Ludwig Boltzmann Institut
Health Technology Assessment

Horizon Scanning in Oncology
40th Prioritization – 3rd quarter 2019

General Information, efficacy and safety data

Nicole Grössmann
Eleen Rothschedl
Sarah Wolf

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 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 40th prioritisation (July 2019), eleven drugs were filtered out of 570 identified and were sent to prioritisation. Of these, 6 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 – 40th prioritisation 3rd quarter 2019	Overall category
1.	Alpelisib (Piqray®, BYL719) for PIK3CA-mutated, hormone receptor (HR) – positive advanced breast cancer	Highly relevant
2.	Overall survival with ribociclib (Kisqali®, LEE011) plus endocrine therapy in breast cancer	Highly relevant
3.	Trastuzumab emtansine (Kadcyla®, T-DM1) for residual invasive HER2-positive breast cancer	Highly relevant
4.	Apalutamide (Erleada®) for metastatic, castration-sensitive prostate cancer	Highly relevant
5.	Enzalutamide (Xtandi®) with standard first-line therapy in metastatic prostate cancer	Highly relevant
6.	Daratumumab (Darzalex®) plus lenalidomide and dexamethasone for untreated myeloma	Relevant
7.	Pomalidomide (Imnovid®, Pomalyst®), bortezomib, and dexamethasone for patients with relapsed or refractory MM previously treated with lenalidomide	Relevant
8.	Lenalidomide (Revlimid®) plus rituximab versus placebo plus rituximab in relapsed or refractory indolent lymphoma	Highly relevant
9.	Maintenance olaparib (Lynparza®) for germline breast cancer gene (BRCA)-mutated metastatic pancreatic cancer	Relevant
10.	Pembrolizumab (Keytruda®) versus chemotherapy for previously untreated, programmed death ligand 1 (PD-L1)-expressing, locally advanced or metastatic non-small-cell lung cancer (NSCLC)	Highly relevant
11.	Venetoclax (Venclyxto®, Venclexta®,) and obinutuzumab in patients with chronic lymphocytic leukemia (CLL) and coexisting conditions	Highly relevant

Breast cancer

Alpelisib (Piqray®, BYL719) for PIK3CA-mutated, hormone receptor (HR) – positive advanced breast cancer

Overview

Drug Description	an orally bioavailable, small-molecule, α-specific PI3K inhibitor that selectively inhibits p110α approximately 50 times as strongly as other isoforms
Patient Indication	men and postmenopausal women who had locally confirmed HR-positive, human epidermal growth factor receptor (HER) 2-negative advanced breast cancer, were eligible to receive further endocrine therapy after relapse or progression, and were receiving or had received aromatase inhibitor treatment in the context of neoadjuvant or adjuvant therapy or for advanced disease.
Incidence in Austria	breast cancer: 5,558 newly diagnosed women and 88 newly diagnosed men per year (2016), 119.4/100,000 women/year and 2.3/100,000 men/year (European Standard Population, 2013) [1]
Current standard treatment	the National Institute for Health and Care Excellence (NICE) guidelines for managing HR+, HER2- advanced breast cancer recommend the following treatments: endocrine therapy or chemotherapy: • offer endocrine therapy as a first-line treatment for the majority of patients with HR+ advanced breast cancer • offer chemotherapy as first-line treatment for patients with HR+ advanced breast cancer whose disease is imminently life-threatening or requires early relief of symptoms because of significant visceral organ involvement, providing they understand and are prepared to accept the toxicity • for patients with HR+ advanced breast cancer who have been treated with chemotherapy as their first-line treatment, offer endocrine therapy following the completion of chemotherapy ✪ endocrine therapy: • offer an aromatase inhibitor (either non-steroidal or steroidal) to: ○ postmenopausal women with ER-positive breast cancer and no prior history of endocrine therapy ○ postmenopausal women with ER-positive breast cancer previously treated with tamoxifen • offer tamoxifen and ovarian suppression as first-line treatment to premenopausal and perimenopausal women with ER-positive advanced breast cancer not previously treated with tamoxifen • offer ovarian suppression to premenopausal and perimenopausal women who have previously been treated with tamoxifen and then experience disease progression • offer tamoxifen as first-line treatment to men with HR+ advanced breast cancer ✪ chemotherapy: • on disease progression, offer systemic sequential therapy to the majority of patients with advanced breast cancer who have decided to be treated with chemotherapy • consider using combination chemotherapy to treat patients with advanced breast cancer for whom a greater

		probability of response is important and who understand and are likely to tolerate the additional toxicity • for patients with advanced breast cancer who are not suitable for anthracyclines, systemic chemotherapy should be offered in the following sequence: ○ first line: single-agent docetaxel ○ second line: single-agent vinorelbine or capecitabine ○ third line: single-agent capecitabine or vinorelbine (whichever was not used as second-line treatment) ✪ other second-line treatments: • everolimus: everolimus, in combination with exemestane, is recommended within its marketing authorisation, as an option for treating advanced HR+, HER2- breast cancer in postmenopausal women without symptomatic visceral disease that has recurred or progressed after a non-steroidal aromatase inhibitor. Everolimus is recommended only if the company provides it with the discount agreed in the patient access scheme. • fulvestrant: fulvestrant is not recommended within its licensed indication, as an alternative to aromatase inhibitors for the treatment of oestrogen-receptor-positive, locally advanced or metastatic breast cancer in postmenopausal women whose cancer has relapsed on or after adjuvant anti-oestrogen therapy, or who have disease progression on anti-oestrogen therapy. Post-menopausal women currently receiving fulvestrant within its licensed indication as an alternative to aromatase inhibitors for the treatment of oestrogen-receptor-positive, locally advanced or metastatic breast cancer whose cancer has relapsed on or after adjuvant anti-oestrogen therapy, or who have disease progression on anti-oestrogen therapy, should have the option to continue treatment until they and their clinicians consider it appropriate to stop. ✪ other third-line treatments: • eribulin: eribulin is recommended as an option for treating locally advanced or metastatic breast cancer in adults, only when: ○ it has progressed after at least 2 chemotherapy regimens (which may include an anthracycline or a taxane, and capecitabine) ○ the company provides eribulin with the discount agreed in the patient access scheme (this guidance is not intended to affect the position of patients whose treatment with eribulin was started within the NHS before this guidance was published; treatment of those patients may continue without change to whatever funding arrangements were in place for them before this guidance was published until they and their NHS clinician consider it appropriate to stop) [2].
Ongoing Phase III		NCT02437318 (SOLAR-1) ongoing until 09/2020 [3]
Approval status for this indication	**EMA**	-
	FDA	according to label information (05/2019) alpelisib is indicated in: ○ in combination with fulvestrant for the treatment of postmenopausal women, and men, with HR-positive, HER2-negative, PIK3CA-mutated, advanced or metastatic breast cancer as detected by an

		FDA-approved test following progression on or after an endocrine-based regimen [4].
Approval status for other indications	**EMA**	-
	FDA	-
Costs		-

Published articles (PubMed):

NEJM; 380:1929-40, May 16, 2019 (André et al.): *"Alpelisib for PIK3CA-Mutated, Hormone Receptor–Positive Advanced Breast Cancer"* [5]

Background
PIK3CA mutations occur in approximately 40% of patients with hormone receptor (HR) – positive, human epidermal growth factor receptor 2 (HER2)–negative breast cancer. The PI3Kα-specific inhibitor alpelisib has shown antitumor activity in early studies.

Methods
In a randomized, phase 3 trial, we compared alpelisib (at a dose of 300 mg per day) plus fulvestrant (at a dose of 500 mg every 28 days and once on day 15) with placebo plus fulvestrant in patients with HR-positive, HER2-negative advanced breast cancer who had received endocrine therapy previously. Patients were enrolled into two cohorts on the basis of tumor-tissue *PIK3CA* mutation status. The primary end point was progression- free survival, as assessed by the investigator, in the cohort with *PIK3CA*-mutated cancer; progression-free survival was also analyzed in the cohort without *PIK3CA*mutated cancer. Secondary end points included overall response and safety.

Findings
A total of 572 patients underwent randomization, including 341 patients with confirmed tumor-tissue PIK3CA mutations. In the cohort of patients with PIK3CA-mutated cancer, progression-free survival at a median follow-up of 20 months was 11.0 months (95% confidence interval [CI], 7.5 to 14.5) in the alpelisib–fulvestrant group, as compared with 5.7 months (95% CI, 3.7 to 7.4) in the placebo–fulvestrant group (hazard ratio for progression or death, 0.65; 95% CI, 0.50 to 0.85; P<0.001); in the cohort without PIK3CA-mutated cancer, the hazard ratio was 0.85 (95% CI, 0.58 to 1.25; posterior probability of hazard ratio <1.00, 79.4%). Overall response among all the patients in the cohort without PIK3CA-mutated cancer was greater with alpelisib–fulvestrant than with placebo–fulvestrant (26.6% vs. 12.8%); among patients with measurable disease in this cohort, the percentages were 35.7% and 16.2%, respectively. In the overall population, the most frequent adverse events of grade 3 or 4 were hyperglycemia (36.6% in the alpelisib–fulvestrant group vs. 0.7% in the placebo–fulvestrant group) and rash (9.9% vs. 0.3%). Diarrhea of grade 3 occurred in 6.7% of patients in the alpelisib– fulvestrant group, as compared with 0.3% of those in the placebo–fulvestrant group; no diarrhea of grade 4 was reported. The percentages of patients who discontinued alpelisib and placebo owing to adverse events were 25.0% and 4.2%, respectively.

Interpretation
Treatment with alpelisib–fulvestrant prolonged progression-free survival among patients with PIK3CA-mutated, HR-positive, HER2-negative advanced breast cancer who had received endocrine therapy previously. (Funded by Novartis Pharmaceuticals; SOLAR-1 ClinicalTrials.gov number, NCT02437318.)

Overall survival with ribociclib (Kisqali®, LEE011) plus endocrine therapy in breast cancer

Overview

Drug Description		ribociclib is a selective, orally available inhibitor of cyclin-dependent kinases 4 and 6 (CDK4/6)
Patient Indication		premenopausal or perimenopausal women with HR–positive, HER2-negative advanced breast cancer.
Incidence in Austria		breast cancer: 5,558 newly diagnosed women and 88 newly diagnosed men per year (2016), 119.4/100,000 women/year and 2.3/100,000 men/year (European Standard Population, 2013)
Current standard treatment		❂ treatment for patients with advanced breast cancer aims to slow disease progression, manage symptoms and improve quality of life ❂ current practice for HR-positive breast cancer is usually focused on endocrine anti-oestrogen treatments before moving onto chemotherapy, unless the patient is resistant or has developed rapidly life-threatening disease ❂ most premenopausal women have aggressive cancers requiring chemotherapy when there is visceral disease recurrence ❂ treatment options for women with advanced HR-positive/HER2-negative breast cancer include: - endocrine therapies – tamoxifen and ovarian suppression as first-line treatment to premenopausal and perimenopausal women with ER-positive advanced breast cancer not previously treated with tamoxifen - chemotherapy – single agents are recommended: anthracycline- or taxane-based regimens, capecitabine, vinorelbine, gemcitabine (with paclitaxel), cyclophosphamide, platinum-based treatments; eribulin (not recommended by NICE) - bisphosphonates – for women undergoing ovarian suppression and for treatment-related bone loss. - surgery or radiotherapy with adjuvant systemic therapy may be considered for patients with bone metastases and pain, or those with a single or small number of potentially resectable brain metastases, a good performance status and who have no or well-controlled other metastatic disease.
Ongoing Phase III		NCT02278120 (MONALEESA-7) until 12/2020 NCT02422615 until 02/2020 NCT01958021 until 08/2021 NCT02941926 until 05/2021 NCT03425838 until 10/2022 NCT03096847 until 02/2020
Approval status for this indication	**EMA**	-
	FDA	-
Approval status for other indications	**EMA**	according to product information (01/2019), ribociclib is indicated: ❂ for the treatment of women with HR-positive, HER2-negative locally advanced or metastatic breast cancer in combination with an aromatase inhibitor or fulvestrant as initial endocrine-based therapy, or in women who have received prior endocrine therapy. In pre- or perimenopausal women, the endocrine therapy should be combined with a luteinising hormone-releasing hormone (LHRH) agonist.

	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 HR-positive, HER2-negative advanced or metastatic breast cancer, as initial endocrine-based therapy; or ✪ 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		63 Kisqali® tablets (200 mg) = € 3,350.00 (ex-factory price) MONALEESA-7 trial patients (ribociclib group) received ribociclib at a dose of 600 mg, administered orally once daily for 21 consecutive days followed by 7 days off, for a complete cycle of 28 days → costs of € 3,350.00/cycle. Both groups received goserelin and either a nonsteroidal aromatase inhibitor or tamoxifen administered orally once daily continuously → additional costs. The median duration of exposure to trial treatment in the ribociclib group was approx. 2 years → approx. € 80,400.00.

1.1.1 Published articles (PubMed):

NEJM; available online June 4, 2019 (Im et al.): *"Overall Survival with Ribociclib plus Endocrine Therapy in Breast Cancer" [6]*

Background
An earlier analysis of this phase 3 trial showed that the addition of a cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor to endocrine therapy provided a greater benefit with regard to progression-free survival than endocrine therapy alone in premenopausal or perimenopausal patients with advanced hormone-receptor–positive, human epidermal growth factor receptor 2 (HER2)–negative breast cancer. Here we report the results of a protocol-specified interim analysis of the key secondary end point of overall survival.

Methods
We randomly assigned patients to receive either ribociclib or placebo in addition to endocrine therapy (goserelin and either a nonsteroidal aromatase inhibitor or tamoxifen). Overall survival was evaluated with the use of a stratified log-rank test and summarized with the use of Kaplan–Meier methods.

Findings
A total of 672 patients were included in the intention-to-treat population. There were 83 deaths among 335 patients (24.8%) in the ribociclib group and 109 deaths among 337 patients (32.3%) in the placebo group. The addition of ribociclib to endocrine therapy resulted in significantly longer overall survival than endocrine therapy alone. The estimated overall survival at 42 months was 70.2% (95% confidence interval [CI], 63.5 to 76.0) in the ribociclib group and 46.0% (95% CI, 32.0 to 58.9) in the placebo group (hazard ratio for death, 0.71; 95% CI, 0.54 to 0.95; P = 0.00973 by log-rank test). The survival benefit seen in the subgroup of 495 patients who received an aromatase inhibitor was consistent with that in the overall intention-to-treat population (hazard ratio for death, 0.70; 95% CI, 0.50 to 0.98). The percentage of patients who received subsequent antineoplastic therapy was balanced between the groups (68.9% in the ribociclib group and 73.2% in the placebo group). The time from randomization to disease progression during receipt of second-line therapy or to death was also longer in the ribociclib group than in the placebo group (hazard ratio for disease progression or death, 0.69; 95% CI, 0.55 to 0.87).

Interpretation
This trial showed significantly longer overall survival with a CDK4/6 inhibitor plus endocrine therapy than with endocrine therapy alone among patients with advanced hormone-receptor–positive, HER2-negative breast cancer. No new concerns regarding toxic effects emerged with longer follow-up. (Funded by Novartis; MONALEESA-7 ClinicalTrials.gov number, NCT02278120.)

Trastuzumab emtansine (Kadcyla®, T-DM1) for residual invasive HER2-positive breast cancer

Overview

Drug Description		trastuzumab emtansine is an antibody–drug conjugate of trastuzumab and the cytotoxic agent emtansine, a maytansine derivative and microtubule inhibitor
Patient Indication		patients were eligible if they had HER2- positive, nonmetastatic, invasive primary breast cancer (clinical tumor stage T1 to T4, nodal stage N0 to N3, and metastasis stage M0 excluding clinical stage T1aN0 or T1bN0) at presentation and if residual invasive disease was detected pathologically in the surgical specimen of the breast or axillary lymph nodes after completion of taxane-based neoadjuvant chemotherapy administered with trastuzumab
Incidence in Austria		breast cancer: 5,558 newly diagnosed women and 88 newly diagnosed men per year (2016), 119.4/100,000 women/year and 2.3/100,000 men/year (European Standard Population, 2013) [1]
Current standard treatment		❁ NICE recommends to consider adjuvant therapy for all patients with early invasive breast cancer after surgery. Adjuvant chemotherapy or radiotherapy needs to be started as soon as clinically possible, within 31 days of completion of surgery in patients with early breast cancer having these treatments ❁ trastuzumab, given at three-week intervals for one year or until disease recurrence (whichever is the shorter period), is recommended by NICE as a treatment option for women with early-stage HER2-positive breast cancer following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable) ❁ for patients with lymph node-positive breast cancer, NICE recommends docetaxel as part of an adjuvant chemotherapy regimen. Docetaxel, when given concurrently with doxorubicin and cyclophosphamide (the TAC regimen) as per its licensed indication, is recommended as an option for the adjuvant treatment of women with early node-positive breast cancer ❁ for patients with early invasive breast cancer who have had a mastectomy and are at a high risk of local recurrence (include those with four or more positive axillary lymph nodes or involved resection margins), NICE recommends offering adjuvant chest wall radiotherapy [7].
Ongoing Phase III		NCT01772472 (KATHERINE) until 04/2023 NCT01966471 until 01/2024 NCT01702571 until 09/2019 [3]
Approval status for this indication	**EMA**	-
	FDA	according to label information (05/2019), trastuzumab is indicated as a single agent for: ❁ the adjuvant treatment of patients with HER2-positive early breast cancer who have residual invasive disease after neoadjuvant taxane and trastuzumab-based treatment [4].
Approval status for other indications	**EMA**	according to product information (09/2018), trastuzumab emtansine is indicated: ❁ as a single agent for the treatment of adult patients with HER2-positive, unresectable locally advanced or metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination. Patients should have either: - received prior therapy for locally advanced or metastatic disease, or - developed disease recurrence during or within six months of completing adjuvant therapy [8].

	FDA	according to label information (05/2019), trastuzumab is indicated as a single agent for: ❁ the treatment of patients with HER2-positive, metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination. Patients should have either: - received prior therapy for metastatic disease, or - developed disease recurrence during or within six months of completing adjuvant therapy [4].
Costs		Kadcyla® concentrate for solution for infusion (100 mg) = € 1,700.00 (ex-factory price) [9] KATHERINE trial patients assigned to the T-DM1 group received T-DM1 at a dose of 3.6 mg per kilogram of body weight intravenously every 3 weeks for 14 cycles. Assuming an average body weight of 70 kg, 252 mg would be needed for one dose, costing € 5,100.00 (costs for 14 cycles → approx. € 71,400.00) A loading dose of 8 mg of trastuzumab per kilogram was administered if more than 6 weeks had elapsed since the preceding dose of trastuzumab.

Published articles (PubMed):

NEJM; available online December 5, 2018 (Minckwitz et al.): *"Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer"* [10]

Background
Patients who have residual invasive breast cancer after receiving neoadjuvant chemotherapy plus human epidermal growth factor receptor 2 (HER2)–targeted therapy have a worse prognosis than those who have no residual cancer. Trastuzumab emtansine (T-DM1), an antibody–drug conjugate of trastuzumab and the cytotoxic agent emtansine (DM1), a maytansine derivative and microtubule inhibitor, provides benefit in patients with metastatic breast cancer that was previously treated with chemotherapy plus HER2-targeted therapy.

Methods
We conducted a phase 3, open-label trial involving patients with HER2-positive early breast cancer who were found to have residual invasive disease in the breast or axilla at surgery after receiving neoadjuvant therapy containing a taxane (with or without anthracycline) and trastuzumab. Patients were randomly assigned to receive adjuvant T-DM1 or trastuzumab for 14 cycles. The primary end point was invasive disease–free survival (defined as freedom from ipsilateral invasive breast tumor recurrence, ipsilateral locoregional invasive breast cancer recurrence, contralateral invasive breast cancer, distant recurrence, or death from any cause).

Findings
At the interim analysis, among 1486 randomly assigned patients (743 in the T-DM1 group and 743 in the trastuzumab group), invasive disease or death had occurred in 91 patients in the T-DM1 group (12.2%) and 165 patients in the trastuzumab group (22.2%). The estimated percentage of patients who were free of invasive disease at 3 years was 88.3% in the T-DM1 group and 77.0% in the trastuzumab group. Invasive disease–free survival was significantly higher in the T-DM1 group than in the trastuzumab group (hazard ratio for invasive disease or death, 0.50; 95% confidence interval, 0.39 to 0.64; P<0.001). Distant recurrence as the first invasive-disease event occurred in 10.5% of patients in the T-DM1 group and 15.9% of those in the trastuzumab group. The safety data were consistent with the known safety profile of T-DM1, with more adverse events associated with T-DM1 than with trastuzumab alone.

Interpretation
Among patients with HER2-positive early breast cancer who had residual invasive disease after completion of neoadjuvant therapy, the risk of recurrence of invasive breast cancer or death was 50% lower with adjuvant T-DM1 than with trastuzumab alone. (Funded by F. Hoffmann–La Roche/Genentech; KATHERINE ClinicalTrials.gov number, NCT01772472.)

Prostate cancer

Apalutamide (Erleada®) for metastatic, castration-sensitive prostate cancer

Overview

Drug Description		apalutamide is an inhibitor of the ligand-binding domain of the androgen receptor
Patient Indication		patients with an adenocarcinoma of the prostate and distant metastatic disease documented on the basis of at least one lesion on bone scanning, with or without visceral or lymph-node involvement.
Incidence in Austria		5,245 newly diagnosed per year (2016), 138.3/100,000 men/year (European Standard Population, 2013) [11]
Current standard treatment		✪ for men with metastatic hormone-sensitive prostate cancer (mHSPC), NICE guidelines recommend: - bilateral orchidectomy or continuous luteinising-hormone-releasing hormone (LHRH)-agonist therapy - anti-androgen monotherapy with bicalutamide; or - combined androgen blockade (not first-line) ✪ NICE has also published an evidence summary for the off-label use of docetaxel in combination with androgen deprivation therapy (ADT) for the treatment of mHSPC. Docetaxel is licensed in the UK for the treatment of metastatic hormone-resistant prostate cancer. ✪ a draft of an update to the NICE guideline for prostate cancer recommends offering docetaxel to people who do not have significant comorbidities, starting treatment within 12 weeks of starting ADT, to be administered in six 3-weekly cycles with or without daily prednisolone ✪ although not currently recommended by NICE, abiraterone is licensed for the treatment of newly diagnosed, high risk mHSPC in adult men in combination with ADT plus prednisone or prednisolone [12].
Ongoing Phase III		NCT02489318 (TITAN) until 07/2022 [3]
Approval status for this indication	**EMA**	-
	FDA	-
Approval status for other indications	**EMA**	according to product information (03/2019), apalutamide is indicated: ✪ in adult men for the treatment of non-metastatic castration-resistant prostate cancer (nmCRPC) who are at high risk of developing metastatic disease [8]
	FDA	according to label information (02/2018), apalutamide is indicated: ✪ for the treatment of patients with nmCRPC [4]
Costs		112 Erleada® tablets (60mg) = € 3,040.00 (ex-factory price) [9] TITAN trial patients received apalutamide at a dose of 240 mg per day (orally, added to ADT → additional costs); the median duration of the trial intervention was 20.5 months in patients of the apalutamide group. 28 days of treatment = € 3,040.00, 20.5 months of treatment = € 62,320.00.

Published articles (PubMed):

NEJM; available online May 31, 2019 (Chi et al.): *"Apalutamide for Metastatic, Castration-Sensitive Prostate Cancer"* [13]

Background
Apalutamide is an inhibitor of the ligand-binding domain of the androgen receptor. Whether the addition of apalutamide to androgen-deprivation therapy (ADT) would prolong radiographic progression–free survival and overall survival as compared with placebo plus ADT among patients with metastatic, castration-sensitive prostate cancer has not been determined.

Methods
In this double-blind, phase 3 trial, we randomly assigned patients with metastatic, castration-sensitive prostate cancer to receive apalutamide (240 mg per day) or placebo, added to ADT. Previous treatment for localized disease and previous docetaxel therapy were allowed. The primary end points were radiographic progression–free survival and overall survival.

Findings
A total of 525 patients were assigned to receive apalutamide plus ADT and 527 to receive placebo plus ADT. The median age was 68 years. A total of 16.4% of the patients had undergone prostatectomy or received radiotherapy for localized disease, and 10.7% had received previous docetaxel therapy; 62.7% had high-volume disease, and 37.3% had low-volume disease. At the first interim analysis, with a median of 22.7 months of follow-up, the percentage of patients with radiographic progression–free survival at 24 months was 68.2% in the apalutamide group and 47.5% in the placebo group (hazard ratio for radiographic progression or death, 0.48; 95% confidence interval [CI], 0.39 to 0.60; P<0.001). Overall survival at 24 months was also greater with apalutamide than with placebo (82.4% in the apalutamide group vs. 73.5% in the placebo group; hazard ratio for death, 0.67; 95% CI, 0.51 to 0.89; P = 0.005). The frequency of grade 3 or 4 adverse events was 42.2% in the apalutamide group and 40.8% in the placebo group; rash was more common in the apalutamide group.

Interpretation
In this trial involving patients with metastatic, castration-sensitive prostate cancer, overall survival and radiographic progression–free survival were significantly longer with the addition of apalutamide to ADT than with placebo plus ADT, and the side-effect profile did not differ substantially between the two groups. (Funded by Janssen Research and Development; TITAN ClinicalTrials.gov number, NCT02489318.)

Enzalutamide (Xtandi®) with standard first-line therapy in metastatic prostate cancer

Overview

Drug Description		enzalutamide is an orally administered, small molecule inhibitor of the androgen receptor that is designed to overcome acquired resistance to first-generation nonsteroidal antiandrogens
Patient Indication		men with mHSPC
Incidence in Austria		5,245 newly diagnosed per year (2016), 138.3/100,000 men/year (European Standard Population, 2013) [11]
Current standard treatment		✪ for men with mHSPC, NICE guidelines recommend: - bilateral orchidectomy or continuous luteinising-hormone-releasing hormone (LHRH)-agonist therapy - anti-androgen monotherapy with bicalutamide; or - combined androgen blockade (not first-line) ✪ NICE has also published an evidence summary for the off-label use of docetaxel (in combination with ADT) for the treatment of mHSPC. Docetaxel is licensed in the UK for the treatment of metastatic hormone-resistant prostate cancer. ✪ a draft of an update to the NICE guideline for prostate cancer recommends offering docetaxel to people who do not have significant comorbidities, starting treatment within 12 weeks of starting ADT, to be administered in six 3-weekly cycles with or without daily prednisolone ✪ although not currently recommended by NICE, abiraterone is licensed for the treatment of newly diagnosed, high risk mHSPC in adult men in combination with ADT plus prednisone or prednisolone [12].
Ongoing Phase III		NCT02446405 (ENZAMET) until 12/2020 NCT02677896 until 12/2023 NCT02294461 until 03/2020 NCT00268476 until 09/2024 [3]
Approval status for this indication	**EMA**	-
	FDA	-
Approval status for other indications	**EMA**	according to product information (01/2019), enzalutamide is indicated for ✪ the treatment of adult men with high-risk non-metastatic castration-resistant prostate cancer (CRPC) ✪ the treatment of adult men with metastatic CRPC who are asymptomatic or mildly symptomatic after failure of ADT in whom chemotherapy is not yet clinically indicated ✪ the treatment of adult men with metastatic CRPC whose disease has progressed on or after docetaxel therapy [8].
	FDA	according to label information (07/2018), enzalutamide is indicated for ✪ the treatment of patients with CRPC [4].
Costs		112 Xtandi® soft capsules (40 mg) = € 2,895.35 (ex-factory price) [9] ENZAMET trial patients received enzalutamide at a dose of 160 mg until the occurrence of clinical disease progression or prohibitive toxic effects. Based on the trial regimen, 28 days of enzalutamide treatment would cost € 2,895.35.

Published articles (PubMed):

NEJM; available online June 2, 2019 (Davis et al.): *"Enzalutamide with Standard First-Line Therapy in Metastatic Prostate Cancer"* [14]

Background
Enzalutamide, an androgen-receptor inhibitor, has been associated with improved overall survival in men with castration-resistant prostate cancer. It is not known whether adding enzalutamide to testosterone suppression, with or without early docetaxel, will improve survival in men with metastatic, hormone-sensitive prostate cancer.

Methods
In this open-label, randomized, phase 3 trial, we assigned patients to receive testosterone suppression plus either open-label enzalutamide or a standard nonsteroidal antiandrogen therapy (standard-care group). The primary end point was overall survival. Secondary end points included progression-free survival as determined by the prostate-specific antigen (PSA) level, clinical progression-free survival, and adverse events.

Findings
A total of 1125 men underwent randomization; the median follow-up was 34 months. There were 102 deaths in the enzalutamide group and 143 deaths in the standard-care group (hazard ratio, 0.67; 95% confidence interval [CI], 0.52 to 0.86; P = 0.002). Kaplan–Meier estimates of overall survival at 3 years were 80% (based on 94 events) in the enzalutamide group and 72% (based on 130 events) in the standard-care group. Better results with enzalutamide were also seen in PSA progression-free survival (174 and 333 events, respectively; hazard ratio, 0.39; P<0.001) and in clinical progression-free survival (167 and 320 events, respectively; hazard ratio, 0.40; P<0.001). Treatment discontinuation due to adverse events was more frequent in the enzalutamide group than in the standard-care group (33 events and 14 events, respectively). Fatigue was more common in the enzalutamide group; seizures occurred in 7 patients in the enzalutamide group (1%) and in no patients in the standard-care group.

Interpretation
Enzalutamide was associated with significantly longer progression-free and overall survival than standard care in men with metastatic, hormone-sensitive prostate cancer receiving testosterone suppression. The enzalutamide group had a higher incidence of seizures and other toxic effects, especially among those treated with early docetaxel. (Funded by Astellas Scientific and Medical Affairs and others; ENZAMET (ANZUP 1304) ANZCTR number, ACTRN12614000110684; ClinicalTrials.gov number, NCT02446405; and EU Clinical Trials Register number, 2014-003190-42.)

Lenalidomide (Revlimid®) plus rituximab versus placebo plus rituximab in relapsed or refractory indolent lymphoma

Overview

Drug Description	lenalidomide is an immunomodulatory drug that binds to the cereblon E3 ubiquitin ligase complex, resulting in ubiquitination of the transcription factors Aiolos and Ikaros, leading to antilymphoma effects.
Patient Indication	patients with marginal zone lymphoma (MZL) or follicular lymphoma (FL) (grades 1 to 3a) requiring treatment per investigator assessment; at least one prior chemotherapy, immunotherapy, or chemoimmunotherapy and two or more previous doses of rituximab; and relapsed, refractory, or progressive disease and not rituximab refractory disease
Incidence in Austria	NHLs: 1,133 newly diagnosed per year (2016), 15.5/100,000 persons/year (European Standard Population, 2013) The most common indolent NHL types, FL and MZL, account for 22% and 7% of adult NHL, respectively.
Current standard treatment	✪ FL usually grows slowly. Although it is difficult to cure, it is usually kept under control for many years, with treatment needed only occasionally ✪ once the condition has progressed to the extent that patients need treatment, many have first-line induction with rituximab in combination with chemotherapy (R-chemotherapy) that induces a response in most people. This is followed by rituximab maintenance therapy. Other patients are treated with rituximab alone, without the addition of chemotherapy. ✪ second-line treatment for FL depends on the timing of relapse following first-line treatment and the chemotherapy agents used first-line - R-chemotherapy should be offered to patients who are rituximab-naïve, and should also be given if the patient had previously responded to rituximab - disease that remains under control for some time on rituximab maintenance, or after it has stopped, is likely to be treated with further R-chemotherapy (in combination with another chemotherapy agent) in preference to bendamustine monotherapy - rituximab monotherapy, within its marketing authorisation, is recommended as an option for the treatment of people with relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma, when all alternative treatment options have been exhausted - in clinical practice, bendamustine monotherapy may be offered to patients with FL that does not respond to induction treatment with R-chemotherapy, or for disease that relapses early-on in the 2-year rituximab maintenance period. However, NICE was unable to recommend the use in the NHS of bendamustine for the treatment of indolent non-Hodgkin's lymphoma that is refractory to rituximab or a rituximab-containing regimen because no evidence submission was received from the manufacturer or sponsor of the technology. - Y-Ibritumomab radio-immunotherapy may be offered to patients with relapsed FL, especially those who are refractory to rituximab or chemotherapy and for those who are intolerant or unwilling to have further chemotherapy. - In August 2017, NICE recommended obinutuzumab in combination with bendamustine followed by obinutuzumab maintenance as an option for treating adults with refractory follicular lymphoma that did not respond or progressed during or up to 6 months after treatment with rituximab or a

		rituximab-containing regimen, if the conditions in the managed access agreement for obinutuzumab are followed. - NCCN guidelines recommend chemoimmunotherapy, rituximab monotherapy, lenalidomide +/- rituximab, radioimmunotherapy, idelalisib, or fludarabine + rituximab.
Ongoing Phase III		NCT01938001 (AUGMENT) until 12/2021 NCT02390869 until 03/2022 NCT01996865 until 07/2024 NCT01865110 until 03/2024
Approval status for this indication	**EMA**	-
	FDA	according to label information (05/2019), lenalidomide is indicated for the treatment of: ❁ previously treated FL, in combination with a rituximab product ❁ previously treated MZL, in combination with a rituximab product
Approval status for other indications	**EMA**	according to product information (06/2019), lenalidomide is indicated in ❁ MM: - as monotherapy for the maintenance treatment of adult patients with newly diagnosed MM who have undergone ASCT - as combination therapy with dexamethasone, or bortezomib and dexamethasone, or melphalan and prednisone for the treatment of adult patients with previously untreated MM who are not eligible for transplant. - in combination with dexamethasone for the treatment of MM in adult patients who have received at least one prior therapy. ❁ myelodysplastic syndromes (MDS): - as monotherapy for the treatment of adult patients with transfusion-dependent anaemia due to low- or intermediate-1-risk MDS associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate. ❁ mantle cell lymphoma (MCL): - as monotherapy for the treatment of adult patients with relapsed or refractory MCL.
	FDA	according to label information (05/2019), lenalidomide is indicated for the treatment of: ❁ MM in combination with dexamethasone ❁ MM, as maintenance following autologous HSCT ❁ transfusion-dependent anaemia due to low- or intermediate-1-risk MDS associated with a deletion 5q abnormality with or without additional cytogenetic abnormalities ❁ MCL in patients whose disease has relapsed or progressed after two prior therapies, one of which included bortezomib.
Costs		21 Revlimid® hard capsule 20 mg = € 6,093.50 (ex-factory price) Patients of the AUGMENT trial (lenalidomide + rituximab group) received oral lenalidomide at a dose of 20 mg daily on days 1-21 (plus intravenous rituximab → additional costs). Treatment continued for 12 cycles or relapse, progressive disease, withdrawal of consent, or unacceptable toxicity. According to the AUGMENT trial regimen, one month of lenalidomide treatment would cost € 6,093.50 (12 cycles → € 73,122.00).

Published articles (PubMed):

J Clin Oncol 37:1188-1199; 2019 (Leonard et al.): *"AUGMENT: A Phase III Study of Lenalidomide Plus Rituximab Versus Placebo Plus Rituximab in Relapsed or Refractory Indolent Lymphoma" [15]*

Background
Patients with indolent non-Hodgkin lymphoma typically respond well to first-line immunochemotherapy. At relapse, single-agent rituximab is commonly administered. Data suggest the immunomodulatory agent lenalidomide could increase the activity of rituximab.

Methods
A phase III, multicenter, randomized trial of lenalidomide plus rituximab versus placebo plus rituximab was conducted in patients with relapsed and/or refractory follicular or marginal zone lymphoma. Patients received lenalidomide or placebo for 12 cycles plus rituximab once per week for 4 weeks in cycle 1 and day 1 of cycles 2 through 5. The primary end point was progression-free survival per independent radiology review.

Findings
A total of 358 patients were randomly assigned to lenalidomide plus rituximab (n = 178) or placebo plus rituximab (n = 180). Infections (63% v. 49%), neutropenia (58% v. 23%), and cutaneous reactions (32% v. 12%) were more common with lenalidomide plus rituximab. Grade 3 or 4 neutropenia (50% v. 13%) and leukopenia (7% v. 2%) were higher with lenalidomide plus rituximab; no other grade 3 or 4 adverse event differed by 5% or more between groups. Progression-free survival was significantly improved for lenalidomide plus rituximab versus placebo plus rituximab, with a hazard ratio of 0.46 (95% CI, 0.34 to 0.62; P < .001) and median duration of 39.4 months (95% CI, 22.9 months to not reached) versus 14.1 months (95% CI, 11.4 to 16.7 months), respectively.

Interpretation
Lenalidomide improved efficacy of rituximab in patients with recurrent indolent lymphoma, with an acceptable safety profile.

Lung cancer

Pembrolizumab (Keytruda®) versus chemotherapy for previously untreated, programmed death ligand 1 (PD-L1)-expressing, locally advanced or metastatic non-small-cell lung cancer (NSCLC)

Overview

Drug Description	pembrolizumab is a humanised IgG4 monoclonal antibody against PD-1
Patient Indication	patients with locally advanced or metastatic NSCLC and a PD-L1 tumour proportion score (TPS) of 1% or greater, without a sensitizing epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) translocation and who had received no previous therapy for locally advanced or metastatic disease
Incidence in Austria	cancer of the trachea, lung and bronchia: 4,877 newly diagnosed per year (2016), 57.3/100,000 persons/year (European Standard Population, 2013) [16]. NSCLC is the most common type of lung cancer (85-90% of lung cancer cases).
Current standard treatment	✪ the aim of treatment for locally advanced or metastatic NSCLC is to prolong survival, improve quality of life, and control disease-related. ✪ current guidelines recommend that chemotherapy should be offered to patients with stage IV NSCLC and good performance status (WHO 0 or 1 or a Karnofsky score of 80–100) ✪ induction chemotherapy for advanced NSCLC should be a combination of a single third generation drug (docetaxel, gemcitabine, paclitaxel, or vinorelbine) plus a platinum drug (either carboplatin or cisplatin) ✪ if patients cannot tolerate a platinum combination (or are WHO performance status 2), single agent chemotherapy with a third generation drug is recommended ✪ in the first and subsequent treatment line setting, afatinib, erlotinib, and gefitinib (not recommend by NICE) are all options for epidermal growth factor receptor tyrosine kinase mutation (EGFR-TK) positive metastatic NSCLC patients ✪ pemetrexed in combination with cisplatin is recommended if the tumour has been confirmed as adenocarcinoma or large-cell carcinoma on the basis of best survival figures and toxicity profile. ✪ pemetrexed is recommended as maintenance therapy after treatment with platinum-based chemotherapy in combination with gemcitabine, paclitaxel and docetaxel (switch maintenance) if the tumour is adenocarcinoma or large-cell carcinoma ✪ it is recommended that patients progressing after first line chemotherapy be offered docetaxel or erlotinib monotherapy as a second line treatment option, or crizotinib for previously treated ALK-positive advanced NSCLC, though this is not currently recommended by NICE [17].
Ongoing Phase III	NCT02220894 (KEYNOTE-042) until 03/2021 NCT02142738 until 05/2020 NCT03302234 until 02/2024 NCT03631199 until 10/2022 NCT03976362 until 05/2024 NCT03950674 until 01/2020 NCT03875092 until 02/2021 NCT03850444 until 03/2021 NCT03829332 until 03/2024 NCT03302234 until 02/2024 NCT02775435 until 02/2021 [3]

Approval status for this indication	**EMA**	-
	FDA	according to label information (06/2019), pembrolizumab is indicated: ✪ as a single agent for the first-line treatment of patients with NSCLC expressing PD-L1 (TPS ≥1%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations, and is: - stage III where patients are not candidates for surgical resection or definitive chemoradiation, or - metastatic [4].
Approval status for other indications	**EMA**	according to product information (05/2019), pembrolizumab is indicated ✪ as monotherapy for the treatment of advanced (unresectable or metastatic) melanoma in adults ✪ as monotherapy for the adjuvant treatment of adults with Stage III melanoma and lymph node involvement who have undergone complete resection ✪ as monotherapy for the first-line treatment of metastatic NSCLC in adults whose tumours express PD-L1 with a ≥ 50% 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 ✪ in combination with carboplatin and either paclitaxel or nab-paclitaxel for the first-line treatment of metastatic squamous NSCLC in adults ✪ 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 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 (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 [8].
	FDA	according to label information (06/2019), pembrolizumab is indicated in: ✪ melanoma: - for the treatment of patients with unresectable or metastatic melanoma - for the adjuvant treatment of patients with melanoma with involvement of lymph node(s) following complete resection ✪ 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 - in combination with carboplatin and either paclitaxel or paclitaxel protein-bound, as first-line treatment of patients with metastatic squamous NSCLC - 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 ❁ head and neck squamous cell cancer (HNSCC): - in combination with platinum and FU for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC - as a single agent for the first line treatment of patients with metastatic or with unresectable, recurrent HNSCC whose tumors express PD-L1 (CPS) ≥1 as determined by an FDA-approved test - as a single agent for the treatment of patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy ❁ classical Hodgkin lymphoma (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 (limitations 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 (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 (MSI-H): - for the treatment of adult and pediatric patients with unresectable or metastatic (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 (limitations of use: The safety and effectiveness of pembrolizumab in paediatric 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 ✪ Merkel cell carcinoma (MCC): - for the treatment of adult and paediatric patients with recurrent locally advanced or metastatic MCC ✪ renal cell carcinoma (RCC)**:** - in combination with axitinib, for the first-line treatment of patients with advanced RCC (accelerated approval) [4].
Costs		Keytruda® 50 mg powder for concentrate for solution for infusion = € 1,714.00 (ex-factory price) [9]. KEYNOTE-042 patients (pembrolizumab group) received pembrolizumab at a dose of 200 mg (€ 6,856.00 per dose) administered intravenously every 3 weeks up to a maximum of 35 cycles.

Published articles (PubMed):

The Lancet; available online April 4, 2019 (Mok et al.): "*Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial"* [18]

Background
First-line pembrolizumab monotherapy improves overall and progression-free survival in patients with untreated metastatic non-small-cell lung cancer with a programmed death ligand 1 (PD-L1) tumour proportion score (TPS) of 50% or greater. We investigated overall survival after treatment with pembrolizumab monotherapy in patients with a PD-L1 TPS of 1% or greater.

Methods
This randomised, open-label, phase 3 study was done in 213 medical centres in 32 countries. Eligible patients were adults (≥18 years) with previously untreated locally advanced or metastatic non-small-cell lung cancer without a sensitising EGFR mutation or ALK translocation and with an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1, life expectancy 3 months or longer, and a PD-L1 TPS of 1% or greater. Randomisation was computer generated, accessed via an interactive voice-response and integrated web-response system, and stratified by region of enrolment (east Asia vs. rest of world), ECOG performance status score (0 vs. 1), histology (squamous vs. non-squamous), and PD-L1 TPS (≥50% vs. 1–49%). Enrolled patients were randomly assigned 1:1 in blocks of four per stratum to receive pembrolizumab 200 mg every 3 weeks for up to 35 cycles or the investigator's choice of platinum-based chemotherapy for four to six cycles. Primary endpoints were overall survival in patients with a TPS of 50% or greater, 20% or greater, and 1% or greater (one-sided significance thresholds, p=0.0122, p=0.0120, and p=0.0124, respectively) in the intention-to-treat population, assessed sequentially if the previous findings were significant. This study is registered at ClinicalTrials.gov, number NCT02220894.

Findings
From Dec 19, 2014, to March 6, 2017, 1274 patients (902 men, 372 women, median age 63 years [IQR 57–69]) with a PD-L1 TPS of 1% or greater were allocated to pembrolizumab (n=637) or chemotherapy (n=637) and included in the intention-to-treat population. 599 (47%) had a TPS of 50% or greater and 818 patients (64%) had a TPS of 20% or greater. As of Feb 26, 2018, median follow-up was 12.8 months. Overall survival was significantly longer in the pembrolizumab group than in the chemotherapy group in all three TPS populations (≥50% hazard ratio 0.69, 95% CI 0.56–0.85, p=0.0003; ≥20% 0.77, 0.64–0.92, p=0.0020, and ≥1% 0.81, 0.71–0.93, p=0.0018). The median survival values by TPS population were 20.0 months (95% CI 15.4–24.9) for pembrolizumab versus 12.2 months (10.4–14.2) for chemotherapy, 17.7 months (15.3–22.1) versus 13.0 months (11.6–15.3), and 16.7 months (13.9–19.7) versus 12.1 months (11.3–13.3), respectively. Treatment-related adverse events of grade 3 or worse occurred in 113 (18%) of 636 treated patients in the pembrolizumab group and in 252 (41%) of 615 in the chemotherapy group and led to death in 13 (2%) and 14 (2%) patients, respectively.

Interpretation
The benefit-to-risk profile suggests that pembrolizumab monotherapy can be extended as first-line therapy to patients with locally advanced or metastatic non-small-cell lung cancer without sensitising EGFR or ALK alterations and with low PD-L1 TPS.

Leukaemia

Venetoclax (Venclyxto®, Venclexta®,) and obinutuzumab in patients with chronic lymphocytic leukemia (CLL) and coexisting conditions

Overview

Drug Description		venetoclax is an orally administered, BCL2 homology domain 3 (BH3)–mimetic compound that disrupts anti-apoptotic signaling through BCL2, thereby inducing programmed cell death of CLL cells
Patient Indication		patients with previously untreated CD20+ CLL that had been diagnosed in accordance with the criteria of the International Workshop on CLL and had been determined by the treating clinician and confirmed during the central screening process to require therapy (Binet stage C [low haemoglobin or platelet count from bone marrow infiltration of CLL cells] or symptomatic disease)
Incidence in Austria		leukaemia: 1,007 newly diagnosed per year (2016), 11.8/100,000 persons/year (European Standard Population, 2013) [19] CLL: 5,600 newly diagnosed per year (Germany) [20]; CLL is the most common leukaemia in adults.
Current standard treatment		suggested treatment regimens for patients with CLL/SLL without del(17p)/TP53 mutation: ✪ frail patients with significant comorbidity (not able to tolerate purine analogs) OR Patients age ≥65 y and younger patients with significant comorbidities: - preferred regimens: ibrutinib or venetoclax + obinutuzumab - other recommended regimens: ▪ bendamustine + anti-CD20 monoclonal antibody (not recommended for frail patients) ▪ chlorambucil + anti-CD20 monoclonal antibody ▪ high-dose methylprednisolone (HDMP) + rituximab ▪ ibrutinib + obinutuzumab ▪ obinutuzumab ▪ chlorambucil ▪ rituximab ✪ patients aged <65 years without significant comorbidities: - preferred regimen: ibrutinib - other recommended regimens: ▪ bendamustine + anti-CD20 monoclonal antibody ▪ FCR (fludarabine, cyclophosphamide, rituximab) ▪ FR (fludarabine, rituximab) ▪ HDMP + rituximab ▪ ibrutinib + rituximab ▪ venetoclax + obinutuzumab ▪ PCR (pentostatin, cyclophosphamide, rituximab) [21].
Ongoing Phase III		NCT02242942 until 09/2021 NCT03701282 until 10/2025 NCT03462719 until 04/2024 NCT02950051 until 01/2024 NCT03836261 until 04/2024 NCT03737981 until 06/2027 [3]
Approval status for this indication	**EMA**	-
	FDA	according to label information (05/2019), venetoclax is indicated: ✪ for the treatment of adult patients with CLL or small lymphocytic lymphoma (SLL) [4].

Approval status for other indications	**EMA**	according to product information (12/2018), venetoclax is indicated: ❁ in combination with rituximab for the treatment of adult patients with CLL who have received at least one prior therapy ❁ as monotherapy for the treatment of 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, or - in the absence of 17p deletion or TP53 mutation in adult patients who have failed both chemoimmunotherapy and a B-cell receptor pathway inhibitor [8].
	FDA	according to label information (05/2019), venetoclax is indicated: ❁ in combination with azacitidine or decitabine or low-dose cytarabine for the treatment of newly-diagnosed acute myeloid leukemia (AML) in adults who are age 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy [4].
Costs		14 Venclyxto® tablets 10 mg = € 74.94 7 Venclyxto® tablets 50 mg = €187.34 7 Venclyxto® tablets 100 mg = €374.69 14 Venclyxto® tablets 100 mg = € 749.38 112 Venclyxto® tablets 100 mg 4x28 = €5,954.00 (ex-factory prices) [9] Trial patients: the treatment duration in both groups consisted of 12 cycles lasting 28 days each. The daily oral venetoclax regimen was initiated on day 22 of cycle 1, starting with a 5-week dose ramp-up (1 week each of 20, 50, 100, and 200 mg, then 400 mg daily for 1 week, costing € 2, 135.73), thereafter continuing at 400 mg daily until completion of cycle 12 (5,954.00/cycle). In addition, costs for obinutuzumab incur.

Published articles (PubMed):

NEJM; available online June 4, 2019 (Fischer et al.): *"Venetoclax and Obinutuzumab in Patients with CLL and Coexisting Conditions"* [22]

Background
The BCL2 inhibitor venetoclax has shown activity in patients with chronic lymphocytic leukemia (CLL), but its efficacy in combination with other agents in patients with CLL and coexisting conditions is not known.

Methods
In this open-label, phase 3 trial, we investigated fixed-duration treatment with venetoclax and obinutuzumab in patients with previously untreated CLL and coexisting conditions. Patients with a score of greater than 6 on the Cumulative Illness Rating Scale (scores range from 0 to 56, with higher scores indicating more impaired function of organ systems) or a calculated creatinine clearance of less than 70 ml per minute were randomly assigned to receive venetoclax–obinutuzumab or chlorambucil– obinutuzumab. The primary end point was investigator-assessed progression- free survival. The safety of each regimen was also evaluated.

Findings
In total, 432 patients (median age, 72 years; median Cumulative Illness Rating Scale score, 8; median creatinine clearance, 66.4 ml per minute) underwent randomization, with 216 assigned to each group. After a median follow-up of 28.1 months, 30 primary end-point events (disease progression or death) had occurred in the venetoclax–obinutuzumab group and 77 had occurred in the chlorambucil–obinutuzumab group (hazard ratio, 0.35; 95% confidence interval [CI], 0.23 to 0.53; P<0.001). The Kaplan–Meier estimate of the percentage of patients with progression- free survival at 24 months was significantly higher in the venetoclax–obinutuzumab group than in the chlorambucil–obinutuzumab group: 88.2% (95% CI, 83.7 to 92.6) as compared with 64.1% (95% CI, 57.4 to 70.8). This benefit was also observed in patients with TP53 deletion, mutation, or both and in patients with unmutated immunoglobulin heavy-chain genes. Grade 3 or 4 neutropenia occurred in 52.8% of patients in the venetoclax–obinutuzumab group and in 48.1% of patients in the chlorambucil–obinutuzumab group, and grade 3 or 4 infections occurred in 17.5% and 15.0%,

respectively. All-cause mortality was 9.3% in the venetoclax–obinutuzumab group and 7.9% in the chlorambucil–obinutuzumab group. These differences were not significant.

Interpretation
Among patients with untreated CLL and coexisting conditions, venetoclax–obinutuzumab was associated with longer progression-free survival than chlorambucil– obinutuzumab. (Funded by F. Hoffmann–La Roche and AbbVie; ClinicalTrials.gov number, NCT02242942.)

REFERENCES

[1] Statistik Austria. Krebserkrankungen.Brust. [07/2019]; Available from: http://www.statistik-austria.at/web_de/statistiken/menschen_und_gesellschaft/gesundheit/krebserkrankungen/brust/index.html.

[2] National Institute for Health Research. Alpelisib in combination with fulvestrant for advanced HR positive, HER2-negative breast cancer in men and postmenopausal women. [07/2019]; Available from: http://www.io.nihr.ac.uk/wp-content/uploads/2017/12/9191-Alpelisib-fulvestrant-for-breast-cancer.pdf.

[3] U.S. National Library of Medicine. ClinicalTrials.gov. [07/2019]; Available from: https://clinicaltrials.gov/.

[4] U.S. Food and Drug Administration (FDA). [07/2019]; Available from: https://www.accessdata.fda.gov/scripts/cder/daf/.

[5] André F, Ciruelos E, Rubovszky G, Campone M, Loibl S, Rugo HS, et al. Alpelisib for PIK3CA-Mutated, Hormone Receptor–Positive Advanced Breast Cancer. N Engl J Med 2019;380:1929-40.

[6] Im S-A, Lu Y-S, Bardia A, Harbeck N, Colleoni M, Franke F, et al. Overall Survival with Ribociclib plus Endocrine Therapy in Breast Cancer. New England Journal of Medicine. 2019.

[7] National Institute for Health Research. Trastuzumab Emtansine for HER2-positive breast cancer - adjuvant. [07/2019]; Available from: http://www.io.nihr.ac.uk/wp-content/uploads/2018/08/15119-Trastuzumab-Emtansine-for-HER2-Breast-cancer-V1.0-JUL2018-NON-CONF.pdf.

[8] European Medicines Agency (EMA). [07/2019]; Available from: https://www.ema.europa.eu/en.

[9] Apotheker-Verlag. Warenverzeichnis online. [07/2019]; Available from: https://warenverzeichnis.apoverlag.at/.

[10] von Minckwitz G, Huang CS, Mano MS, Loibl S, Mamounas EP, Untch M, et al. Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer. NEJM, published online on December 5, 2018.

[11] Statistik Austria. Krebserkrankungen. Prostata. [07/2019]; Available from: https://www.statistik.at/web_de/statistiken/menschen_und_gesellschaft/gesundheit/krebserkrankungen/prostata/index.html.

[12] National Institute for Health Research. Trastuzumab Emtansine for HER2-positive breast cancer - adjuvant. [cited 07/2019]; Available from: http://www.io.nihr.ac.uk/wp-content/uploads/2018/08/15119-Trastuzumab-Emtansine-for-HER2-Breast-cancer-V1.0-JUL2018-NON-CONF.pdf.

[13] Chi KN, Agarwal N, Bjartell A, Chung BH, Pereira de Santana Gomes AJ, Given R, et al. Apalutamide for Metastatic, Castration- Sensitive Prostate Cancer. NEJM, published online on May 31, 2019.

[14] Davis D, Martin AJ, Stockler MR, Begbie S, Chi KN, Chowdhury S, et al. Enzalutamide with Standard First-Line Therapy in Metastatic Prostate Cancer. NEJM, published on June 2, 2019.

[15] Leonard JP, Trneny M, Izutsu K, Fowler NH, Hong X, Zhu J, et al. AUGMENT: A Phase III Study of Lenalidomide Plus Rituximab Versus Placebo Plus Rituximab in Relapsed or Refractory Indolent Lymphoma. Journal of Clinical Oncology. 2019;37(14):1188-99.

[16] Statistik Austria. Krebserkrankungen. Luftröhre, Bronchien, Lunge. [07/2019]; Available from: http://www.statistik-austria.at/web_de/statistiken/menschen_und_gesellschaft/gesundheit/krebserkrankungen/luftroehre_bronchien_lunge/index.html.

[17] National Institute for Health Research. Pembrolizumab (Keytruda) for PD-L1 strong-positive metastatic non-small cell lung cancer – first line. [07/2019]; Available from: http://www.io.nihr.ac.uk/wp-content/uploads/migrated/Pembrolizumab-July2015.pdf.

[18] Mok TS, Wu Y-L, Kudaba I, Kowalski DM, Chul Cho B, Turna HZ, et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-

small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. The Lancet Published Online April 4, 2019.

[19] Statistik Austria. Krebserkrankungen. Leukämie. [07/2019]; Available from: https://www.statistik.at/web_de/statistiken/menschen_und_gesellschaft/gesundheit/krebserkrankungen/leukaemie/index.html.

[20] Onkopedia. Chronische Lymphatische Leukämie (CLL). [07/2019]; Available from: https://www.onkopedia.com/de/onkopedia/guidelines/chronische-lymphatische-leukaemie-cll/@@guideline/html/index.html.

[21] National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Chronic Lymphocytic Leukemia/ Small Lymphocytic Lymphoma. Version 5.2019 — May 23, 2019. [07/2019]; Available from: www.nccn.org.

[22] Statistik Austria. Krebserkrankungen. Luftröhre, Bronchien, Lunge. [cited 07/2019]; Available from: http://www.statistik-austria.at/web_de/statistiken/menschen_und_gesellschaft/gesundheit/krebserkrankungen/luftroehre_bronchien_lunge/index.html.