A Phase 2, Open-Label, multi-center Study of AL101 in patients with adenoid cystic carcinoma (ACC) bearing activating Notch mutations

Published: 08-07-2019
Last updated: 10-04-2024

Primary objective:To assess the clinical activity of AL101 using radiographic assessments and RECIST v1.1 in ACC patients with activating Notchmutations.Secundary objectives:• To assess quality of life in ACC patients with activating mutations.• To...

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

Summary

ID

NL-OMON49242

Source
ToetsingOnline

Brief title
ACCURACY

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
Adenoid cystic carcinoma, saliva gland cancer

Research involving
Human

Sponsors and support

Primary sponsor: Ayala Pharmaceuticals, Inc.
Source(s) of monetary or material Support: Ayala Pharmaceuticals;Inc.

Intervention

Keyword: Activating Notch mutations, Adenoid cystic carcinoma, AL101

Outcome measures

Primary outcome

Objective response rate (ORR; CR and PR) by RECIST v1.1 as determined by an Independent Central Review (ICR). For patients with bone-exclusive disease, the modified MDA bone criteria will be used to access response.

Secondary outcome

Secundary outcomes:

• ORR by Investigator review based on RECIST v1.1. For patients with boneexclusive disease, the modified MDA bone criteria will be used to access response.

• Duration of response (DOR) by ICR and Investigator review based on RECIST v1.1.

• Progression free survival (PFS) by ICR and Investigator review based on RECIST v1.1.

• Overall survival (OS).

• Frequency, duration and severity of adverse events (AEs) and serious adverse events (SAEs).

• Incidence of clinically significant laboratory abnormalities; safety laboratory evaluations includes complete blood count (CBC), blood biochemistry

and urinalysis.

• A population (mixed-effects) PK approach will be used to analyze the concentration data.

• Change from baseline in EORTC QLQ-C30

Exploratory objectives:

• Predictive biomarkers of response or resistance to the study drug will be explored:

- Immunohistochemistry (IHC): Tumor specimens will be stained for the NICD1 and other biomarkers such as but not limited to: programmed death ligand (PD-L1), Ki-67 and FBXW7.

- Next generation sequencing (NGS): Mutational analysis will be performed in tissues samples as well as in cfDNA.

• Pharmacodynamic markers indicative of drug activity will be measured, including HES-1 and others such as, but not limited to: HES-4, HES-5, HEY-1, 2, HEYL, HIF1 alpha, and others.

Study description

Background summary

Adenoid cystic carcinoma (ACC) is a rare cancer most often occurring in the salivary glands. ACC is characterized by an indolent but persistent course, with high rates of both local-regional recurrence and distant metastasis. Multiple studies have been conducted to discover genetic mutations and biomarkers specific for ACC. It was specifically demonstrated that Notch 1 mutations significantly correlate with solid histology, advanced disease stage at diagnosis, higher incidence of liver and bone metastasis, and shorter relapse-free and overall survival.

Notch receptors are highly conserved, Type 1 transmembrane glycoproteins that regulate critical cellular functions, including differentiation, proliferation, self-renewal, survival and cell fate determination. The Notch family has 4 members, Notch 1 to Notch 4. Notch receptors are activated by 4 transmembrane-bound ligands. The Notch signaling pathway relies on regulated proteolysis. Upon ligand binding to the Notch receptor, a series of steps leads to cleavage by gamma secretase within the transmembrane domain. This frees the Notch intracellular domain (NICD), which translocates to the nucleus to form a transcriptional activation complex with the DNA-binding factor CSL (CBF1/Suppressor of Hairless/Lag1) and coactivators belonging to the mastermind-like family of proteins.

Experimental evidence supports the causal role of Notch pathway deregulation in tumorigenesis. In ACC, sequencing of tumor samples revealed genomic alterations in the Notch 1 pathway in a subset of patients with distinct ACC phenotype. ACC patients with Notch 1 mutations have an aggressive disease with a distinct pattern of metastasis and worse prognosis.

Most ACC primary tumors are treated with surgical resection and postoperative radiotherapy, yet local and repeated recurrences are common. In advanced stage, conventional chemotherapy regimens are still utilized as first-line therapy although antitumor activity across a variety of chemotherapy classes is poor. Few of these regimens have shown efficacy, therefore the need for new therapeutic options remains. To date, no agent has been formally tested in ACC tumors that harbor Notch activation.

AL101 (BMS-906024) is a potent and selective inhibitor of gamma secretase-mediated Notch signaling that is currently under development as an antitumor/antiangiogenic agent for single use or in combination with other targeted agents in treatment of tumor growth and metastasis. AL101 can block the final step in Notch activation, the formation of NICD.
It is expected that AL101 is showing antitumor activity in patients with ACC bearing activation Notch mutations. The study is designed to evaluate the safety and efficacy of AL101.

Study objective

Primary objective:
To assess the clinical activity of AL101 using radiographic assessments and RECIST v1.1 in ACC patients with activating Notch mutations.

Secundary objectives:
• To assess quality of life in ACC patients with activating mutations.
• To confirm safety and tolerability of AL101 in ACC patients with activating Notch mutations.
• To obtain a set of population parameters and to identify covariates that

affect systemic exposure to AL101 and metabolite(s).

Exploratory objectives:
• To establish correlation between positive Notch intracellular domain (NICD1) stain and Notch1 activating mutations
• To establish the correlation between mutations in Notch and associated genes and response or resistance to study drug

Study design

This is a Phase 2, non-comparative, open-label, multicenter study of AL101 in patients with recurrent or metastatic ACC who harbor NOTCH 1,2,3,4 activating mutations.

The study includes 2 cohorts, ran in a sequential fashion: Cohort 1 - AL101 4 mg once weekly (QW) intravenously (IV); Cohort 2 - AL101 6 mg QW IV.

Prior to entering the study, to determine eligibility, potential candidates will undergo pre-screening assessment and confirmation for the presence of activating Notch mutations. Patients with activating Notch mutations will then undergo a 28-day screening period from the time of informed consent followed by active treatment (28 day cycle) with either AL101 4 mg QW IV or 6 mg QW IV in Cohorts 1 and 2, respectively. All patients will undergo end of study (EOS) visit 30 days post last treatment and will be contacted by phone every 3 months thereafter to determine survival status.

Throughout the study, the independent DMC will monitor safety and efficacy parameters at approximately quarterly intervals, after at least 3 patients have been treated for at least 2 cycles (after the first on-treatment radiographic assessment)

Intervention

The study IMP AL101 will be administered via IV infusion once a week in 28-days cycles.

Radiologic imaging will be performed at screening and every 8 weeks as of cycle 3 (day 1), at the End of Study visit and, if a patient discontinues from treatment due to toxicity, every 3 months during the Long Term Follow Up period.

A tumor biopsy will be performed at the pre-screening and at the End of Study visit. If at pre-screening archival tumor tissue is available <3 years old, this can be used as screening sample.

During the study several blood draws will be performed for determination of pharmacokinetics, clinical chemistry, hematology, coagulation, PSA, hepatitis

and HIV serology and biomarker (cfDNA, farmacodynamiek, mRNA) analysis.
A test for pregnancy will be performed in blood or urine, depending on the test method of the participating site.
A urine sample will be collected for standard urinalysis testing at screening and the End of Study visit.

Study burden and risks

Most Adenoid Cystic Carcinoma (ACC) primary tumors are treated with surgical resection and postoperative radiotherapy, yet local and repeated recurrences are common. In advanced stage, conventional chemotherapy regimens are still utilized as first-line therapy although anti-tumor activity across a variety of chemotherapy classes is poor. Few of these regimens have shown efficacy. AL101 is a potent and selective inhibitor of gamma secretase-mediated Notch signaling that is currently under development as an anti-tumor/anti-angiogenic agent. It is expected that AL101 will show anti-tumor activity in patients with ACC bearing activation Notch mutations.

The study medication AL101 will be administered via a once weekly infusion.
AL101 can cause the following side effects:
- Nausea, or feeling like throwing up,
- Diarrhea, or increase in the number of stools
- Fatigue
- Vomiting,
- Irritation/damage to the lining of the gastrointestinal tract which can result in abdominal discomfort and/or pain, decreased appetite, and/or diarrhea.
- Electrolyte and/or key blood component abnormalities. Severe abnormalities can cause muscle cramping, nausea, or in very severe cases, problems with heart function.
- Decreased platelets which can lead to bleeding or bruising more easily.
- Nose bleeding
- Decreased white blood cells with risk to infection development.
- Change in taste.
- Skin changes; rash, dryness, cracking, bleeding.
- Insomnia or change in sleep pattern
- Liver damage/failure accompanied by abdominal pain, nausea, decreased appetite, itching of the skin, yellow discoloration of the eyes and/or skin and in severe cases irritation of the brain. Events generally resolve with stopping drug, but a few were fatal.
- Weight loss
- Hoarseness.
- Infusion allergic-like reaction.
- Skin cancer.

Risks/burden associated with procedures:
- CT/MRI: contrast fluid can cause side effects like nausea, headache or an allergic reaction.

- Blood draws: The risks of blood draws may include fainting, pain and/or bruising. Rarely there may be an infection at the site of the needle puncture.
- Tumor biopsy: Risks of biopsy include pain, discomfort and infection.
- ECG: redness or itching caused by sticky pads.

The following procedures are performed:
- Tumor biopsy at pre-screening and End of Study visit (if archival tumor tissue is available at screening which is < 3 years old, than this may be used).
- NGS assay at pre-screening;
- Physical examination at all visits;
- Vital signs and weight at all visits, height at screening only;
- ECG at screening, cycle 3 day 1 and every 12 weeks thereafter, and End of Study visit;
- Pregnancy test at screening, day 1 of every cycle, and End of Study visit;
- Hematology blood draw all visits;
- Peripheral blood lymphocyte subsets at cycle 1 day1, cycle 2 day2, cycle 3 day 1 and every 8 weeks thereafter;
- Chemistry blood draw all visits (tryglycerides every cycle day 1 only);
- Thyroid function at cycle 1 day 1, cycle 3 day 1 and every 12 weeks thereafter;
- HbA1c at cycle 1 day 1 and every odd cycle thereafter;
- PSA, HIV and Hepatitis B and C serology at screening;
- Coagulation blood draw at screening and at day 1 of every odd cycle;
- Blood samples for biomarkers: mRNA & pharmacodynamics at cycle 1 day 1, 8 and 22, cycle 2 day 1, cycle 3 day 22 and thereafter every 8 weeks and End of Study visit;
- Blood for biomarkers cfDNA at cycle 1 day 1, cycle 2 day, cycle 3 day 22 and every 8 weeks thereafter and End of Study visit;
- MRI or CT brain at screening;
- MRI or CT of the neck, chest, abdomen and pelvis at screening, cycle 3 day 1 and thereafter every 8 weeks, End of Study visit and if the patient discontinues due to toxicity every 3 months during the Long Term Follow Up period.
- PK sampling at cycle 1 day 1 pre-dose, end of infusion and 2, 4 and 7 hours after infusion, cycle 1 day 2 or 3 (24 - 48 hours after infusion), cycle 1 day 8 pre-dose, cycle 1 day 15 pre-dose, cycle 1 day 22 pre-dose, end of infusion and 2, 4 and 7 hours after infusion, cycle 1 day 23 or 24 (24 - 48 hours after infusion), cycle 2 day 1 pre-dose.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Inclusion criteria

In order to be eligible for participation in this study, the patient must meet all of the following:
1. Age >18 years old.
2. Histologically confirmed ACC with known NOTCH 1/2/3/4 activating mutation that is
recurrent or metastatic, not amenable to potentially curative surgery or radiotherapy.
3. Evidence of radiographic or clinical disease progression within 6-months of signing informed
consent; newly diagnosed metastatic patients will be allowed.
4. Patients must have FFPE tissue available (please refer to laboratory manual for number of
slides required). Archived5 (within 3 years) or fresh core or punch needle biopsied are
acceptable.
5. Must have at least 1 target lesion that is measurable per RECIST v1.1 for patients with nodal
or visceral metastasis. Patients with bone exclusive disease will also be eligible after consultation and approval with Sponsor's Medical Monitor and only if bone
lesions are evaluable by CT or MRI as per modified MDA Criteria. (see Table 9 in

Appendix C).
6. Resolution of clinically significant toxicities related to prior therapy to National Cancer
Institute (NCI) - Common Terminology Criteria for Adverse Events (CTCAE v5.0) <= Grade 1, except for sensory neuropathy with resolution to <= Grade 2 and alopecia.

Exclusion criteria

The patient must be excluded from participating in the study if meet any of the following:
Medical Conditions
1. Diagnosed with a malignancy in the past 2 years.
2. Current or recent gastrointestinal disease. Nonchronic conditions that are completely resolved for at least 2 weeks prior to starting investigational product are not exclusionary.
3. Evidence of uncontrolled, active infection, requiring systemic anti-bacterial, anti-viral or
anti-fungal therapy <=7 days prior to administration of investigational product at Screening.
4. Symptomatic central nervous system (CNS) metastases. Patients with asymptomatic CNS
metastases as well as those with previously treated CNS metastases are eligible for
enrollment in the study if at least four weeks has elapsed since last whole brain radiation
treatment or at least two weeks has elapsed since last focal radiation treatment, steroid
therapy is not required, and the patient is deemed clinically stable by the Investigator.
5. Unstable or severe uncontrolled medical condition or any important medical illness or abnormal laboratory finding that would, in the investigator*s judgment, increase the risk to the patient associated with his or her participation in the study.
6. Female patients who are pregnant or breastfeeding.
7. Completed palliative radiation therapy < 7 days prior to initiating study drug.
8. Prior treatment with gamma secretase inhibitors.
9. Last chemotherapy, biologic, or investigational therapy agent <4 weeks or 5 half-lives (whichever is shorter) prior to initiating investigational product;
6 weeks if the last regimen included BCNU or mitomycin C.
10. Eastern Cooperative Oncology Group (ECOG) performance status >=2.
11. Abnormal organ and marrow function defined as:
a. neutrophils <1500/mm3,
b. platelet count <100,000/mm3,

c. hemoglobin <9 g/dL,
d. total bilirubin >1.5 x upper limit of normal (ULN) (except known Gilbert's syndrome),
e. aspartate aminotransferase (AST) and alanine aminotransferase (ALT) >2.5 x ULN OR >5 x ULN for patients with liver metastases,
f. serum creatinine > ULN and creatinine clearance <50 mL/min (Calculation of CrCl will be based on acceptable institution standard),
g. uncontrolled triglyceride =Grade 2 elevations per CTCAE v5.0 (>300 mg/dL or >3.42 mmol/L)
12. Myocardial infarction within 6 months prior to enrollment or has NYHA Class III or IV heart failure, uncontrolled angina, severe uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities.
13. Mean QT interval corrected for heart rate using Fridericia's formula (QTcF) >=480 msec.

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):	29-05-2020
Enrollment:	5
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	AL 101

Generic name:	Not applicable

Ethics review

Approved WMO Date:	08-07-2019
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	31-10-2019
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	24-02-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	04-05-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	20-05-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	26-11-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	14-12-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	16-02-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Approved WMO Date:	17-02-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	21-03-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	31-03-2022
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	EUCTR2019-000309-64-NL
ClinicalTrials.gov	NCT03691207
CCMO	NL70336.091.19