Purpose

This is a Phase 1, open-label, dose-escalation trial of avelumab [antibody targeting programmed death ligand 1 (anti PD-L1)] with consecutive parallel group expansion in subjects with selected tumor indications. New recruitment is open for all active cohorts.

Active cohorts: urothelial carcinoma (efficacy) and gastric/gastroesophageal junction (GEJ) cancer (third line).

Closed cohorts: Non-small cell lung cancer (NSCLC, first line), NSCLC (post-platinum), metastatic breast cancer (MBC), colorectal cancer (CRC), urothelial carcinoma (secondary), mesothelioma, gastric/GEJ cancer (first line switch maintenance and second line), and ovarian cancer (secondary and platinum refractory + liposomal doxorubicin), renal cell carcinoma (second line) melanoma and head, neck squamous cell carcinoma (HNSCC), castrate-resistant prostate cancer (CRPC), adrenocortical carcinoma (ACC), and renal cell carcinoma (RCC, first line).

<table>
<thead>
<tr>
<th>Condition</th>
<th>Intervention</th>
<th>Phase</th>
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<tbody>
<tr>
<td>Solid Tumors</td>
<td>Drug: Avelumab</td>
<td>Phase 1</td>
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</tbody>
</table>

Study Type: Interventional
Study Design: Endpoint Classification: Safety Study
             Intervention Model: Single Group Assignment
             Masking: Open Label
             Primary Purpose: Treatment

Official Title: A Phase I, Open-label, Multiple-ascending Dose Trial to Investigate the Safety, Tolerability, Pharmacokinetics, Biological and Clinical Activity of Avelumab (MSB0010718C) in Subjects With Metastatic or Locally Advanced Solid Tumors and Expansion to Selected Indications

Resource links provided by NLM:

- Genetics Home Reference related topics: head and neck squamous cell carcinoma, lung cancer
- MedlinePlus related topics: Cancer
- Genetic and Rare Diseases Information Center resources: Adrenocortical Carcinoma, Kidney Cancer, Ovarian Cancer, Renal Cancer, Squamous Cell Carcinoma of the Head and Neck, Transitional Cell Carcinoma
- U.S. FDA Resources

Further study details as provided by EMD Serono:
Primary Outcome Measures:

- Dose Limiting Toxicity [Time Frame: Up to 3 weeks] [Designated as safety issue: Yes]
- Confirmed Best Overall Response as per Response Evaluation Criteria in Solid Tumors (RECIST Version 1.1) for Efficacy Expansion Cohorts [Time Frame: Every 6 weeks until end of treatment (52 months)] [Designated as safety issue: No]

Secondary Outcome Measures:

- Number of subjects with Treatment-Emergent Adverse Events according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.0 [Time Frame: Screening up to 10 weeks after last treatment] [Designated as safety issue: Yes]
- Pharmacokinetic parameters: AUC (0-t), AUC (0-infinity), λz, Cmax, Tmax, T(1/2) of avelumab [Time Frame: Every 6-week up to Week 25] [Designated as safety issue: No]
- Immune-related Best Overall Response (irBOR) and Best Overall Response (BOR) according to modified Immune-related response criteria (irRC) and RECIST version 1.1, respectively [Time Frame: Time from inclusion in the trial until the date of first documented progression or discontinuation from the study due to any cause, up to 1 year after last treatment] [Designated as safety issue: No]
- Immune-related Progression-Free Survival (irPFS) time and Progression-Free Survival (PFS) time according to modified irRC and RECIST version 1.1, respectively [Time Frame: Time from inclusion in the trial until first observation of progressive disease or death when death occurs within 12 weeks of the last tumor assessment or first administration of trial treatment (whichever is later) up to 1 year after last treatment] [Designated as safety issue: No]
- Overall Survival Time [Time Frame: Time from randomization to death anticipated up to 2 years after last treatment] [Designated as safety issue: No]
- Pharmacodynamic profile of avelumab to include serum levels of cytokines [Time Frame: Up to Week 25] [Designated as safety issue: No]
- Number of subjects with anti-avelumab antibodies [Time Frame: Every 6-week up to Week 25] [Designated as safety issue: No]
- Level of PD-L1 tumor expression [Time Frame: Every 6-week up to Week 25] [Designated as safety issue: No]
- Unconfirmed response according to RECIST 1.1 per investigator assessment for Primary expansion cohort [Time Frame: Week 13] [Designated as safety issue: No]
- Duration of response according to modified irRC and RECIST 1.1 per investigator assessment [Time Frame: Time from inclusion in the trial until the date of first documented disease progression or discontinuation from the study due to any cause, up to 1 year after last treatment] [Designated as safety issue: No]
- Progression Free Survival time according to RECIST 1.1 for Efficacy Expansion Cohorts [Time Frame: Time from inclusion in the trial until the date of first documented disease progression or discontinuation from the study due to any cause, up to 1 year after last treatment] [Designated as safety issue: No]
- Duration of response according to RECIST 1.1 for Efficacy Expansion cohorts [Time Frame: Time from inclusion in the trial until the date of first documented disease progression or discontinuation from the study due to any cause, up to 1 year after last treatment] [Designated as safety issue: No]

Estimated Enrollment: 1670
Study Start Date: January 2013
Estimated Study Completion Date: April 2017
Estimated Primary Completion Date: April 2017 (Final data collection date for primary outcome measure)

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<thead>
<tr>
<th>Arms</th>
<th>Assigned Interventions</th>
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<tbody>
<tr>
<td>Experimental:</td>
<td>Drug: Avelumab</td>
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<tr>
<td>Avelumab</td>
<td>Avelumab will be administered in study location using a protocol-defined dose escalation scheme until confirmed progression, unacceptable toxicity, or if any criterion for withdrawal from the trial or investigational medicinal product occurs. After determination of the dose and regimen for Expansion Phase, avelumab will be administered to subjects divided into 4 primary cohorts: Non-small cell lung cancer (NSCLC) post platinum doublet, NSCLC first-line, gastric/gastroesophageal junction (GEJ) cancer and metastatic breast cancer (MBC); 8 secondary cohorts: Colorectal cancer (CRC), castrate-resistant prostate cancer (CRPC), melanoma, ovarian cancer, adrenocortical carcinoma (ACC) mesothelioma, uterine carcinoma, and renal cell carcinoma (RCC); and 4 efficacy expansion cohorts: gastric and GEJ cancer (third line), ovarian cancer (second-line only), uterine carcinoma, and head and neck squamous cell carcinoma (HNSCC).</td>
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<tr>
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<td>Other Names:</td>
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<tr>
<td></td>
<td>MSB0010718C</td>
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<td>Anti PD-L1</td>
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Eligibility

Ages Eligible for Study: 18 Years and older
Genders Eligible for Study: Both
Accepts Healthy Volunteers: No

Criteria

Inclusion Criteria for dose escalation and expansion phase:

- Signed written informed consent
- Male or female subjects aged greater than or equal to 18 years
- Subjects must have histologically or cytologically proven metastatic or locally advanced solid tumors, for which no standard therapy exists or standard therapy has failed. Availability of tumor archival material or fresh biopsies is optional for subjects in dose escalation
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1 at trial entry and an estimated life expectancy of at least 3 months
- Disease must be measurable with at least 1 uni-dimensional measurable lesion by RECIST 1.1, except for subjects with metastatic castrate-resistant prostate cancer (mCRPC) or metastatic breast cancer (MBC) who may be enrolled with objective evidence of disease without a measurable lesion
- Adequate hematological, hepatic and renal function as defined in the protocol
- Effective contraception for both male and female subjects if the risk of conception exists
- Other protocol defined inclusion criteria could apply

Inclusion Criteria for expansion phase:

- Subjects must have relapsed, refractory, or progressive disease following last line of treatment (with the exception of the gastric and gastroesophageal junction (GEJ) cancer cohort, which does not require progression). Availability of tumor archival material or fresh biopsies (excluding bone biopsies) is mandatory for eligibility in the expansion cohorts. For subjects in the MBC cohort, the biopsy or surgical specimen must have been collected within 90 days prior to the first investigational medicinal product (IMP) administration. Specifically, the following will be required:
  - NSCLC post platinum doublet: Histologically or cytologically confirmed stage IIIB or stage IV NSCLC that has progressed after 1 line of platinum-containing doublet chemotherapy. Subjects should have received only 1 line of platinum-containing treatment for metastatic disease (i.e., adjuvant treatment with a platinum-containing regimen is not sufficient for eligibility because not received in the context of a metastatic disease). Subjects in the NSCLC cohort will only be enrolled in USA
  - NSCLC first line: Stage IV (per 7th International Association for the Study of Lung Cancer [IASLC] classification) or recurrent NSCLC that is histologically proven. Subjects must not have received treatment for their metastatic or recurrent disease. No activating epidermal growth factor receptor (EGFR) mutation nor ALK translocation/re-arrangement
  - Gastric and GEJ cancer: Histologically confirmed, unresectable locally advanced or metastatic adenocarcinoma of the gastric and gastroesophageal junction, treated with first-line chemotherapy combination with or without disease progression. Subjects should have received no more than 1 line of treatment for metastatic disease. Subjects should not have been treated with trastuzumab (but can be Human Epidermal growth factor Receptor 2 [HER2] positive). Subjects who received any platinum containing doublet or triplet as a neoadjuvant chemotherapy strategy, but are not ultimately candidates for surgery will also be eligible, as long as they did not have progressive disease after completion of the neoadjuvant chemotherapy. In addition, subjects with gastric cancer can enter in the study if their white blood cell (WBC) and lymphocyte count is as defined in the protocol
  - MBC: Subjects must have histologically confirmed locally advanced or MBC and have tumor that is refractory to or progressive after standard of care therapy. Subjects must have received no more than 3 prior lines of cytotoxic therapy for metastatic disease. Subjects must have received a taxane and an anthracycline, unless contra-indicated
  - Secondary expansion cohorts: Metastatic colorectal cancer (mCRC), Metastatic castrate-resistant prostate cancer (mCRPC), melanoma, ovarian cancer, ACC, mesothelioma, urothelial carcinoma and renal cell carcinoma as defined in the protocol
  - Efficacy expansion cohorts: Gastric and GEJ cancer (third line), ovarian cancer (platinum refractory + liposomal doxorubicin), urothelial carcinoma, and HNSCC as defined in the protocol
- Other protocol defined inclusion criteria for expansion phase could apply

Exclusion Criteria for dose escalation and expansion phase:

- Concurrent treatment with a non-permitted drug
- Prior therapy with specific antibody/drug targeting T cell co-regulatory proteins (immune checkpoints)
- Concurrent antitumor treatment, major surgery, or use of any investigational drug within 28 days before the start of trial treatment; or concurrent systemic therapy with immunosuppressive agents, use of hormonal agents within 7 days before the start of trial treatment as defined in the protocol. Note: Subjects receiving bisphosphonate or denosumab are eligible provided treatment was initiated at least 14 days before the first dose of avelumab.
- Previous malignant disease other than the target malignancy to be investigated in this trial within the last 5 years with the exception of basal or squamous cell carcinoma of the skin or cervical carcinoma in situ
- Rapidly progressive disease (for example, tumor lysis syndrome)
- Active or history of central nervous system metastases
- Receipt of any organ transplantation including allogeneic stem-cell transplantation
- Significant acute or chronic infections as defined in the protocol
- Active or history of any autoimmune disease (subjects with diabetes Type 1, vitiligo, psoriasis, hypo- or hyperthyroid disease not requiring immunosuppressive treatment are eligible) or immunodeficiencies
- Known severe hypersensitivity reactions to monoclonal antibodies, any history of anaphylaxis, or uncontrolled asthma
- Persisting toxicity related to prior therapy greater than Grade 1 NCI-CTCAE v4.0, however sensory neuropathy less than or equal to Grade 2 is acceptable
- Pregnancy or lactation period
- Known alcohol or drug abuse
- Clinically significant (that is, active) cardiovascular disease
- All other significant diseases (for example, inflammatory bowel disease), which, in the opinion of the investigator, might impair the subject's tolerance of trial treatment
- Any psychiatric condition that would prohibit the understanding or rendering of informed consent
- Legal incapacity or limited legal capacity
- Non-oncology vaccine therapies for prevention of infection disease (for example, seasonal flu vaccine, human papilloma virus vaccine) within 4 weeks of study drug administration. Vaccination while on study is also prohibited except for administration of the inactivated influenza vaccine

**Contacts and Locations**

Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff using the Contacts provided below. For general information, see [Learn About Clinical Studies](#).

Please refer to this study by its ClinicalTrials.gov identifier: NCT01772004

**Contacts**

Contact: US Medical Information 888-275-7376

Contact: Merck KGaA Communication Center +49 6151 72 5200 service@merckgroup.com

**Locations**

**United States, Massachusetts**

For Recruiting Locations in the United States, please Contact U.S. Medical Information

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Sponsors and Collaborators

EMD Serono
Merck KGaA

Investigators

Study Director: Medical Responsible EMD Serono Inc., an affiliate of Merck KGaA, Darmstadt, Germany

More Information

No publications provided

Responsible Party: EMD Serono
ClinicalTrials.gov Identifier: NCT01772004 History of Changes
Other Study ID Numbers: EMR 100070-001 2013-002834-19
Study First Received: January 14, 2013
Last Updated: February 12, 2016
Health Authority: United States: Food and Drug Administration
Belgium: Federal Agency for Medicines and Health Products, FAMHP
Czech Republic: State Institute for Drug Control
France: Agence Nationale de Sécurité du Médicament et des produits de santé
Germany: Federal Institute for Drugs and Medical Devices
Hungary: Ministry of Health, Social and Family Affairs
Poland: Ministry of Health
United Kingdom: Medicines and Healthcare Products Regulatory Agency
Korea: Ministry of Food and Drug Safety
Taiwan: Food and Drug Administration

Keyw ords provided by EMD Serono:
Solid Tumors
MSB0010718C Phase 1 Pharmacokinetic anti PD-L1 Non-small cell lung cancer (NSCLC) Metastatic breast cancer (MBC) Gastric and gastroesophageal junction (GEJ) cancer Ovarian cancer

Colorectal cancer (CRC)
Castrate-resistant prostate cancer (CRPC)
Melanoma
Urothelial carcinoma
Bladder cancer
Head and neck squamous cell carcinoma (HNSCC)
Renal cell carcinoma (RCC)
Adrenocortical carcinoma (ACC)

ClinicalTrials.gov processed this record on February 21, 2016