who had verified disease progression. The primary end points were overall survival and progression-free survival, as assessed by blinded, independent central radiologic review.

Findings
After a median follow-up of 10.5 months, the estimated rate of overall survival at 12 months was 69.2% (95% confidence interval [CI], 64.1 to 73.8) in the pembrolizumab- combination group versus 49.4% (95% CI, 42.1 to 56.2) in the placebo-combination group (hazard ratio for death, 0.49; 95% CI, 0.38 to 0.64; P<0.001). Improvement in overall survival was seen across all PD-L1 categories that were evaluated. Median progression-free survival was 8.8 months (95% CI, 7.6 to 9.2) in the pembrolizumab-combination group and 4.9 months (95% CI, 4.7 to 5.5) in the placebo-combination group (hazard ratio for disease progression or death, 0.52; 95% CI, 0.43 to 0.64; P<0.001). Adverse events of grade 3 or higher occurred in 67.2% of the patients in the pembrolizumab-combination group and in 65.8% of those in the placebo-combination group.

Interpretation
In patients with previously untreated metastatic nonsquamous NSCLC without EGFR or ALK mutations, the addition of pembrolizumab to standard chemotherapy of pemetrexed and a platinum-based drug resulted in significantly longer overall survival and progression-free survival than chemotherapy alone. (Funded by Merck; KEYNOTE-189 ClinicalTrials.gov number, NCT02578680.)

3 Leukaemia

3.1 Blinatumomab (Blincyto®) for minimal residual disease (MRD) in adults with B-cell precursor acute lymphoblastic leukaemia (ALL)

Overview

Drug Description		a bispecific T cell–engager antibody construct that directs T cells to $CD19^+$ cells
Patient Indication		patients with B-cell precursor ALL in first or later haematologic complete remission (CR) and with persistent or recurrent MRD $\geq 10^{-3}$ after a minimum of 3 blocks of intensive chemotherapy.
Incidence in Austria		ALL total incidence rate: 1.1/100,000/year
Ongoing Phase III		NCT01207388 (BLAST) ongoing until 01/2019 NCT03476239 until 11/2021 NCT02101853 until 03/2022 NCT02393859 until 12/2022
Approval status for this indication	**EMA**	07/2009: orphan designation was granted for blinatumomab for the treatment of ALL 11/2015: approved for the treatment of adults with Philadelphia chromosome negative relapsed or refractory B-precursor ALL
	FDA	12/2014: indicated for treatment of Philadelphia chromosomenegative relapsed or refractory B-cell precursor ALL 03/2018: indicated for the treatment of adults and children with B-cell precursor ALL in first or second CR with MRD greater than or equal to 0.1% (accelerated approval)
Approval status for other indications	**EMA**	-
	FDA	-
Costs		Blincyto® 38.5 micrograms powder for concentrate and solution for infusion, one vial = € 2826.08 (ex-factory price). BLAST-trial: patients received 15 μg/m^2/day (IV) of blinatumumab for 4 weeks, followed by 2 treatment-free weeks (=1 cycle). 1 dose = 25.95 μg/day. Costs for one cycle = € 84,782.4.

Phase III results

Blood Journal (2018); 131(14):1522-1531 Gökbuget N et al.: *"Blinatumomab for minimal residual disease in adults with B-cell precursor acute lymphoblastic leukemia"*

Background
Approximately 30% to 50% of adults with acute lymphoblastic leukemia (ALL) in hematologic complete remission after multiagent therapy exhibit minimal residual disease (MRD) by reverse transcriptase–polymerase chain reaction or flow cytometry.MRD is the strongest predictor of relapse in ALL.

Methods
In this open-label, single-arm study, adults with B-cell precursor ALL in hematologic complete remission with MRD ($\geq 10^{-3}$) received blinatumomab 15 μg/m2 per day by continuous IV infusion for up to 4 cycles. Patients could undergo allogeneic hematopoietic stem-cell transplantation any time after cycle 1. The primary end point was complete MRD response status after 1 cycle of blinatumomab.

Findings
One hundred sixteen patients received blinatumomab. Eighty-eight (78%) of 113 evaluable patients achieved a complete MRD response. In the subgroup of 110 patients with Ph-negative ALL in hematologic remission, the Kaplan- Meier estimate of relapse-free survival (RFS) at 18 months was 54%. Median overall survival (OS) was 36.5 months. In landmark analyses, complete MRD responders had longer RFS (23.6 vs. 5.7 months; P = .002) and OS (38.9 vs. 12.5 months; P = .002) compared with MRD nonresponders. Adverse events were consistent with previous studies of blinatumomab. Twelve (10%) and 3 patients (3%) had grade 3 or 4 neurologic events, respectively. Four patients (3%) had cytokine release syndrome grade 1, n 5 2; grade 3, n 5 2), all during cycle 1.

Interpretation
After treatment with blinatumomab in a population of patients with MRD-positive B-cell precursor ALL, a majority achieved a complete MRD response, which was associated with significantly longer RFS and OS compared with MRD nonresponders. This study is registered at www.clinicaltrials.gov as #NCT01207388. (Blood. 2018;131(14):1522-1531).

3.2 Venetoclax (Venclyxto®, Venclexta®) plus rituximab in relapsed or refractory chronic lymphocytic leukemia (CLL)

Overview

Drug Description		an inhibitor of BCL2, an antiapoptotic protein that is pathologically overexpressed and that is central to the survival of chronic lymphocytic leukemia cells
Patient Indication		Patients with relapsed or refractory CLL that required therapy; and had received one to three previous treatments (including at least one chemotherapy- containing regimen)
Incidence in Austria		7.4/100,000 men/year, 4.8/100,000 women/year (2011)
Ongoing Phase III		NCT02005471 ongoing until 09/2018
Approval status for this indication	**EMA**	orphan designation was granted for the treatment of CLL (12/2012), for the treatment of acute myeloid leukaemia (02/2016), for the treatment of diffuse large B-cell carcinoma and multiple myeloma (10/2016) and for the

		treatment of mantle cell lymphoma (12/2017) 10/2016: venetoclax monotherapy is indicated for the treatment of chronic lymphocytic leukaemia (CLL) in the presence of 17p deletion or TP53 mutation in adult patients who are unsuitable for or have failed a B cell receptor pathway inhibitor. Venetoclax monotherapy is indicated for the treatment of CLL in the absence of 17p deletion or TP53 mutation in adult patients who have failed both chemoimmunotherapy and a B cell receptor pathway inhibitor
	FDA	04/2016: indicated for the treatment of patients with chronic lymphocytic leukemia (CLL) with 17p deletion as detected by an FDA approved test who have received at least one prior therapy (accelerated approval)
Approval status for other indications	**EMA**	-
	FDA	-
Costs		10 Venclyxto® tablets á 10 mg = € 53.53 (ex-factory price) 14 Venclyxto® tablets á 100 mg = € 749.38 (ex-factory price) Trial patients received venetoclax according to a 5-week schedule of a gradual increase in the dose from 20 mg per day to 400 mg per day.

Phase III results

NEJM;378:1107-20; 2018 (Seymour et al): *"Venetoclax‑rituximab in relapsed or refractory chronic lymphocytic leukemia"*

Background
Venetoclax inhibits BCL2, an antiapoptotic protein that is pathologically overexpressed and that is central to the survival of chronic lymphocytic leukemia cells. We evaluated the efficacy of venetoclax in combination with rituximab in patients with relapsed or refractory chronic lymphocytic leukemia.

Methods
In this randomized, open-label, phase 3 trial, we randomly assigned 389 patients to receive venetoclax for up to 2 years (from day 1 of cycle 1) plus rituximab for the first 6 months (venetoclax‑rituximab group) or bendamustine plus rituximab for 6 months (bendamustine‑rituximab group). The trial design did not include crossover to venetoclax plus rituximab for patients in the bendamustine‑rituximab group in whom progression occurred. The primary end point was investigator-assessed progression-free survival.

Findings
After a median follow-up period of 23.8 months, the rate of investigator-assessed progression-free survival was significantly higher in the venetoclax‑rituximab group (32 events of progression or death in 194 patients) than in the bendamustine‑rituximab group (114 events in 195 patients); the 2-year rates of progression-free survival were 84.9% and 36.3%, respectively (hazard ratio for progression or death, 0.17; 95% confidence interval [CI], 0.11 to 0.25; P<0.001 by the stratified log-rank test). The benefit was maintained across all clinical and biologic subgroups, including the subgroup of patients with chromosome 17p deletion; the 2-year rate of progression-free survival among patients with chromosome 17p deletion was 81.5% in the venetoclax‑rituximab group versus 27.8% in the bendamustine‑rituximab group (hazard ratio, 0.13; 95% CI, 0.05 to 0.29), and the 2-year rate among those without chromosome 17p deletion was 85.9% versus 41.0% (hazard ratio, 0.19; 95% CI, 0.12 to 0.32). The benefit of venetoclax plus rituximab over bendamustine plus rituximab was confirmed by an independent review committee assessment of progression-free survival and other secondary efficacy end points. The rate of grade 3 or 4 neutropenia was higher in the venetoclax‑ rituximab group than in the bendamustine‑rituximab group, but the rates of grade 3 or 4 febrile neutropenia and infections or

infestations were lower with venetoclax than with bendamustine. The rate of grade 3 or 4 tumor lysis syndrome in the venetoclax‐rituximab group was 3.1% (6 of 194 patients).

Interpretation
Among patients with relapsed or refractory chronic lymphocytic leukemia, venetoclax plus rituximab resulted in significantly higher rates of progression-free survival than bendamustine plus rituximab. (Funded by Genentech and AbbVie; ClinicalTrials.gov number, NCT02005471.)

4 Melanoma

4.1 Adjuvant pembrolizumab (Keytruda®) versus placebo in resected stage III melanoma

Overview

Drug Description		a programmed death 1 (PD-1) inhibitor
Patient Indication		patients with cutaneous melanoma with metastasis to regional lymph nodes; the patients had to have either stage IIIA melanoma (patients with stage N1a melanoma had to have at least one micrometastasis measuring >1 mm in greatest diameter) or stage IIIB or IIIC disease with no in-transit metastases
Incidence in Austria		1,779 newly diagnosed per year (2015), 20.7/100,000 persons/year (European Standard Population, 2013)
Ongoing Phase III		NCT02362594 (Keynote-054) ongoing until 07/2025 NCT02506153 until 09/2023
Approval status for this indication	**EMA**	-
	FDA	-
Approval status for other indications	**EMA**	according to product information (updated 04/2018), pembrolizumab is indicated: - as monotherapy for the treatment of advanced (unresectable or metastatic) melanoma in adults - as monotherapy for the first-line treatment of metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express PD-L1 with a ≥ 50% tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations - as monotherapy for the treatment of locally advanced or metastatic NSCLC in adults whose tumours express PD-L1 with a ≥ 1% TPS and who have received at least one prior chemotherapy regimen; patients with EGFR or ALK positive tumour mutations should also have received targeted therapy before receiving pembrolizumab - as monotherapy for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL) who have failed autologous stem cell transplant (ASCT) and brentuximab vedotin (BV), or who are transplant -ineligible and have failed BV - as monotherapy for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum -containing chemotherapy - as monotherapy for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin -containing chemotherapy
	FDA	according to label information (11/2017), pembrolizumab is indicated: - for the treatment of patients with unresectable or metastatic melanoma

		- as a single agent for the first-line treatment of patients with metastatic NSCLC whose tumors have high PD -L1 expression [(Tumor Proportion Score (TPS) ≥50%)] as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations - as a single agent for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥1%) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy; patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA -approved therapy for these aberrations prior to receiving pembrolizumab - in combination with pemetrexed and carboplatin, as first-line treatment of patients with metastatic nonsquamous NSCLC (accelerated approval) - for the treatment of patients with recurrent or metastatic head and neck squamous cell cancer (HNSCC) with disease progression on or after platinum-containing chemotherapy (accelerated approval) - for the treatment of adult and pediatric patients with refractory classical Hodgkin lymphoma (cHL), or who have relapsed after 3 or more prior lines of therapy (accelerated approval) - for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy (accelerated approval) - for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy - for the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options, or colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan (accelerated approval). Limitation of Use: The safety and effectiveness of pembrolizumab in pediatric patients with MSI-H central nervous system cancers have not been established - for the treatment of patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by an FDA-approved test, with disease progression on or after two or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2/neu-targeted therapy (accelerated approval).
Costs		Keytruda® 50 mg powder for concentrate for solution for infusion = € 1,714.00 (ex-factory price). Trial patients received either 200 mg (€ 6,856.00/ per dose) of pembrolizumab or placebo intravenously every 3 weeks for a total of 18 doses (€ 123,408.00/18 doses)

Phase III results

NEJM; available online 15 April, 2018 (Eggermont et al.): *"Adjuvant pembrolizumab versus placebo in resected stage III melanoma"*

Background
The programmed death 1 (PD-1) inhibitor pembrolizumab has been found to prolong progression-free and overall survival among patients with advanced melanoma. We conducted a phase 3 double-blind trial to evaluate pembrolizumab as adjuvant therapy in patients with resected, high-risk stage III melanoma.

Methods
Patients with completely resected stage III melanoma were randomly assigned (with stratification according to cancer stage and geographic region) to receive 200 mg of pembrolizumab (514 patients) or placebo (505 patients) intravenously every 3 weeks for a total of 18 doses (approximately 1 year) or until disease recurrence or unacceptable toxic effects occurred. Recurrence-free survival in the overall intention-to-treat population and in the subgroup of patients with cancer that was positive for the PD-1 ligand (PD-L1) were the primary end points. Safety was also evaluated.

Findings
At a median follow-up of 15 months, pembrolizumab was associated with significantly longer recurrence-free survival than placebo in the overall intention-to-treat population (1-year rate of recurrence-free survival, 75.4% [95% confidence interval {CI}, 71.3 to 78.9] vs. 61.0% [95% CI, 56.5 to 65.1]; hazard ratio for recurrence or death, 0.57; 98.4% CI, 0.43 to 0.74; P<0.001) and in the subgroup of 853 patients with PD-L1–positive tumors (1-year rate of recurrence-free survival, 77.1% [95% CI, 72.7 to 80.9] in the pembrolizumab group and 62.6% [95% CI, 57.7 to 67.0] in the placebo group; hazard ratio, 0.54; 95% CI, 0.42 to 0.69; P<0.001). Adverse events of grades 3 to 5 that were related to the trial regimen were reported in 14.7% of the patients in the pembrolizumab group and in 3.4% of patients in the placebo group. There was one treatment-related death due to myositis in the pembrolizumab group.

Interpretation
As adjuvant therapy for high-risk stage III melanoma, 200 mg of pembrolizumab administered every 3 weeks for up to 1 year resulted in significantly longer recurrence-free survival than placebo, with no new toxic effects identified. (Funded by Merck; ClinicalTrials.gov number, NCT02362594; EudraCT number, 2014-004944-37.)

5 Kidney Cancer

5.1 Nivolumab (Opdivo®) plus ipilimumab versus sunitinib in advanced renal cell carcinoma (RCC)

Overview

Drug Description		nivolumab is a programmed death 1 (PD-1) immune checkpoint inhibitor antibody
Patient Indication		patients with previously untreated advanced renal-cell carcinoma with a clear-cell component
Incidence in Austria		kidney cancer: 1,258 newly diagnosed per year (2015), 14.8/100,000 persons/year (European Standard Population, 2013); approx. 80% of all kidney cancers are RCCs
Ongoing Phase III		NCT02231749 (CheckMate 214) ongoing until 09/2019 NCT03138512 until 07/2023 NCT01668784 until 09/2018 NCT03141177 until 04/2023
Approval status for this indication	**EMA**	-
	FDA	-
Approval status for other indications	**EMA**	approved indications (product information, updated 05/2018): - as monotherapy or in combination with ipilimumab for the treatment of advanced (unresectable or metastatic) melanoma in adults - as monotherapy for the treatment of locally advanced or metastatic non-small cell lung cancer after prior chemotherapy in adults - as monotherapy for the treatment of advanced RCC after prior therapy in adults - as monotherapy for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin - as monotherapy for the treatment of squamous cell cancer of the head and neck in adults progressing on or after platinum-based therapy - as monotherapy for the treatment of locally advanced unresectable or metastatic urothelial carcinoma in adults after failure of prior platinum-containing therapy.
	FDA	approved indications (label information 04/2018) for the treatment of: - patients with BRAF V600 wild-type unresectable or metastatic melanoma, as a single agent - patients with BRAF V600 mutation-positive unresectable or metastatic melanoma, as a single agent (accelerated approval) - patients with unresectable or metastatic melanoma, in combinati

		on with ipilimumab (accelerated approval) - patients with melanoma with lymph node involvement or metastatic disease who have undergone complete resection, in the adjuvant setting. - patients with metastatic non-small cell lung cancer and progres sion on or after platinum-based chemotherapy; patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving nivolumab - patients with advanced renal cell carcinoma who have received prior anti-angiogenic therapy in patients with intermediate or poor risk, previously untreated advanced renal cell carcinoma, in combination with ipilimumab - adult patients with classical Hodgkin lymphoma that has relapsed or progressed after (accelerated approval) autologous hematopoietic stem cell transplantation (HSCT) and brentuximab vedotin, or 3 or more lines of systemic therapy that includes autologous HSCT - patients with recurrent or metastatic squamous cell carcinoma of the head and neck with disease progression on or after platinum-based therapy - patients with locally advanced or metastatic urothelial carcino - ma who (accelerated approval) have disease progression during or following platinum-containing chemotherapy or have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy - adult and pediatric (12 years and older) patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan (accelerated approval) - patients with hepatocellular carcinoma who have been previously treated with sorafenib (accelerated approval).
Costs		One vial of 4 mL contains 40 mg of nivolumab = € 572.00 one vial of 10 mL contains 100 mg of nivolumab = € 1,430.00 (ex-factory prices) CheckMate 214 – patients received 3 mg/kg of body weight (240 mg* nivolumab per dose/ € 3,432.00) IV every 3 weeks for 4 doses (induction phase) and 3 mg/kg of body weight every 2 weeks (maintenance phase). Median treatment duration in the CheckMate trial was 7.9 months (approx. 14 doses of nivolumab costing ~ € 48,048. *assuming a body weight of 80 kg

Phase III results

NEJM; available online 21 March 2018 (Motzer et al.): *"Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma"*

Background
Nivolumab plus ipilimumab produced objective responses in patients with advanced renal-cell carcinoma in a pilot study. This phase 3 trial compared nivolumab plus ipilimumab with sunitinib for previously untreated clear-cell advanced renal-cell carcinoma.

Methods
We randomly assigned adults in a 1:1 ratio to receive either nivolumab (3 mg per kilogram of body weight) plus ipilimumab (1 mg per kilogram) intravenously every 3 weeks for four doses, followed by nivolumab (3 mg per kilogram) every 2 weeks, or sunitinib (50 mg) orally once daily for 4 weeks (6-

week cycle). The coprimary end points were overall survival (alpha level, 0.04), objective response rate (alpha level, 0.001), and progression-free survival (alpha level, 0.009) among patients with intermediate or poor prognostic risk.

Findings
A total of 1096 patients were assigned to receive nivolumab plus ipilimumab (550 patients) or sunitinib (546 patients); 425 and 422, respectively, had intermediate or poor risk. At a median follow-up of 25.2 months in intermediate- and poor-risk patients, the 18-month overall survival rate was 75% (95% confidence interval [CI], 70 to 78) with nivolumab plus ipilimumab and 60% (95% CI, 55 to 65) with sunitinib; the median overall survival was not reached with nivolumab plus ipilimumab versus 26.0 months with sunitinib (hazard ratio for death, 0.63; P<0.001). The objective response rate was 42% versus 27% (P<0.001), and the complete response rate was 9% versus 1%. The median progression-free survival was 11.6 months and 8.4 months, respectively (hazard ratio for disease progression or death, 0.82; P = 0.03, not significant per the prespecified 0.009 threshold). Treatment-related adverse events occurred in 509 of 547 patients (93%) in the nivolumab-plus-ipilimumab group and 521 of 535 patients (97%) in the sunitinib group; grade 3 or 4 events occurred in 250 patients (46%) and 335 patients (63%), respectively. Treatment-related adverse events leading to discontinuation occurred in 22% and 12% of the patients in the respective groups.

Interpretation
Overall survival and objective response rates were significantly higher with nivolumab plus ipilimumab than with sunitinib among intermediate- and poor-risk patients with previously untreated advanced renal-cell carcinoma. (Funded by Bristol-Myers Squibb and Ono Pharmaceutical; CheckMate 214 ClinicalTrials.gov number, NCT02231749.)