Ludwig Boltzmann Institut
Health Technology Assessment

Horizon Scanning in Oncology
27th Prioritization – 2nd quarter 2016

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 and conference abstracts of phase III trials, assessing the safety and efficacy of the drugs of interest.

At the very end of each chapter we have provided a table containing the prioritization criteria and a drop-down field to apply the provided criteria.

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 27th prioritisation (June 2016), 12 drugs were filtered out of 282 identified and were sent to prioritisation. Of these, 5 drugs were ranked as ‘highly relevant’ by the expert panel, 7 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 – 27th prioritisation 2nd quarter 2016	Overall category
1.	Combined chemotherapy with cisplatin, etoposide, and irinotecan versus topotecan alone as second-line treatment for patients with sensitive relapsed small-cell lung cancer	Relevant
2.	Erlotinib (Tarceva®) alone or with bevacizumab (Avastin®) as first-line therapy in patients with advanced non-squamous non-small-cell lung cancer harbouring EGFR mutations	Relevant
3.	Oral ixazomib (MLN9708, Ninlaro®), lenalidomide, and dexamethasone for multiple myeloma	Highly relevant
4.	Phase III trial evaluating letrozole (Femara®) as first-line endocrine therapy with or without bevacizumab (Avastin®) for the treatment of postmenopausal women with hormone receptor–positive advanced-stage breast cancer	Relevant
5.	Fulvestrant plus palbociclib (Ibrance®) versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy	Relevant
6.	Atezolizumab (Tecentriq®) in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy	Highly relevant
7.	Randomized, double-blind, placebo-controlled phase III study of tasquinimod in men with metastatic castration-resistant prostate cancer	Relevant
8.	Lenvatinib (Lenvima®), everolimus (Afinitor®), and the combination in patients with metastatic renal cell carcinoma	Relevant
9.	Nivolumab (Opdivo®) in classical Hodgkin lymphoma after autologous stem cell transplant and brentuximab vedotin	Highly relevant
10.	Brentuximab vedotin (Adcetris®) as consolidation therapy after autologous stem-cell transplantation in patients with Hodgkin's lymphoma at risk of relapse or progression (AETHERA)	Relevant
11.	Venetoclax (Venclexta™) in relapsed or refractory chronic lymphocytic leukaemia with 17p deletion	Highly relevant
12.	Inotuzumab ozogamicin versus standard therapy for acute lymphoblastic leukemia	Highly relevant

1 Multiple Myeloma

1.1 Oral ixazomib (MLN9708, Ninlaro®), lenalidomide, and dexamethasone for multiple myeloma

Overview

Drug Description		is a reversible proteasome inhibitor that preferentially binds and inhibits the chymotrypsin-like activity of the beta 5 subunit of the 20S proteasome
Patient Indication		ixazomib plus lenalidomide–dexamethasone for relapsed, refractory, or relapsed and refractory multiple myeloma
Incidence in Austria		627 newly diagnosed per year (2012), 5.6 /100,000/year
Ongoing Phase III		NCT01564537 - until 05/2019
Approval status for this indication	**EMA**	On 26 May 2016, the Committee for Medicinal Products for Human Use (CHMP) adopted a negative opinion, recommending the refusal of the marketing authorisation for the medicinal product Ninlaro, intended for the treatment of multiple myeloma. → Update of 24 June 2016: The company that applied for a marketing authorisation for Ninlaro has requested a re-examination of the CHMP's May 2016 opinion. Upon receipt of the grounds of the request, the CHMP will re-examine its opinion and issue a final recommendation.
	FDA	11/2015: for the treatment of patients with multiple myeloma who have received at least one prior therapy
Approval status for other indications	**EMA**	Ninlaro was designated an 'orphan medicine' on 27 September 2011, for the treatment of multiple myeloma.
	FDA	01/2005: approved for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated. 09/2013: approved for metastatic adenocarcinoma of the pancreas as first-line treatment, in combination with gemcitabine. 10/2012: Locally advanced or metastatic Non-Small Cell Lung Cancer (NSCLC), as first-line treatment in combination with carboplatin, in patients who are not candidates for curative surgery or radiation therapy.
Costs		-

Phase III results

NEJM (2016) 374:1621-1634 (Moreau et al.): *"Oral Ixazomib, Lenalidomide, and Dexamethasone for Multiple Myeloma"*

Background

Ixazomib is an oral proteasome inhibitor that is currently being studied for the treatment of multiple myeloma.

Methods
In this double-blind, placebo-controlled, phase 3 trial, we randomly assigned 722 patients who had relapsed, refractory, or relapsed and refractory multiple myeloma to receive ixazomib plus lenalidomide–dexamethasone (ixazomib group) or placebo plus lenalidomide–dexamethasone (placebo group). The primary end point was progression-free survival.

Results
Progression-free survival was significantly longer in the ixazomib group than in the placebo group at a median follow-up of 14.7 months (median progression-free survival, 20.6 months vs. 14.7 months; hazard ratio for disease progression or death in the ixazomib group, 0.74; P=0.01); a benefit with respect to progression-free survival was observed with the ixazomib regimen, as compared with the placebo regimen, in all prespecified patient subgroups, including in patients with high-risk cytogenetic abnormalities. The overall rates of response were 78% in the ixazomib group and 72% in the placebo group, and the corresponding rates of complete response plus very good partial response were 48% and 39%. The median time to response was 1.1 months in the ixazomib group and 1.9 months in the placebo group, and the corresponding median duration of response was 20.5 months and 15.0 months. At a median follow-up of approximately 23 months, the median overall survival has not been reached in either study group, and follow-up is ongoing. The rates of serious adverse events were similar in the two study groups (47% in the ixazomib group and 49% in the placebo group), as were the rates of death during the study period (4% and 6%, respectively); adverse events of at least grade 3 severity occurred in 74% and 69% of the patients, respectively. Thrombocytopenia of grade 3 and grade 4 severity occurred more frequently in the ixazomib group (12% and 7% of the patients, respectively) than in the placebo group (5% and 4% of the patients, respectively). Rash occurred more frequently in the ixazomib group than in the placebo group (36% vs. 23% of the patients), as did gastrointestinal adverse events, which were predominantly low grade. The incidence of peripheral neuropathy was 27% in the ixazomib group and 22% in the placebo group (grade 3 events occurred in 2% of the patients in each study group). Patient-reported quality of life was similar in the two study groups.

Conclusions
The addition of ixazomib to a regimen of lenalidomide and dexamethasone was associated with significantly longer progression-free survival; the additional toxic effects with this all-oral regimen were limited. (Funded by Millennium Pharmaceuticals; TOURMALINE-MM1 ClinicalTrials.gov number, NCT01564537.)

2 Urothelial carcinoma

2.1 Atezolizumab (Tecentriq®) in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy

Overview

Drug Description	a programmed death-ligand 1 (PD-L1) blocking antibody
Patient Indication	atezolizumab for metastatic urothelial carcinoma after failure of platinum-based chemotherapy
Incidence in Austria	1,496 newly diagnosed per year (2012), 8.9 /100,000/year

Ongoing Phase III		NCT02589717 - until 2016
Approval status for this indication	**EMA**	-
	FDA	05/2016: approved for the treatment of patients with locally advanced or metastatic urothelial carcinoma who: • have disease progression during or following platinum-containing chemotherapy. • have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.
Approval status for other indications	**EMA**	-
	FDA	-
Costs		-

Phase II results

The Lancet, Published Online March 4, 2016 (Rosenberg et al.): *"Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial"*

Background
Patients with metastatic urothelial carcinoma have few treatment options after failure of platinum-based chemotherapy. In this trial, we assessed treatment with atezolizumab, an engineered humanised immunoglobulin G1 monoclonal antibody that binds selectively to programmed death ligand 1 (PD-L1), in this patient population.

Methods
For this multicentre, single-arm, two-cohort, phase 2 trial, patients (aged ≥18 years) with inoperable locally advanced or metastatic urothelial carcinoma whose disease had progressed after previous platinum-based chemotherapy were enrolled from 70 major academic medical centres and community oncology practices in Europe and North America. Key inclusion criteria for enrolment were Eastern Cooperative Oncology Group performance status of 0 or 1, measurable disease defined by Response Evaluation Criteria In Solid Tumours version 1.1 (RECIST v1.1), adequate haematological and end-organ function, and no autoimmune disease or active infections. Formalin-fixed paraffin-embedded tumour specimens with sufficient viable tumour content were needed from all patients before enrolment. Patients received treatment with intravenous atezolizumab (1200 mg, given every 3 weeks). PD-L1 expression on tumour-infiltrating immune cells (ICs) was assessed prospectively by immunohistochemistry. The co-primary endpoints were the independent review facility-assessed objective response rate according to RECIST v1.1 and the investigator-assessed objective response rate according to immune-modified RECIST, analysed by intention to treat. A hierarchical testing procedure was used to assess whether the objective response rate was significantly higher than the historical control rate of 10% at an α level of 0·05. This study is registered with ClinicalTrials.gov, number NCT02108652.

Findings
Between May 13, 2014, and Nov 19, 2014, 486 patients were screened and 315 patients were enrolled into the study. Of these patients, 310 received atezolizumab treatment (five enrolled patients later did not meet eligibility criteria and were not dosed with study drug). The PD-L1 expression status

on infiltrating immune cells (ICs) in the tumour microenvironment was defined by the percentage of PD-L1-positive immune cells: IC0 (<1%), IC1 (≥1% but <5%), and IC2/3 (≥5%). The primary analysis (data cut-off May 5, 2015) showed that compared with a historical control overall response rate of 10%, treatment with atezolizumab resulted in a significantly improved RECIST v1.1 objective response rate for each prespecified immune cell group (IC2/3: 27% [95% CI 19–37], p<0·0001; IC1/2/3: 18% [13–24], p=0·0004) and in all patients (15% [11–20], p=0·0058). With longer follow-up (data cut-off Sept 14, 2015), by independent review, objective response rates were 26% (95% CI 18–36) in the IC2/3 group, 18% (13–24) in the IC1/2/3 group, and 15% (11–19) overall in all 310 patients. With a median follow-up of 11·7 months (95% CI 11·4–12·2), ongoing responses were recorded in 38 (84%) of 45 responders. Exploratory analyses showed The Cancer Genome Atlas (TCGA) subtypes and mutation load to be independently predictive for response to atezolizumab. Grade 3–4 treatment-related adverse events, of which fatigue was the most common (five patients [2%]), occurred in 50 (16%) of 310 treated patients. Grade 3–4 immune-mediated adverse events occurred in 15 (5%) of 310 treated patients, with pneumonitis, increased aspartate aminotransferase, increased alanine aminotransferase, rash, and dyspnoea being the most common. No treatment-related deaths occurred during the study.

Interpretation
Atezolizumab showed durable activity and good tolerability in this patient population. Increased levels of PD-L1 expression on immune cells were associated with increased response. This report is the first to show the association of TCGA subtypes with response to immune checkpoint inhibition and to show the importance of mutation load as a biomarker of response to this class of agents in advanced urothelial carcinoma.

3 Lymphoma

3.1 Nivolumab (Opdivo®) in classical Hodgkin lymphoma after autologous stem cell transplant and brentuximab vedotin

Overview

Drug Description		humanized IgG4 anti-PD-1 monoclonal antibody
Patient Indication		nivolumab for classical Hodgkin lymphoma (cHL) that has relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) and post-transplantation brentuximab vedotin
Incidence in Austria		161 newly diagnosed per year (2012), 1.8/100,000/year
Ongoing Phase III		NCT02572167 - until 2020 NCT01822509 - until 2016
Approval status for this indication	**EMA**	-
	FDA	On May 17, 2016 nivolumab received accelerated approval for the treatment of patients with classical Hodgkin lymphoma (cHL) that has relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) and post-transplantation brentuximab vedotin. Based on the results of the CheckMate-205 and the CheckMate-039 trial.
Approval status for other indications	**EMA**	05/2016: for the treatment of advanced melanoma as a monotherapy or in combination with ipilimumab 02/2016: for the treatment of non-small cell lung cancer (NSCLC) that has spread locally or to other parts of the body in patients who have previously

		been treated 04/2016: as a monotherapy for advanced renal cell carcinoma in previously treated patients
	FDA	09/2015: BRAF V600 wild-type unresectable or metastatic melanoma, as a single agent. 09/2015: BRAF V600 mutation-positive unresectable or metastatic melanoma, as a single agent. 09/2015: Unresectable or metastatic melanoma, in combination with ipilimumab. 10/2015: Metastatic non-small cell lung cancer and progression on or after platinum based chemotherapy. Patients with EGFR or ALK genomic tumour aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving OPDIVO. 11/2015: Advanced renal cell carcinoma after prior anti-angiogenic therapy.
Costs		→ nivolumab conc. 10mg/ml 40 ml €626; nivolumab conc. 10mg/ml 100 ml: €1,517.50. The recommended dose-schedule of nivolumab is 3 mg/kg intravenously every 2 weeks until disease progression or unacceptable toxicity; assuming an average body weight of 70 kg, a dose of 210mg nivolumab would be needed, costing €3,186.75 per 2-week cycle and €6,373.5 per month.

Abstracts

ASCO 2016 Annual Meeting (Younes et al.)

Background

cHL is characterized by amplification at 9p24.1, causing overexpression of PD-1 ligands. Thus, cHL may be uniquely sensitive to PD-1 blockade. Nivo is a fully human IgG4 immune checkpoint inhibitor targeting PD-1 that showed promising results in a phase 1b study (NCT01592370) in pts with relapsed/refractory cHL (Ansell SM et al NEJM 2015;372:311–9), who currently have limited treatment options.

Methods

This study evaluated the efficacy and safety of nivo in pts with cHL who had received BV after failed ASCT, as Cohort B of the larger Phase 2 Checkmate 205 study (NCT02181738). Nivo was given at 3 mg/kg IV q2w. Response was assessed by independent radiologic review committee (IRRC) and investigators (Inv), using 2007 IWG criteria. Primary endpoint was IRRC ORR.

Results

The main characteristics of 80 treated cHL pts were: median age 37 y, median (range) 4 prior regimens (3–15). 90% of pts had drug-related AEs: 25% G3–4, 1% G5 (multi-organ failure). Most common drug-related AEs were fatigue (25%), infusion reaction (IR; 20%) and rash (16%). Most common SAEs were pyrexia, tumour progression, arrhythmia, IR, septic meningitis, and pneumonia (≤ 4% each). Select immune-related AEs, all G1–2, occurred in 26%. At database lock (DBL; October 2015), median (range) follow-up was 8.9 mo (1.9–11.7). 64% of pts remained on therapy; main reason for discontinuation was disease progression (16%). IRRC ORR (95% CI) was 66% (54.8–76.4); CR and PR rates were 8.8% (3.6–17.2) and 57.5% (45.9–68.5), respectively. Inv ORR, a pre-specified secondary endpoint, was 73% (61.4–81.9); CR and PR rates were 27.5% (18.1–38.6) and 45.0% (33.8–56.5). 62% (33/53) of IRRC responders remained in response at DBL. 6 pts elected to stop nivo

and undergo stem cell transplant, all of these pts were alive at data cut-off. IRRC 6-mo PFS was 77%; OS was 99%. In 43 pts who had no prior BV response, nivo treatment resulted in an IRRC ORR of 72% (31/43).

Conclusions
Nivo demonstrated a high response rate, long-lasting responses, and an acceptable safety profile in pts with cHL after ASCT and BV, including pts with no prior BV response. PFS and OS are encouraging in this heavily pre-treated population. Clinical trial information: NCT02181738

2015 ASH 2015 Annual Meeting (Ansell et al.)

Introduction
The programmed death-1 (PD-1) immune checkpoint pathway regulates T-cell–mediated antitumor immune responses in solid tumours and hematologic malignancies. Nivolumab (Bristol-Myers Squibb, Ono Pharmaceutical) is a fully human IgG4 PD-1–blocking monoclonal antibody with demonstrated efficacy in a range of tumors. Results from an independent cohort of 23 pts with R/R cHL in a phase 1 study (CA209-039) showed that nivolumab was well tolerated and yielded an overall response rate (ORR) of 87% (Ansell et al, *N Engl J Med*, 2015). This raises important questions including the necessary duration of treatment, the relevance of the depth of response (complete response [CR] vs partial response [PR]), the duration of response, and the feasibility of retreatment. Here, we present the clinical course and post-treatment outcomes from extended follow-up of these pts to shed some light on these questions.

Methods
Pts with R/R cHL received nivolumab 3 mg/kg at weeks (wks) 1 and 4, and then every 2 wks for up to 2 years (yrs). Therapy was stopped earlier in pts with intolerance to treatment or progressive disease (PD) without evidence of clinical benefit. Pts who discontinued treatment due to toxicity were followed for up to 120 days after discontinuation; other pts were followed for 1 yr after discontinuation. Responding pts discontinued after confirmed CR or 16 wks after unconfirmed CR, or continued treatment for up to 2 yrs if they had PR or stable disease (SD). Pts who discontinued treatment with ongoing CR, PR, or SD could be retreated for confirmed PD occurring <1 yr after nivolumab discontinuation. Responses were evaluated using the Revised Response Criteria for Malignant Lymphoma (Cheson et al, *J Clin Oncol*, 2007). The primary endpoint was safety, and the key secondary endpoint was antitumor activity.

Results
A total of 23 pts with R/R cHL were treated. The median follow-up observation time is now 86 wks (range: 32–107 wks). Of 20 responders (14 PR, 6 CR), 10 have had durable responses per protocol assessment; their treatment durations and response characteristics are shown in Table 1. Responses were maintained in 2 pts (#5 and #6) after discontinuing nivolumab for >40 wks and in 1 pt (#7) after stopping due to toxicity. Eight pts with durable responses have received nivolumab for >1 yr, including 7 pts who have been in response for >1.5 yrs. One pt (#2) with an initial CR experienced a relapse 43 wks after treatment was discontinued, and achieved a second response (CR) after retreatment with nivolumab. Of the 10 remaining responders, 4 eventually progressed (time to progression [TTP] range: 21.4–92 wks), 1 discontinued treatment due to toxicity with no PD within the 120-day follow-up period, and 5 discontinued nivolumab to undergo stem cell transplant (SCT; 4 allogeneic, 1 autologous) after achieving remission. Time to CR for all responders ranged from 3–88 wks after starting nivolumab, including 2 pts with initial PRs that converted to CRs with continued treatment. All 5 pts who proceeded to SCT had responded to nivolumab within 16 wks of starting treatment (4 PR, 1 CR).

Three pts had a best overall response of SD (1 discontinued due to toxicity without documented PD within the 120-day follow-up period; 2 subsequently discontinued for PD [TTP: 15 and 15.3 wks, respectively]). Overall, 3 pts discontinued nivolumab due to adverse events (AEs; Grade 2 peripheral neuropathy, Grade 3 myelodysplastic syndrome, Grade 3 pancreatitis). Grade 1 or 2 immune-related AEs (IR-AEs) occurred in 4 of 10 pts and resolved without treatment in 2 pts. The incidence of IR-AEs did not increase with time on treatment.

Conclusions
In pts with R/R cHL, nivolumab was well tolerated and produced a high ORR. Responses occurred within 16 wks of nivolumab initiation in 15 of 20 pts. Early responses to nivolumab allowed 5 pts to proceed to SCT and lasted ≥1 yr in 7 of 10 pts who did not pursue SCT. One pt achieved CR again after retreatment with nivolumab when relapse occurred within 1 yr of discontinuing treatment following an initial CR.

4 Leukemia

4.1 Venetoclax (Venclexta™) in relapsed or refractory chronic lymphocytic leukaemia with 17p deletion

Overview

Drug Description		is a selective and orally bioavailable small-molecule inhibitor of BCL-2, an anti-apoptotic protein.
Patient Indication		venetoclax for relapsed or refractory del(17p) chronic lymphocytic leukaemia
Incidence in Austria		1,265 newly diagnosed per year (2012), 9.0 /100,000/year
Ongoing Phase III		NCT02756611 - until 2020
Approval status for this indication	**EMA**	-
	FDA	04/2016: for the treatment of patients with chronic lymphocytic leukemia (CLL) who have a chromosomal abnormality called 17p deletion and who have been treated with at least one prior therapy.
Approval status for other indications	**EMA**	On 17 February 2016, orphan designation (EU/3/16/1617) was granted by the European Commission to Abbvie Ltd., United Kingdom, for venetoclax for the treatment of acute myeloid leukaemia.
	FDA	-
Costs		-

Phase II results

The Lancet Published Online May 10, 2016 (Stilgenbauer et al.): *"Venetoclax in relapsed or refractory chronic lymphocytic leukaemia with 17p deletion: a multicentre, open-label, phase 2 study"*

Background
Deletion of chromosome 17p (del[17p]) in patients with chronic lymphocytic leukaemia confers very poor prognosis when treated with standard chemo-immunotherapy. Venetoclax is an oral small-

molecule BCL2 inhibitor that induces chronic lymphocytic leukaemia cell apoptosis. In a previous first-in-human study of venetoclax, 77% of patients with relapsed or refractory chronic lymphocytic leukaemia achieved an overall response. Here we aimed to assess the activity and safety of venetoclax monotherapy in patients with relapsed or refractory del(17p) chronic lymphocytic leukaemia.

Methods
In this phase 2, single-arm, multicentre study, we recruited patients aged 18 years and older with del(17p) relapsed or refractory chronic lymphocytic leukaemia (as defined by 2008 Modified International Workshop on Chronic Lymphocytic Leukemia guidelines) from 31 centres in the USA, Canada, UK, Germany, Poland, and Australia. Patients started once daily venetoclax with a weekly dose ramp-up schedule (20, 50, 100, 200, 400 mg) over 4–5 weeks. Patients were then given daily 400 mg continuous dosing until disease progression or discontinuation for another reason. The primary endpoint was the proportion of patients achieving an overall response, assessed by an independent review committee. Activity and safety analyses included all patients who received at least one dose of study drug (per protocol). This study is registered with ClinicalTrials.gov, number NCT01889186. Follow-up is ongoing, and patients are still receiving treatment.

Findings
Between May 27, 2013, and June 27, 2014, 107 patients were enrolled into the study. At a median follow-up of 12·1 months (IQR 10·1–14·2), an overall response by independent review was achieved in 85 (79·4%; 95% CI 70·5–86·6) of 107 patients. The most common grade 3–4 adverse events were neutropenia (43 [40%]), infection (21 [20%]), anaemia (19 [18%]), and thrombocytopenia (16 [15%]). Serious adverse events occurred in 59 (55%) patients, irrespective of their relationship to treatment, with the most common (≥5% of patients) being pyrexia and autoimmune haemolytic anaemia (seven [7%] each), pneumonia (six [6%]), and febrile neutropenia (five [5%]). 11 patients died in the study within 30 days of the last dose of venetoclax; seven due to disease progression and four from an adverse event (none assessed as treatment related).

Interpretation
Results of this trial show that venetoclax monotherapy is active and well tolerated in patients with relapsed or refractory del(17p) chronic lymphocytic leukaemia, providing a new therapeutic option for this very poor prognosis population. Additionally, in view of the distinct mechanism-of-action of venetoclax, combinations or sequencing with other novel targeted agents should be investigated to further advance treatment of del(17p) chronic lymphocytic leukaemia.

4.2 Inotuzumab ozogamicin versus standard therapy for acute lymphoblastic leukemia

Overview

Drug Description		is an antibody–drug conjugate that consists of a cytotoxic moiety (derivative of calicheamicin) attached to a humanized monoclonal anti-CD22 antibody
Patient Indication		inotuzumab ozogamicin in acute lymphoblastic leukemia
Incidence in Austria		1,265 newly diagnosed per year (2012), 9.0 /100,000/year
Ongoing Phase III		NCT01564784 until 07/2017
Approval status for this indication	**EMA**	-
	FDA	-
Approval status for other	**EMA**	On 7 June 2013, orphan designation (EU/3/13/1127) was granted by the European Commission to Pfizer Limited, United Kingdom, for inotuzumab ozogamicin for the treatment of B-cell acute lymphoblastic leukaemia.

indications	**FDA**	-
Costs		-

Phase III results

NEJM, published on June 12 2016, and updated on June 23, 2016 (Kantarjian et al.):
"Inotuzumab Ozogamicin versus Standard Therapy for Acute Lymphoblastic Leukemia"

Background
The prognosis for patients with acute lymphoblastic leukemia is poor. We sought to determine whether inotuzumab ozogamicin, an anti-CD22 antibody conjugated to calicheamicin, results in better outcomes in patients with relapsed or refractory acute lymphoblastic leukemia than does standard therapy.

Methods
In this phase 3 trial, we randomly assigned adults with relapsed or refractory acute lymphoblastic leukemia to receive either inotuzumab ozogamicin (inotuzumab ozogamicin group) or standard intensive chemotherapy (standard-therapy group). The primary end points were complete remission (including complete remission with incomplete hematologic recovery) and overall survival.

Results
Of the 326 patients who underwent randomization, the first 218 (109 in each group) were included in the primary intention-to-treat analysis of complete remission. The rate of complete remission was significantly higher in the inotuzumab ozogamicin group than in the standard-therapy group (80.7% [95% confidence interval {CI}, 72.1 to 87.7] vs. 29.4% [95% CI, 21.0 to 38.8], P<0.001). Among the patients who had complete remission, a higher percentage in the inotuzumab ozogamicin group had results below the threshold for minimal residual disease (0.01% marrow blasts) (78.4% vs. 28.1%, P<0.001): the duration of remission was longer in the inotuzumab ozogamicin group (median, 4.6 months [95% CI, 3.9 to 5.4] vs. 3.1 months [95% CI, 1.4 to 4.9]; hazard ratio, 0.55 [95% CI, 0.31 to 0.96]; P=0.03). In the survival analysis, which included all 326 patients, progression-free survival was significantly longer in the inotuzumab ozogamicin group (median, 5.0 months [95% CI, 3.7 to 5.6] vs. 1.8 months [95% CI, 1.5 to 2.2]; hazard ratio, 0.45 [97.5% CI, 0.34 to 0.61]; P<0.001); the median overall survival was 7.7 months (95% CI, 6.0 to 9.2) versus 6.7 months (95% CI, 4.9 to 8.3), and the hazard ratio was 0.77 (97.5% CI, 0.58 to 1.03) (P=0.04). In the safety population, the most frequent grade 3 or higher no hematologic adverse events with inotuzumab ozogamicin were liver-related. Veno-occlusive liver disease of any grade occurred in 15 patients (11%) who received inotuzumab ozogamicin and in 1 patient (1%) who received standard therapy.

Conclusions
The rate of complete remission was higher with inotuzumab ozogamicin than with standard therapy, and a higher percentage of patients in the inotuzumab ozogamicin group had results below the threshold for minimal residual disease. Both progression-free and overall survival was longer with inotuzumab ozogamicin. Veno-occlusive liver disease was a major adverse event associated with inotuzumab ozogamicin. (Funded by Pfizer; INO-VATE ALL ClinicalTrials.gov number, NCT01564784.)