**Annex to the main manuscript.**

**Criteria for inclusion in the drug program in Poland (according to the decision of the Minister of Health).**

1. **Qualification criteria for vemurafenib:**
2. Unresectable diagnosis (3rd degree) or generalized (4th degree) skin melanoma;
3. confirmation of BRAF V600 mutation in cancer cells using a validated test;
4. cancerous changes to assess the response to treatment according to the criteria of the current version of RECIST;
5. age ≥ 18;
6. lack of symptomatic metastases to the central nervous system or asymptomatic state after surgery or radiotherapy of brain metastases;
7. size of QTC interval of ECG ≤ 500 ms;
8. results of morphology and biochemical tests of blood allowing treatment according to the current Summary of Product Characteristics, and in particular:
9. leukocytes count ≥ 2000/μl;
10. neutrophils count ≥ 1500/μl;
11. platelets count 100 x 103/μl;
12. hemoglobin concentration ≥ 9 g/dl (Possible transfusion of blood / blood products);
13. creatinine concentration ≤ 1,5 x ULN (upper limit of normal –ULN);
14. activity of AST / ALT, alkaline phosphatase (ALP) ≤ 3.0 x ULN in patients without liver metastases and ≤ 5 x ULN in patients with liver metastases (or in case of ALP to the bone);
15. bilirubin concentration ≤ 1,5 x ULN (Except for patients with Gilbert syndrome who must have a total bilirubin concentration of less than 3.0 mg / dl)
16. there are no contraindications for the use of Zelboraf and Cotellic medicines as defined in the current Summary of Product Characteristics;
17. start of the treatment in the program is possible within the time of > 14 days after palliative radiotherapy or major surgery;
18. ophthalmic diseases exclusion during the interview: central serous choroidoretinopathy, the closure of retinal vein or exudative macular degeneration, uncontrolled glaucoma;
19. no significant cardiovascular loads: unstable coronary artery disease, NYHA ≥ 2 cardiovascular insufficiency;
20. left ventricular ejection fraction ≥ 50%;
21. lack of accompanying diseases or disorders that prevent treatment;
22. exclusion of coexisting other malignancy with the exception of malignant skin cancers;
23. exclusion of pregnancy or breast-feeding in patients;
24. no previous BRAF treatment;

**Criteria must be met together.**

**B. Qualification criteria for ipilimumab:**

1. histologically confirmed melanoma skin or of mucous membranes in stage III (non-

operational) or stage IV;

2. Insufficient prior systemic treatment of melanoma or non-tolerance not allowing further

treatment (not applicable to patients who received complementary postoperative treatment -

the patients may be eligible for ipilimumab after the aforementioned complementary

treatment and one option of systemic treatment due to the generalization of the tumor);

3. initiating therapy with ipilimumab at the time of reversal of all clinically significant side

effects of earlier treatment (chemotherapy, immunotherapy, biochemotherapy, radiotherapy,

surgical treatment);

4. absence metastases in the brain or asymptomatic state after surgery or radiotherapy of brain

metastases;

5. performance level 0-1 according to ECOG criteria

6. age ≥ 18

7. contraceptive prevention in women of childbearing age throughout the period of application of

treatment and 26 weeks after the last dose ipilimumabem

8. laboratory tests (before treatment) with values:

1. white blood cells count ≥ 2000/μl;
2. neutrophils count ≥ 1000/μl;
3. platelets count ≥ 75 x 103/μl;
4. haemoglobin concentration ≥ 9 g/dl (Possible transfusion of blood / blood products);
5. creatinine concentration ≤ 2 x ULN (upper limit of normal –ULN);
6. activity of AST / ALT, ≤ 2,5 x ULN in patients without liver metastases and ≤ 5 x ULN in patients with liver metastases;
7. bilirubin concentration ≤ 1,5 x ULN (Except for patients with Gilbert syndrome who must have a total bilirubin concentration of less than 3.0 mg / dl)

**Criteria must be met together.**

**C. Qualification criteria for dabrafenib:**

1. Unresectable diagnosis (3rd degree) or generalized (4th degree) skin melanoma
2. confirmation of BRAF V600 mutation in cancer cells using a validated test
3. cancerous changes to assess the response to treatment according to the criteria of the current version of RECIST;
4. age ≥ 18;
5. performance level 0-1 according to Zubroda-WHO classification or ECOG criteria;
6. If new CNS metastases are identified, the condition for inclusion in the program is their asymptomatic state. Patients previously treated for CNS metastases, lack of symptoms due to the CNS metastases and metastatic CNS changes stable for ≥ 1 month after surgery or after stereotactic radiotherapy;
7. size of QTC interval of ECG ≤ 500 ms;
8. results of morphology and biochemical tests of blood allowing treatment according to the current Summary of Product Characteristics dabrafenib and trametynib, and in particular:
9. white blood cells count ≥ 2000/μl;
10. neutrophils count ≥ 1500/μl;
11. platelets count 100 x 103/μl;
12. hemoglobin concentration ≥ 9 g/dl (Possible transfusion of Packed red blood cells (PRBC));
13. creatinine concentration ≤ 1,5 x ULN (upper limit of normal - ULN);
14. activity of AST / ALT, alkaline phosphatase (ALP) ≤ 2.5 x ULN in patients without liver metastases and ≤ 5 x ULN in patients with liver metastases;
15. bilirubin concentration ≤ 1,5 x ULN (except for patients with Gilbert syndrome who must have a total bilirubin concentration of less than 3.0 mg/dl)
16. there are no contraindications for the use of dabrafenib i trametynib medicines as defined in the

current Summary of Product Characteristics;

10. lack of accompanying diseases or disorders that prevent treatment;

11. exclusion of concurrent chemotherapy;

12. exclusion of coexisting other malignancy with the exception of malignant skin cancers;

13. exclusion of pregnancy or breast-feeding in patients.

**Criteria must be met together.**