A Phase III, Randomized, Double-Blind, Placebo Controlled, Multi-Center, International Study of Durvalumab Given Concurrently With Definitive Chemoradiation Therapy in Patients With Locally Advanced, Unresectable Esophageal Squamous Cell Carcinoma (KUNLUN)
NOTE: Official Title should have no more than 240 characters

Published: 29-10-2020
Last updated: 08-04-2024

Primary Objectives:- To assess the efficacy of durvalumab + dCRT compared with placebo + dCRT in all randomized patients based on PFS (per RECIST 1.1 as assessed by BICR)- To assess the efficacy of durvalumab + dCRT compared with placebo + dCRT in...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Respiratory and mediastinal neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON50948

Source
ToetsingOnline

Brief title
KUNLUN

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified

Synonym
esophageal cancer, Unresectable Esophageal Squamous Cell Carcinoma

Research involving
Human

Sponsors and support

Primary sponsor: Astra Zeneca
Source(s) of monetary or material Support: opdrachtgever/sponsor: AstraZeneca

Intervention

Keyword: Definitive chemoradiation therapy, Durvalumab, Esophageal squamous cell carcinoma

Outcome measures

Primary outcome

Primary Objectives:

- To assess the efficacy of durvalumab + dCRT compared with placebo + dCRT in

all randomized patients based on PFS (per RECIST 1.1 as assessed by BICR)

- To assess the efficacy of durvalumab + dCRT compared with placebo + dCRT in

patients with PD-L1 High tumors based on PFS (per RECIST 1.1 as assessed by

BICR)

Secondary outcome

Key Secondary Objectives:

- To assess the efficacy of durvalumab + dCRT compared to placebo + dCRT in

terms of OS in all randomized patients

- To assess the efficacy of durvalumab + dCRT compared to placebo + dCRT in

terms of OS in patients with PD-L1 High tumors

Study description

Background summary

In the past 20 years, curative intent definitive radiotherapy concurrent with cisplatin plus fluorouracil has evolved as a standard modality for patients with inoperable, locally advanced esophageal cancer. However, the survival outcomes of definitive chemoradiation therapy (dCRT) with cisplatin plus fluorouracil regimen are sub optimal with a 40% 5-year overall survival (OS) rate, and >50% patients progressing within 2 years after dCRT, highlighting high unmet medical need. As such, a new treatment modality to improve patient outcome is warranted.

PD-1/PD-L1 inhibition in combination with chemoradiotherapy has demonstrated synergistic antitumor activity in both preclinical models and in clinical trials. As such, triggering or augmenting an antigenic antitumor response with CRT and combining this treatment with an PD-L1 therapy, may result in enhanced antitumor activity by improving local control and decreasing systemic spread.

Durvalumab is a human mAb of the IgG 1 kappa subclass that blocks the interaction of PD-L1 with PD-1 on T cells and CD80 (B7.1) on immune cells. Given this, it is hypothesized that the administration of durvalumab in combination with dCRT may have added clinical benefit, and demonstrate improved outcome for ESCC patients versus dCRT alone.

Study objective

Primary Objectives:
- To assess the efficacy of durvalumab + dCRT compared with placebo + dCRT in all randomized patients based on PFS (per RECIST 1.1 as assessed by BICR)
- To assess the efficacy of durvalumab + dCRT compared with placebo + dCRT in patients with PD-L1 High tumors based on PFS (per RECIST 1.1 as assessed by BICR)

Secondary Objectives:
- To assess the efficacy of durvalumab + dCRT compared to placebo + dCRT in terms of OS in all randomized patients
- To assess the efficacy of durvalumab + dCRT compared to placebo + dCRT in terms of OS in patients with PD-L1 High tumors

Study design

This is a Phase III, randomized, double-blind, placebo-controlled, multi-center international study to assess the efficacy and safety of durvalumab administered concurrently with dCRT in patients with locally advanced, unresectable esophageal squamous cell carcinoma.

Approximately 600 patients with locally advanced, unresectable ESCC (AJCC 8th cStage IIIVA) will be randomized in a 2:1 ratio to receive either durvalumab + dCRT or placebo + dCRT. Patients will be stratified by geographical region [Asia versus Non-Asia], cStage: [II versus III
+IVA] and level of PD-L1 expression [PD-L1 High versus PD-L1 Low].

Randomization of patients with cervical ESCC will be capped at approximately 10% of the planned total number of randomized patients.

Intervention

Patients will be randomized in a 2:1 ratio to receive either durvalumab + dCRT or placebo + dCRT:
- Durvalumab + dCRT: Durvalumab 1500 mg Q4W will be administered concurrently with dCRT. Patients without PD after completion of CRT will continue to receive durvalumab 1500 mg Q4W up to 24 months from the date of randomization.
- Placebo + dCRT: Placebo Q4W will be administered concurrently with dCRT. Patients without PD after completion of dCRT will continue to receive placebo Q4W up to 24 months from the date of randomization.

Chemotherapy regimen as part of dCRT choice of 2 options:
- Cisplatin + Capecitabine: Cisplatin 30 mg/m2 IV on Day 1 weekly for 5 weeks and Capecitabine 800 mg/m2 PO BID on Days 1-5 weekly for 5 weeks
- Cisplatin + Fluorouracil: Cisplatin 75-100 mg/m2 on Day 1 of each cycle and Fluorouracil 750-1000 mg/m2 IV continuous infusion over 24 hours daily on Days 1*4 q28 days × 2 cycles. Optional: 2 consolidation cycles after radiotherapy is completed

Radiation regimen as part of dCRT:
- Total 50-64Gy (1.8-2.0 Gy/d) 25Fr-36Fr, 5 fractions/week for 5-8 weeks

Study burden and risks

Patients are subject to the following assessments throughout the study:
- Anamnesis (at screening, including medical history)
- Physical examination
- ECOG performance status
- Vital functions (blood pressure, heart rate, body temperature, respiratory rhythm)
- Measurement of body weight
- FDG-PET/CT scan

- CT/MRI-scan
- ECG
- Blood and urine examination
- Questionnaires (EORTC QLQ-C30, QLQ-OES18, EQ-5D-5L, PGIS en PGI-TT)
- Pregnancy test when applicable
- AE/SAE assessment
- IP administration
- Biopsy (new biopsy or archival (<3 months old))

The side effects of durvalumab can range from mild to severe or in some cases even life-threatening. Conditions have been built into the study to identify serious side effects as early as possible.

Very common (seen in more than 1 in 10 people):
Fatigue/tiredness, diarrhea, rash/dry itchy skin, liver problems, nausea, vomiting and abdominal pain, oedema, upper respiratory tract infections, decreased appetite, shortness of breath, cough, pain in muscles and joints, fever

Common (seen in more than 1 in 100 people):
Pneumonitis, colitis, low or high thyroid (hypothyroidism or hyperthyroidism), kidney injury, nervous system problems, infusion related reactions and allergic reactions, pneumonia, influenza, hoarse voice, painful urination, night sweats, oral thrush, dental infections, soft tissue infections.

Moreover, the study procedures could also have risks:
- Pain or bruises through collection of blood/tumor biopy
- Rash through ECG stickers
- Health risks through radiation of CT/MRI scan

Contacts

Public
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

* 18 years or older at the time of signing the ICF.
* Histologically or cytologically confirmed esophageal squamous cell carcinoma, and present with locally advanced disease (Stage II-IVA).
* Unresectable and has been deemed suitable for definitive chemoradiation therapy.
* Patients with at least 1 lesion that qualifies as a RECIST 1.1 Target Lesion at baseline.
* Mandatory provision of available tumor tissue for PD-L1 expression analysis.
* ECOG PS 0 or 1.
* Adequate organ and marrow function.
* Life expectancy of more than 3 months.

Exclusion criteria

* Histologically or cytologically confirmed small cell esophageal carcinoma, esophageal adenocarcinoma or other mixed carcinoma.
* Prior anti-cancer treatment, including but not limited to, chemotherapy and/or radiation therapy, immunotherapy, and investigational agents.
* Patient with a great risk of perforation and massive bleeding.
* History of allogeneic organ transplantation.
* Active or prior documented autoimmune or inflammatory disorders.
* Uncontrolled intercurrent illness.
* History of another primary malignancy.
* Active infection including tuberculosis, hepatitis B, hepatitis C, or human immunodeficiency virus.
* Known allergy or hypersensitivity to any of the study drugs or any of the

study drug excipients.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	18
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Capecitabine
Generic name:	Capecitabine
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Cisplatin
Generic name:	Cisplatin
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Fluorouracil
Generic name:	5-FU
Registration:	Yes - NL outside intended use
Product type:	Medicine

Brand name:	Imfinzi
Generic name:	Durvalumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	29-10-2020
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	18-03-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	30-03-2021
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	02-06-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	05-07-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	08-07-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	21-01-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2020-001001-22-NL
ClinicalTrials.gov	NCT04550260
CCMO	NL75376.091.20