A Phase 2 Study to Evaluate Safety and Anti-tumor Activity of Avelumab in Combination with Talazoparib In Patients with BRCA or ATM Mutant Tumors

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Primary Objective:* To evaluate ORR of avelumab in combination with talazoparib, in patients with locally advanced or metastatic solid tumors harboring BRCA1, BRCA2 or ATM defect.Secondary Objective:* To assess the overall safety and tolerability of...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Miscellaneous and site unspecified neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON48840

Source
ToetsingOnline

Brief title
JAVELIN BRCA/ATM

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
locally advanced or metastatic solid tumors, maligne tumor

Research involving
Human

Sponsors and support

Primary sponsor: Pfizer
Source(s) of monetary or material Support: Farmaceutische industrie

Intervention

Keyword: ATM-mutation, BRCA-mutation, Phase II, Solid tumors

Outcome measures

Primary outcome

* Confirmed OR in patients with locally advanced or metastatic solid tumors with BRCA 1/2 or ATM defect, as assessed by Blinded Independent Central Review (BICR), using RECIST v1.1 and, in patients with mCRPC, RECIST v1.1 and PCWG3 (bone).

Secondary outcome

* Adverse Events as characterized by type, severity (as graded by National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v.4.03), timing, seriousness, and relationship to study therapy.

* Laboratory abnormalities as characterized by type, severity (as graded by NCI CTCAE v.4.03) and timing.

* PK parameters including: pre dose/trough concentrations (Ctrough) for avelumab and talazoparib and post dose concentrations (for talazoparib) and maximum concentrations (Cmax) for avelumab.

* Avelumab Anti drug antibody (ADA) levels and neutralizing antibodies (Nab) against avelumab.

* Confirmed OR as assessed by the investigator, using RECIST v1.1 (Appendix 3) and, in patients with mCRPC, RECIST v1.1 and PCWG3.

* Time to event endpoints: Endpoints as assessed by BICR and as assessed by the investigator, using RECIST v1.1 and in patients with mCRPC, RECIST v1.1 and PCWG3, including time to tumor response (TTR), duration of response (DR), and progression free survival (PFS). Additional time to event endpoints include overall survival (OS) for all patients and time to prostate specific antigen (PSA) progression (*25% increase) for mCRPC patients.

* PSA response 50% decrease and CTC count conversion for patients with mCRPC.

* Cancer antigen (CA) 125 response 50% decrease for patients with ovarian cancer.

* PD L1 expression level in baseline tumor tissue

* Presence of defects in a panel of key oncogenes, including BRCA1/2 and ATM, and TMB in ctDNA and tumor tissue at baseline, during treatment, and at the end of treatment.

Study description

Background summary

Avelumab, as a single agent, has demonstrated efficacy in patients across different tumor types, including previously untreated and treated non small cell lung cancer (NSCLC), urothelial cancer, ovarian cancer, breast cancer, mMCC, gastric/gastroesophageal junction cancer (GC/GEJ) and castration resistant prostate cancer (mCRPC). The efficacy findings for avelumab are summarized in the table in the protocol synopsis.
These studies have also shown an acceptable safety profile for avelumab single agent treatment; most frequently observed treatment related adverse events from pooled data have been fatigue (17.7%), infusion related reaction (17.0%), nausea (8.6%), diarrhea (7.1%), chills (6.7%), pyrexia (6.1%), decreased appetite (5.2%), and hypothyroidism (5.0%).
While subsets of patients in a growing number of tumor types respond to treatment with a single agent PD 1 or PD L1 inhibitor, most patients with advanced disease either do not respond to single agent therapy or experience

only a partial response. Further, the majority of those patients who do respond will ultimately progress. These findings of somewhat limited responses are observed regardless of either the PD 1 or PD L1 inhibitor that is being tested or the tumor type in which the immune checkpoint inhibitor is being evaluated.

Talazoparib, as a single agent, has demonstrated efficacy as well as an acceptable toxicity profile in patients with multiple types of solid tumors with DNA repair pathway abnormalities, particularly those associated with BRCA and phosphatase and tensin homolog gene (PTEN) dysfunction. In the Phase 1 Study PRP 001, in patients treated with talazoparib 1.0 mg/day with advanced breast cancer, ovarian/peritoneal cancer, and pancreatic cancer, an objective response rate (ORR) of 50.0% (7 of 14; 95% confidence interval [CI]: 23.0, 77.0), 41.7% (5 of 12; 95% CI: 15.2, 72.3), and 20% (2 of 10) was observed, respectively.33 In the ongoing Phase 2 study in patients with locally advanced or metastatic breast cancer harboring BRCA mutations (Study 673 201), independently assessed OR has been observed in 20.8% of 48 patients with disease progression after prior response to platinum containing regimens and in 37.1% of 35 patients with disease progression after 3 or more non platinum cytotoxic regimens.

Data from the ongoing EMBRACA study presented in December 2017 (287 patients in talazoparib arm, 144 patients in physician*s choice therapy [PCT] arm) showed that median PFS was 8.6 months (95% CI: 7.2, 9.3) for patients treated with talazoparib and 5.6 months (95% CI: 4.2, 6.7) for those treated with chemotherapy (hazard ratio [HR]=0.54; 95% CI: 0.41, 0.71; p<0.0001). Also, ORR was 62.6% for talazoparib vs 27.2% for chemotherapy (odds ratio for OR=4.99; 95% CI: 2.9, 8.8; p<0.0001; per RECIST 1.1, confirmation of CR/PR was not required) and median duration of response (DOR) was 5.4 months (interquartile range [IQR]: 2.8 11.2) for talazoparib and 3.1 months (IQR: 2.4 6.7) for PCT. The overall survival (OS) data are still immature (38% deaths in each arm) and OS time was not statistically different between arms. The most common adverse events (AEs) observed with talazoparib (>20%, all grade) were anemia (52.8%), fatigue (50.3%), nausea (48.6%), neutropenia (34.6%), headache (32.5%), thrombocytopenia (26.9%), alopecia (25.2%), vomiting (24.8%), diarrhea (22%), constipation (22%), decreased appetite (21.3%), and back pain (21%). The incidence of serious AEs was 31.8% in the talazoparib arm and 29.4% in the chemotherapy arm. Discontinuations due to AEs occurred in 7.7% of patients in the talazoparib arm and 9.5% of patients in the chemotherapy arm.24

Talazoparib is proposed for evaluation in combination with avelumab in patients with locally advanced (primary or recurrent) or metastatic solid tumors with a pathogenic or likely pathogenic germline or loss of function somatic BRCA1, or BRCA2, or ATM gene defect who have received at least 1 line of standard of care (SOC) treatment for locally advanced or metastatic disease unless prior treatment requirements are otherwise specified. This is based on the acceptable safety and pharmacokinetic (PK) profiles observed for each of the investigational products when administered as single agents, on the clinical activity that has been observed for these investigational products, or an agent of the same class, and on proposed complementary mechanisms of action, detailed

below.
The activity of avelumab depends on generation of a productive immune response. DNA damage via talazoparib is expected to promote inflammation and prime an immune response by enhancing effective recognition and infiltration of tumors by immune cells. Additionally, talazoparib treatment has been shown to lead to two to three fold increased expression of PD L1 by tumor cells, suggesting that this may represent a means by which tumors function to inhibit talazoparib mediated anti tumor immunity. Based on these interactions between DNA damage, PD L1 expression and the immune response, the combination of talazoparib and avelumab is expected to lead to additive or synergistic anti tumor activity.
Preliminary data from other PARP and PD L1 inhibitor combination studies for treatment of advanced tumors currently tested in clinical trials have shown promising activity and suggest that the combination has an acceptable safety profile.25,26,45
This expectation is supported by preclinical studies in syngeneic mouse models of ovarian and colorectal cancers, which demonstrated a significant improvement in overall survival (OS) in mice treated with the combination of talazoparib and an anti mouse PD L1, but not in mice treated with either talazoparib or anti mouse PD L1 alone.40
Clinical studies have indicated that the greatest sensitivity to PARP inhibitors, such as talazoparib, is observed in tumors with defective repair of DNA double strand breaks (DSBs); such breaks accumulate following PARP inhibition and in the absence of effective repair lead to cell death.41 One underlying reason for defective DSB repair is the presence of mutations in key genes, either at the germline or somatic level. The BRCA1, BRCA2 and ATM genes are three of the best evidenced examples of such genes. Mutations in either the BRCA1 or BRCA2 gene have been associated with increased response, or improved outcome, following treatment with a number of PARP inhibitors including olaparib, rucaparib, and niraparib while mutations in ATM have been associated with increased response to olaparib.42,43,44,54 Clinical development of most PARP inhibitors has been focused up to now in tumor types with a relatively high prevalence of BRCA1/2 defects, such as ovarian, breast, prostate and pancreatic cancers. However, analysis of publicly available data within The Cancer Genome Atlas (TCGA56), indicates that mutations in BRCA 1/2 and ATM occur with variable frequency in many other tumor types, with an average prevalence across solid tumors of 7.7%. It is expected that all tumors with such defects will present with increased sensitivity to talazoparib mediated DNA damage, and therefore have the potential to benefit from the combination of talazoparib and avelumab.
The primary purpose of this study is to assess the efficacy and safety of the avelumab plus talazoparib combination in approximately 200 patients with locally advanced (primary or recurrent) or metastatic solid tumors with a pathogenic or likely pathogenic germline or somatic BRCA1, or BRCA2, or ATM gene defect who have received at least 1 line of standard of care (SOC) treatment for locally advanced or metastatic disease unless prior treatment requirements are otherwise specified. It is anticipated that these patients,

who have limited therapeutic options after progression on chemotherapy, and whose tumors harbor sensitizing defects in BRCA 1/2, or ATM, will be most likely to benefit from the combination treatment, independent of their tumor type. There remains a high unmet need in the management of these patients.

Study objective

Primary Objective:
* To evaluate ORR of avelumab in combination with talazoparib, in patients with locally advanced or metastatic solid tumors harboring BRCA1, BRCA2 or ATM defect.

Secondary Objective:
* To assess the overall safety and tolerability of avelumab in combination with talazoparib.
* To characterize the PK of avelumab and talazoparib when given in combination.
* To evaluate the immunogenicity of avelumab when given in combination with talazoparib.
* To assess other measures of the anti tumor activity of avelumab in combination with talazoparib.
* To assess the correlation of anti tumor activity of avelumab in combination with talazoparib with PD L1 expression in baseline tumor tissue.
* To assess the correlation of anti tumor activity and emergence of resistance with defects in a panel of key oncogenes, including BRCA 1/2 and ATM, and TMB in circulating tumor DNA (ctDNA) and tumor tissue at baseline, during treatment and at the end of treatment.

Exploratory Objectives:
* To explore potential predictive and/or pharmacodynamic biomarkers in peripheral blood, and tumor tissue that may be relevant to the mechanism of action, response to or resistance to avelumab in combination with talazoparib. Specific markers will include but are not limited to biomarkers related to the immune response and to DDR.
* To assess the effects of avelumab in combination with talazoparib on patient reported outcomes including assessments of disease related symptoms, treatment side effects, functioning, and health status.
* To evaluate patient reported symptomatic AEs for avelumab in combination with talazoparib.
* To enable exploratory research through collection of banked biospecimens, unless prohibited by local regulations or ethics committee decision.

Study design

This is a Phase 2b, open label, multi center, non randomized study of avelumab in combination with talazoparib in adult patients with locally advanced (primary or recurrent) or metastatic solid tumors with pathogenic or likely

pathogenic germline or loss of function somatic BRCA1 or BRCA2, or ATM gene defect who have received at least 1 line of SOC treatment for locally advanced or metastatic disease unless prior treatment requirements are otherwise specified.

Intervention

All patients enrolled will receive avelumab and talazoparib.

Study burden and risks

- Blood draws (see E6)
- Study visits
- questionnaires
- Scans: CT/MRI/bone scan
- Adverse events (see section E9)

Risks and possible discomforts you might have from the study procedures include:
* Tumor Biopsy: The risk of a tumor biopsy depends on the size, type and location of your cancer. The risks include discomfort and bruising at the place where the biopsy needle is inserted. Significant bleeding and infection may occur but are uncommon. To reduce these risks, sterile techniques will be used and your doctor may give you antibiotics to prevent or treat any infection.
* Blood draws: During the study, your blood will be collected for blood tests. The risks of taking blood samples include temporary discomfort from the needle in your arm, bruising, swelling at the needle site. There is also a slight chance of infection.
* Contrast dye for CT scans: Contrast dye is usually injected when you get a CT scan. The contrast dye may cause pain or burning when it is injected, and may worsen kidney function in people who already have kidney disease or who are dehydrated (have not had enough liquids that day). The contrast dye may also cause an allergic reaction, which could be severe and life threatening.
* CT Scans and Bone scans: There are risks associated with the use of this test. CT scans and bone scans expose you to a small dose of radiation. Although all radiation you receive builds up over your lifetime, this amount of radiation should not create a significant risk to your health.
* MRI: There are risks associated with an MRI, especially if you are pregnant or have one of the following: an artificial heart valve, pacemaker, metal plate, pin, or other metallic objects in your body (including gun shot or shrapnel). You may also become anxious from lying in a tight space without moving. The MRI scan does not cause any pain and does not expose you to x ray radiation.
* ECG: The risks from an ECG can include skin irritation and a rash from the gel that is used or from wearing or removing the patches on your chest.
* Testing of DNA and/or RNA: This research may involve studying your biology and the likelihood that a particular biological feature (including genes) may

increase the chance of developing a disease. Genes are pieces of DNA that, through material called RNA, give instructions for building the proteins that make our bodies work. These instructions are stored in the form of a code. This is the code that you inherit from your parents and that you pass on to your children. DNA, RNA, and proteins can be studied as part of genetic research. The sponsor and researchers will put measures in place to minimize the possibility for the results from this research being linked to you, but there is always the remote possibility that information from your participation in the research may be disclosed.
* Intravenous Catheter: The use of an intravenous (IV) catheter may cause pain, bruising, clotting, bleeding, leakage of drug solution, and possibly infection at the catheter site.

Contacts

Public
Pfizer

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Scientific
Pfizer

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Patients must meet all of the following inclusion criteria to be eligible for enrollment into the study:
1. Pathogenic or likely pathogenic germline or somatic gene defect as determined by local assessment and classification:
* One or more BRCA1 or BRCA2 gene defect (Cohort 1);
* ATM gene defect in the absence of concurrent BRCA 1/2 defect (Cohort 2).
Note: in the event that a patient has concomitant defects in more than 1 of the three genes (BRCA1 or BRCA2 or ATM), they will be enrolled in Cohort 1.
The presence of gene defects must have been determined by local assessment and classification using a test of either germline or tumor DNA which was performed in a CAP/CLIA certified (or comparable local or regional certification) laboratory.
2. Histological diagnosis of locally advanced (primary or recurrent) or metastatic solid tumors that are not amenable for treatment with curative intent, as follows:
a. Recurrent Epithelial Ovarian Cancer:
* Patients must have received at least 1 but no more than 5 total prior cytotoxic chemotherapy regimens, including at least 1 course of platinum based therapy;
* Patients must not have progressed during or within 1 month after the last dose of the most recent platinum based chemotherapy;
* Platinum sensitivity requirements:
* If previously treated with *2 prior cytotoxic chemotherapy regimens, patients must have had disease progression within 6 months after the last dose of platinum based chemotherapy, also termed *platinum resistant recurrent disease*;
* If previously treated with >2 prior cytotoxic chemotherapy regimens, platinum sensitive recurrent disease is allowed.
* Any treatment regimen that began with cytotoxic chemotherapy and continued with another regimen for maintenance therapy following best response to initial cytotoxic regimen will count as one line of prior therapy.
b. TNBC (defined as ER and PgR negative [IHC nuclear staining <5%] and HER2 negative [IHC 0, 1+, or 2+ and/or ISH non amplified with ratio less than 2.0]) or hormone receptor positive (HR+), HER2 negative breast cancer:
* Have been previously treated with no more than 3 prior chemotherapy regimens for locally advanced or metastatic breast cancer;
* There is no limit on the number of prior endocrine therapies or targeted anti cancer therapies such as mammalian target of rapamycin (mTOR) or cyclin dependent kinase (CDK)4/6 inhibitors, or vascular endothelial growth factor inhibitors (VEGF);
* Previous neo adjuvant/adjuvant treatment counts as 1 line of prior chemotherapy if disease progression occurred while on treatment or within 6 months after the last treatment dose;
* Patients must have received treatment with a taxane or anthracycline containing chemotherapy regimen in the neo adjuvant, adjuvant, or advanced setting, unless deemed unsuitable for these treatments;
* Patients that have previously been treated with platinum based chemotherapy in the neo adjuvant/adjuvant setting must not have had disease progression while on treatment or within 6 months after the last dose of platinum based chemotherapy;
* Patients that have previously been treated with platinum based chemotherapy in the

advanced/metastatic setting must not have had disease progression within 6 months of initiation of a platinum-containing regimen;
* Patients with HR+ breast cancer must have received at least 1 prior endocrine therapy (adjuvant or metastatic), unless deemed not suitable for endocrine therapy.
c. Metastatic castration resistant prostate cancer (mCRPC) without small cell features:
* Patients with disease spread limited to regional pelvic lymph nodes (below the aortic bifurcation) are not eligible unless bone metastasis is present on bone scan;
* Progressed on at least 1 line of second generation anti androgen therapy (enzalutamide and/or abiraterone acetate/prednisone) for treatment of mCRPC;
* Have received no more than 2 prior chemotherapy regimens for mCRPC. Patients may have received radium 223, which does not count for a line of prior chemotherapy regimen;
* Serum testosterone *1.73 nmol/L (50 ng/dL);
* Bilateral orchiectomy or ongoing androgen deprivation therapy with a gonadotropin releasing hormone (GnRH) agonist/antagonist (surgical or medical castration);
* Progressive disease at enrollment defined as 1 or more of the following 3 criteria:
* A minimum of 3 consecutive rising PSA values with an interval of at least 1 week between determinations. The screening PSA value must be *2 *g/L (2 ng/mL) if qualifying solely by PSA progression;
* Disease progression as defined by RECIST v1.1;
* Bone disease progression defined by Prostate Cancer Working Group 3 (PCWG3) with 2 or more new metastatic lesions on bone scan (confirm ambiguous results by other imaging modalities).
d. Metastatic ductal adenocarcinoma of the pancreas:
* Have been previously treated with at least 1 but no more than 2 prior cytotoxic chemotherapy regimens (including at least one of the following: FOLFIRINOX or a gemcitabine containing regimen) unless deemed unsuitable or patient declined these therapies;
* Patients must not have had disease progression within 6 months of initiation of a platinum containing regimen.
e. Any other advanced solid tumor:
* Have received at least 1 prior SOC regimen, if it exists, as appropriate for the respective tumor type unless deemed unsuitable, or declined these therapies;
* Patients must not have had disease progression within 6 months of initiation of a platinum-containing regimen;
* Patients with NSCLC harboring B Raf proto oncogene (BRAF)V600 mutations or ALK and c Ros oncogene 1 (ROS1) translocations/rearrangements must have received the appropriate targeted therapy as approved by the relevant health care authority. Patients with activating EGFR mutations are not eligible; non squamous cell histologies require testing if EGFR status is unknown.
3. Availability of a fresh or recent tumor tissue sample from a diagnostic biopsy/surgery or a metastatic tumor biopsy; the sample must have been obtained within 24 months prior to study enrollment. When only bone disease is present, an archival tumor tissue sample obtained within 5 years prior to study enrollment may be accepted for non-prostate cancer patients and a fresh bone biopsy may be accepted for prostate cancer patients only). (See Section 7.4.1 for details).
4. Have progressive disease at study enrollment as defined by RECIST v1.1 (except for mCRPC, who must meet criterion 2c above).

5. Must have measurable disease by RECIST v1.1 with at least 1 measurable lesion that has not been previously irradiated (patients with mCRPC may have only non measurable disease).
6. Age *18 years (except in Japan, where patients must be *20 years old).
7. Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 or 1.
8. Adequate bone marrow function (without hematopoietic growth factor or transfusion support within 14 days prior to study enrollment), including:
a. Absolute Neutrophil Count (ANC) *1,500/mm3 or *1.5 x 109/L.
b. Platelets *100,000/mm3 or *100 x 109/L.
c. Hemoglobin *9 g/dL (*5.6 mmol/L).
9. Adequate renal function defined by an estimated creatinine clearance *30 mL/min according to the Cockcroft Gault formula as:
* CLCR<={[(140*age) × weight)]/(72 x SCR)} × 0.85 (if female), where CLCR (creatinine clearance) is measured in mL/min, age is expressed in years, weight in kilograms (kg), and SCR (serum creatinine) in mg/dL;
* Or as measured by 24h urine assessment.
NOTE: Patients with moderate renal impairment (30 59 mL/min) will receive a reduced starting dose for talazoparib (see section 5.4.2).
10. Adequate liver function, including:
a. Total serum bilirubin *1.5 × the upper limit of normal range (ULN);
b. Aspartate and Alanine aminotransferase (AST and ALT) *2.5 x ULN.
11. Female patients of childbearing potential must have negative serum pregnancy or urine pregnancy test at screening.
Women in the following categories are not considered to be women of child-bearing potential (WOCBP):
1. Premenopausal female with 1 of the following :
* Documented hysterectomy;
* Documented bilateral salpingectomy;
* Documented bilateral oophorectomy.
For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity),
investigator discretion should be applied to determining study entry. Note: Documentation for any of the above categories can come from the site
personnel*s review of the participant*s medical records, medical examination, or medical history interview. The method of documentation should be
recorded in the participant*s medical record for the study.;2. Postmenopausal female: ;* A postmenopausal state is defined as age 60 years or older or no menses for 12 months without an alternative medical cause.
* A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT).
* Females on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception
methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal
status before study enrollment.;12. Evidence of a personally signed and dated informed consent document indicating that the patient has been informed of all pertinent aspects of

the study.
13. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

Exclusion criteria

1. Prior treatment with a PARP inhibitor.;2. Prior immunotherapy with anti-PD-1, anti-PD-L1, anti-PD-L2, or anti-CTLA-4 antibody.;3. Prior anti-cancer therapy within 2 weeks prior to study enrollment or prior radiation therapy within 2 weeks prior to study enrollment. Prior palliative radiotherapy to metastatic lesion(s) is permitted, provided it has been completed at least 2 days prior to study enrollment and no clinically significant toxicities are expected (eg, mucositis, esophagitis).;4. Major surgery within 4 weeks prior to study enrollment.;5. Current use of immunosuppressive medication at the time of study enrollment, EXCEPT for the following permitted steroids: see Section 4.2.;6. Known prior severe hypersensitivity to investigational products or any component in their formulations, including known severe hypersensitivity reactions to monoclonal antibodies ([NCI CTCAE] v4.03 Grade * 3).;7. Known history of immune-mediated colitis, inflammatory bowel disease, pneumonitis, pulmonary fibrosis.;8. Active or prior autoimmune disease that might deteriorate when receiving an immunostimulatory agent. Patients with diabetes type I, vitiligo, psoriasis, or hypoor hyperthyroid disease not requiring immunosuppressive treatment are eligible.;9. Prior organ transplantation including allogenic stem-cell transplantation.;10. Administration of live attenuated vaccines within 4 weeks of study enrollment.;11. Diagnosis of myelodysplastic syndrome (MDS).;12. Known symptomatic brain metastases requiring steroids. Patients with previously diagnosed brain metastases are eligible if they have completed their treatment and have recovered from the acute effects of radiation therapy or surgery prior to study enrollment, have discontinued corticosteroid treatment for these metastases for at least 4 weeks, and are neurologically stable.;13. Participation in other studies involving investigational drug(s) within 4 weeks prior to study entry and/or during study participation.;14. Persisting toxicity related to prior therapy (NCI CTCAE v4.03 Grade >1); however, alopecia and sensory neuropathy Grade * 2, or other Grade * 2 AEs not constituting a safety risk, based on investigator's judgment, are acceptable.;15. Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS).;16. Hepatitis B virus (HBV) or hepatitis C virus (HCV) infection at screening (positive HBV surface antigen or HCV RNA if anti-HCV antibody screening test positive).;17. Active infection requiring systemic therapy. Minor infections, eg, periodontal or urinary tract infection (UTI) infection, which may be treated with short term oral antibiotics are allowed.;18. Clinically significant (ie, active) cardiovascular disease: cerebral vascular;accident/stroke (<6 months prior to study enrollment), myocardial infarction;(<6 months prior to study enrollment), unstable angina, congestive heart failure (* New York Heart Association Classification Class II), or a serious cardiac arrhythmia requiring medication.;19. Current or anticipated use of strong P-gp inhibitors within 7 days prior to enrollment,or anticipated use during the study. For a list of strong P-gp inhibitors, refer to Section 5.7.10.;20. Inability to swallow capsules, known intolerance to talazoparib or its excipients, known malabsorption syndrome, or other condition that may impair absorption of talazoparib.;21. Bisphosphonate or denosumab dosage that was not stable (ie, not the same)

for at least 2 weeks before study enrollment for patients receiving these therapies.;22. Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.;23. Diagnosis of any other malignancy within 2 years prior to study enrollment, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ of the breast, bladder, or cervix, or low-grade (Gleason * 6) prostate cancer on surveillance without any plans for treatment intervention (eg, surgery, radiation, or castration), or other early-stage low-risk cancers.;24. Pregnant female patients, breastfeeding female patients, and female patients of childbearing potential who are unwilling or unable to use a method of highly effective contraception as outlined in this protocol during treatment and for at least 30 days after the last dose of avelumab and for at least 7 months after the last dose of talazoparib; fertile male patients with female partners of reproductive potential or pregnant partners, unwilling to use a condom (even after vasectomy) during treatment and for at least 4 months after the last dose of talazoparib.;25. Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or patients who are Pfizer employees, including their family members, directly involved in the conduct of the study.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	23-05-2019
Enrollment:	22
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Bavencio
Generic name:	Avelumab
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	MDV3800, BMN 673
Generic name:	Talazoparib

Ethics review

Approved WMO Date:	09-08-2018
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	14-11-2018
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	11-03-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	21-03-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	16-05-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	27-06-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

Approved WMO Date:	29-07-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	06-08-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	26-02-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	09-03-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2018-000345-39-NL
ClinicalTrials.gov	NCT03565991
CCMO	NL66360.028.18