DRUP – Drug specific study manual for ATEZOLIZUMAB + BEVACIZUMAB (Tecentriq + Avastin)

1. Drug specific in- and exclusion criteria

Atezolizumab + bevacizumab specific criteria are highlighted in light grey.

Inclusion criteria	Yes	No	n.a.
1. Patients must be ≥18 years of age.			
2. Histologically-proven locally advanced or metastatic solid tumor, multiple myeloma or non-Hodgkin lymphoma, with symptomatic disease progression or progression according to RECIST-criteria after standard anti-cancer therapy, or for whom on such treatment is available or indicated.			
a. <u>For patients with a primary brain tumor</u>: histologically confirmed recurrent or de novo primary brain tumor, with unequivocal progression after prior therapy, at least 3 months after radiotherapy (either first line chemo-radiotherapy or re-irradiation), and with stable or decreasing dosage of steroids for at least 7 days prior to the baseline MRI scan.			
3. Presence of an oncogenic mutation or profile that can potentially be targeted by atezolizumab + bevacizumab (please refer to the list of drugs and acceptable profiles for further definitions). A complete pathology or sequencing report, confirming the actionable variant, has to be submitted for patient enrollment.			
4. ECOG performance status 0-1			
5. Patients must have normal organ and bone marrow function measured within 4 weeks prior to administration of study treatment as defined below:			
a. Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L			
b. Hemoglobin > 6.2 mmol/l			
c. Platelet count > 100 x 10^9/L			
d. Total bilirubin < 1.5 x ULN (exception: elevated bilirubin due to Gilbert's disease or a similar syndrome involving slow conjugation of bilirubin)			
e. Alkaline phosphatase < 2.5x institutional ULN (or < 5 x ULN in case of liver metastases, and < 7 x ULN in case of bone metastases)			
f. AST (SGOT) and ALT (SGPT) < 2.5 x institutional ULN (or < 5 x ULN in patients with known hepatic metastases)			
g. Serum creatinine ≤ 1.5 × ULN or calculated or measured creatinine clearance ≥ 50 mL/min/1.73 m^2			
h. INR < 1.5 and APTT normal, unless patient is on stable anti-coagulant treatment for at least two weeks with a low molecular weight heparine or coumarine, then an INR within the target range (usually between 2 and 3) is allowed.			
6. Objectively measurable disease (by physical or radiographic examination, according to RECIST v1.1 for patients with solid tumors, or according to IMWG, Lugano, RANO or GCIG criteria, resp., for patients with multiple myeloma, non-Hodgkin lymphoma, glioblastoma or ovarian cancer in case of CA125-based evaluation).			

Inclusion criteria	Yes	No	n.a.
7. A new (obtained ≤2 months before inclusion, and without any type of anti-cancer therapy within those ≤2 months) fresh frozen tumor biopsy specimen for extensive biomarker testing is mandatory before the start of treatment with a targeted agent included in the protocol. Alternatively, fresh frozen tumor tissue acquired in the context of a standard care procedure may be used, provided that no systemic anti-cancer treatment was given between the procedure and start of study treatment within DRUP. The following exceptions are made: a. An exception is made for patients with a primary brain tumor, only if the mandatory DRUP pre-treatment biopsy for biomarker analysis cannot safely be obtained: i. The fresh frozen tumor biopsy sample may be replaced by fresh frozen tumor tissue, obtained earlier from recurrent disease, as part of standard of care surgical procedure (i.e., performed at progression) ii. If no fresh frozen tumor tissue is available for NGS, and the risk of obtaining a new tumor biopsy is considered too high, no biopsy will be required. In this case, the study coordinators must be informed in advance, and there will be no reimbursement for the biopsy procedure. b. In case WGS is performed on tumor tissue outside the context of a clinical trial before inclusion, and without any type of anti-cancer therapy between the collection of tissue and inclusion in DRUP, this can replace the DRUP pre-treatment biopsy, provided that the patient gives consent to use his/her WGS data for biomarker analysis in DRUP. c. An exception is made for patients that underwent an allogeneic hematopoietic stem cell transplantation prior to study enrollment, since this will prevent a correct WGS analysis due to a mismatch between the biopsy specimen and the required blood sample			
8. Ability to understand and the willingness to sign a written informed consent document.			
9. Women of child-bearing potential must agree to use adequate contraception for the duration of study participation, and for five months following completion of study therapy. Men receiving atezolizumab + bevacizumab must agree to use contraception for a period of 7 months after the last dose of atezolizumab + bevacizumab. Females should not breastfeed while receiving the combination and for any subsequent protocol-specified period.			

Exclusion criteria	Yes	No	n.a.
1. Patients that are eligible for on-label treatment with atezolizumab and/or bevacizumab or for ongoing phase 2 / 3 trials with atezolizumab and/or bevacizumab are excluded from treatment with the combination within the DRUP trial.			
2. Prior treatment with an anti-PD1 or anti-PDL1 agent.			
3. Known hypersensitivity to the active substances or to any of the excipients.			
4. Use of systemic corticosteroids and other immunosuppressants at baseline (before starting atezolizumab + bevacizumab). Exception: The use of low dose corticosteroids (prednisone ≤10 mg daily or equivalent) is allowed.			

Exclusion criteria	Yes	No	n.a.
5. Active autoimmune disease requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease, or a syndrome requiring systemic or immunosuppressive agents. Note: Patients with vitiligo, Type 1 diabetes, resolved childhood asthma/atopy are eligible. Patients who require intermittent use of bronchodilators, inhaled steroids, or local steroid injections are eligible. Patients with hypothyroidism stable on hormone replacement or Sjogren's syndrome are eligible. Replacement therapy (such as: thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc) is not considered a form of systemic therapy.			
6. Positive test for HIV.			
7. Active hepatitis B (defined as having a positive hepatitis B surface antigen [HBsAg] test at screening) or hepatitis C. Patients with past hepatitis B virus (HBV) infection or resolved HBV infection (defined as having a negative HBsAg test and a positive antibody to hepatitis B core antigen [anti-HBc] antibody test) are eligible. Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA.			
8. Administration of live, attenuated vaccine within 4 weeks prior to enrollment.			
9. Patients with wound healing complications in the last 3 months before enrollment, or who had major surgery in the last 28 days before enrollment.			
10. Patients with active fistula of the gastrointestinal tract, gynaecological organs or bronchus/trachea, or a high risk of fistula formation. Patients with active intraabdominal inflammatory processes are not eligible.			
11. Patients with haemoptysis or pulmonary haemorrhage within the past 3 months before enrollment.			
12. Patients with an arterial thromboembolism in the past 6 months before enrollment are not eligible. Patients with a history of arterial thromboembolism > 6 months ago are eligible, but close monitoring is advised.			
13. Patients with a history of venous thromboembolism are eligible, but close monitoring is advised.			
14. Ongoing toxicity > grade 2, other than alopecia.			
15. Patient is receiving any other anti-cancer therapy (cytotoxic, biologic, radiation, or hormonal other than for replacement). Required wash out period prior to starting study treatment is at least two weeks. An exception is made for patients suffering from CRPC, who are allowed to continue androgen deprivation therapy.			
16. Patient is pregnant or nursing.			
17. Patients with known active progressive brain metastases. Patients with previously treated brain metastases are eligible, provided that the patient has not experienced a seizure or had a clinically significant change in neurological status within the 3 months prior to registration. All patients with previously treated brain metastases must be stable for at least 1 month after completion of treatment and off steroid treatment prior to study enrollment.			
a. <u>For patients with a primary brain tumor</u>: (I) Patients who require anti-convulsant therapy must be taking non-enzyme inducing antiepileptic drugs (non-EIAED). EIAED are prohibited. Patients previously on EIAED must be switched to non-EIAED at least 2 weeks prior to randomization. (II) No radiotherapy within the three months prior to the diagnosis of progression. (III) No radiotherapy with a dose over 65 Gy, stereotactic radiosurgery or brachytherapy unless the recurrence is histologically proven.			

Exclusion criteria	Yes	No	n.a.
18. Patients with clinically significant preexisting cardiac conditions, including uncontrolled or symptomatic angina, uncontrolled atrial or ventricular arrhythmias, or symptomatic congestive heart failure are not eligible.			
19. Patients with known left ventricular ejection fraction (LVEF) < 40% are not eligible.			
20. Patients with stroke (including TIA) or acute myocardial infarction within 3 months before the first dose of study treatment are not eligible.			
21. Patients with any other clinically significant medical condition which, in the opinion of the treating physician, makes it undesirable for the patient to participate in the study or which could jeopardize compliance with study requirements including, but not limited to: ongoing or active infection, significant uncontrolled hypertension, or severe psychiatric illness/social situations.			

NB Please note that official prescription instructions, as outlined in the Summary of Product Characteristics (SPC, most recent version can be downloaded from https://www.ema.europa.eu/en/medicines) and / or any other official documents concerning this drug, will always take precedence over this manual. This manual is provided for practical support; treatment can be performed according to local standard-of-care protocols.

2. Treatment schedule

	Screening (≤28 days before start)	After screening, before start	D1 of every treatment cycle 1 treatment cycle = 21 days[3]	After every 9 weeks of treatment[3,4]	After end of treatment (≤30 days after stop)
Concurrent meds	X		X		
Adverse events			X		
Physical exam	X		X[1]		
Vital signs	X		X[1,2]		
Performance Status	X		X		
CBC w/diff, platelets	X		X[1]		
Serum chemistry	X[3]		X[3]		
Serum pregnancy test	X[7]				
Urine analysis	X[4]		X		
ECG	X				
Tumor biopsy		X[6]			X[6]
Atezolizumab (Tecentriq)			X		
Bevacizumab (Avastin)			X		
Response evaluation	X[5]			X[5]	

1. According to local standard clinical practice, or as clinically indicated.
2. Monitored for the development or worsening of hypertension.
3. Patients should be monitored for signs and symptoms of immune-related hepatitis, pancreatitis, renal dysfunction and endocrinopathies. Regular monitoring of the following is recommended: bilirubin, ALAT, ASAT, GGT, AF, CRP, serum creatinine, GFR, urea, sodium, potassium, phosphate, magnesium, glucose, total protein, albumin, calcium, T-amylase, lipase, chloride, uric acid, bi-carbonate, HDL and LDL-cholesterol, triglycerides, ACTH, cortisol, TSH, free thyroxine. During the screening, INR and APTT should also be checked.
4. Patients should be monitored for signs and symptoms of proteinuria.
5. A baseline scan should be performed <28 days before start of treatment. Tumor assessments will initially be repeated every 9 weeks after treatment initiation. If the patient continues study treatment beyond 3 response evaluations (i.e., 24 weeks), response evaluation will thereafter be performed at the end of every 12 weeks.
6. If screening is positive, a mandatory DRUP pre-treatment biopsy will be performed. After end of treatment a post-treatment biopsy can be obtained. The post-treatment biopsy is optional.
7. In women of child-bearing potential.

3. Administration and starting dosage

The recommended dose of atezolizumab is 1200 mg (flat dose) administered intravenously every 3 weeks. The initial dose should be administered over 60 minutes. If the first infusion is well tolerated, all subsequent infusions may be administered over 30 minutes.

The recommended dose of bevacizumab is 15 mg/kg, administered intravenously every 3 weeks. The initial dose should be administered over 90 minutes. If the first infusion is well tolerated, the second infusion may be administered over 60 minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be administered over 30 minutes.

Treatment should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient.

Atezolizumab is for intravenous use only. It is to be administered as an intravenous infusion over a period of 30-60 minutes. The use of in-line filter membranes is optional. Atezolizumab must **not** be administered as an intravenous push or bolus injection. Twenty ml of atezolizumab concentrate should be withdrawn from the vial and diluted into 250 ml sodium chloride 9 mg/ml (0.9%) solution for injection. After dilution, 1 ml of solution should contain approximately 4.4 mg of atezolizumab (1200 mg/270 ml). The bag should be gently inverted to mix the solution in order to avoid foaming. Once infusion is prepared it should be administered immediately. Vials of atezolizumab injection must be stored at 2ºC to 8ºC and protected from light and freezing. They must be kept in the original outer carton. The unopened vials can be stored at room temperature (up to 25ºC) and room light for up to 48 hours. The administration of atezolizumab infusion must be completed within 24 hours of preparation. If not used immediately, the infusion solution may be stored under refrigeration conditions (2°C to 8°C) for up to 24 hours, and a maximum of 8 hours of the total 24 hours can be at room temperature (20°C to 25°C) and room light. The maximum of 8 hours under room temperature and room light conditions included the product administration period.

Bevacizumab is for intravenous use only. It is to be administered as an intravenous infusion over a period of 30-90 minutes. Bevacizumab must not be administered as an intravenous push or bolus injection. The necessary amount of bevacizumab should be withdrawn and diluted to the required administration volume with sodium chloride 9 mg/ml (0.9%) solution for injection. The concentration of the final bevacizumab solution should be kept within the range of 1.4 mg/ml to 16.5 mg/ml. In the majority of the occasions the necessary amount of bevacizumab can be diluted with 0.9 % sodium chloride solution for injection to a total volume of 100 ml.

Bevacizumab should not be diluted with glucose solutions (5%). Once infusion is prepared it should be administered immediately. Vials of bevacizumab injection must be stored at 2ºC to 8ºC and protected from light and freezing. They must be kept in the original outer carton. The administration of bevacizumab infusion must be completed within 24 hours of preparation. If not used immediately, the infusion solution may be stored under refrigeration conditions (2°C to 8°C) for up to 24 hours.

For other instructions on the handling of the medicinal product before administration, see SPC section 6.6.

4. How supplied

Atezolizumab is supplied as 60 mg/mL concentrate for solution for infusion. One vial of 20 mL contains 1200 mg of atezolizumab.

Bevacizumab is supplied as 25 mg/mL concentrate for solution for infusion. One vial of 4 ml contains 100 mg of bevacizumab. One vial of 16 ml contains 400 mg of bevacizumab.

Drugs can be (re-)ordered by filling in the required fields in the eCRF. Drugs will be shipped to the site's pharmacy. Per shipment, sufficient drug can be ordered to treat the patient until the next response evaluation (and 1 cycle beyond for the first order, to cover the period in between response evaluation and re-supply).

5. Dose modifications for toxicity

Dose escalation or reduction of atezolizumab and bevacizumab is not recommended. Dosing delay or discontinuation may be required based on individual safety and tolerability. For more information on permanent discontinuation or withholding of doses, please refer to the Summary of Product Characteristics (SPC) of both drugs, table 1 and section 4.4 and 4.8.

In case toxicity occurs that is clearly attributed to only one of the drugs, it is allowed to continue with atezolizumab or bevacizumab monotherapy.

6. Treatment interruption

For patients who have ongoing clinical benefit (CR, PR or SD) after 1 year of treatment with atezolizumab and bevacizumab, an interruption of treatment can be considered. After treatment discontinuation, response evaluations need to be performed every 8-12 weeks or as clinically indicated. If radiological or clinical progression occurs, treatment with atezolizumab and bevacizumab can be restarted within DRUP. A new "baseline" scan must be performed, defining RECIST 1.1 evaluable target lesion(s). Assessment of the in- and exclusion criteria (section 1 in this manual) needs to be performed, before restarting the treatment. An optional new pre-treatment biopsy is recommended. Treatment can only be interrupted after consultation with the central DRUP study team.

	Before interruption of atezo/beva	During interruption	At clinical/radiological progression
Consult DRUP study team	X		X
Response evaluation		X[1]	X[1]
Re-screening			X
Biopsy			X (optional)

1. During the first two years following the discontinuation of the atezolizumab and bevacizumab treatment, radiological response evaluation should be performed every 12 weeks. Thereafter, response evaluation should be performed every 6 months or as clinically indicated.

7. Warnings and precautions

For Atezolizumab a Patient Card is available from Roche, which must be handed out to all patients treated with Atezolizumab. The latest version can be downloaded from the website:

https://www.roche.nl/producten/medicijnen/tecentriq

Immune-related adverse reactions: patients should be monitored continuously (at least up to 5 months after the last dose) as an adverse reaction with atezolizumab may occur at any time during or after discontinuation of atezolizumab therapy.

- Immune-related pneumonitis: patients should be monitored for signs and symptoms of pneumonitis such as radiographic changes (e.g., focal ground glass opacities, patchy filtrates), dyspnea, and hypoxia.
- Immune-related colitis: patients should be monitored for diarrhea and additional symptoms of colitis, such as abdominal pain and mucus or blood in stool.
- Immune-related hepatitis: patients should be monitored for signs and symptoms of hepatitis such as transaminase and total bilirubin elevations.
- Immune-related nephritis or renal dysfunction: patients should be monitored for signs and symptoms of nephritis and renal dysfunction. Most patients present with asymptomatic increases in serum creatinine.
- Immune-related endocrinopathies: patients should be monitored (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) for clinical signs and symptoms of endocrinopathies and for changes in thyroid function , including hypothyroidism, adrenal insufficiency, hypophysitis and diabetes. Patients may present with fatigue, headache, mental status changes, abdominal pain, unusual bowel habits, and hypotension, or nonspecific symptoms which may resemble other causes such as brain metastasis or underlying disease. Unless an alternate etiology has been identified, signs or symptoms of endocrinopathies should be considered immune-related.
- Immune-related pancreatitis: patients should be closely monitored for signs and symptoms that are suggestive of acute pancreatitis, including monitoring of serum amylase and lipase levels.
- Immune-related neuropathies: patients should be monitored for symptoms of motor and sensory neuropathy, such as myasthenic syndrome/myasthenia gravis or Guillain-Barré syndrome.
- Immune-related meningoencephalitis: patients should be monitored for clinical signs and symptoms of meningitis or encephalitis.
- Other immune-mediated adverse events: cases of myotoxicity (myositis, myocarditis, and rhabdomyolysis), some with fatal outcome, have been reported with atezolizumab. Any cases with cardiac or cardio-pulmonary symptoms should undergo prompt diagnostic work-up to evaluate for myocarditis with close monitoring.

For an overview of management of toxicities from immunotherapy, we would like to refer you to the **ESMO Clinical Practice Guidelines**: J. B. A. G. Haanen et al. Annals of Oncology 28 (Supplement 4): iv119–iv142, 2017. 'Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up'. http://www.esmo.org/Guidelines/Supportive-and-Palliative-Care/Management-of-Toxicities-from-Immunotherapy

For detailed information on recommended supportive therapy and dose reductions, delays or discontinuation, please refer to SPC table 1 and sections 4.4 and 4.8. For suspected immune-related adverse reactions, adequate evaluation should be performed to confirm etiology or exclude other causes. Based on the severity of the adverse reaction, atezolizumab should be withheld and corticosteroids administered. If immunosuppression with corticosteroids is used to treat an adverse reaction, a taper of at least 1 month duration should be initiated upon improvement to Grade ≤ 1. Non-corticosteroid immunosuppressive therapy should be added if there is worsening or no improvement despite corticosteroid use.

Atezolizumab must be permanently discontinued for any Grade 3 immune-related adverse reaction that recurs and for any Grade 4 immune-related adverse reactions, except for endocrinopathies that are controlled with replacement hormones (see SPC sections 4.2 and 4.8).

Gastrointestinal perforation and fistulae: bevacizumab should be permanently discontinued in patients who develop a gastrointestinal perforation, tracheoesophageal (TE-)fistula or any Grade 4 fistula.

Surgery and wound healing complications: bevacizumab should be withheld in case of wound healing complications until the wound is fully healed. Bevacizumab should be withheld for elective surgery.

Thromboembolic events: bevacizumab should be permanently discontinued in patients who develop an arterial thromboembolic reaction and in patients who develop a life-threatening (Grade 4) venous thromoboembolic reaction, including pulmonary embolism. Patients who develop a Grade ≤ 3 venous thromboembolism should be closely monitored.

Infusion related reactions: the rate of infusion should be reduced or treatment should be interrupted in patients with Grade 1 or 2 infusion-related reactions. Atezolizumab should be permanently discontinued in patients with Grade 3 or 4 infusion-related reactions. Patients with Grade 1 or 2 infusion-related reactions may continue to receive atezolizumab with close monitoring; premedication with antipyretic ant antihistamines may be considered.

Haemorrhage: bevacizumab should be permanently discontinued in patients who develop a Grade ≥ 3 bleeding or any Grade intracranial bleeding during therapy.

Interactions: as monoclonal antibodies like atezolizumab are not metabolized by cytochrome P450 (CYP) enzymes or other drug metabolizing enzymes, inhibition or induction of these enzymes by co-administered medicinal products is not anticipated to affect the pharmacokinetics of atezolizumab.

The use of systemic corticosteroids and other immunosuppressants at baseline, before starting atezolizumab, should be avoided because of their potential interference with the pharmacodynamics activity. However, systemic corticosteroids and other immunosuppressants can be used after starting atezolizumab to treat immune-related adverse reactions.

Adverse Events of Special Interest (AESI): the following AE's are considered AESI. Regardless of whether they meet the seriousness criteria, AESI should **always** be reported within 1 working day (using the SAE form, conform the SAE procedure):

- Immune-mediated severe cutaneous reaction
- Immune-mediated ocular inflammatory toxicity
- Immune-mediated vasculitis
- Systemic lupus erythematosus (SLE)
- Cytokine-release syndrome (CRS)
- Hemophagocytic lymphohistiocytosis (HLH)

8. Special populations:

Elderly patients: No dose adjustment of atezolizumab or bevacizumab is required in patients ≥ 65 years of age.

Renal impairment: no dose adjustment of atezolizumab is required in patients with mild or moderate renal impairment. Data from patients with severe renal impairment are too limited to draw conclusions on this population. Bevacizumab has not been studied in patients with renal impairment.

Hepatic impairment: no dose adjustment of atezolizumab is required in patients with mild hepatic impairment. Atezolizumab has not been studied in patients with moderate or severe hepatic impairment. Bevacizumab has not been studied in patients with hepatic impairment.