Purpose

This is an open label Phase 1a/1b, dose escalation, and dose expansion trial designed to explore the safety, tolerability, pharmacokinetic (PK) and pharmacodynamics (PD) profile, and clinical activity of MSC2490484A in combination with radiotherapy (RT). An ancillary clinical Proof-of-Principle (cPoP) study will be conducted in parallel with the Phase 1a/1b core trial to explore the PD effect of MSC2490484A in combination with RT on target engagement in tumor tissue.

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<thead>
<tr>
<th>Condition</th>
<th>Intervention</th>
<th>Phase</th>
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<tbody>
<tr>
<td>Solid Tumors</td>
<td>Drug: MSC2490484A</td>
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<td>Radiation: Fractionated palliative RT</td>
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Study Type: Interventional
Study Design: Endpoint Classification: Safety/Efficacy Study
Intervention Model: Single Group Assignment
Masking: Open Label
Primary Purpose: Treatment

Official Title: An Open Label, Phase 1a/1b Trial of the DNA-PK Inhibitor MSC2490484A in Combination With Radiotherapy in Patients With Advanced Solid Tumors

Further study details as provided by EMD Serono:

Primary Outcome Measures:

- Phase 1a: Number of Subjects Experiencing at Least one Dose-limiting Toxicity (DLT) [ Time Frame: Up to 21 days after last dose of MSC2490484A in combination with palliative fractionated RT ] [ Designated as safety issue: Yes ]
  DLT is defined as any of the following toxicities assessed as at least possibly related to MSC2490484A by the investigator and/or the Sponsor up to 21 days after the end of radiotherapy (RT): A treatment-emergent adverse event (TEAE) of potential clinical significance; evidence of possible treatment-related hepatocellular injury for more than 3 days as defined in the protocol; any Grade greater than or equal to (>=) 3 toxicity, but excluding the conditions mentioned in the protocol; any Grade 4 neutropenia of greater than (>5 days duration or Grade >3 febrile neutropenia; any Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with bleeding; any toxicity related to trial drug that causes the subject to receive less than 80 percent (% ) of planned MSC2490484A and/or RT dose.

- Phase 1b: Number of subjects experiencing at least one DLT [ Time Frame: Up to 21 days after last dose of MSC2490484A in combination with curatively intended fractionated RT ] [ Designated as safety issue: Yes ]
  DLT is defined as any of the following toxicities assessed as at least possibly related to MSC2490484A by the investigator and/or the Sponsor up to 21 days after the end of radiotherapy (RT): A Treatment-Emergent Adverse Event (TEAE) of potential clinical significance; evidence of possible treatment-related hepatocellular injury for more than 3 days as defined in the protocol; any Grade greater than or
equal to (>= 3) toxicity, but excluding the conditions mentioned in the protocol; any Grade 4 neutropenia of greater than (>)=5 days duration or Grade >=3 febrile neutropenia; any Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with bleeding; any toxicity related to trial drug that causes the subject to receive less than 80 percent (%) of planned MSC2490484A and/or RT dose. Assessment was done in first 3 subjects of the phase 1b.

- Phase 1b: Number of subjects experiencing treatment emergent adverse events (TEAEs) [ Time Frame: From first dose of investigational medicinal product administration up to 30 days after the end of treatment ] [ Designated as safety issue: Yes ]

An Adverse Event (AE) is defined as any new untoward medical occurrences/worsening of pre-existing medical condition w ithout regard to possibility of causal relationship. A Serious AE (SAE) was an AE that resulted in any of the following outcomes: death; life threatening; persistent/significant disability/incapacity; initial or prolonged inpatient hospitalization; congenital anomaly/birth defect. TEAEs are events between first dose of study drug and up to 30 days after last dose that were absent before treatment or that worsened relative to pretreatment state.

Secondary Outcome Measures:

- Number of Subjects with Treatment Emergent Adverse Events (TEAEs), Serious TEAEs, TEAEs Leading to Treatment Discontinuation, and TEAEs Leading to Death [ Time Frame: Up to 30 days after end of treatment ] [ Designated as safety issue: Yes ]

Best Overall Response Rate [ Time Frame: Time from first dose to disease progression or death, whichever occurs first, assessed until 1 year after end of RT ] [ Designated as safety issue: No ]

Best overall response is defined as occurrence of complete response (CR) or partial response (PR) based on the Investigator’s assessment according to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 confirmed at a repeat assessment performed no less than 28 days after the criteria for response are first met. Complete response (CR) is defined as disappearance of all target and non-target lesions. Partial response (PR) is defined as at least 30% decrease in the sum of the diameters of target or non-target lesions taking as reference the baseline sum diameters, with no evidence of progressive disease (PD). PD is defined as at least 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on trial, or unequivocal progression of existing non-target lesions.

- Tumor Size Measurement [ Time Frame: Time from first dose to disease progression or death, whichever occurs first, assessed until 1 year after end of RT ] [ Designated as safety issue: No ]

- Progression-free Survival (PFS) Time [ Time Frame: Time from first dose to disease progression or death, whichever occurs first, assessed until 1 year after end of RT ] [ Designated as safety issue: No ]

PFS time will be evaluated According to RECIST Version 1.1.

- Overall Survival (OS) Time [ Time Frame: Time from first dose to death, assessed until 1 year after end of RT ] [ Designated as safety issue: No ]

Overall Survival (OS) Time will be evaluated according to RECIST Version 1.1.

- Phase 1a: Maximum plasma concentration (Cmax) of MSC2490484A [ Time Frame: Predose, 0.5, 1, 1.5, 2, 3, 4, 6 (Day 1, 10); 8 hours postdose on Day 1 ] [ Designated as safety issue: No ]

- Phase 1a: Time to reach maximum plasma concentration (tmax) of MSC2490484A [ Time Frame: Predose, 0.5, 1, 1.5, 2, 3, 4, 6 (Day 1, 10); 8 hours postdose on Day 1 ] [ Designated as safety issue: No ]

- Phase 1a: Area under the plasma concentration curve from zero to last sampling time AUC (0-1) of MSC2490484A [ Time Frame: Predose, 0.5, 1, 1.5, 2, 3, 4, 6 (Day 1, 10); 8 hours postdose on Day 1 ] [ Designated as safety issue: No ]

- Phase 1a: Area under the plasma concentration curve from zero to infinity AUC (0-inf) of MSC2490484A [ Time Frame: Predose, 0.5, 1, 1.5, 2, 3, 4, 6 (Day 1, 10); 8 hours postdose on Day 1 ] [ Designated as safety issue: No ]

- Phase 1a: Terminal half life (t1/2) of MSC2490484A [ Time Frame: Predose, 0.5, 1, 1.5, 2, 3, 4, 6 (Day 1, 10); 8 hours postdose on Day 1 ] [ Designated as safety issue: No ]

- Phase 1a: Apparent total body clearance (CL/F) of MSC2490484A [ Time Frame: Predose, 0.5, 1, 1.5, 2, 3, 4, 6, and 8 hours postdose on Day 1 ] [ Designated as safety issue: No ]

- Phase 1a: Volume of distribution (Vz/F) of MSC2490484A [ Time Frame: Predose, 0.5, 1, 1.5, 2, 3, 4, 6, and 8 hours postdose on Day 1 ] [ Designated as safety issue: No ]

- Phase 1a: Area under the plasma concentration-time curve over the dosing interval after multiple dosing (AUC0-tau) of MSC2490484A [ Time Frame: Predose, 0.5, 1, 1.5, 2, 3, 4, 6 hours postdose on Day 10 ] [ Designated as safety issue: No ]

- Phase 1a: Oral clearance of MSC2490484A at steady state (CLss/F) in Plasma [ Time Frame: Predose, 0.5, 1, 1.5, 2, 3, 4, and 6 hours postdose on Day 10 ] [ Designated as safety issue: No ]

- Phase 1a: Apparent volume of distribution at steady state (Vss/F) of MSC2490484A in plasma [ Time Frame: Predose, 0.5, 1, 1.5, 2, 3, 4, and 6 hours postdose on Day 10 ] [ Designated as safety issue: No ]

- Phase 1a: Accumulation ratio for area under the concentration-time curve (Racc[AUC]) [ Time Frame: Predose, 0.5, 1, 1.5, 2, 3, 4, and 6 hours postdose on Day 10 ] [ Designated as safety issue: No ]
Phase 1a: Accumulation ratio for maximum concentration (Racc\([C_{\text{max}}]\)) [ Time Frame: Predose, 0.5, 1, 1.5, 2, 3, 4, and 6 hours postdose on Day 10 ] [ Designated as safety issue: No ]

Estimated Enrollment: 68
Study Start Date: September 2015
Estimated Study Completion Date: November 2019
Estimated Primary Completion Date: November 2019 (Final data collection date for primary outcome measure)

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<th>Assigned Interventions</th>
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| Experimental: MSC2490484A + Fractionated palliative RT | Drug: MSC2490484A
Phase 1a: Subjects will receive a starting dose of 100 milligram (mg) of MSC2490484A orally once daily 1.5 hours prior each radiotherapy (RT) fraction (3 Gray [Gy]) for up to 10 fractions. Dose escalation will continue from MSC2490484A 100 mg/day up to a maximum dose of MSC2490484A 800 mg/day until one of the following stopping rules apply: a maximum number of 30 subjects are included, more than three cohorts are assigned to the same dose level or the estimate for dose limiting toxicity (DLT) probability of the maximum tolerated dose (MTD) reaches sufficient precision.
Phase 1b: Subjects will receive the assigned dose of MSC2490484A once daily orally.
cPoP Study: Subjects will receive a single oral dose of MSC2490484A (planned doses of 100 mg, 200 mg and 400 mg) on Day 2, 1.5 hours before the start of RT.

Other Name: M3814
Radiation: Fractionated palliative RT
Phase 1a: Subjects will receive fractionated palliative RT (3 Gy x 10, 5 fractions per week [F/W]).
Phase 1b: Subjects will receive fractionated RT (2 Gy x 30, 5 F/W).
cPoP study: Subjects will receive a single high dose of RT (10-25 Gy) on Day 1 given on Lesion 1 and one dose of MSC2490484A followed by a single high dose of RT (10-25 Gy) on Day 2 given on Lesion 2.|

Eligibility

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

Criteria

Inclusion Criteria:
- All subjects in Phase 1a and cPoP must agree to have tumor biopsies collected
- For subjects in Phase 1b, archival tumor material must be available, either as a block or slides
- To be eligible the subject must fulfill all of the following criteria:

Subjects must have:
- Phase 1a part: advanced solid tumors or metastases including lymphoma localized in the head and neck region with an indication for fractionated palliative RT
- Phase 1b part: treatment-naïve Stage III A/B non-small cell lung cancer (NSCLC) not eligible for concurrent chemoradiation
cPoP study: any tumor with at least 2 (sub) cutaneous tumor/metastases at least 2 centimeter (cm) apart which are RT naïve with an indication for high dose palliative RT
- Measurable or evaluable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (not required for the cPoP study)
- Male or female subjects at least 18 years of age
- Eastern Cooperative Oncology Group performance status (ECOG PS) less than or equal to (\(\leq\)) 2
- Must have read, well understood, and signed and dated the Informed Consent Form; the subject fully understands the requirements of the trial and is willing to comply with all trial visits and assessments
- Women of childbearing potential must have a negative serum pregnancy test at the screening visit. For the purposes of this trial, women of childbearing potential are defined as all female subjects after puberty unless they are postmenopausal for at least 2 years, are surgically sterile or are not sexually active
- Female subjects of childbearing potential and male subjects with female partners of childbearing potential must agree to use effective contraception defined as an intrauterine device or 2 barrier methods continuously from 2 weeks prior to first investigational medicinal product (IMP) administration, throughout the trial, and for 3 months after the last dose of IMP
Phase 1a/1b parts only: life expectancy of greater than or equal to (>=)3 months

Exclusion Criteria:

Subjects are not eligible for the Phase 1a or 1b parts of the trial if they fulfill any of the following exclusion criteria:

- Prior treatment consisting of: a. Chemotherapy, immunotherapy, hormonal therapy, biologic therapy, or any other anticancer therapy or IMP with in 28 days prior to the first dose of IMP (6 weeks for nitrosoureas or mitomycin C) for Phase 1a subjects, and any prior therapy for Phase 1b subjects. For subjects with rapidly growing tumors localized in the head and neck region where the treating physician cannot wait for 28 days, inclusion may take place if there is no residual toxicity from previous treatment (maximum Common Terminology Criteria for Adverse Events [CTCAE] Grade 1) b. Prior RT to the same region at any time previously (Phase 1b; treatment-naïve Stage III A/B NSCLC subjects) or within 12 months (Phase 1a; subjects with tumors localized in the head and neck region) c. Extensive prior RT on >= 30 percent (%) of bone marrow reserve as judged by the investigator or prior bone marrow/stem cell transplantation within 5 years before trial start
- Residual toxicity due to prior therapy with no return to baseline or less than or equal to (<=) Grade 1 (except alopecia according to Common Terminology Criteria for Adverse Events [CTCAE] v4.03)
- Surgical intervention, including biopsies and dental root surgeries, within 28 days prior to the first dose of IMP administration or having participated in an interventional clinical trial within 28 days prior to the first dose of IMP administration for Phase 1a/1b
- Poor vital organ functions as defined in the protocol
- Significant cardiac conduction abnormalities as defined in the protocol
- Hypertension uncontrolled by medication
- Known central nervous system (CNS) metastases unless previously treated by RT, stable by computed tomography (CT) scan for at least 3 months without evidence of cerebral edema and no requirement for corticosteroids or anticonvulsants
- Subjects currently receiving H2-blocker or proton pump inhibitors (or unable to stop at least 5 days prior to the first treatment).
- Other protocol-defined criteria could apply

Subjects are not eligible for the cPoP part if they fulfill any of the following exclusion criteria:

- History of difficulty swallowing, malabsorption or other chronic gastrointestinal disease or conditions that may hamper compliance and/or absorption of the IMP
- History of any other significant medical disease such as major gastric or small bowel surgery, recent drainage of significant volumes of ascites or pleural effusion or a psychiatric condition that might impair the subject’s well-being or preclude full participation in the trial
- Known hypersensitivity to the trial treatment or to one or more of the excipients used
- Other protocol-defined criteria could apply

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: NCT02516813

Contacts

Contact: US Medical Information 888-275-7376
Contact: Merck KGaA Communication Center +49-6151-72-5200 service@merckgroup.com

Locations

United States, Massachusetts
Please Contact U.S. Medical Information Recruiting
Rockland, Massachusetts, United States

Germany
Please contact the Merck KGaA Communication Center Recruiting
Darmstadt, Germany

Sponsors and Collaborators

EMD Serono

Investigators

Study Director: Medical Responsible Merck KGaA
More Information

No publications provided

Responsibility Party: EMD Serono
ClinicalTrials.gov Identifier: NCT02516813  History of Changes
Other Study ID Numbers: 100036-002  2015-000673-12
Study First Received: August 4, 2015
Last Updated: October 20, 2015
Health Authority:
  Netherlands: The Central Committee on Research Involving Human Subjects (CCMO)
  Belgium: Federal Agency for Medicinal Products and Health Products
  Denmark: Danish Health and Medicines Authority
  Germany: Federal Institute for Drugs and Medical Devices
  Sweden: Medical Products Agency
  Norway: Norwegian Medicines Agency
  United States: Food and Drug Administration

Keywords provided by EMD Serono:
  M3814
  Solid Tumors

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