Ludwig Boltzmann Institut
Health Technology Assessment

Horizon Scanning in Oncology
38th Prioritization – 1st quarter 2019

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), nine information sources are scanned frequently to identify emerging anticancer drugs.

Every three 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 five 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 38th prioritisation (January 2019), ten drugs were filtered out of 502 identified and were sent to prioritisation. Of these, three drugs were ranked as ‘highly relevant’ by the expert panel, seven 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 – 38th prioritisation 1st quarter 2019	Overall category
1.	Atezolizumab (Tecentriq®) and nab-paclitaxel in advanced triple-negative breast cancer	Highly relevant
2.	First-line atezolizumab (Tecentriq®) plus chemotherapy in extensive-stage small-cell lung cancer (SCLC)	Relevant
3.	Brigatinib (Alunbrig®) versus crizotinib in ALK-positive NSCLC	Relevant
4.	Pembrolizumab (Keytruda®) plus chemotherapy for squamous NSCLC	Highly relevant
5.	Frontline bortezomib (Velcade®), rituximab, cyclophosphamide, doxorubicin, and prednisone (VR-CAP) versus rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in transplantation-ineligible patients with newly diagnosed mantle cell lymphoma (MCL)	Relevant
6.	Duvelisib (Copiktra®) versus ofatumumab in relapsed and refractory (RR) chronic lymphocytic leukemia (CLL)/ small lymphocytic lymphoma (SLL)	Relevant
7.	Addition of lomustine (Gleostine®) to conventional chemotherapy for elderly patients with acute myeloid leukaemia (AML) without unfavorable cytogenetics	Relevant
8.	Elotuzumab (Empliciti®) plus pomalidomide and dexamethasone for MM	Relevant
9.	Maintenance olaparib (Lynparza®) in patients with newly diagnosed advanced ovarian cancer	Highly relevant
10.	Trifluridine/tipiracil (TAS-102, Lonsurf®) versus placebo in patients with heavily pretreated metastatic gastric cancer	Relevant

Breast Cancer

Atezolizumab (Tecentriq®) and nab-paclitaxel in advanced triple negative breast cancer

Overview

Drug Description		atezolizumab selectively targets programmed death ligand 1 (PD-L1) to prevent interaction with the receptors PD-1 and B7-1 (a co-stimulatory cell-surface protein), reversing T-cell suppression
Patient Indication		patients with untreated metastatic triple-negative breast cancer
Incidence in Austria		breast cancer: 5,480 newly diagnosed per year (2015), 116.7/100,000 women/year (2015) (European Standard Population 2013) [1]
Ongoing Phase III		NCT02425891(IMpassion 130) until 04/2020 NCT03125902 until 06/2021 NCT03281954 until 06/2024 NCT03498716 until 12/2024 NCT03371017 until 01/2021
Approval status for this indication [2, 3]	**EMA**	-
	FDA	-
Approval status for other indications [2, 3]	**EMA**	according to product information (09/2018) atezolizumab is indicated ✪ as monotherapy for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC) - after prior platinum-containing chemotherapy, or - who are considered cisplatin ineligible, and whose tumours have a PD-L1 expression ≥ 5% ✪ as monotherapy for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy. Patients with epidermal growth factor receptor (EGFR) activating mutations or anaplastic lymphoma kinase (ALK)-positive tumour mutations should also have received targeted therapy before receiving atezolizumab.
	FDA	according to label information (12/2018) atezolizumab is indicated in ✪ UC: - for the treatment of patients with locally advanced or metastatic UC who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 (PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥ 5% of the tumor area), as determined by an FDA-approved test, or who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status, or who have disease progression during or following any platinum-containing chemotherapy, or within 12 months of neoadjuvant or adjuvant chemotherapy (indication is approved under accelerated approval)

		✪ NSCLC: - in combination with bevacizumab, paclitaxel, and carboplatin, for the first-line treatment, of patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations - for the treatment of patients with metastatic NSCLC who have disease progression during or following platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for NSCLC harboring these aberrations prior to receiving atezolizumab.
Costs		Tecentriq® is available as concentrate for solution for infusion (1200 mg) at € 4,799.20 (ex-factory price) [4]. Impassion 130 patients received atezolizumab at a dose of 840 mg or placebo, administered intravenously (IV), on days 1 and 15 of every 28-day cycle -> € 9,598.4/cycle. Median duration of atezolizumab treatment among Impassion 130 patients was 24.1 weeks -> approx. 57,590.4 for 6 months of atezolizumab treatment. In addition, costs for nab-paclitaxel incur.

1.1.1 Published articles (PubMed):

NEJM; available online October 20, 2018 (Schmid et al.): *"Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer" [5]*

Background
Unresectable locally advanced or metastatic triple-negative (hormone-receptor–negative and human epidermal growth factor receptor 2 [HER2]–negative) breast cancer is an aggressive disease with poor outcomes. Nanoparticle albumin-bound (nab)–paclitaxel may enhance the anticancer activity of atezolizumab.

Methods
In this phase 3 trial, we randomly assigned (in a 1:1 ratio) patients with untreated metastatic triple-negative breast cancer to receive atezolizumab plus nab-paclitaxel or placebo plus nab-paclitaxel; patients continued the intervention until disease progression or an unacceptable level of toxic effects occurred. Stratification factors were the receipt or nonreceipt of neoadjuvant or adjuvant taxane therapy, the presence or absence of liver metastases at baseline, and programmed death ligand 1 (PD-L1) expression at baseline (positive vs. negative). The two primary end points were progression-free survival (in the intention-to-treat population and PD-L1–positive subgroup) and overall survival (tested in the intention-to-treat population; if the finding was significant, then it would be tested in the PD-L1–positive subgroup).

Findings
Each group included 451 patients (median follow-up, 12.9 months). In the intention to-treat analysis, the median progression-free survival was 7.2 months with atezolizumab plus nab-paclitaxel, as compared with 5.5 months with placebo plus nab-paclitaxel (hazard ratio for progression or death, 0.80; 95% confidence interval [CI], 0.69 to 0.92; P = 0.002); among patients with PD-L1–positive tumors, the median progression- free survival was 7.5 months and 5.0 months, respectively (hazard ratio, 0.62; 95% CI, 0.49 to 0.78; P<0.001). In the intention-to-treat analysis, the median overall survival was 21.3 months with atezolizumab plus nab-paclitaxel and 17.6 months with placebo plus nab-paclitaxel (hazard ratio for death, 0.84; 95% CI, 0.69 to 1.02; P = 0.08); among patients with PD-L1–positive tumors, the median overall survival was 25.0 months and 15.5 months, respectively (hazard ratio, 0.62; 95% CI, 0.45 to 0.86). No new adverse effects were identified. Adverse events that led to the discontinuation of any agent occurred in 15.9% of the patients who received atezolizumab plus nab-paclitaxel and in 8.2% of those who received placebo plus nab-paclitaxel.

Interpretation
Atezolizumab plus nab-paclitaxel prolonged progression-free survival among patients with metastatic triple-negative breast cancer in both the intention-to-treat population and the PD-L1–positive subgroup. Adverse events were consistent with the known safety profiles of each agent. (Funded by F. Hoffmann–La Roche/Genentech; IMpassion130 ClinicalTrials.gov number, NCT02425891.

Lung Cancer

Pembrolizumab (Keytruda®) plus chemotherapy for squamous NSCLC

Overview

Drug Description		PD-1 inhibitor
Patient Indication		patients with stage IV squamous NSCLC 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 (2015) (European Standard Population 2013) including lung, trachea and bronchial tumours [6]
Ongoing Phase III		NCT02775435 (KEYNOTE-407) until 02/2021 NCT03631199 until 10/2022 NCT03515629 until 03/2023
Approval status for this indication [2, 3]	**EMA**	-
	FDA	10/2018: pembrolizumab, in combination with carboplatin and either paclitaxel or nab-paclitaxel, is indicated for the first-line treatment of patients with metastatic squamous NSCLC
Approval status for other indications [2, 3]	**EMA**	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 NSCLC in adults whose tumours express PD-L1 with a ≥ 50% tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations. - in combination with pemetrexed and platinum chemotherapy, for the first-line treatment of metastatic non-squamous NSCLC in adults whose tumours have no EGFR or ALK positive mutations. - as monotherapy is 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 UC in adults who have received prior platinum-containing chemotherapy. - as monotherapy for the treatment of locally advanced or metastatic UC in adults who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD L1 with a combined positive score (CPS) ≥ 10. - as monotherapy for the treatment of recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) in adults whose tumours express PD-L1 with a ≥ 50% TPS and progressing on or after platinum-containing chemotherapy. In October 2017, the manufacturer officially notified the Committee for Medicinal Products for Human Use (CHMP) that it wishes to withdraw its application to extend the use of pembrolizumab in NSCLC to include metastatic non-squamous NSCLC in combination with chemotherapy. Pembrolizumab was also expected to be used in combination with the chemotherapy medicines pemetrexed and carboplatin in NSCLC patients with metastatic non-squamous NSCLC, irrespective of whether their tumour produced the PD-L1 protein.
	FDA	pembrolizumab is indicated in • melanoma: for the treatment of patients with unresectable or metastatic melanoma • NSCLC: - in combination with pemetrexed and platinum chemotherapy, as first-line treatment of patients with metastatic nonsquamous NSCLC, with no EGFR or ALK genomic tumor aberrations. - as a single agent for the first-line treatment of patients with metastatic NSCLC whose tumors have high PD-L1 expression [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. • HNSCC: - for the treatment of patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy. • cHL: - for the treatment of adult and pediatric patients with refractory cHL, or who have relapsed after 3 or more prior lines of therapy. • primary mediastinal large B-cell lymphoma (PMBCL): - for the treatment of adult and pediatric patients with refractory PMBCL, or who have relapsed after 2 or more prior lines of therapy. Limitation of Use: pembrolizumab is not recommended for treatment of patients with PMBCL who require urgent cytoreductive therapy. • UC: - for the treatment of patients with locally advanced or metastatic UC who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 [Combined Positive Score (CPS) ≥10] as determined by an FDA-

		approved test, or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status. - for the treatment of patients with locally advanced or metastatic UC who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. • Microsatellite Instability-High Cancer: - 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. Limitation of Use: The safety and effectiveness of pembrolizumab in pediatric patients with MSI-H central nervous system cancers have not been established. • Gastric Cancer: - for the treatment of patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma whose tumors express PD-L1 [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. • Cervical Cancer: for the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test. • Hepatocellular Carcinoma (HCC): for the treatment of patients with HCC who have been previously treated with sorafenib.
Costs		Keytruda® 50 mg powder for concentrate for solution for infusion = € 1,714.00 (ex-factory price) [4]. KEYNOTE-407 patients received 200 mg of pembrolizumab (€ 6,856.00/ per dose) or placebo on day 1 for up to 35 3-week cycles. In addition (for the first 4 cycles) costs for carboplatin and either paclitaxel or nab-paclitaxel incur. The patients who received paclitaxel also received premedication with a glucocorticoid, a type 1 antihistamine, and a type 2 antihistamine according to local guidelines.

1.1.2 Published articles (PubMed):

NEJM; available online September 25, 2018 (Paz-Ares et al.): *"Pembrolizumab plus chemotherapy for squamous non‐small-cell lung cancer" [7]*

Background
Standard first-line therapy for metastatic, squamous non–small-cell lung cancer (NSCLC) is platinum-based chemotherapy or pembrolizumab (for patients with programmed death ligand 1 [PD-L1] expression on ≥50% of tumor cells). More recently, pembrolizumab plus chemotherapy was shown to significantly prolong overall survival among patients with nonsquamous NSCLC.

Methods
In this double-blind, phase 3 trial, we randomly assigned, in a 1:1 ratio, 559 patients with untreated metastatic, squamous NSCLC to receive 200 mg of pembrolizumab or saline placebo for up to 35 cycles; all the patients also received carboplatin and either paclitaxel or nanoparticle albumin-bound

[nab]–paclitaxel for the first 4 cycles. Primary end points were overall survival and progression-free survival.

Findings
After a median follow-up of 7.8 months, the median overall survival was 15.9 months (95% confidence interval [CI], 13.2 to not reached) in the pembrolizumab-combination group and 11.3 months (95% CI, 9.5 to 14.8) in the placebo-combination group (hazard ratio for death, 0.64; 95% CI, 0.49 to 0.85; P<0.001). The overall survival benefit was consistent regardless of the level of PD-L1 expression. The median progression-free survival was 6.4 months (95% CI, 6.2 to 8.3) in the pembrolizumab-combination group and 4.8 months (95% CI, 4.3 to 5.7) in the placebo-combination group (hazard ratio for disease progression or death, 0.56; 95% CI, 0.45 to 0.70; P<0.001). Adverse events of grade 3 or higher occurred in 69.8% of the patients in the pembrolizumab-combination group and in 68.2% of the patients in the placebo-combination group. Discontinuation of treatment because of adverse events was more frequent in the pembrolizumab-combination group than in the placebo-combination group (13.3% vs. 6.4%).

Interpretation
In patients with previously untreated metastatic, squamous NSCLC, the addition of pembrolizumab to chemotherapy with carboplatin plus paclitaxel or nab-paclitaxel resulted in significantly longer overall survival and progression-free survival than chemotherapy alone. (Funded by Merck Sharp & Dohme; KEYNOTE-407 ClinicalTrials.gov number, NCT02775435.)

Ovarian Cancer

Maintenance olaparib (Lynparza®) in patients with newly diagnosed advanced ovarian cancer

Overview

Drug Description		an oral poly(adenosine diphosphate‑ribose) polymerase inhibitor
Patient Indication		patients with newly diagnosed advanced (International Federation of Gynecology and Obstetrics stage III or IV) high-grade serous or endometrioid ovarian cancer, primary peritoneal cancer, or fallopian-tube cancer (or a combination thereof) with a mutation in *BRCA1*, *BRCA2*, or both (*BRCA1/2*) who had a complete or partial clinical response after platinum-based chemotherapy.
Incidence in Austria		ovarian cancer: 659 newly diagnosed per year (2015), 14.1/100,000/year (2015) (European Standard Population 2013) [8]
Ongoing Phase III		NCT01844986 (SOLO-1) until 06/2023 NCT02477644 until 06/2022 NCT03737643 until 07/2025 NCT03740165 until 08/2025
Approval status for this indication [2, 3]	**EMA**	05/2018 (extension of indication): olaparib is indicated as monotherapy for the maintenance treatment of adult patients with platinum -sensitive relapsed BRCA-mutated (germline and/or somatic) high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response or partial response) to platinum -based chemotherapy.

	FDA	-
Approval status for other indications [2, 3]	**EMA**	-
	FDA	olaparib is indicated for the treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy.
Costs		112 Lynparza tablets (150 mg) = € 5,059.29 [4] Patients of SOLO-1 trial received olaparib tablets (300 mg twice daily) or placebo. Based on this dosing regimen, 28 days of olaprib treatment would cost € 5,059.29. The median duration of the trial intervention in the olaparib group was 24.6 months -> approx. € 124,458.53.

1.1.3 Published articles (PubMed):

NEJM; available online October 21, 2018 (Moore et al.): *"Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer" [9]*

Background
Most women with newly diagnosed advanced ovarian cancer have a relapse within 3 years after standard treatment with surgery and platinum-based chemotherapy. The benefit of the oral poly(adenosine diphosphate–ribose) polymerase inhibitor olaparib in relapsed disease has been well established, but the benefit of olaparib as maintenance therapy in newly diagnosed disease is uncertain.

Methods
We conducted an international, randomized, double-blind, phase 3 trial to evaluate the efficacy of olaparib as maintenance therapy in patients with newly diagnosed advanced (International Federation of Gynecology and Obstetrics stage III or IV) high-grade serous or endometrioid ovarian cancer, primary peritoneal cancer, or fallopian-tube cancer (or a combination thereof) with a mutation in BRCA1, BRCA2, or both (BRCA1/2) who had a complete or partial clinical response after platinum-based chemotherapy. The patients were randomly assigned, in a 2:1 ratio, to receive olaparib tablets (300 mg twice daily) or placebo. The primary end point was progression- free survival.

Findings
Of the 391 patients who underwent randomization, 260 were assigned to receive olaparib and 131 to receive placebo. A total of 388 patients had a centrally confirmed germline BRCA1/2 mutation, and 2 patients had a centrally confirmed somatic BRCA1/2 mutation. After a median follow-up of 41 months, the risk of disease progression or death was 70% lower with olaparib than with placebo (Kaplan–Meier estimate of the rate of freedom from disease progression and from death at 3 years, 60% vs. 27%; hazard ratio for disease progression or death, 0.30; 95% confidence interval, 0.23 to 0.41; P<0.001). Adverse events were consistent with the known toxic effects of olaparib.

Interpretation
The use of maintenance therapy with olaparib provided a substantial benefit with regard to progression-free survival among women with newly diagnosed advanced ovarian cancer and a BRCA1/2 mutation, with a 70% lower risk of disease progression or death with olaparib than with placebo. (Funded by AstraZeneca and Merck; SOLO1 ClinicalTrials.gov number, NCT01844986.)

References

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