# A phase 1 study of phospholipid ether [$^{131}$I]-CLR1404 in patients with advanced solid tumors.

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## Background

Preclinical data suggest that tumor cells of many types selectively accumulate and retain phospholipid ethers. To capitalize on this, a radiolabeled phospholipid ether [$^{131}$I]-CLR1404 was developed with the goal of improving tumor imaging specificity and as a novel approach to therapy. Preclinical experiments with [$^{131}$I]-CLR1404 (Figure 1) in mouse models demonstrated safety and efficacy. Imaging trials with different radioisotopes coupled to CLR-1404 have demonstrated a high degree of tumor specificity. Results from a dosimetric phase 1a study demonstrated the ability to image tumor uptake at a dose of 10 mCi/m$^2$. (Image 1)

We conducted a phase 1 study of escalating doses of [$^{131}$I]-CLR1404 in patients with advanced solid tumors. The primary objective of this study was to determine a recommended dose of [$^{131}$I]-CLR1404 for treating advanced solid malignancies. The secondary objectives were to expand the safety and pharmacokinetic profile, determine anti-tumor activity, and obtain tumor imaging with [$^{131}$I]-CLR1404.

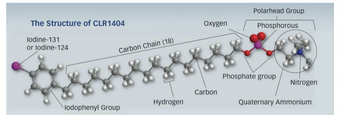


Figure 1: Chemical structure of [$^{131}$I]-CLR1404

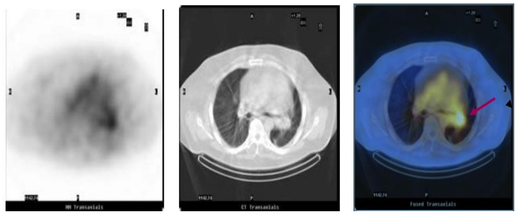


Image 1: SPECT, CT, and fused SPECT-CT of a patient with metastatic colorectal cancer received $^{131}$I]-CLR1404

## Materials/Methods

Patients with advanced solid tumors, measurable disease by RECIST 1.1, ECOG performance status 0-2 and adequate bone marrow, cardiac, renal and hepatic function were eligible. Patients were first given a dosimetric dose of [$^{131}$I]-CLR1404 followed by a treatment dose 1-2 weeks later in an algorithmic escalation design starting at 12.5 mCi/m2. Toxicity follow up included weekly laboratory and clinical assessment. Patients had SPECT scans to assess [$^{131}$I]-CLR1404 biodistribution. Imaging followup to assess response was performed at 8 weeks.

Toxicity follow up included q 7 day laboratory and clinical assessment. Patients had single photon emission computed tomography (SPECT) scans to assess [$^{131}$I]-CLR1404 biodistribution. Imaging follow up was performed at treatment day 56 with CT.

## Results

Twelve patients were enrolled at 3 open centers. Two patients withdrew from study before receiving drug; 10 patients received protocol therapy and were used for the safety analysis (Table 1). Myelosuppression was common and dose-related, with the highest-grade toxicities occurring 4-6 weeks post-infusion, and resolving within 2 weeks with growth factor support. The per-protocol dose-limiting toxicities (DLT) related to drug were grade 4 thrombocytopenia and grade 4 neutropenia at 37.5mCi/m$^2$ (2/2 pts). For further safety analysis, an intermediate dose level was opened at 31.25 mCi/m$^2$; 2/4 patients suffered DLTs. No DLTs were seen at 12.5 mCi/m$^2$ or 25 mCi/m$^2$. Other common toxicities included low-grade fatigue, and a dose-dependent, asymptomatic elevation in GGT. (Table 2)

Response assessments demonstrated 4 patients with stable disease (SD). Patients with stable disease included a patient with heavily pretreated ovarian cancer (2 systemic chemotherapies, 1 intraperitoneal chemotherapy), one patient with triple-negative breast cancer, and two patients with castrate-resistant prostate cancer with SD for 2-6 months. There were no complete or partial responses by RECIST 1.1.

SPECT imaging confirmed selective [$^{131}$I]-CLR1404 accumulation in known tumors of a variety of histologic subtypes. Solid intraparenchymal tumors were able to be visualized, and a pleural effusion was SPECT-avid in a patient with metastatic triple negative breast cancer (see images 2-6).

Table 1: Patient Demographics/Characteristics (N=10)

| Characteristic | N |
|---|---|
| Median age | 55<br>(Range 40-70) |
| Gender | Male-5<br>Female-5 |
| Tumor type | Colorectal-3<br>Breast-2<br>Prostate-2<br>Esophageal-2<br>Ovarian-1 |
| Lines of systemic cytotoxic therapy | 3 lines: 6<br>2 lines: 2<br>1 line: 0<br>0 lines: 2 |
| ECOG PS | 0: 6<br>1: 4<br>2: 0 |
| Race | White-9<br>Asian-1 |

Table 2: Toxicities at least possibly related to therapy (N=10); * Denotes DLT

| Dose (mCi/m$^2$) (N) | Toxicity | Grade 1-2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| 12.5 mCi/m$^2$ N=2 | Thrombocytopenia | 2 | 0 | 0 |
| | Leukopenia/Neutropenia | 1 | 0 | 0 |
| | Fatigue | 2 | 0 | 0 |
| 25 mCi/m$^2$ N=2 | Thrombocytopenia | 2 | 0 | 0 |
| | Leukopenia/Neutropenia | 1 | 1 | 0 |
| | Anemia | 0 | 1 | 0 |
| | Elevated GGT | 0 | 1 | 0 |
| | Fatigue | 2 | 0 | 0 |
| 37.5 mCi/m$^2$ N=2 | Thrombocytopenia | 0 | 1 | 1* |
| | Leukopenia/Neutropenia | 0 | 0 | 2* |
| | Anemia | 0 | 2 | 0 |
| | Elevated GGT | 0 | 2 | 0 |
| | Fatigue | 1 | 0 | 0 |
| 31.25 mCi/m$^2$ N=4 | Thrombocytopenia | 0 | 2 | 2* |
| | Leukopenia/Neutropenia | 1 | 2 | 1* |
| | Anemia | 1 | 1 | 0 |
| | Fatigue | 3 | 0 | 0 |

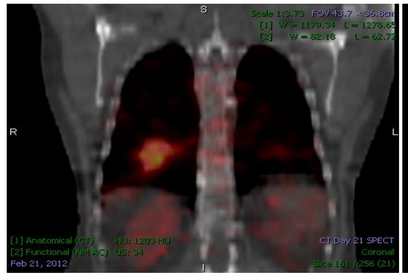


Image 2: SPECT-CT fused images from a patient (001) with colorectal cancer with lung and liver metastases.

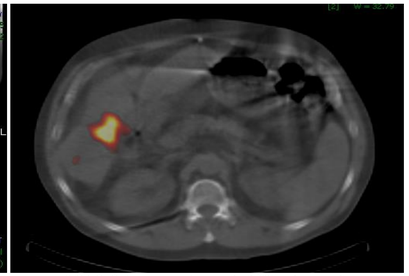

Image 3: SPECT-CT fused images from a patient (001) with colorectal cancer with lung and liver metastases.

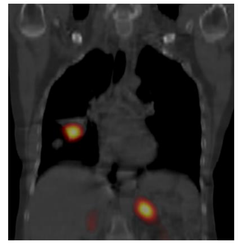

Image 4: SPECT-CT fused images from a patient (007) with lung and nodal metastases from colon cancer

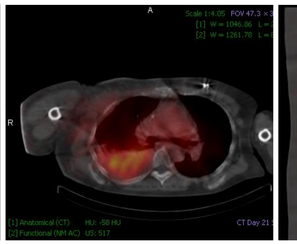


Image 5: SPECT-CT fused image of a malignant pleural effusion in a patient with triple negative breast cancer

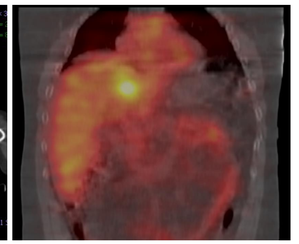

Image 6: SPECT-CT fused image from a patient (012) with metastatic esophageal cancer to the liver

## Conclusions

At a dose of 31.25 mCi/m$^2$, dose-limiting toxicities were thrombocytopenia and neutropenia. Studies exploring the mechanism(s) of action of [$^{131}$I]-CLR1404 toxicity are ongoing to minimize myelosuppression. Disease-specific phase II protocols will further explore the toxicity profile of the compound and are also underway to identify patients most likely to benefit from [$^{131}$I]-CLR1404.

In this study, there was a suggestion of [$^{131}$I]-CLR1404 anti-tumor activity (4 pts with SD) in a heavily pretreated population that merits further study. Future studies may examine different response evaluation, as assessing response by RECIST 1.1 in a compound for which the primary method of action is delivery of ionizing radiation has its limitations.

From the standpoint of tumor imaging, there was sustained uptake in tumors by SPECT. Tumor uptake and delayed excretion of phospholipid ether demonstrates the potential diagnostic and therapeutic capability of this compound.

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