



Horizon Scanning in Oncology 39th Prioritization – 2nd 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>), nine information sources are scanned frequently to identify emerging anticancer drugs.

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

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

For the 39th prioritisation (April 2019), 10 drugs were filtered out of 507 identified and were sent to prioritisation. Of these, three drugs were ranked as ‘highly relevant’ by the expert panel, seven as ‘relevant’ and none as ‘not relevant’. For ‘highly relevant’ drugs, further information including, for example, abstracts of phase III studies and licensing status is contained in this document.

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

No	Filtered Drugs – 39 th prioritisation 2 nd quarter 2019	Overall category
1.	Avelumab (Bavencio®) plus axitinib versus sunitinib for advanced renal-cell carcinoma (RCC)	Relevant
2.	Pembrolizumab (Keytruda®) plus axitinib versus sunitinib for advanced RCC	Relevant
3.	Brentuximab vedotin (Adcetris®) with chemotherapy for CD30-positive, peripheral T-cell lymphoma	Highly relevant
4.	Darolutamide (ODM-201) in nonmetastatic, castration-resistant prostate cancer (CRPC)	Highly relevant
5.	Adjuvant denosumab (Xgeva®, Prolia®) in postmenopausal patients with hormone receptor-positive breast cancer	Relevant
6.	Ibrutinib (Imbruvica®) plus obinutuzumab versus chlorambucil plus obinutuzumab in first-line treatment of chronic lymphocytic leukaemia (CLL)	Highly relevant
7.	Oral ixazomib (Ninlaro®) maintenance following ASCT (TOURMALINE-MM3)	Relevant
8.	PD-1 blockade with pembrolizumab (Keytruda®) in advanced Merkel-cell carcinoma (MCC)	Relevant
9.	Ramucirumab (Cyramza®) after sorafenib in patients with advanced hepatocellular carcinoma (HCC) and increased α -fetoprotein concentrations	Relevant
10.	Sorafenib (Nexavar®) for advanced and refractory desmoid tumours	Relevant

Lymphoma

Brentuximab vedotin (Adcetris®) with chemotherapy for CD30-positive, peripheral T-cell lymphoma

Overview

Drug Description		brentuximab vedotin is an antibody-drug conjugate composed of a CD30-directed monoclonal antibody that is covalently linked to the antimicrotubule agent monomethyl auristatin E (MMAE)
Patient Indication		patients with previously untreated, CD30-positive peripheral T-cell lymphoma
Incidence in Austria		approx. 10% of newly diagnosed non-Hodgkin-lymphomas (NHLs) are T-cell lymphomas. NHL: 1,333 newly diagnosed per year (2016), 15.5/100,000 persons/year (2016) (European Standard Population 2013) [1]
Current standard treatment		<ul style="list-style-type: none"> ✧ the most common peripheral T-cell lymphomas are nodal peripheral T-cell lymphomas, including peripheral T-cell lymphoma not otherwise specified, angioimmunoblastic T-cell lymphoma, and ALK-positive or ALK-negative systemic anaplastic large cell lymphoma. ✧ for the first-line treatment, strategies should be adapted according to factors such as age, international prognostic index (IPI), and comorbidity that define a patient's eligibility for dose-intensified approaches ✧ whenever possible, inclusion in a clinical trial is recommended ✧ cyclophosphamide, hydroxydaunorubicin, vincristine and prednisone (CHOP), or variants of it, has been the most commonly used regimen in nodal peripheral T-cell lymphomas [2, 3]
Ongoing Phase III		NCT01777152 (ECHELON-2) until 12/2019 [4]
Approval status for this indication [5, 6]	EMA	-
	FDA	-
Approval status for other indications [5, 6]	EMA	<p>according to product information (03/2019), brentuximab vedotin is indicated:</p> <ul style="list-style-type: none"> ✧ for adult patients with previously untreated CD30+ Stage IV Hodgkin lymphoma (HL) in combination with doxorubicin, vinblastine and dacarbazine (AVD) ✧ for the treatment of adult patients with CD30+ HL at increased risk of relapse or progression following ASCT ✧ for the treatment of adult patients with relapsed or refractory CD30+ HL <ul style="list-style-type: none"> - following ASCT, or - following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option. Brentuximab vedotin is indicated for the treatment of adult patients with relapsed or refractory systemic anaplastic large cell lymphoma (sALCL) ✧ for the treatment of adult patients with CD30+ cutaneous T-cell lymphoma (CTCL) after at least 1 prior systemic therapy
	FDA	<p>according to label information (11/2018), brentuximab vedotin is indicated for the treatment of adult patients with:</p> <ul style="list-style-type: none"> ✧ previously untreated Stage III or IV cHL, in combination with doxorubicin, vinblastine, and dacarbazine

	<ul style="list-style-type: none"> ✧ cHL at high risk of relapse or progression as post-autologous hematopoietic stem cell transplantation (auto-HSCT) consolidation ✧ cHL after failure of auto-HSCT or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not auto-HSCT candidates ✧ previously untreated sALCL or other CD30-expressing peripheral T-cell lymphomas (PTCL), including angioimmunoblastic T-cell lymphoma and PTCL not otherwise specified, in combination with cyclophosphamide, doxorubicin, and prednisone ✧ sALCL after failure of at least one prior multi-agent chemotherapy regimen ✧ primary cutaneous anaplastic large cell lymphoma (pcALCL) or CD30-expressing mycosis fungoides (MF) who have received prior systemic therapy.
Costs	<p>Adcetris[®] 50 mg powder for concentrate for solution for infusion = € 3,333.00 (ex-factory price) [7].</p> <p>ECHELON-2 patients received cyclophosphamide 750 mg/m² and doxorubicin 50 mg/m² on day 1 of each cycle intravenously and prednisone 100 mg once daily on days 1 to 5 of each cycle orally, followed by either brentuximab vedotin 1.8 mg/kg and a placebo form of vincristine intravenously (A+CHP group) or vincristine 1.4 mg/m² and a placebo form of brentuximab vedotin intravenously (CHOP group) on day 1 of each cycle. The number of the 21-day cycles (six or eight) was decided at the investigator's discretion at registration.</p> <p>Based on study treatment and assuming an average body weight of 70 kg, one dose of brentuximab vedotin would cost approx. € 9,999.00 (6 cycles = approx. € 59,994.00) .</p>

1.1.1 Published articles (PubMed):

The Lancet; available online December 4, 2018 (Horwitz et al.): *“Brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECHELON-2): a global, double-blind, randomised, phase 3 trial” [2]*

Background

Based on the encouraging activity and manageable safety profile observed in a phase 1 study, the ECHELON-2 trial was initiated to compare the efficacy and safety of brentuximab vedotin, cyclophosphamide, doxorubicin, and prednisone (A+CHP) versus cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) for the treatment of CD30-positive peripheral T-cell lymphomas.

Methods

ECHELON-2 is a double-blind, double-dummy, randomised, placebo-controlled, active-comparator phase 3 study. Eligible adults from 132 sites in 17 countries with previously untreated CD30-positive peripheral T-cell lymphomas (targeting 75% with systemic anaplastic large cell lymphoma) were randomly assigned 1:1 to receive either A+CHP or CHOP for six or eight 21-day cycles. Randomisation was stratified by histological subtype according to local pathology assessment and by international prognostic index score. All patients received cyclophosphamide 750 mg/m² and doxorubicin 50 mg/m² on day 1 of each cycle intravenously and prednisone 100 mg once daily on days 1 to 5 of each cycle orally, followed by either brentuximab vedotin 1.8 mg/kg and a placebo form of vincristine intravenously (A+CHP group) or vincristine 1.4 mg/m² and a placebo form of brentuximab vedotin intravenously (CHOP group) on day 1 of each cycle. The primary endpoint, progression-free survival according to blinded independent central review, was analysed by intent-to-treat. This trial is registered with ClinicalTrials.gov, number NCT01777152.

Findings

Between Jan 24, 2013, and Nov 7, 2016, 601 patients assessed for eligibility, of whom 452 patients were enrolled and 226 were randomly assigned to both the A+CHP group and the CHOP group. Median progression-free survival was 48.2 months (95% CI 35.2–not evaluable) in the A+CHP

group and 20.8 months (12.7–47.6) in the CHOP group (hazard ratio 0.71 [95% CI 0.54–0.93], $p=0.0110$). Adverse events, including incidence and severity of febrile neutropenia (41 [18%] patients in the A+CHP group and 33 [15%] in the CHOP group) and peripheral neuropathy (117 [52%] in the A+CHP group and 124 [55%] in the CHOP group), were similar between groups. Fatal adverse events occurred in seven (3%) patients in the A+CHP group and nine (4%) in the CHOP group.

Interpretation

Front-line treatment with A+CHP is superior to CHOP for patients with CD30-positive peripheral T-cell lymphomas as shown by a significant improvement in progression-free survival and overall survival with a manageable safety profile.

Prostate Cancer

Darolutamide (ODM-201) in nonmetastatic, castration-resistant prostate cancer (CRPC)

Overview

Drug Description	darolutamide is an androgen-receptor antagonist	
Patient Indication	men with nonmetastatic CRPC	
Incidence in Austria	5,245 newly diagnosed per year (2016), 138.3/100,000 men/year (2016) (European Standard Population, 2013) [8]	
Current standard treatment	<ul style="list-style-type: none"> ✧ there are several treatment options available to patients with non-metastatic CRPC ✧ many men with localised prostate cancer will not benefit from definitive treatment, and 45% of men with prostate-specific antigen (PSA)-detected prostate cancer are candidates for deferred management (watchful waiting) ✧ in men with comorbidity and limited life expectancy, treatment of localized prostate cancer may be deferred to avoid loss of quality ✧ European Association of Urology (EAU) - European Society for Radiotherapy & Oncology (ESTRO) - International Society of Geriatric Oncology (SIOG) - guidelines recommend the use of: <ul style="list-style-type: none"> - watchful waiting or observation - radical prostatectomy (surgical removal of the entire prostate gland between the urethra and bladder) - external beam radiotherapy - brachytherapy (trans-perineal implantation of radioactive seeds into the prostate) - cryotherapy (local or general use of low temperatures in medical therapy) - hormone therapy (androgen deprivation or anti-androgens) ✧ treatment recommendations are dependent on the disease and patient characteristics, currently there is no standard treatment for castrated patients with rising PSA and no evidence of metastases [9]. 	
Ongoing Phase III [4]	NCT02200614 (ARAMIS) until 06/2020	
Approval status for this indication [5, 6]	EMA	-
	FDA	-
Approval status for other indications [5, 6]	EMA	-
	FDA	-
Costs	-	

1.1.2 Published articles (PubMed):

NEJM; available online February 14, 2019 (Fizazi et al.): "Darolutamide in Nonmetastatic, Castration-Resistant Prostate Cancer" [10]

Background

Darolutamide is a structurally unique androgen-receptor antagonist that is under development for the treatment of prostate cancer. We evaluated the efficacy of darolutamide for delaying metastasis and death in men with nonmetastatic, castration-resistant prostate cancer.

Methods

We conducted a randomized, 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 darolutamide (600 mg [two 300-mg tablets] twice daily) or placebo while continuing androgen-deprivation therapy. The primary end point was metastasis-free survival, with the presence of metastasis determined by independent central review of radiographic imaging every 16 weeks.

Findings

In total, 1509 patients underwent randomization (955 to the darolutamide group and 554 to the placebo group). In the planned primary analysis, which was performed after 437 primary end-point events had occurred, the median metastasis-free survival was 40.4 months with darolutamide, as compared with 18.4 months with placebo (hazard ratio for metastasis or death in the darolutamide group, 0.41; 95% confidence interval, 0.34 to 0.50; $P < 0.001$). Darolutamide was also associated with benefits with regard to all secondary end points, including overall survival, time to pain progression, time to cytotoxic chemotherapy, and time to a symptomatic skeletal event. The incidence of adverse events that occurred or worsened during the treatment period and had a frequency of 5% or more or were of grade 3 or higher was similar in the two groups; all such events except fatigue occurred in less than 10% of patients in either group. The percentage of patients who discontinued the assigned regimen because of adverse events was 8.9% in the darolutamide group and 8.7% in the placebo group. Darolutamide was not associated with a higher incidence of seizures, falls, fractures, cognitive disorder, or hypertension than placebo.

Interpretation

Among men with nonmetastatic, castration-resistant prostate cancer, metastasis-free survival was significantly longer with darolutamide than with placebo. The incidence of adverse events was similar for darolutamide and placebo. (Funded by Bayer HealthCare and Orion Pharma; ARAMIS ClinicalTrials.gov number, NCT02200614.)

Leukaemia

Ibrutinib (Imbruvica®) plus obinutuzumab versus chlorambucil plus obinutuzumab in first-line treatment of chronic lymphocytic leukaemia (CLL)

Overview

Drug Description		ibrutinib is an oral inhibitor of tyrosine-protein kinase (BTK)
Patient Indication		patients with untreated, active CLL or small lymphocytic lymphoma (SLL)
Incidence in Austria	leukaemia: 1,007 newly diagnosed per year (2016), 11.8/100,000 persons/year (2016) (European Standard Population, 2013) [11]	
Current standard treatment	<ul style="list-style-type: none"> ✧ the choice of first-line therapy of patients with CLL depends on the presence of any comorbidities, genetic status, renal function and to a lesser extent patient age ✧ wherever possible, the therapy should take place within the framework of a clinical trial ✧ patients without del(17p13) or TP53 mutation: <ul style="list-style-type: none"> - physically fit patients: combination therapy with fludarabine, cyclophosphamide and rituximab (FCR); alternatively: combination of bendamustine with rituximab - unfit patients: chlorambucil or bendamustine - frail patients: supportive therapy is paramount (this may also include administration of antineoplastic drugs such as steroids, chlorambucil, bendamustine or rituximab at adapted doses) ✧ patients with a confirmed del(17p13) or TP53 mutation: <ul style="list-style-type: none"> - in patients without relevant comorbidity but with CLL requiring therapy there are alternative approaches available for first-line therapy such as ibrutinib, idelalisib/rituximab or alemtuzumab - the indication for allogeneic blood stem cell transplantation should be given critical consideration after weighing up of individual risks considering age, comorbidities, and the availability of perfectly matched donors. 	
Ongoing Phase III [4]	NCT02264574 (iLLUMINATE) until 01/2020 NCT03701282 until 10/2025 NCT02863718 until 04/2022 NCT02048813 until 03/2020 NCT01886872 until 02/2019 NCT03737981 until 06/2027 NCT02950051 until 01/2024	
Approval status for this indication [5, 6]	EMA	-
	FDA	according to label information (01/2019), ibrutinib is indicated for the treatment of adult patients with: <ul style="list-style-type: none"> ✧ CLL/SLL ✧ CLL/SLL with 17p deletion
Approval status for other indications [5, 6]	EMA	according to product information (08/2018), ibrutinib is indicated: <ul style="list-style-type: none"> ✧ 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 CLL ✧ as a single agent or in combination with bendamustine and

		<p>rituximab for the treatment of adult patients with CLL who have received at least one prior therapy</p> <ul style="list-style-type: none"> ✧ as a single agent for the treatment of adult patients with Waldenström's macroglobulinaemia (WM) who have received at least one prior therapy, or in first line treatment for patients unsuitable for chemo-immunotherapy.
	FDA	<p>according to label information (01/2019), ibrutinib is indicated for the treatment of adult patients with:</p> <ul style="list-style-type: none"> ✧ MCL who have received at least one prior therapy ✧ Waldenström's macroglobulinaemia (WM) ✧ marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy ✧ chronic graft versus host disease (cGVHD) after failure of one or more lines of systemic therapy
Costs		<p>90 Imbruvica[®] hard capsules 140 mg = € 5474.70 (ex-factory price) [7] 120 Imbruvica[®] hard capsules 140 mg = € 7299.60 (ex-factory price) [7]</p> <p>iLLUMINATE trial patients received oral ibrutinib at a dose of 420 mg once daily continuously combined with intravenous obinutuzumab for a total of 6 (28-day-)cycles. Based on study treatment, one month of ibrutinib treatment would cost approx. € 5474.70 (6 cycles = € 32,848.20); additionally, costs for obinutuzumab treatment would incur.</p>

1.1.3 Published articles (PubMed):

Lancet Oncol 2019; 20: 43–56, 3 December 2018 (Moreno et al.): *“Ibrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab in first-line treatment of chronic lymphocytic leukaemia (iLLUMINATE): a multicentre, randomised, open-label, phase 3 trial”* [12]

Background

Both single-agent ibrutinib and chlorambucil plus obinutuzumab have shown superior efficacy to chlorambucil monotherapy and are standard first-line treatments in chronic lymphocytic leukaemia. We compared the efficacy of the combination of ibrutinib plus obinutuzumab with chlorambucil plus obinutuzumab in first-line chronic lymphocytic leukaemia or small lymphocytic lymphoma.

Methods

iLLUMINATE is a multicentre, randomised, open-label, phase 3 trial done at 74 academic and community hospitals in Australia, Canada, Israel, New Zealand, Russia, Turkey, the EU, and the USA in patients with previously untreated chronic lymphocytic leukaemia or small lymphocytic lymphoma, either aged 65 years or older or younger than 65 years with coexisting conditions. Patients were randomly assigned (1:1) using a blocked randomisation schedule, stratified by Eastern Cooperative Oncology Group performance status and cytogenetics, to receive ibrutinib plus obinutuzumab (oral ibrutinib [420 mg once daily continuously] combined with intravenous obinutuzumab [100 mg on day 1, 900 mg on day 2, 1000 mg on day 8, and 1000 mg on day 15 of cycle 1 and on day 1 of subsequent 28-day cycles, for a total of six cycles]) or chlorambucil plus obinutuzumab (oral chlorambucil [0.5 mg/kg bodyweight on days 1 and 15 of each 28-day cycle for six cycles] combined with the same obinutuzumab regimen). Allocation concealment was achieved using an interactive web response system. Patients and investigators were not masked to treatment assignment. The primary endpoint was progression-free survival assessed by a masked independent review committee in the intention-to-treat population. Safety was assessed in all patients who received at least one dose of study treatment. This study is registered with ClinicalTrials.gov (NCT02264574), and patient enrolment is complete.

Findings

Between Oct 6, 2014, and Oct 12, 2015, 229 patients were enrolled and randomly assigned to receive ibrutinib plus obinutuzumab (n=113) or chlorambucil plus obinutuzumab (n=116). After a median follow-up of 31.3 months (IQR 29.4–33.2), median progression-free survival was significantly longer in the ibrutinib plus obinutuzumab group (median not reached [95% CI 33.6–

non-estimable]) than in the chlorambucil plus obinutuzumab group (19.0 months [15.1–22.1]; hazard ratio 0.23; 95% CI 0.15–0.37; $p < 0.0001$). Estimated 30-month progression-free survival was 79% (95% CI 70–85) in the ibrutinib plus obinutuzumab group and 31% (23–40) in the chlorambucil plus obinutuzumab group. The most common grade 3 or 4 adverse events in both groups were neutropenia and thrombocytopenia. Serious adverse events occurred in 65 (58%) of 113 patients treated with ibrutinib plus obinutuzumab and 40 (35%) of 115 patients treated with chlorambucil plus obinutuzumab. Ibrutinib or chlorambucil treatment-related deaths were reported in one (1%) of 113 patients in the ibrutinib plus obinutuzumab group (sudden death) and one (1%) of 115 patients in the chlorambucil plus obinutuzumab group (neuroendocrine carcinoma of the skin).

Interpretation

Ibrutinib plus obinutuzumab is an efficacious and safe chemotherapy-free combination treatment in previously untreated patients with chronic lymphocytic leukaemia or small lymphocytic lymphoma independent of high-risk features and provides an alternative first-line treatment option for these patients.

References

- [1] Statistik Austria. Krebserkrankungen. Non-Hodgkin. [cited 04/2019]; Available from: https://www.statistik.at/web_de/statistiken/menschen_und_gesellschaft/gesundheit/krebs_erkrankungen/non-hodgkin/021786.html.
- [2] Horwitz S, O'Connor OA, Pro B, Illidge T, Fanale M, Advani R, et al. Brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECHOLON-2): a global, double-blind, randomised, phase 3 trial. This article was published online December 4, 2018 at www.thelancet.com.
- [3] d'Amore F, Gaulard P, Trümper L, Corradini P, Kim WS, Specht L, et al. Peripheral T-cell lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology* 26 (Supplement 5): v108–v115, 2015.
- [4] U.S. National Library of Medicine. ClinicalTrials.gov. Available from: <https://clinicaltrials.gov/>.
- [5] European Medicines Agency. Medicines. Available from: <https://www.ema.europa.eu/en/medicines>.
- [6] U.S. Food and Drug Administration. Drugs@FDA: FDA Approved Drug Products.; Available from: <https://www.accessdata.fda.gov/scripts/cder/daf/>.
- [7] Warenverzeichnis Apothekerverlag Online. [cited 04/2019]; Available from: <https://warenverzeichnis.apoverlag.at/>.
- [8] Statistik Austria. Krebserkrankungen.Prostata. [cited 04/2019]; Available from: https://www.statistik.at/web_de/statistiken/menschen_und_gesellschaft/gesundheit/krebs_erkrankungen/prostata/021791.html.
- [9] National Institute for Health Research (NIHR). Darolutamide for non-metastatic, castrationresistant prostate cancer. Available from: http://www.io.nihr.ac.uk/wp-content/uploads/2018/02/7531-Darolutamide_prostate-cancer_V2.0-FEB2018-NON-CONF.pdf.
- [10] Fizazi K, Shore N, Tammela TL, Ulys A, Vjaters E, Polyakov S, et al. Darolutamide in Nonmetastatic, Castration-Resistant Prostate Cancer. This article was published on February 14, 2019, at NEJM.org.
- [11] Statistik Austria. Krebserkrankungen.Leukämie. [cited 04/2019]; Available from: https://www.statistik.at/web_de/statistiken/menschen_und_gesellschaft/gesundheit/krebs_erkrankungen/leukaemie/021761.html.
- [12] Moreno C, Greil R, Demirkan F, Tedeschi A, Anz B, Larratt L, et al. Ibrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab in first-line treatment of chronic lymphocytic leukaemia (iLLUMINATE): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol* 2019; 20: 43–56.