IPAX-1: PHASE 1/2 STUDY OF 4-L-[^{131}I] IODO-PHENYLALANINE (^{131}I-IPA) COMBINED WITH EXTERNAL RADIATION THERAPY (XRT) AS TREATMENT FOR PATIENTS WITH GLIOBLASTOMA MULTIFORME

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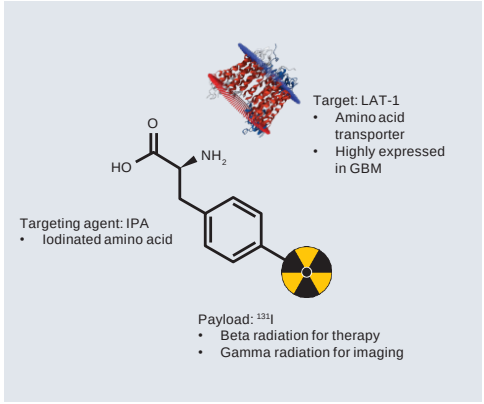
Background

- Each year, approximately 300 000 people globally are diagnosed with brain or nervous system cancer and 240 000 die as a result of the disease.[1]
- Glioblastoma multiforme (GBM) is the most common and aggressive form of primary malignant brain tumor in adults.[2]
- The prognosis for patients with GBM is poor.[3]
- There is a substantial unmet need for therapies able to extend survival in GBM.
- Molecularly targeted radiation (MTR) is a novel therapeutic approach that utilizes a specific molecular target to deliver a radionuclide payload to tumor cells.
  - Many tumor types, including GBM, overexpress the L-type amino acid transporter 1 (LAT-1).[4]
  - The small-molecule amino acid derivative 4-L-[^{131}I] iodo-phenylalanine (^{131}I-IPA) is internalized by LAT-1.
  - ^{131}I-IPA has received an orphan designation in the USA (10-3287) and European Union (EU/3/06/363) for the treatment of glioma.
- **Figure 1** shows the mechanism underlying the molecularly targeted radiation of GBM cells with ^{131}I-IPA.

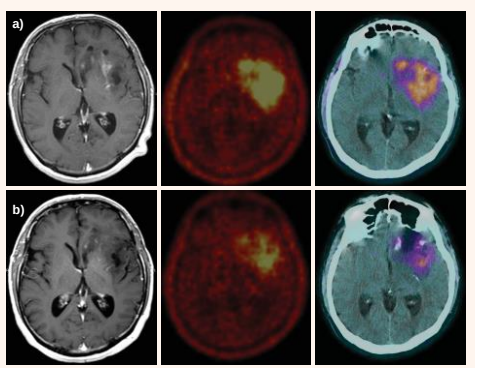
Figure 1. Molecularly targeted radiation of GBM cells with ^{131}I-IPA.



GBM, glioblastoma multiforme; ^{131}I, radioactive iodine; IPA, iodo-phenylalanine; LAT-1, L-type amino acid transporter 1.

- In preclinical research, combining ^{131}I-IPA with external radiation therapy (XRT) yielded additive cytotoxic effects.[5]
- Imaging results from the use of ^{131}I-IPA as a single agent in a patient with refractory high-grade glioma treated on a named-patient basis highlighted the potential for tumor shrinkage with this therapeutic approach (**Figure 2**).[6]
- Tumor accumulation of ^{131}I-IPA was shown in a proof-of-principle study[7] and confirmed with single dosing of 2–7 GBq ^{131}I-IPA in combination with XRT in patients with recurrent GBM.[8]

Figure 2. Contrast-enhanced T1 MRI (*left*), ^{18}F-FET-PET (*middle*) and ^{18}F-FET-PET/CT (*right*) in a patient with refractory high-grade glioma treated with ^{131}I-IPA as a single agent at a) baseline and b) 10 months after therapy.



Courtesy of Andreas Kluge, ABX-CRO advanced pharmaceutical services Forschungsgesellschaft.
^{18}F-FET-PET, [^{18}F]2-fluoroethyl-L-tyrosine positron emission tomography; CT, computed tomography; ^{131}I-IPA, 4-L-[^{131}I] iodo-phenylalanine; MRI, magnetic resonance imaging.

- The ^{131}I-IPA + XRT as Treatment for Patients with Glioblastoma Multiforme (IPAX-1) study is evaluating the safety, tolerability, dosing schedule and preliminary efficacy of ^{131}I-IPA in combination with second-line XRT in patients with recurrent GBM (NCT03849105).
- Primary and secondary study objectives are shown in **Table 1**.

Methods

Study design

- IPAX-1 is a multicenter, open-label, single-arm, dose-finding phase 1/2 study.
- The study was stopped after enrollment of the initial 10 patients.

Patients

- The key study eligibility criteria are listed in **Table 2**.

Treatment

- In phase 1 of the study, patients receive intravenous ^{131}I-IPA at a starting dose level of 2 GBq, followed by dose escalation.
  - The ^{131}I-IPA starting dose of 2 GBq is administered in one of three different dosing regimens:.
  - XRT is delivered in 18 fractions of 2 Gy each.
  - The optimal dosing regimen from the 2 GBq dose level will be implemented during dose escalation.
  - Dose escalation is performed in 2 GBq increments until maximum tolerated dose is reached.
  - Preliminary efficacy will be assessed via FET imaging

^{131}I-IPA, 4-L-[^{131}I] iodo-phenylalanine; IPAX-1, ^{131}I-IPA + XRT as Treatment for Patients with Glioblastoma Multiforme; MTD, maximum tolerated dose; XRT, external radiation therapy; IMP, Investigational Medicinal Product.

I-IPA in Combination with XRT is Well Tolerated

- The prognosis for patients with glioblastoma multiforme (GBM) is poor.
- Molecularly targeted radiation with ^{131}I-IPA in combination with XRT is a novel therapeutic approach for patients with GBM.
- The IPAX-1 study is to evaluate the safety and tolerability of intravenous ^{131}I-IPA administered concomitantly to second-line XRT in patients with recurrent GBM.
- Overall Survival shows median 15.97 months to date

Phase 2 of the study was planned to assess whether therapy with ^{131}I-IPA + XRT at the maximum tolerated dose possesses clinically relevant antineoplastic potential.

Table 1. IPAX-1 study objectives.

Primary objective
• To assess the safety and tolerability of ^{131}I-IPA + XRT
Secondary objectives
• To assess the feasibility of fractionated administration of ^{131}I-IPA • To evaluate the radiation absorbed dose to tumor from ^{131}I-IPA • To evaluate biodistribution and absorbed doses to whole body and organs from ^{131}I-IPA • To explore the antineoplastic effect of ^{131}I-IPA + XRT combination therapy • To assess the occurrence and frequency of pseudoprogression in response to ^{131}I-IPA + XRT • To explore cognitive function before, during and after therapy

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IPAX-1

Table 2. Key inclusion and exclusion criteria.

Key inclusion criteria	Key exclusion criteria
• Age ≥ 18 years • Previously confirmed histological diagnosis of GBM, with evidence of first recurrence • History of GBM standard therapy • At least 6 months since end of first-line XRT • Pathologically increased amino acid tumor uptake shown by molecular imaging • Current indication for repeat radiation • GTV of up to 4.8 cm diameter	• Primary XRT dose > 60 Gy • Doses to organs at risk exceeded/reached by prior radiation therapy • Multifocal distant recurrence, defined as tumor lesion outside the primary XRT field • Prior treatment with brachytherapy or bevacizumab

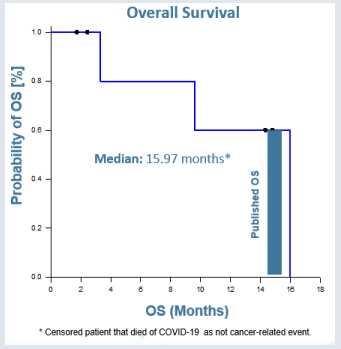
Table 3. Total Injected Activity Dose.

- This Phase 1/2 study determined the most suitable dose of 36 Gy administered in 18 fractions of 2Gy, concomitantly to 2nd line XRT.
- All patients evaluated in these preliminary results received similar total activity dose of about 2GBq (2000 MBq) of IMP, and the total injected activity doses were comparable for all groups. The mean total body effective doses were 150.67 ± 59.01 µSv/MBq in the 1f group, 165.00±49.12µSv/MBq in the 3Fp group, and 215.00 µSv/MBq in the one patient in the 3Fs group. The overall mean (±SD) was 166.00 ± 49.83µSv/MBq.

Injected Activity (MBq) (mean±SD)	Single dose 1f (n=4)	Fractionated dose 3f-parallel (n=3)	Fractionated dose 3f-sequential (n=1)	Total (N=8)
Dose 1	1915.00 ± 63.41	661.00 ± 82.02	688.00 ±.NA	–
Dose 2	–	682.00 ± 81.07	688.00 ± NA	–
Dose 3	–	643.67 ± 63.09	696.00 ± NA	–
Overall Total	1915.00 ± 63.41	1986.67 ± 223.74	2072.00 ± NA	1968.14 ± 146.31

XRT is administered in 18 fractions in total, given at 2 Gy per fraction.
^{131}I-IPA, 4-L-[^{131}I] iodo-phenylalanine; XRT, external radiation therapy

Figure 3. Preliminary Overall Survival.



N=9

Overall survival shows median 15.97 months to date with three patients exhibiting stable disease at day 135 and two with stable disease at 6 months.

Safety Summary and Conclusion

- The most frequent treatment-related TEAE was fatigue which occurred in three patients (37.5%), followed by diarrhea, decreased lymphocyte count, headache, and cerebral oedema, which all occurred in two patients, each (25%).
- With the exception of cerebral oedema, all the events had an intensity of grade 1 or grade 2.
- **In conclusion**, injections of single or fractionated doses of 131I-IPA containing a total activity of 2GBq in combination with XRT in patients with recurrent GBM were safe and well tolerated.

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Disclosures

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