Ludwig Boltzmann Institut
Health Technology Assessment

Horizon Scanning in Oncology
37th Prioritization – 4th 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 37th prioritisation (October 2018), 14 drugs were filtered out of 477 identified and were sent to prioritisation. Of these, 6 drugs were ranked as ‘highly relevant’ by the expert panel, 7 as ‘relevant’ and 1 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 – 37th prioritisation 4th quarter 2018	Overall category
1.	Apalutamide (Erleada®) treatment and metastasis-free survival in prostate cancer	Highly relevant
2.	Enzalutamide (Xtandi®, MDV3100) in men with nonmetastatic, castration-resistant prostate cancer	Highly relevant
3.	Blinatumomab (Blincyto®) for minimal residual disease (MRD) in adults with B-cell precursor acute lymphoblastic leukaemia (ALL)	Highly relevant
4.	Adjuvant pembrolizumab (Keytruda®) versus placebo in resected stage III melanoma	Highly relevant
5.	Adjuvant bevacizumab (Avastin®) for melanoma patients at high risk of recurrence	Not relevant
6.	Combined nivolumab (Opdivo®, BMS-936558, MDX1106, ONO4538) and ipilimumab in melanoma metastatic to the brain	Relevant
7.	Atezolizumab (Tecentriq®) for first-line treatment of metastatic nonsquamous non-small-cell lung cancer (NSCLC)	Relevant
8.	Cabozantinib (Cometriq®, Cabometyx®) in patients with advanced and progressing hepatocellular carcinoma (HCC)	Relevant
9.	Pembrolizumab (Keytruda®) in patients with advanced hepatocellular carcinoma (HCC) previously treated with sorafenib	Relevant
10.	Ibrutinib (Imbruvica®) plus rituximab in Waldenstrom’s macroglobulinemia	Highly relevant
11.	Mogamulizumab (Poteligeo®, KW-0761) versus vorinostat in previously treated cutaneous T-cell lymphoma	Relevant
12.	Ribociclib (Kisqali®) and fulvestrant in hormone receptor–positive, human epidermal growth factor receptor 2–negative advanced breast cancer	Relevant
13.	Ribociclib (Kisqali®) plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer	Highly relevant
14.	Talazoparib (BMN 673) in patients with advanced breast cancer and a germline BRCA mutation	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 08/2019 NCT02489318 until 07/2022 NCT02257736 until 08/2021
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		-

Published articles (PubMed):

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%).

Interpretation
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.)

1.2 Enzalutamide (Xtandi®, MDV3100) in men with nonmetastatic, castration-resistant prostate cancer

Overview

Drug Description		enzalutamide binds directly to the androgen receptor and inhibits the binding of androgens, androgen-receptor nuclear translocation, and androgen-receptor–mediated DNA binding
Patient Indication		patients with nonmetastatic, castration-resistant prostate cancer
Incidence in Austria		4,854 newly diagnosed per year (2015), 130.6/100,000 men/year (European Standard Population, 2013)
Ongoing Phase III		NCT02003924 (PROSPER) until 05/2020 NCT02987543 until 02/2021 NCT02288247 until 12/2019 NCT03016312 until 07/2022 NCT03395197 until 03/2024 NCT01949337 until 12/2019
Approval status for this indication	**EMA**	-
	FDA	according to label information (07/2018) enzalutamide is indicated for the treatment of patients with castration-resistant prostate cancer
Approval status for other indications	**EMA**	according to product information (updated 04/2018), enzalutamide is indicated for - the treatment of adult men with metastatic castration-resistant prostate cancer who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated - the treatment of adult men with metastatic castration-resistant

		prostate cancer whose disease has progressed on or after docetaxel therapy
	FDA	-
Costs		112 Xtandi® soft capsules (40mg) = € 2,895.35 (ex-factory price) PROSPER study patients received enzalutamide at a dose of 160 mg once daily, the median duration of treatment was 18.4 months. Based on study treatment, 28 days of enzalutamide treatment would cost € 2,895.35; 18.4 months of treatment would cost € 53,274.44.

Published articles (PubMed):

NEJM 2018; 378:2465-74 (Hussain et al.): *"Enzalutamide in men with nonmetastatic, castration-resistant prostate cancer"*

Background
Men with nonmetastatic, castration-resistant prostate cancer and a rapidly rising prostate-specific antigen (PSA) level are at high risk for metastasis. We hypothesized that enzalutamide, which prolongs overall survival among patients with metastatic, castration-resistant prostate cancer, would delay metastasis in men with nonmetastatic, castration-resistant prostate cancer and a rapidly rising PSA level.

Methods
In this double-blind, phase 3 trial, we randomly assigned, in a 2:1 ratio, men with nonmetastatic, castration-resistant prostate cancer and a PSA doubling time of 10 months or less who were continuing androgen-deprivation therapy to receive enzalutamide (at a dose of 160 mg) or placebo once daily. The primary end point was metastasis-free survival (defined as the time from randomization to radiographic progression or as the time to death without radiographic progression).

Findings
A total of 1401 patients (median PSA doubling time, 3.7 months) underwent randomization. As of June 28, 2017, a total of 219 of 933 patients (23%) in the enzalutamide group had metastasis or had died, as compared with 228 of 468 (49%) in the placebo group. The median metastasis-free survival was 36.6 months in the enzalutamide group versus 14.7 months in the placebo group (hazard ratio for metastasis or death, 0.29; 95% confidence interval, 0.24 to 0.35; P<0.001). The time to the first use of a subsequent antineoplastic therapy was longer with enzalutamide treatment than with placebo (39.6 vs. 17.7 months; hazard ratio, 0.21; P<0.001; such therapy was used in 15% vs. 48% of patients) as was the time to PSA progression (37.2 vs. 3.9 months; hazard ratio, 0.07; P<0.001; progression occurred in 22% vs. 69% of patients). At the first interim analysis of overall survival, 103 patients (11%) receiving enzalutamide and 62 (13%) receiving placebo had died. Adverse events of grade 3 or higher occurred in 31% of the patients receiving enzalutamide, as compared with 23% of those receiving placebo.

Interpretation
Among men with nonmetastatic, castration-resistant prostate cancer with a rapidly rising PSA level, enzalutamide treatment led to a clinically meaningful and significant 71% lower risk of metastasis or death than placebo. Adverse events were consistent with the established safety profile of enzalutamide. (Funded by Pfizer and Astellas Pharma; PROSPER ClinicalTrials.gov number, NCT02003924.)

2 Leukaemia

2.1 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/m²/day (IV) of blinatumomab for 4 weeks, followed by 2 treatment-free weeks (=1 cycle). 1 dose = 25.95 μg/day. Costs for one cycle = € 84,782.4.

Published articles (PubMed):

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 Melanoma

3.1 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)

Published articles (PubMed):

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.)

4 Lymphoma

4.1 Ibrutinib (Imbruvica®) plus rituximab in Waldenstrom's macroglobulinemia

Overview

Drug Description		a tyrosine kinase inhibitor
Patient Indication		patients with Waldenstrom´s macroglobulinemia who had not received previous treatment and patients with disease recurrence
Incidence in Austria		Waldenstrom´s macroglobulinemia accounts for approx. 1-3% of all non-Hodgkin´s lymphomas (NHL). NHL: 1,318 newly diagnosed per year (2015), 15.5/100,000 persons/year (European Standard Population)
Ongoing Phase III		NCT02165397 until 01/2019 NCT03053440 until 06/2021
Approval status for this indication	**EMA**	-
	FDA	according to label information (02/2018) ibrutinib is indicated for the treatment of adult patients with Waldenström's macroglobulinemia
Approval status for other indications	**EMA**	according to product information (updated 08/2018) ibrutinib is indicated - as a single agent for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) - as a single agent for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) - as a single agent or in combination with bendamustine and rituximabfor the treatment of adult patients with CLL who have received at least one prior therapy - as a single agent for the treatment of adult patients with Waldenström's macroglobulinaemia who have received at least one prior therapy, or in first line treatment for patients unsuitable for chemo-immunotherapy
	FDA	according to label information, ibrutinib is indicated for the treatment of adult patients with: - mantle cell lymphoma (MCL) who have received at least one prior therapy (accelerated approval) - chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) - chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) with 17p deletion - marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy (accelerated approval) - chronic graft versus host disease (cGVHD) after failure of one or more lines of systemic therapy

Costs		90 Imbruvica® hard capsules 140 mg = € 5474.70 120 Imbruvica® hard capsules 140 mg = € 7299.60 Study patients assigned to the ibrutinib-rituximab-group received 420 mg of ibrutinib orally once daily; the median duration of treatment among patients of this group was 25.8 months. One month (30 days) of ibrutinib treatment would cost € 5474.70, for 25.8 months of treatment, costs of € 141,247.26 would incur (plus additional costs for rituximab)

Published articles (PubMed):

NEJM; available online June 1, 2018 (Dimopoulos et al.): *"Phase 3 trial of ibrutinib plus rituximab in Waldenstrom's macroglobulinemia"*

Background
Single-agent ibrutinib has shown substantial activity in patients with relapsed Waldenstrom's macroglobulinemia, a rare form of B-cell lymphoma. We evaluated the effect of adding ibrutinib to rituximab in patients with this disease, both in those who had not received previous treatment and in those with disease recurrence.

Methods
We randomly assigned 150 symptomatic patients to receive ibrutinib plus rituximab or placebo plus rituximab. The primary end point was progression-free survival, as assessed by an independent review committee. Key secondary end points were response rates, sustained hematologic improvement from baseline, and safety. The mutational status of *MYD88* and *CXCR4* was assessed in bone marrow samples.

Findings
At 30 months, the progression-free survival rate was 82% with ibrutinib–rituximab versus 28% with placebo–rituximab (hazard ratio for progression or death, 0.20; P<0.001). The benefit in the ibrutinib–rituximab group over that in the placebo–rituximab group was independent of the *MYD88* or *CXCR4* genotype. The rate of major response was higher with ibrutinib–rituximab than with placebo–rituximab (72% vs. 32%, P<0.001). More patients had sustained increases in hemoglobin level with ibrutinib–rituximab than with placebo–rituximab (73% vs. 41%, P<0.001). The most common adverse events of any grade with ibrutinib–rituximab included infusion-related reactions, diarrhea, arthralgia, and nausea. Events of grade 3 or higher that occurred more frequently with ibrutinib–rituximab than with placebo–rituximab included atrial fibrillation (12% vs. 1%) and hypertension (13% vs. 4%); those that occurred less frequently included infusion reactions (1% vs. 16%) and any grade of IgM flare (8% vs. 47%). The major hemorrhage rate was the same in the two trial groups (4%).

Interpretation
Among patients with Waldenstrom's macroglobulinemia, the use of ibrutinib– rituximab resulted in significantly higher rates of progression-free survival than the use of placebo–rituximab, both among those who had received no previous treatment and among those with disease recurrence. Atrial fibrillation and hypertension were more common with ibrutinib–rituximab, whereas infusion reactions and IgM flare were more common with placebo–rituximab. (Funded by Pharmacyclics and Janssen Research and Development; ClinicalTrials.gov number, NCT02165397.)

5 Breast Cancer

5.1 Ribociclib (Kisqali®) plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer

Overview

Drug Description		a highly selective small-molecule inhibitor of CDK4 and 6
Patient Indication		premenopausal women with advanced, HR-positive breast cancer
Incidence in Austria		5,480 newly diagnosed per year (2015), 116.7/100,000 women/ year (European Standard Population, 2013)
Ongoing Phase III		-
Approval status for this indication	**EMA**	-
	FDA	according to label information (07/2018) ribociclib is indicated in combination with: - an aromatase inhibitor for the treatment of pre/perimenopausal or postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer, as initial endocrine -based therapy
Approval status for other indications	**EMA**	according to product information (07/2018) ribociclib (in combination with an aromatase inhibitor) is indicated for the treatment of postmenopausal women with hormone receptor (HR) –positive, human epidermal growth factor receptor 2 (HER2) -negative locally advanced or metastatic breast cancer as initial endocrine -based therapy
	FDA	according to label information (07/2018) ribociclib is indicated in combination with: - fulvestrant for the treatment of postmenopausal women with HR-positive, HER2 -negative advanced or metastatic breast cancer, as initial endocrine based therapy or following disease progression on endocrine therapy
Costs		21 Kisqali® 200 mg tablets = € 1,116.67 42 Kisqali® 200 mg tablets = € 2,233.33 63 Kisqali® 200 mg tablets = € 3,350.00 Study patients received oral ribociclib (600 mg/day) on a 3-weeks-on, 1-week-off schedule. Median duration of exposure to study treatment was 15.2 months in patients of the ribociclib group. Based on study treatment, one month of ribociclib treatment costs € 3,350.00.

Published articles (PubMed):

Lancet Oncology; available May 24, 2018 (Tripathy et al.): *"Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): a randomised phase 3 trial"*

Background
In MONALEESA-2, ribociclib plus letrozole showed improved progression-free survival compared with letrozole alone as first-line treatment for postmenopausal patients with hormone receptor (HR)-positive, HER2-negative, advanced breast cancer. MONALEESA-7 aimed to assess the efficacy and safety of ribociclib plus endocrine therapy in premenopausal women with advanced, HR-positive breast cancer.

Methods
This phase 3, randomised, double-blind, placebo-controlled trial was done at 188 centres in 30 countries. Eligible patients were premenopausal women aged 18–59 years who had histologically or cytologically confirmed HR-positive, HER2-negative, advanced breast cancer; an Eastern Cooperative Oncology Group performance status of 0 or 1; measurable disease as per Response Evaluation Criteria in Solid Tumors version 1.1 criteria, or at least one predominantly lytic bone lesion; and had not received previous treatment with cyclin-dependent kinases 4 and 6 inhibitors. Endocrine therapy and chemotherapy in the adjuvant or neoadjuvant setting was permitted, as was up to one line of chemotherapy for advanced disease. Patients were randomly assigned (1:1) via interactive response technology to receive oral ribociclib (600 mg/day on a 3-weeks-on, 1-week-off schedule) or matching placebo with either oral tamoxifen (20 mg daily) or a non-steroidal aromatase inhibitor (letrozole 2.5 mg or anastrozole 1 mg, both oral, daily), all with goserelin (3.6 mg administered subcutaneously on day 1 of every 28-day cycle). Patients and investigators were masked to treatment assignment. Efficacy analyses were by intention to treat, and safety was assessed in all patients who received at least one dose of any study treatment. The primary endpoint was investigator-assessed progression-free survival. MONALEESA-7 is registered with ClinicalTrials.gov, NCT02278120 and is ongoing, but no longer enrolling patients.

Findings
Between Dec 17, 2014, and Aug 1, 2016, 672 patients were randomly assigned: 335 to the ribociclib group and 337 to the placebo group. Per investigator's assessment, median progression-free survival was 23.8 months (95% CI 19.2–not reached) in the ribociclib group compared with 13.0 months (11.0–16.4) in the placebo group (hazard ratio 0.55, 95% CI 0.44–0.69; p<0.0001). Grade 3 or 4 adverse events reported in more than 10% of patients in either group were neutropenia (203 [61%] of 335 patients in the ribociclib group and 12 [4%] of 337 in the placebo group) and leucopenia (48 [14%] and four [1%]). Serious adverse events occurred in 60 (18%) of 335 patients in the ribociclib group and 39 (12%) of 337 in the placebo group, of which 15 (4%) and six (2%), respectively, were attributed to the study regimen. 12 (4%) of 335 patients in the ribociclib group and ten (3%) of 337 in the placebo group discontinued treatment because of adverse events. No treatment-related deaths occurred. 11 deaths occurred (five [1%] in the ribociclib group and six [2%] in the placebo group) during or within 30 days after treatment, most of which were due to progression of the underlying breast cancer (three [1%] and six [2%]). The remaining two deaths in the ribociclib group were due to an intracranial haemorrhage in an anticoagulated patient, and a pre-existing wound haemorrhage in another patient.

Interpretation
Ribociclib plus endocrine therapy improved progression-free survival compared with placebo plus endocrine therapy, and had a manageable safety profile in patients with premenopausal, HR-positive, HER2-negative, advanced breast cancer. The combination could represent a new first-line treatment option for these patients.