Horizon Scanning in Oncology

Atezolizumab (Tecentriq™) for the treatment of locally advanced and metastatic urothelial carcinoma

Ludwig Boltzmann Institut
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1 Research questions

The HTA Core Model® for Rapid Relative Effectiveness Assessment of Pharmaceuticals was used for structuring this report [1]. The Model organises HTA information according to pre-defined generic research questions. Based on these generic questions, the following research questions were answered in the assessment.

EUnetHTA HTA Core Model®

Element ID	Research question
Description of the technology	
B0001	What is atezolizumab?
A0022	Who manufactures atezolizumab?
A0007	What is the target population in this assessment?
A0020	For which indications has atezolizumab received marketing authorisation?
Health problem and Current use	
A0002	What is locally advanced and MUC?
A0004	What is the natural course of locally advanced and MUC?
A0006	What are the consequences of locally advanced and MUC for the society?
A0023	How many people belong to the target population?
A0005	What are the symptoms and the burden of locally advanced and MUC?
A0003	What are the known risk factors for locally advanced and MUC?
A0024	How are locally advanced and MUC currently diagnosed according to published guidelines and in practice?
A0025	How are locally advanced and MUC currently managed according to published guidelines and in practice?
Clinical Effectiveness	
D0001	What is the expected beneficial effect of atezolizumab on mortality?
D0005	How does atezolizumab affect symptoms and findings (severity, frequency) of locally advanced and MUC?
D0006	How does atezolizumab affect progression (or recurrence) of locally advanced and MUC?
D0011	What is the effect of atezolizumab on patients' body functions?
D0012	What is the effect of atezolizumab on generic health-related quality of life?
D0013	What is the effect of atezolizumab on disease-specific quality of life?
Safety	
C0008	How safe is atezolizumab in relation to no intervention?
C0002	Are there harms related to dosage or frequency of applying atezolizumab?
C0005	What are the susceptible patient groups that are more likely to be harmed through the use of atezolizumab?
A0021	What is the reimbursement status of atezolizumab?

2 Drug description

Generic/Brand name/ATC code:

Atezolizumab/Tecentriq™/MPDL3280A

B0001: What is atezolizumab?

PD-L1 humanized monoclonal antibody

Up-regulation of the programmed death ligand 1 (PD-L1) in patients with haematological malignancies and solid tumours increases the propensity for cancer cells to evade immune surveillance. Atezolizumab, a monoclonal antibody designed to inhibit PD-L1, enables T-cell activation, restoring their ability to effectively detect and destroy tumour cells [2].

1,200 mg IV over 60 minutes every 3 weeks

Atezolizumab is available in 1,200 mg/20 mL (60 mg/mL) single-use vials. It is administered as an intravenous infusion over 60 minutes, at a fixed dose of 1,200 mg, every three weeks until disease progression or unacceptable toxicity [2].

A0022: Who manufactures atezolizumab?

Genentech Inc, a subsidiary of F Hoffmann-La Roche Ltd

3 Indication

A0007: What is the target population in this assessment?

≥ second-line for locally advanced or MUC

Atezolizumab is indicated as second-line treatment for patients with locally advanced or metastatic urothelial carcinoma (MUC) who have disease progression during or following platinum-based chemotherapy.

4 Current regulatory status

A0020: For which indications has atezolizumab received marketing authorisation?

FDA: licensed for locally advanced or MUC in May 2016

Atezolizumab was granted its first global approval on May 18, 2016. The US Food and Drug Administration (FDA) issued accelerated approval of atezolizumab for the treatment of patients with locally advanced or metastatic UC whose disease progressed during or following platinum-based chemotherapy, or within 12 months of neoadjuvant or adjuvant platinum-based

chemotherapy. As a complementary diagnostic the Ventana PD-L1 (SP142) assay by Roche, was approved by the FDA. Atezolizumab is the first drug approved for urothelial carcinoma in over 20 years, and the first PD-L1 inhibitor to receive FDA approval based on the tumour response rate and response durability reported in a phase II trial [3-5]. Continued approval is contingent upon randomized phase III studies assessing median overall survival [2, 3].

Atezolizumab is also under FDA review for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) who express PD-L1 and have progressed following platinum-based chemotherapy. Under the expedited priority program, a final decision regarding approval is expected by 19 October 2016 [4, 6].

FDA: awaiting NSCLC approval in October 2016

Currently, atezolizumab does not have marketing authorization in Europe for any indication.

no marketing authorisation for Europe

5 Burden of disease

A0002: What is locally advanced and MUC?

Urothelial cancer, also known as transitional cell carcinoma, typically occurs in the kidney, bladder or accessory organs. It is the most common type of bladder cancer and the second most common type of kidney cancer. Urothelial cancer arises from the transitional cells lining the inner surface of these organs and may extend from the kidney collecting system to the bladder. Approximately 25% of patients will develop locally advanced (National Cancer Institute stage T3/T4 or N1) muscle-invasive disease or MUC [7].

most common type of bladder cancer, second most common kidney cancer

A0004: What is the natural course of locally advanced and MUC?

Urothelial cancer cells commonly travel through the lymphatic system and bloodstream forming metastatic tumours in bone, liver and lungs. Stage IV bladder cancers, that have spread to distant parts of the body, have a poor prognosis with five year survival rates of less than 15% [7].

metastasize to bone, liver, lungs, lymph nodes; ≤5 year survival

A0006: What are the consequences of locally advanced and MUC for the society?

Patients presenting with locally advanced muscle-invasive disease may either progress or further metastasize, causing significant mortality [8].

metastasize causing mortality

A0023: How many people belong to the target population?

Urothelial cancer accounts for 90% of all bladder cancers in the US and Europe. In Austria, 1,496 new cases of bladder cancer were diagnosed in 2012, with a corresponding incidence rate of 8.9 cases per 100,000 persons. Approximately 540 Austrians died due to bladder cancer, leading to a mortality rate of 2.7 cases per 100,000 persons. Bladder cancer accounted for 4% of all

1,496 new cases of bladder cancer in Austria in 2012, 540 deaths

newly diagnosed cancers, and 3% of all deaths due to cancer. The median age of diagnosis is 73 (range 75-84). In Austria, men have higher incidence and mortality rates than women; 70% of deaths and newly diagnosed cases occurred in men [9].

PD-L1 is more active in tumours with high mutation rates than those with lower mutation rates. According to The Cancer Genome Atlas, urothelial carcinoma carries the third highest mutation rate of all studied cancers [5].

A0005: What are the symptoms and the burden of locally advanced and MUC?

main symptom: blood in urine

Haematuria, blood in the urine, is the most common symptom of bladder cancer. Patients may also experience burning during urination, increased urinary frequency or urgency, and pain in the lower abdomen or back [10].

A0003: What are the known risk factors for locally advanced and MUC?

main risk factors: smoking and occupational exposure

Bladder cancer occurs more commonly in people aged over 60 years; smoking and occupational exposure to chemicals are primary risk factors. It is estimated that up to half of all bladder cancers are due to smoking. Smokers with less functional polymorphisms of N-acetyltransferas-2, slow acetylators, have a higher risk due to their reduced ability to detoxify carcinogens. Higher rates of bladder cancer have been reported in textile, tire, leather, iron, aluminium and steel workers [10].

A0024: How are locally advanced and MUC currently diagnosed according to published guidelines and in practice?

diagnostics: cytoscopy, biopsy, transurethral resection, CT scan

Cytoscopy, a diagnostic procedure used to examine the lining of the bladder, is used to evaluate patients with suspected bladder cancer. During cytoscopy, cells may be collected for biopsy or transurethral resection of the tumour may be performed. If locally advanced cancer is identified, the patient is staged with a computed tomography (CT scan) of the abdomen and pelvis and either a chest x-radiation or CT scan. Patients with non-hepatic elevation of alkaline phosphatase or symptoms suggestive of bone metastases may undergo a bone scan. The stages of bladder cancer progress from stage I to stage IV. Stage I cancer is confined to the inner lining of the bladder. Stage II cancer invades the bladder wall. Stage III cancer spreads through the muscle wall to surrounding tissue; and stage IV cancer spreads to lymph nodes, bones, liver or lungs [10].

6 Current treatment

A0025: How are locally advanced and MUC currently managed according to published guidelines and in practice?

first-line therapy: cystectomy, radiation, chemotherapy

Muscle-invasive cancer is generally treated by cystectomy, with partial or complete bladder removal, or by treating the bladder with radiation and chemotherapy. While systemic platinum-based chemotherapy is the stand-

ard of care for patients with inoperable locally advanced or MUC, there is no standard second-line therapy for those who fail.

first-line chemotherapy: platinum-based chemotherapy

First-line chemotherapy regimens include gemcitabine with cisplatin or carboplatin, gemcitabine with paclitaxel, and dose dense methotrexate, vinblastine, doxorubicin and cisplatin (MVAC). However, a substantial proportion of patients are ineligible for cisplatin-based chemotherapy due to renal impairment or comorbidities [11]. Despite response rates of 40% to 60% with cisplatin-based therapy, most cases progress at a median of 8 months [12].

no standard second-line therapy: taxane-based, combinations

Current second-line treatment options involving paclitaxel or docetaxel, gemcitabine, pemetrexed, nab-paclitaxel, ifosfamide, methotrexate, gemcitabine and paclitaxel or cisplatin, dose dense MVAC or ifosfamide, doxorubicin, and gemcitabine result in median progression-free survival (PFS) of 2 to 4 months, and overall survival (OS) of 6 to 9 months [12]. While responses to combined chemotherapy are often better than single agents, they are often associated with toxicity [13].

vinflunine: EMA licensed second-line for MUC

In Europe, vinflunine, a microtubule inhibitor, is approved for second-line systemic treatment of urothelial cancer based on a phase III trial demonstrating a 2.3 month improvement in survival over supportive care. However, this result was not statistically significant in the intent-to-treat population. Vinflunine has not been approved for use in North America, resulting in a disparity in clinical practice and lack of standard second-line treatment options for MUC [13]. Immunotherapies, designed to restore immune-mediated tumour destruction, are under investigation in an attempt to improve outcomes for MUC patients who progress beyond first-line chemotherapy [12].

7 Evidence

59 citations; 1 phase II and one phase I expansion included

A literature search was conducted on 3 August 2016 in five databases: the Cochrane Library, CRD Database, Embase, Ovid Medline and PubMed. Search terms included “Atezolizumab”, “Tecentriq”, “MPDL3280A”, “urothelial carcinoma”, and “bladder cancer”. The manufacturer was also contacted and submitted nine references, of which six were already identified through the literature search. Manual searching yielded an FDA approval document [2], a press release [6], a clinical study record [14], a cost editorial [15], statistical information, two clinical guidance documents [10, 11], and three additional clinical study reports [16-18]. Overall, 59 citations were identified; a single-arm, phase II trial and a phase I expansion study contributed to the evidence regarding the efficacy and safety of atezolizumab for the treatment of locally advanced and MUC [5, 19].

quality of evidence assessed using a modified Downs and Black instrument

The methodological quality of the evidence was assessed using a Downs and Black [20] instrument that was modified to include the source of funding for studies. Evidence was assessed based on reporting of trial characteristics, external and internal validity, and confounding. The form used to assess study quality is reported in Table 4 of the appendix. Study strengths

and limitations were reported in preference to a numeric score and can be found in Table 3.

7.1 Clinical efficacy and safety – phase II studies

IMvigor 210, single-arm, two-cohort, open-label, multicentre phase II

An expanded phase IA study provided initial evidence of the safety and efficacy of atezolizumab [19]; results were expanded in a phase II study [5]. IMvigor 210, a single-arm, two-cohort phase II, open-label, global multicentre study, was conducted in either a first-line setting for cisplatin-unfit patients in cohort 1, or a second-line setting following failed platinum-based chemotherapy in cohort 2 [5].

efficacy and safety of atezolizumab in 310 MUC patients

In Cohort 2, 310 patients with locally advanced or MUC whose disease progressed during or after prior platinum-based chemotherapy were treated with atezolizumab. Inclusion criteria were Eastern Cooperative Oncology Group (ECOG) 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 without autoimmune disease or active infections. The primary endpoint was confirmed objective response rate (ORR) as assessed by independent review; secondary endpoints included duration of response (DOR), progression free survival (PFS), overall survival (OS), and safety. The primary analysis data cut-off of May 5, 2015 was based on a minimum of 24 weeks of follow-up from time of final patient enrolment; however, a later data cut-off of September 14, 2015 was used to explore DOR [5].

median age of 66 years, stratification of randomisation was based upon PD-L1 status

In this cohort, the median age was 66 years, 78% were male, 91% were Caucasian, 26% had non-bladder urothelial carcinoma, 78% had visceral metastases (liver, lung, bone, non-lymph node or soft tissue), and 21% received at least two prior systemic regimens in a metastatic setting. PD-L1 expression on tumour-infiltrating immune cells (IC) was assessed prospectively using the Ventana PD-L1 (SP142) Assay. Patients were stratified based on the percentage of PD-L1 positive IC: IC0 (<1%), IC1 (≥1% but <5%), IC2/3 (≥5%). Of the 310 patients, 100 (32%) were classified as having PD-L1 expression ≥5%; and 210 (68%) were classified as having PD-L1 <5%. Patients received an intravenous infusion of 1,200 mg of atezolizumab every 3 weeks until disease progression or unacceptable toxicity; median duration of treatment was 12 weeks (range 0–66) [5]. Detailed patient characteristics including inclusion and exclusion criteria are reported in Table 4 of the appendix.

7.1.1 Clinical efficacy

D0001: What is the expected beneficial effect of atezolizumab on mortality?

median OS of 9 months

The 12-month OS rate was 36% (95% CI 30–41) in the intent-to-treat population of cohort 2 in IMvigor 210. The OS was 48% (95% CI 38-58) in the IC2/3 group, 30% (95% CI 20-39) in the IC1 group, and 29% (95% CI 20-39) in the IC0 group. The median OS was 11.4 months (95% CI 9-not estimable) in the IC2/3 group, 6.7 months (95% CI 5.1-8.8) in the IC1 group, and 6.5

months (95% CI 4.4-8.3) in the IC0 group. Patients who received only one previous line of therapy in the metastatic setting without prior adjuvant or neoadjuvant therapy (n = 124), had a median OS of 9.0 months (95% CI 7.1–10.9). The median response rate had not been reached after a median follow-up of 11.7 months [5].

D0006: How does atezolizumab affect progression (or recurrence) of locally advanced and MUC?

At final follow-up, 44 (44%) of the IC2/3 patients, 107 (52%) of the IC1/2/3 patients, and 159 (51%) of intent-to-treat patients experienced disease progression. With a median survival follow-up of 11.7 months, the median PFS according to RECIST v1.1 was 2.1 months (95% CI 2.1–2.1) in all patients.

median DOR was not reached; PFS of 2.1 months

D0005: How does atezolizumab affect symptoms and findings (severity, frequency) of locally advanced and MUC?

Compared to a historical ORR of 10%, treatment with atezolizumab significantly improved ORR in each pre-specified IC group (IC2/3: 27% [95% CI 19–37], p<0.0001; IC1/2/3: 18% [95% CI 13–24], p = 0.0004; all patients: 15% [95% CI 11–20], p = 0.0058). An updated analysis showed an ORR of 26% (95% CI 18–36) in the IC2/3 group, including 11 (11%) patients who had a complete response. In the IC1/2/3 group, the ORR was 18% (95% CI 13–24) with complete response in 13 (6%) of patients. The absence of visceral metastasis was associated with the highest complete response rate (1% for those with visceral metastasis versus 18% without). Response was more common in patients with higher levels of PD-L1 expression on IC than those with lower expression [5].

statistically significant improvement in ORR compared to a historical control

D0011: What is the effect of the atezolizumab on patients' body functions?

Atezolizumab may affect body functions by causing immune-mediated adverse events, including pneumonitis, hepatitis, colitis, endocrinopathies, meningoencephalitis, ocular inflammatory toxicity, pancreatitis, infection, infusion-related reactions, rash and immune-related fetus rejection. The use of therapeutic proteins may result in immunogenicity. Among 275 patients in cohort 2, 114 (41.5%) tested positive for treatment-induced anti-therapeutic antibodies (ATA) at one or more post-dose time points; however, ATAs did not have a significant impact on the pharmacokinetics, safety or efficacy [2].

immune-mediated AEs, immunogenicity

D0012: What is the effect of atezolizumab on generic health-related quality of life?

No evidence was found regarding the effect of atezolizumab on generic health-related quality of life.

insufficient evidence for health-related QoL

D0013: What is the effect of atezolizumab on disease-specific quality of life?

No evidence was found regarding the effect of atezolizumab on disease-specific quality of life.

insufficient evidence for disease-specific QoL

Table 1: Efficacy results from cohort 2 of the IMvigor 210 phase II trial [2, 21]

Descriptive statistics and estimate variability	Treatment group	Atezolizumab-treated IC2/3	Atezolizumab-treated IC1/2/3	Atezolizumab-treated all patients
	Number of subjects	100	207	310
	ORR[1], n (%) 95% CI	26 (26%) (18–36)	37 (18%) (13–24)	45 (15%) (11–19)
	CR, n (%) PR, n (%) PD, n (%)	11 (11%) 15 (15%) 44 (44%)	13 (6%) 24 (12%) 107 (52%)	15 (5%) 30 (10%) 159 (51%)
	Median OS, months (95% CI)	11.4 (9.0–NE)	8.8 (7.1–10.6)	7.9 (6.6–9.3)
	12-month OS, % (95% CI)	48% (38–58)	39% (32–46)	36% (30–41)
	Median DOR, months (range)	NR (4.2–13.8$^+$)	12.7 (2.1+–12.7)	NR (2.1+–13.8$^+$)
	Median PFS, months (95% CI)	2.1 (2.1–4.1)	2.1 (2.1–2.1)	2.1 (2.1–2.1)
Effect estimate per comparison	ORR[2], % (95%CI) p-value	27% (19–37) p < 0.0001	18% (13–24) p = 0.004	15% (11–20) p = 0.0058
Notes	✪ Primary analysis (data cut off 2015-05-05) designated based on minimum of 24 weeks of follow-up from final patient enrolled; extended to 2015-09-14 to examine DOR. ✪ Median duration of treatment was 12 weeks (range 0, 66). ✪ ORR was assessed in the objective response population, defined as intent-to-treat, who had measurable disease at baseline according to RECIST v1.1; DOR analyses were done on the subset of patients who achieved an objective response. ✪ As of 2015-09-14, 202 (65%) of 310 patients had discontinued treatment: 193 died, 8 withdrew and one discontinued for other reasons. ✪ At a median follow-up of 11.7 months, the median DOR was not yet reached in any of the PD-L1 IC groups (range 2.0, 13.7), with censored values at these time points. ✪ At 2015-09-14, ongoing responses were reported in 38 (84%) of 45 responders; median time to response was 2.1 months (95% CI: 2.0, 2.2).			

Abbreviations: CI = confidence interval, CR = complete response, DOR = duration of response, IC = immune cells, NE = not estimable, NR = not reached; ORR = objective response rate, OS = overall survival; PD = progressive disease, PFS = progression free survival, PR = partial response, RECIST = Response Evaluation Criteria In Solid Tumours, $^+$ denotes a censored value

[1] assessed by independent review, data cut-off 2015-09-14

[2] compared to historical overall response rate of 10%

7.1.2 Safety

C0008: How safe is atezolizumab in relation to no intervention?

most common AE of any grade: fatigue, reduced appetite, nausea, urinary tract infections

All-cause, any grade adverse events (AE) were reported in 298 (96%) of patients. While 155 (50%) patients experienced a grade 3 or 4 AE, no grade 5 AEs were reported. The most common AEs of any grade, reported in ≥20% atezolizumab users, were fatigue (52%), decreased appetite (26%), nausea (25%), urinary tract infection (22%), pyrexia (21%), and constipation (21%). Half (50%) of all patients experienced AEs of grade 3 or 4. The most common grade 3 or 4 AEs, occurring in ≥2% of patients, include urinary tract infection (9%), anaemia (8%), fatigue (6%), dehydration, intestinal and urinary obstructions, haematuria (3%), dyspnea (4%), acute kidney injury, abdominal pain (4%), venous thromboembolism, sepsis, and pneumonia. Three people (0.9%) experienced sepsis, pneumonitis, or intestinal obstruction that led to death [2].

C0002: Are there harms related to dosage or frequency of applying atezolizumab?

slow rate of infusion to avoid infusion reactions

Patients in cohort 2 received a fixed dose of 1,200mg IV atezolizumab, administered over 60 minutes, every 3 weeks. Severe infusion reactions occurred in 1.3% (25/1978) of patients across clinical trials and in 1.7% (9/523) of patients with urothelial carcinoma. Interrupting or slowing the rate of infusion may be necessary for patients with mild or moderate infusion reactions. Permanently discontinue treatment in patients with grade 3 or 4 infusion reactions [2].

No treatment-related deaths occurred. AEs leading to interruption of atezolizumab treatment occurred in 27% of patients; the most common, occuring in >1% of patients, were increased liver enzymes, urinary tract infection, diarrhea, fatigue, confusional state, urinary obstruction, pyrexia, dyspnea, venous thromboembolism, and pneumonitis [2].

C0005: What are the susceptible patient groups that are more likely to be harmed through the use of atezolizumab?

no immune-mediated renal toxicity

While a substantial proportion of patients are ineligible for cisplatin-based therapy due to renal impairment or comorbidities [11], no immune-mediated renal toxicity was observed following treatment with atezolizumab [5]. Atezolizumab may impair fertility, and cause fetal harm resulting in increased rates of abortion or stillbirth. It is advised that females use effective contraception during treatment with atezolizumab and refrain from breastfeeding for at least 5 months following the last dose [2].

Table 2: Treatment-related adverse events in cohort 2 of the IMvigor 210 phase II trial [2]

Adverse Event (according to CTCAE version 4)	**Atezolizumab** (n = 310)	
AE ≥10% of patients	Any grade n (%)	Grade 3 or 4 n (%)
Any AE	298 (96%)	155 (50%)
Nausea	78 (25%)	6 (2%)
Constipation	65 (21%)	1 (0.3%)
Diarrhoea	56 (18%)	3 (1%)
Abdominal pain	53 (17%)	12 (4%)
Vomiting	53 (17%)	3 (1%)
Fatigue	161 (52%)	19 (6%)
Pyrexia	65 (21%)	3 (1%)
Peripheral edema	56 (18%)	3 (1%)
Urinary tract infection	68 (22%)	28 (9%)
Decreased appetite	81 (26%)	3 (1%)
Back/neck pain	47 (15%)	6 (2%)
Arthralgia	43 (14%)	3 (1%)
Haematuria	43 (14%)	3 (3%)
Dyspnea	50 (16%)	12 (4%)
Cough	43 (14%)	1 (0.3%)
Rash	47 (15%)	1 (0.3%)
Pruritus	40 (13%)	1 (0.3%)
Laboratory abnormalities in ≥1% of patients		Grade 3 or 4 n (%)
Lymphopenia		31 (10%)
Hyponatremia		31 (10%)
Anaemia		25 (8%)
Hyperglycaemia		16 (5%)
Increased Alkaline phosphatase		12 (4%)
Increased Creatinine		9 (3%)
Increased ALT		6 (2%)
Increased AST		6 (2%)
Hypoalbuminemia		3 (1%)

Abbreviations: AE = adverse event; ALT = alanine transaminase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events

7.2 Clinical efficacy and safety – further results

In cohort 1 of the phase II IMvigor 210 study, atezolizumab was used as first-line therapy in 199 MUC patients who were ineligible for cisplatin-based chemotherapy. Preliminary results, presented at the 2016 American Society of Clinical Oncology (ASCO) meeting, suggest that the ORR was 24%; 7% of patients had complete response. At a median follow-up of 14.4 months, continued responses were reported in 21 of 29 (75%) of responders. The median OS was 14.8 months. While most patients had pre-existing renal impairment, there was no evidence of nephrotoxicity. Approximately 6% of patients stopped treatment due to side effects, including hypothyroidism, liver abnormalities, rash and diarrhoea [22].

phase IA expansion study
cohort 1: 199 MUC patients

preliminary results available as an ASCO abstract

The efficacy of atezolizumab was first examined in a phase IA expansion study [19]. Urothelial bladder cancer patients received an IV infusion of 15 mg/kg of atezolizumab every 3 weeks for up to 16 cycles. PD-L1 expression was centrally evaluated and RECIST v1.1 was used to evaluate ORR.

In this cohort, the median patient age was 65 years, 73% were male, visceral and liver metastases were present in 74% and 33% of patients, respectively; 73% had ≥2 prior therapies, and 91% had prior platinum. The cohort was expanded to include patients who were PD-L1 negative to determine whether these patients would also respond to atezolizumab. In this cohort, 33 IC2/3 patients, 36 IC0/1 patients, and 1 PD-L1 patient with unknown IC were evaluable for efficacy. Overall, 68 patients received atezolizumab, many of whom had visceral metastases (n = 50, 75%), ECOG score of 1 (n = 39, 59%), or less than 3 months since previous chemotherapy (n=26, 42%) [19, 23].

median age of 65 years

Patients received a median of 65 days of atezolizumab, 57% reported AEs (4% grade 3, no grade 4 or 5). An ORR of 52% was observed in patients with IC2/3 status at least 12 weeks of follow-up data, and 16 of 17 patients who responded continued treatment at the cut-off point. DOR ranged from 0.1+ to 30.3+ weeks for patients with IC2/3 tumours and from 0.1+ to 6.0+ weeks for patients with IC0/1 tumours. Response was associated with IC scores of tumour-infiltrating IC (p = 0.026) but not to those of the tumour cells (p = 0.93).

AEs of any grade occurred in 57% of patients

Patients with an IC2/3 status achieved an ORR of 52%

Using an adaptive design that allowed for biomarker-positive enriched cohorts, it was demonstrated that tumours expressing PD-L1 positive infiltrating IC had higher rates of response to atezolizumab.

PD-L1 expression correlated with higher response

8 Estimated costs

A0021: What is the reimbursement status of atezolizumab?

Atezolizumab costs approximately US $12,500 per month and may be covered under medical benefit insurance [15]. Genentech Access Solutions offers access and reimbursement assistance to eligible US patients who are un-

estimate: US $12,500/month; no price estimates available for Austria

insured or unable to afford out-of-pocket expenses [6]. Currently, no price estimates for atezolizumab are available yet in Austria.

9 Ongoing research

3 ongoing phase III studies for MUC

In August 2016, a search in www.clinicaltrials.gov and https://www.clinicaltrialsregister.eu was conducted. Three ongoing phase III studies evaluating atezolizumab for the treatment of locally advanced and MUC were identified:

- **NCT02302807:** A study of atezolizumab compared with chemotherapy in participants with locally advanced or metastatic urothelial bladder cancer [IMvigor211]. Estimated completion date is November 2017 [16].
- **NCT02807636:** The effect of atezolizumab in combination with gemcitabine/carboplatin alone in participants with untreated locally advanced or metastatic urothelial carcinoma who are ineligible for cisplatin based therapy [IMvigor130]. Estimated completion date is September 2019 [17].
- **NCT02450331:** A phase III study of atezolizumab treatment versus observation as adjuvant therapy in patients with PD-L1 positive, high-risk muscle invasive bladder cancer after cystectomy [IMvigor010]. Estimated completion date is April 2022 [18].

phase II: atezolizumab for NSCLC with PD-L1 expression

Atezolizumab is also under investigation in three phase II trials (NCT01903993; NCT02031458; NCT01846416) for the treatment of non-small cell lung cancer (NSCLC) [4]. Atezolizumab 1,200 mg once every 3 weeks significantly improved survival compared with docetaxel 75 mg/m^2 once every 3 weeks in patients with previously treated NSCLC according to the randomized phase II POPLAR trial [24]. The phase II FIR (NCT01846416) and BIRCH (NCT02031458) trials evaluated the efficacy of atezolizumab 1,200 mg once every 3 weeks as first-line or subsequent therapy in patients with NSCLC with PD-L1 expression of TC2/3 or IC2/3. Various phase I studies are ongoing in different indications, including breast cancer, renal cell carcinoma and colorectal cancer.

10 Discussion

first global approval by FDA May 2016 for locally advanced or MUC

Atezolizumab was granted its first global approval in May 2016. The US FDA issued accelerated approval of atezolizumab for the treatment of patients with locally advanced or MUC whose disease progressed during or following platinum-based chemotherapy or within 12 months of neoadjuvant or adjuvant platinum-based chemotherapy. While it is the first PD-L1 in-

hibitor to receive approval as second-line treatment for MUC based on the tumour response rate and durability reported in cohort 2 of the phase II trial IMvigor 210, continued approval is contingent upon randomized phase III studies assessing OS [2, 5]. In October 2016, the FDA will decide on the approval of atezolizumab for the treatment of patients with locally advanced or metastatic NSCLC who express PD-L1 and have failed platinum-based chemotherapy [4, 6]. Atezolizumab is currently not marketed in Europe.

not approved in Europe

The safety and efficacy of atezolizumab for the treatment of locally advanced and MUC was evaluated in a phase II study [5]. IMvigor 210, a single-arm, two-cohort, open-label, global multicentre study was conducted in a first-line setting for cisplatin-unfit patients in cohort 1, and in a second-line setting following failed platinum-based chemotherapy in cohort 2. Treatment of cohort 2 with atezolizumab 1,200 mg IV infusion every 3 weeks was associated with a significant improvement in ORR compared to historical controls at 14.4 month follow-up (15% [95% CI 11–20] versus 10%; p = 0.0058). Of the 310 patients treated, 15 (5%) and 30 (10%) demonstrated complete and partial responses, respectively. Response was associated with PD-L1 expression as the ORRs reported in IC2/3 and IC1/2/3 subgroups were 26% (95% CI 18–36, p<0.0001) and 18% (95% CI 13–24, p = 0.004), respectively. The results from the IC3 subgroup were not reported solely, only grouped [5].

IMvigor 210: ORR compared to historical controls 15%, CR: 5% and PR: 10%

At a median follow-up of 11.7 months, the median DOR was not yet reached; continued responses were reported in 38 (84%) of 45 responders. The 12-month OS rate was 48% (95% CI 38–58) in the IC2/3 group, 39% (CI 32–46) in the IC1/2/3 group, and 36% (95% CI 30–41) in the intent-to-treat population. Fatigue, the most common AE, was observed in 50 (16%) patients, and was severe (grade 3 or 4) in 5 (2%). Fifteen (5%) patients experienced severe immune-mediated AE involving pneumonitis, abnormal liver function tests, rash and dyspnea [2]. Atezolizumab showed durable activity and good tolerability; increased PD-L1 expression and absence of visceral metastases was associated with increased response [5].

median DOR was not reached

most common AE: fatigue in 50 patients

The primary endpoint, ORR, was assessed by an independent review facility using RECIST v1.1 and stratification by sub-cohorts may have reduced the potential for confounding by indication. At 14.4 months, 202 (65%) of 310 patients had discontinued treatment; 193 died, 8 withdrew and one discontinued for other reasons [5]. There is a risk of overestimating the effect of atezolizumab on ORR when using historical controls; patients may have been recruited, selected or assessed differently over time. A simultaneous control group would control for more than one confounder. Follow-up was insufficient to determine intended effects including DOR.

risk of overestimating the effect of ORR when using historical controls

The typical median survival for patients who relapse after platinum-based chemotherapy ranges from 5 to 7 months [5]. Patients who received only one line of therapy in a metastatic setting without prior adjuvant or neoadjuvant therapy had a mean OS of 9.0 months (95% CI 7.1–10.9) which is favourable compared to the median survival of 5 to 7 months observed in relapsing patients following platinum-based chemotherapy [5]. However, patients were not followed long enough to determine whether atezolizumab reduces mortality or prolongs survival for some or all responders; or whether atezolizumab affects progression or recurrence of locally advanced and MUC.

mean OS of 9.0 months for patients who received 1 prior therapy

PD-L1 expression correlated with higher response. Compared to historical ORR of 10%, atezolizumab treatment significantly improved ORR in each pre-specified IC group and all intent-to-treat patients. Higher response rates

PD-L1 expression correlated with higher response

were more common in patients with higher levels of PD-L1 expression on IC and patients without visceral metastasis [5]. While evaluating tumour shrinkage (ORR) and disease progression are useful outcomes in clinical trials, patient reported outcomes (PROMs) and patient reported experiences (PREMs) may be useful in determining whether atezolizumab provides adequate clinical benefit in terms of improving the symptoms or severity of local advanced and MUC.

follow-up for potential severe AEs

In terms of safety, follow-up may have been insufficient to identify all potential severe AEs or to evaluate the long-term effects of developing treatment-induced anti-therapeutic antibodies. While no treatment-related deaths were reported, severe infusion reactions occurred in 1.7% (9/523) of MUC patients in clinical trials. AEs leading to interruption of treatment occurred in 27% of patients, most commonly due to increased liver enzymes, urinary tract infection, diarrhoea, fatigue, and pneumonitis. While a substantial proportion (50%) of patients are ineligible for cisplatin-based therapy due to renal impairment or comorbidities [11], no immune-mediated renal toxicity was observed following treatment with atezolizumab[25] [5]. Further studies are needed to determine whether patients incur harm in receiving atezolizumab at higher dosages or frequencies, and which patients may be most susceptible to experiencing AEs.

treatment costs per month in the US $12,500

The cost of atezolizumab is approximately US $12,500 per month [15] and is not yet known for Europe. However, with 1,496 new cases of bladder cancer being diagnosed each year in Austria, it may be difficult to fully determine the value of atezolizumab until clinical benefits are further assessed in randomized phase III studies.

vinflunine therapy option for MUC, but didn´t reach statistical significance

Vinflunine, a microtubule inhibitor, is only approved for use in Europe as a standard chemotherapy treatment option in patients with platinum-refractory MUC [13]. A randomized phase III trial of vinflunine compared with best supportive care in 370 patients, demonstrated an improved survival of 2.3 months with vinflunine; however, the result did not reach statistical significance in the intent-to-treat population [17].

significant improvement of ORR

insufficient follow up for median DOR, mortality, disease progression, AEs

Overall, compared to a historical control of 10%, treatment with atezolizumab significantly improves ORR in patients with locally advanced and MUC with progression following platinum-based chemotherapy. Follow-up was insufficient to adequately determine median DOR, whether atezolizumab reduces mortality or prolongs survival for some or all responders, to define the extent to which treatment may affect disease progression or recurrence, or to identify all potential AEs. Phase III clinical trials are underway to compare atezolizumab with observation as adjuvant therapy in PD-L1 positive patients, atezolizumab with chemotherapy in MUC patients, and atezolizumab in combination with gemcitabine/carboplatin versus gemcitabine/carboplatin alone in patients who are ineligible for cisplatin-based therapy. Further studies are needed to examine PROMs, PREMs, and quality of life measures to determine whether atezolizumab provides adequate clinical benefit in terms of improving the symptoms and severity of locally advanced and MUC.

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12 Appendix

Table 3: Characteristics of IMvigor 210 phase II trial

Title: A study of atezolizumab in patients with locally advanced or metastatic urothelial bladder cancer [IMvigor210] [2, 14, 21]			
Study identifier	NCT02108652, G029293		
Design	IMvigor 210, a single-arm, non-randomized, open-label, two-cohort, phase II global multicentre study, was designed to evaluate the safety and efficacy of atezolizumab for patients with locally advanced and MUC. The study was conducted in either a first-line setting for cisplatin-unfit patients in cohort 1, or a second-line setting following failed platinum-based chemotherapy in cohort 2.		
	Duration of main phase:		2 years, May 2014 to August 2017; primary analysis (data cut off 2015-05-05) designated based on minimum of 24 weeks of follow-up from final patient enrolled; extended to 2015-09-14 to examine DOR. Median duration of treatment was 12.3 weeks (range: 0.1–46 weeks).
	Duration of Run-in phase:		not applicable
	Duration of Extension phase:		not applicable
Hypothesis	Exploratory: treatment efficacy of atezolizumab in patients with locally advanced or MUC		
Funding	Genentech Inc, a subsidiary of F Hoffmann-La Roche Ltd		
Treatments groups	Locally advanced or MUC		1,200 mg atezolizumab IV every 3 weeks until disease progression or unacceptable toxicity Overall enrolment: 439
	Cohort 1: cisplatin ineligible		1,200 mg atezolizumab IV every 3 weeks until disease progression or unacceptable toxicity Treated: 119
	Cohort 2: inoperable locally advanced or MUC with disease progression following platinum-based chemotherapy		1,200 mg atezolizumab IV every 3 weeks until disease progression or unacceptable toxicity Screened: 486; enrolled: 315; treated: 310 Still treated 2015-09-14: 62 Discontinued: 248; progression: 211; AE: 13; withdrawal: 9; other: 15
	Cohort 2[3]	IC0 (n=103)	<1% of cells positive for PD-L1
		IC1 (n=107)	≥1% but ≤ 5% of cells positive for PD-L1
		IC2/3 (n=100)	≥5% of cells positive for PD-L1
Endpoints and definitions	Primary Objective response rate	ORR	Independent review facility-assessed ORR according to RECIST criteria; investigator-assessed ORR according to immune-modified RECIST criteria to better assess atypical response kinetics described with immunotherapy; up to 3 years;
	Secondary Duration of response	DOR	Independent review facility according to RECIST and investigator assessed as per immune-modified RECIST; up to 3 years
	Secondary Progression free survival	PFS	Independent review facility according to RECIST and investigator assessed as per immune-modified RECIST; up to 3 years
	Secondary Overall survival	OS	12 month OS and safety; up to 4 years
Database lock	Last verified: November 2015		
Results and Analysis			

[3] Prospectively stratified by % PD-L1 expression on tumour-infiltrating IC via Ventana PD-L1 (SP142) Assay

Title: A study of atezolizumab in patients with locally advanced or metastatic urothelial bladder cancer [IMvigor210] [2, 14, 21]				
Study identifier	NCT02108652, G029293			
Analysis description	**Primary Analysis** Efficacy analyses on the intention-to-treat population ORR in the objective response-evaluable population, defined as intention-to-treat patients with measurable disease according to RECIST at baseline Historical 10% response rate F. Hoffmann-La Roche Ltd funded, and assisted with study design, data collection, data analysis, data interpretation, and writing of the report.			
Analysis population	Inclusion	✲ Age ≥ 18 years; life expectancy ≥ 12 weeks ✲ ECOG performance status of 0 or 1 ✲ Measurable disease defined by RECIST v1.1 ✲ Adequate haematological and end-organ function ✲ Cohort 1: ineligible for cisplatin-based chemotherapy ✲ Cohort 2: disease progression during or following platinum-based chemotherapy, inoperable locally advanced or MUC		
	Exclusion	✲ Autoimmune disease or active infections ✲ Prior treatment with CD137 agonists, immune checkpoint blockade therapies ✲ Positive for HIV and/or active hepatitis B/C, or tuberculosis ✲ Active or corticosteroid-dependent brain metastases ✲ Administration of vaccines or systemic immune-stimulatory agents or immune-suppressants		
	Characteristics of Cohort 2	Atezolizumab-treated IC2/3 (n=100)	Atezolizumab-treated IC1/2/3 (n=207)	Atezolizumab-treated all patients (n=310)
	Median age (range), years	66 (41-84)	67 (32-91)	66 (32-91)
	Male sex	78 (78%)	160(77%)	241 (78%)
	Caucasian	87 (87%)	184 (89%)	282 (91%)
	Creatinine clearance <60 mL/min	40 (40%)	69 (33%)	110 (34%)
	Haemoglobin <100g/L	24 (24%)	50 (24%)	69 (22%)
	Previous tobacco	60 (60%)	116 (56%)	168 (54%)
	Primary Bladder Renal Pelvis Ureter Urethra Other	 79 (79%) 11 (11%) 5 (5%) 3 (3%) 2 (2%)	 159 (77%) 27 (13%) 12 (6%) 5 (2%) 4 (2%)	 230 (74%) 42 (14%) 23 (7%) 5 (2%) 10 (3%)
	Metastases Visceral Liver	 66 (66%) 27 (27%)	 152 (73%) 61 (30%)	 243 (78%) 96 (31%)
	ECOG Status 0 1	 42 (42%) 58 (58%)	 83 (40%) 124 (60%)	 117 (38%) 193 (62%)
	Cystectomy	44 (44%)	83 (40%)	115 (37%)
	Previous chemotherapy Cisplatin Carboplatin Neoadjuvant/adjuvant progression <12 months	 83 (83%) 17 (17%) 24 (24%)	 161 (78%) 43 (21%) 42 (20%)	 227 (73%) 80 (26%) 57 (18%)
	Number of Previous systemic regimens in metastatic setting 2 3 ≥4	 19 (19%) 11 (11%) 10 (10%)	 41 (20%) 24 (12%) 17 (8%)	 64 (21%) 39 (13%) 24 (8%)

Title: A study of atezolizumab in patients with locally advanced or metastatic urothelial bladder cancer [IMvigor210] [2, 14, 21]	
Study identifier	NCT02108652, G029293
Critical appraisal	
Study strengths	✪ The study objective, patient characteristics, main outcomes, findings, and estimates of variability were clearly described. ✪ Stratification by sub-cohorts may have reduced potential for confounding. ✪ Withdrawals and losses to follow-up were fully reported. ✪ Appropriate statistical tests were used to evaluate results and the probability value was reported for the main outcome. ✪ Outcomes were evaluated using an intent-to-treat analysis based on independent review facility-assessed ORR according to RECIST v1.1, and investigator-assessed ORR according to immune-modified RCIST criteria to better assess atypical response kinetics.
Study limitations	✪ Insufficient follow-up to determine intended effects (DOR) and all potential serious AEs. ✪ Risk of overestimate of effect in using an open-label, sing-arm, cohort study design with historical control to determine overall ORR as patients may have been recruited, selected, or assessed differently over time. A simultaneous control group would control for >1 confounder; a RCT with adequate generation of randomisation, concealment of allocation and blinded assessment would reduce the risk of overestimating the effect. ✪ Study subjects may not be generalizable to the population or representative of the population from whom they were derived. Patient sampling was not fully reported, nor was the proportion of the population sampled. ✪ Industry assisted with study design, data collection, analysis, interpretation and writing the report.

Abbreviations: AE = adverse event; CI = confidence interval; DOR = duration of response: ECOG = Eastern Cooperative Oncology Group; IC= immune cells; IV = intravenous; MUC = metastatic urothelial carcinoma; ORR = objective response rate; PD-L = programmed death ligand-1; PFS = progression free survival; OS = overall survival; RCT: randomised controlled trial; RECIST = Response Evaluation Criteria In Solid Tumour

Table 4: Study quality assessment by Downs and Black

Assessment of study quality, modified Downs and Black checklist for randomised and non-randomised studies		
Reporting	Yes/No/Partially	Score
1. Is the objective of the study clear?	Yes=1, No=0	
2. Are the main outcomes clearly described in the Introduction or Methods?	Yes=1, No=0	
3. Are characteristics of the patients included in the study clearly described?	Yes=1, No=0	
4. Are the interventions clearly described?	Yes=1, No=0	
5. Are the distributions of principal confounders in each group of subjects clearly described?	Yes=2, Partially=1, No=0	
6. Are the main findings of the study clearly described?	Yes=1, No=0	
7. Does the study estimate random variability in data for main outcomes?	Yes=1, No=0	
8. Have all the important adverse events consequential to the intervention been reported?	Yes=1, No=0	
9. Have characteristics of patients lost to follow-up been described?	Yes=1, No=0	
10. Have actual probability values been reported for the main outcomes except probability < 0.001?	Yes=1, No=0	
11. Is the source of funding clearly stated?	Yes=1, No=0	
External validity	Yes/No/Unclear	Score
12. Were subjects asked to participate in the study representative of the entire population recruited?	Yes=1, No=0, Unclear=0	
13. Were those subjects who were prepared to participate representative of recruited the population?	Yes=1, No=0, Unclear=0	
14. Were staff, places and facilities where patients were treated representative of the treatment most received?	Yes=1, No=0, Unclear=0	
Internal validity	Yes/No/Unclear	Score
15. Was an attempt made to blind study subjects to the intervention?	Yes=1, No=0, Unclear=0	
16. Was an attempt made to blind those measuring the main outcomes?	Yes=1, No=0, Unclear=0	
17. If any of the results of the study were based on data dredging, was this made clear?	Yes=1, No=0, Unclear=0	
18. Was the time period between intervention and outcome the same for the intervention and control groups or adjusted for?	Yes=1, No=0, Unclear=0	
19. Were statistical tests used to assess main outcomes appropriate?	Yes=1, No=0, Unclear=0	
20. Was compliance with the interventions reliable?	Yes=1, No=0, Unclear=0	
21. Were main outcome measures used accurate? (valid and reliable)	Yes=1, No=0, Unclear=0	
Internal validity-cofounding (selection bias)	Yes/No/Unclear	Score
22. Were patients in different intervention groups recruited from the same population?	Yes=1, No=0, Unclear=0	
23. Were study subjects in different intervention groups recruited over the same period of time?	Yes=1, No=0, Unclear=0	
24. Were study subjects randomised to intervention groups?	Yes=1, No=0, Unclear=0	
25. Was the randomised intervention assignment concealed from patients and staff until recruitment was complete?	Yes=1, No=0, Unclear=0	
26. Was there adequate adjustment for confounding in the analyses from which main findings were drawn?	Yes=1, No=0, Unclear=0	
27. Were losses of patients to follow-up taken into account?	Yes=1, No=0, Unclear=0	
Power	Size of smallest intervention group Score 0-5	Score
28. Was the study sufficiently powered to detect clinically important effects where the probability value for a difference due to chance is < 5%?		