IRST162.09 _ TeReS

"Phase II Trial of Temozolomide in Patients affected by Relapsed Sensitive or Refractory Small Cell Lung Cancer with MGMT methylation"

IRST162.09_ Report Conclusione Arruolamento

EudraCT number**: 2013-003150-25**

Title**: Phase II Trial of Temozolomide in Patients affected by Relapsed Sensitive or Refractory Small Cell Lung Cancer with MGMT methylation**

Protocol: **ID IRST162.09**

Promoter: **IRCCS Istituto Romagnolo per la Cura dei Tumori "Dino Amadori" IRST S.r.l., Meldola (FC)**

Coordinating Center: IRCCS IRST

Study Chair: **Dr.ssa Claudia Casanova**

Study Activated: **27/01/2015**

First Patient Enrolled: 09/06/2015

Target**: 19 patients**

Accrual: **7 patients**

Rationale

Temozolomide	Temozolomide is a non-classic oral alkylating agent, which produces O6-alkylguanine O6-AG) lesions on DNA. The DNA repair protein O6-AG DNA alkyltransferase, which is encoded by the O6-methylguanine-DNA methyltransferase (MGMT) gene, removes alkyl groups from the O6 position of guanine. Left unrepaired, chemotherapy- induced lesions trigger cytotoxicity and apoptosis. High levels of MGMT activity in cancer cells blunt the therapeutic effects of alkylating agents and thus can be an important determinant of treatment failure. Epigenetic silencing of MGMT via hypermethylation of specific CpG islands of its promoter leads to loss of MGMT activity and improved sensitivity to alkylating agents. Temozolomide is used in patients with glioblastoma multiforme and in refractory astrocytoma. In the phase III study of Temozolomide in glioma, MGMT promoter methylation status was analyzed retrospectively and found to be an independent favorable prognostic factor .
Treatment	Patients were treated with oral Temozolomide 200 mg/m^2/die for 5 consecutive days every 28 days. Treatment were then continued until tumor progression, intolerable toxicity or patient refusal.
Indication and population	Relapsed or refractory small-cell lung cancer patients with MGMT promoter methylation

This study was authorized by AIFA on 12/01/2015 and authorized by the Italian Ethical Committee (CEROM) on 14/10/2014.

Objectives

The primary objective of the study was the evaluation of Overall Response Rate [ORR=CR+PR].

The secondary objectives were:

- Time of Progression (TTP)
- Overall Survival (OS)
- Toxicity
- Correlation between Response Rate (RR) and level of MGMT promoter methylation and/or BER genes alterations.

Primary and Secondary Endpoints/Outcome Measures

The *primary endpoint* was the overall response rate [ORR = CR + PR], which have been evaluated separately in sensitive and refractory cohorts.

The ORR was assessed according to the RECIST 1.1 criteria.

The *secondary end points* were:

- Time to Progression (TTP)
- Overall Survival (OS)
- Toxicity assessed after each cycle using the Common Toxicity Criteria (version 4.0)
- Correlation between Response Rate (RR) and level of MGMT promoter methylation and/or BER genes alterations. In particular BER (base excision repair pathway) genes analysis was:
  - ERCC1, ERCC2, and XRCC1 polymorphisms analyzed by sequencing approach;
  - BER gene alteration profiles were evaluated using a combined approach based on immunohistochemistry and Real Time PCR.

Sample Size

A Minimax Simon 2-stage design was used. At the first stage of 9 patients, if 1 or less responses were observed the trial would be ended. At the second stage, other 10 patienTS (for a total of 19 subjects) will be enrolled. If 5 or less responses were observed in 19 patients, the treatment was considered not active, while if 6 or more responses were observed, the treatment would be considered sufficiently active to warrant further testing. .

Conclusions:

From 01/27/2015 (date of the first Site was opened) to 11/22/2017 (date of closing of enrollment), despite molecular screening of 111 patients, only 7 subjects were found to be eligible and a total of 6 were enrolled. Patients were treated with temozolamide 200mg/m2/day orally for 5 consecutive days every 28 days until disease progression, intolerable toxicity, or patient refusal.
Given the inability to recruit patients on time, the study was closed.
The available data were insufficient to draw major conclusions for eventual publication of the data.

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