Title (Times New Roman, font14)
Phase I/IIa study of concomitant radiotherapy with olaparib and temozolomide in unresectable high grade gliomas patients – OLA-TMZ-RTE-01 protocol

AUTHORS (Times New Roman, font12, Upper-case letters, Italic)

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Purpose
The Stupp protocol is the standard treatment of glioblastoma multiform (GBM). The non-dividing nature of normal brain cells provides an opportunity to enhance the therapeutic ratio by combining radiation with inhibitors of replication-specific DNA repair pathways such PARP inhibitors as olaparib. PARP activity inhibition also increases cellular sensitivity to ionizing radiation and may be more pronounced in tumors than in normal tissue. Progress in technical imaging and intensity-modulated-radiotherapy (IMRT) techniques provide new possibilities for sparing healthy tissues. We propose a phase 1/2a trial to assess the tolerance and efficacy of Olaparib combined with TMZ concomitant with fractionated IMRT as a first line treatment in unresectable GBM patients (pts).

Experimental Design
Based on the Stupp phase 2 design, 2 periods of treatment are considered. The radiotherapy (RT) period occurs after the last surgery: the pt receives IMRT, TMZ and olaparib. TMZ is daily given up to the end of IMRT. Olaparib is given at the same dose until 4 weeks after the end of IMRT. For the maintenance (MT) period, TMZ is given on days 1-5 every 28 days, for 6 cycles. Concomitantly, olaparib is given at the MT dose level and pursued until disease progression or unacceptable toxicities.

For phase 1, pts receive olaparib only during the RT period to separate both periods for DLT (Dose Limiting Toxicities) assessment.
First 15 pts will receive olaparib only during the RT period to determine the MTD1 (Maximum-Tolerated Dose) among 7 dose levels, by assessing DLT on this period. Next 15 pts will all receive MTD1 during the RT period, and a new dose-escalation will determine MTD2 ($\leq$MTD1) during the MT period, assessing DLT from the first 2 cycles. For phase 2a, IMRT and TMZ are given according to the Stupp protocol. For olaparib, the pts will receive the MTD1 during the RT period and the MTD2 during the MT period.

Brain disease is assessed using RANO criteria at baseline, before the MT period, then every 8 weeks.

The protocol includes ancillary studies on tumor biopsies, spectro-MRI and neurocognitive and quality of life assessment before and after IMRT.

Up to 79 pts will be enrolled, including $\leq$30 pts in the phase 1 to define the RP2D and 49 pts in the phase 2a (Case&Morgan two-stage design).

**Results**

This trial (NCT03212742) is granted by the French Cancer Institute and French Health Ministry (PHRC-K15-135) and Astra-Zeneca for olaparib provision. First pt was enrolled on Oct 2017.

**Conclusion**

**References**