A Phase 2 Study of Cemiplimab, an Anti-PD-1 Monoclonal Antibody, and ISA101b Vaccine in Patients with Recurrent/Metastatic HPV16 Cervical Cancer who have Experienced Disease Progression after First Line Chemotherapy

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The primary objective of the study is to estimate the clinical benefit of cemiplimab + ISA101b after progression on first line chemotherapy, as assessed by objective response rate (ORR).The secondary objectives of the study are:• To characterize the...

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

Summary

ID

NL-OMON54112

Source
ToetsingOnline

Brief title
R2810-ONC-ISA-1981 (0456/0376)

Condition

- Reproductive neoplasms female malignant and unspecified

Synonym
cervical cancer; squamous cell cervical cancer

Research involving
Human

Sponsors and support

Primary sponsor: Regeneron Pharmaceuticals, Inc.
Source(s) of monetary or material Support: The study sponsor as listed in B6/7

Intervention

Keyword: Cemiplimab, Cervical cancer, HPV16, ISA101b vaccine

Outcome measures

Primary outcome

Objective response rate (ORR) [Time Frame: Until disease progression, up to 36 months]

Secondary outcome

Secondary Outcome Measures :

1. Incidence and severity of treatment emergent adverse events (TEAEs) [Time Frame: Up to 90 days after the last dose of study treatment]

2. Incidence and severity of adverse events of special interest (AESIs) [Time Frame: Up to 90 days after the last dose of study treatment]

3. Incidence and severity of serious adverse events (SAEs) [Time Frame: Up to 90 days after the last dose of study treatment]

4. Incidence and severity of >= grade 3 laboratory abnormalities [Time Frame: Up to 90 days after the last dose of study treatment]

5. Duration of response (DOR) [Time Frame: Until disease progression, up to 36 months]

6. Progression free survival (PFS) [Time Frame: Until disease progression, up to 36 months]

Overall survival (OS) [Time Frame: Up to 60 months]

Study description

Background summary

Background on Cervical Cancer
The global annual incidence of cervical cancer is approximately 527,000 cases per year, and there are approximately 265,000 deaths (Torre, 2015). The highest incidence rates are in the Caribbean, Africa, Eastern Europe, and South America (Forman, 2012). In the United States (US), there are approximately 13,170 new cases and 4,250 deaths annually (Siegel, 2019). In most cases, causation is due to infection with human papillomavirus (HPV). Although vaccination against high risk strains of HPV is projected to gradually decrease the global incidence of cervical cancer in the next 15 years, the burden of this disease remains profound (Bray, 2012).
Internationally, the etiologic fraction of HPV-associated malignancy, based on HPV detection, varies by geography and anatomic site, but overall suggests that 70% of cervical cancers are caused by HPV16/18, and HPV16 is the primary oncogenic virus in other anogenital and oropharyngeal cancers. In a study of 777 cervical cancer tissue samples, the HPV16 genotype was detected in 50.1% while the HPV18 genotype was detected in 16.1%, comprising 66.2% of HPV-associated cervical cancers. Widespread uptake of HPV16/18 vaccines has already been shown to decrease high-grade cervical lesions and is anticipated to substantially reduce the burden of HPV-associated cancers (Saraiya, 2015).
For patients with locally advanced disease, the curative intent therapy is definitive radiation with concurrent cisplatin. However, recurrent or metastatic disease occurs in approximately one third of cervical cancer patients in the US. For women with recurrent or metastatic disease, the GOG240 study established that standard first line therapy is platinum plus taxane doublet with the addition of bevacizumab, if clinically appropriate. Median survival with the triplet regimen is 17 months (Tewari, 2014).
After progression on first line platinum-taxane based chemotherapy for recurrent or metastatic disease, conventional cytotoxic chemotherapy has limited efficacy. Non-randomized phase 2 trials have demonstrated survival times of 7.4 to 8.1 months (N = 29 and N = 43 patients, respectively) with single agent pemetrexed, gemcitabine, topotecan, vinorelbine, or irinotecan monotherapy (Lorusso, 2010), (Miller, 2008), (Schilder, 2005), (Bookman, 2000), (Muggia, 2004), (Muggia, 2005), (Look, 1998), (Takeuchi, 1991).
Immunotherapy for advanced cervical cancer is a burgeoning field. Almost all cervical cancer is associated with high risk strains of HPV (Cancer Genome Atlas Research, 2017), and the presence of viral antigen may support anti-tumor immune responses. An example of a virally-associated tumor for which immunotherapy has demonstrated efficacy is Merkel Cell carcinoma (Gillison,

2016), (Nghiem, 2016). Cervical squamous cell carcinoma (SCC) may evade immune response by expression of PD-L1 (programmed-death ligand 1), the ligand for the immune-checkpoint receptor PD-1 (programmed death-1) on T cells (Heeren, 2016). A non-randomized phase 2 trial of the anti-PD1 antibody pembrolizumab showed a durable response rate for patients with PD-L1 positive metastatic or recurrent cervical cancer treated with pembrolizumab monotherapy. Response rate for these patients was 14.6% (12/82 patients) with a median follow up time of 10.2 months (0.6 to 22.7 months) (Chung, 2019). These data led to an accelerated approval by the US FDA for patients with PD L1 positive tumors in the United States. A non-randomized phase 1/2 trial showed a durable response rate for patients with metastatic or recurrent cervical cancer treated with nivolumab monotherapy. Response rate for these patients was 26.3% (5/19 patients) with a median follow up of 19.2 months (1.4 to 31.4 months) (Naumann, 2019). An ongoing multicohort phase 1/2 trial showed early signals of durable responses in both first and second line metastatic cervical cancer with combination therapy with nivolumab and ipilimumab, an antibody directed against the CTLA-4 immune checkpoint. Responses ranged from 23.1% (6/26 patients) to 45.8% (11/24 patients) in varying dose levels. Median follow-up time ranged from 10.7 to 13.9 months (Naumann, 2019). The anti-PD1 monoclonal antibody cemiplimab (also known as REGN2810) has also demonstrated preliminary efficacy against cervical cancer, as described in Section 1.2.

These data are reassuring that immunotherapy has a role in recurrent/metastatic cervical cancer. While PD-1/PD-L1 blockade alone has a modest response rate, the consistent durability of these responses make it into a reasonable backbone for future combination therapies.

Taken together, these data support a single arm study of the anti-PD1 antibody cemiplimab in combination with other agents such that may enhance anti-tumor immune responses, such as ISA101b in patients with recurrent or metastatic HPV16+ cervical cancer with SCC and AC histology who have experienced disease progression after first line chemotherapy (Section 1.3).

Background on Cemiplimab

LIBTAYO® (cemiplimab) is approved for the treatment of patients with metastatic cutaneous squamous cell carcinoma or patients with locally advanced cutaneous squamous cell carcinoma who are not candidates for curative surgery or curative radiation. It is also approved for the treatment of patients with locally advanced basal cell carcinoma, and as a first-line treatment option in advanced non-small cell lung cancer. In the United States, it is approved with a suffix as cemiplimab-rwlc.

Cemiplimab is a high-affinity, recombinant human immunoglobulin G (IgG4P) monoclonal antibody that binds to PD-1 and blocks its interaction with programmed death ligand 1 (PD-L1) and programmed death-ligand 2 (PD-L2), countering PD-1-mediated inhibition of the anti-tumor immune response. Cemiplimab is being evaluated in more than 20 phase 1 through phase 3 clinical studies in a variety of tumor types. The safety profile of cemiplimab demonstrated in these clinical trials is consistent with the expected safety profile of an anti-PD-1 antibody.

In the cemiplimab phase 1 study (R2810-ONC-1423), patients with cervical cancer were enrolled in the dose escalation phase and in 2 expansion cohorts. Cumulatively, there were 4/23 (17%) responses. All responses were in SCC patients. Duration of response ranged from 6.4 to 14.7 months (NCT03257267). Cemiplimab is currently under investigation in R2810-ONC-1676, an open-label, randomized, multi-center, phase 3 trial comparing cemiplimab versus investigator*s choice chemotherapy in patients with recurrent or metastatic cervical cancer after platinum-based therapy. The primary objective is to compare overall survival (OS) between the arms. The trial showed a clinically and statistically significant survival benefit in patients with squamous cell carcinoma (SCC) and adenosquamous/adenocarcinoma (AC) histology. A total of 608 patients, including 477 patients with SCC histology and 131 patients with AC histology, were randomized in a 1:1 ratio to receive either monotherapy with cemiplimab or IC chemotherapy. Patients on the cemiplimab arm had a median survival of 12.0 months (95% CI 10.3 months to 13.5 months). Patients on the chemotherapy arm had a median survival of 8.5 months (95% CI 7.5 months to 9.6 months). In addition to a survival benefit, patients had a clinically and statistically significant improvement in progression free survival (PFS) and overall response rate (ORR) (Tewari, 2021). Patients on the cemiplimab arm had an ORR of 16.4% (95% CI 12.5% to 21.1%). Patients on the chemotherapy arm had an ORR of 6.3% (95% CI 3.8 to 9.6%) (Press Release: Phase 3 Trial of Libtayo® (cemiplimab) Monotherapy in Advanced Cervical Cancer Stopped Early for Positive Result on Overall Survival, 2021).
Additional information, including preclinical and clinical safety data, is available in the Investigator*s Brochure.

Background on ISA101b
ISA101/ISA101b is a therapeutic vaccine targeting the HPV type 16 E6/E7 proteins. The HPV16 long peptides in ISA101b act as a therapeutic vaccine that stimulates the actions of both CD4+ T-helper cells and CD8+ cytotoxic T cells against the known oncogenic sequences of the HPV16 virus. These long peptides, containing multiple cytotoxic T-lymphocyte (CTL) and T-helper epitopes, are predominantly processed by professional antigen presenting cells (APCs), the dendritic cells (Bijker, 2007), (Bijker, 2008), (Rosalia, 2013). This leads to presentation of the exact amino acid sequences (epitopes) by human leukocyte antigen (HLA) class I and II molecules on dendritic cells.
ISA101b consists of 9 overlapping long E6 peptides (five 32-mer and four 25-mer E6 peptides) and three 35-mer E7 peptides. These peptides overlap by 10 to 18 residues and cover the complete sequence of HPV16 E6. The E7 oncoprotein sequence is almost completely represented by the peptide sequences (only amino acids 57 to 63 are not covered), due to the omission of 1 poorly manufacturable peptide (G-3980-R).
The peptide sequences are synthetically produced and individually released and stored as bulk drug substances according to current good manufacturing processes.
A dose of 100 µg/peptide has been selected for further study based on both the strength of the induced HPV16 immune response and safety data in clinical

trials.

Study objective

The primary objective of the study is to estimate the clinical benefit of cemiplimab + ISA101b after progression on first line chemotherapy, as assessed by objective response rate (ORR).

The secondary objectives of the study are:
• To characterize the safety profile of cemiplimab + ISA101b
To assess preliminary efficacy of cemiplimab + ISA101b as measured by duration of response (DOR), progression-free survival (PFS), and overall survival (OS)

Study design

This will be a single-arm, phase 2, global study of treatment with cemiplimab + ISA101b in HPV16 positive cervical cancer patients with disease progression on first line chemotherapy in the recurrent or metastatic setting. Study treatment and duration include cemiplimab every 3 weeks (Q3W) (with 3 doses of ISA101b on days 1, 29, and 50) until progression or any reason for early discontinuation. The primary endpoint is ORR.

Patients will undergo screening evaluations to determine eligibility within 28 days prior to first treatment. All patients will receive the following regimen:
• ISA101b 100 µg/peptide by subcutaneous (SC) injection on day 1, day 29, and day 50 (total of 3 doses).
• Cemiplimab 350 mg given by intravenous (IV) infusion over 30 minutes Q3W on days 8 and 29 in cycle 1, on days 1 and 22 in cycle 2 through 4, and on days 1, 22, and 43 in all subsequent cycles or until disease progression or discontinuation of study drug for any other reason.

Note: On days 29 and 50, cemiplimab will be administered first, and ISA101b will be administered approximately 1 hour after the end of the cemiplimab infusion. Patients must be observed for 4 hours after each ISA101b administration.

There will be a 90-day safety follow-up after the last dose of cemiplimab. Patients who discontinue study drug for reasons other than progression will be followed approximately every 4 months by scans (eg, CT scan and/or MRI) until disease progression or until the patient commences another anticancer systemic therapy, whichever comes first. After progression, survival follow-up should occur approximately every 4 months.

Intervention

Study Drug: Cemiplimab

Dose/Route/Schedule: Cemiplimab will be administered IV at a dose of 350 mg over 30 minutes (±10 minutes) Q3W.

Study Drug: ISA101b
Dose/Route/Schedule: ISA101b 100 µg/peptide will be administered by 2 separate SC injections per dose on day 1, day 29, and day 50 (total of 3 doses).

Study burden and risks

The combination of ISA101b and cemiplimab in this study is expected to have a positive benefit risk profile for the treatment of patients with HPV16 positive cervical cancer. Anti-PD1 inhibitors given as monotherapy have shown activity and a well-established acceptable toxicity profile in recurrent/metastatic cervical cancer patients. ISA101b has been demonstrated to induce a robust and persistent T-cell response in patients with HPV16 driven malignancies, including cervical cancer and OPC. The combination of ISA101b with the anti-PD1 nivolumab achieved higher response rates compared to a historical control of nivolumab alone in the treatment of HPV16 positive OPC, albeit in a small number of patients with heterogeneous prior therapy. Finally, the combination of ISA101 with nivolumab has shown no unexpected toxicities in patients with OPC (Massarelli, 2019).
For patients with HPV-16 positive cervical cancer who failed prior platinum containing therapy, the use of cemiplimab in combination with ISA101b is therefore acceptable in order to objectively test the hypothesis of improved efficacy.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Adult patients >=18 years of age (or the legal age of adults to consent to participate in a clinical study per country specific regulations).
2. Has histologically confirmed recurrent or metastatic HPV16 positive cervical cancer as determined by an investigational HPV16 PCR assay by Qiagen, who have experienced disease progression after treatment with platinum containing therapy as defined in the protocol.
3. Patient must be determined to be positive for HPV16 genotype, as determined by a specified central reference laboratory.
4. Patient must have measurable disease as defined by RECIST 1.1.
5. ECOG performance status of 0 or 1.
6. Has adequate organ and bone marrow function as defined in the protocol.
7. Anticipated life expectancy >=20 weeks.

Other protocol-defined Inclusion criteria apply.

Exclusion criteria

1. Prior treatment with an agent that blocks the PD-1/PD-L1 pathway.
2. Prior treatment with other systemic immune-modulating agents as defined in the protocol.
3. Major surgery or radiation therapy within 14 days of first administration of study drug.
4. Has received treatment with an approved systemic therapy within 4 weeks of first dose of study drug, or has not yet recovered (ie, grade <=1 or baseline) from any acute toxicities except for laboratory changes as described in the protocol.
5. Has another malignancy that is progressing or requires active treatment

and/or history of malignancy other than cervical cancer within 3 years of date of first planned dose of study drug as defined in the protocol.
6. Has any condition that requires ongoing/continuous corticosteroid therapy (>10 mg prednisone/day or anti-inflammatory equivalent) within 4 weeks prior to the first dose of study drug.
7. Has ongoing or recent (within 5 years) evidence of significant autoimmune disease that required treatment with systemic immunosuppressive treatments as defined in the protocol.

Other protocol-defined Exclusion criteria apply.

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):	24-01-2022
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	ISA101b
Product type:	Medicine
Brand name:	Libtayo
Generic name:	Cemiplimab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	22-02-2021
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	20-07-2021
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	27-10-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	01-02-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	24-05-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	27-07-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	18-04-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO

Date:	25-05-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

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	EUCTR2020-001239-29-NL
ClinicalTrials.gov	NCT04646005
CCMO	NL75765.000.21