A Novel “Diapeutic” Molecular Agent for Combined Oncologic Diagnosis and Therapy in a Broad Spectrum of Human Cancers: Preliminary Clinical Experience with CLR1404


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Disclosure of Potential COI

The following co-authors either have or recently had a financial relationship with the following commercial organizations:

- **PJ Pickhardt**: Viatronix, Braintree, Mindways, VirtuoCTC, Cellectar
- **M Longino, A Pinchuk, M Banach, J Grudzinski, B Titz, C Jaskowiak, JP Weichert**: Cellectar

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Presented by: Perry J. Pickhardt, MD
Background

- **CLR1404** – an alkylphosphocholine analog
- Capitalizes on over-abundance of phospholipid ethers present in most cancer cells

\[
\text{CH}_3(\text{CH}_2)_{16}\text{CO} \quad \text{O}(\text{CH}_2)_n \quad \text{OPOCH}_2\text{CH}_2\text{N}^+\text{Me}_3 \quad \text{X} = 125, 124, 131
\]
Tumor-targeting not affected by iodine label

PET tumor imaging with $^{124}$I-CLR1404

Molecular radiotherapy with $^{131}$I-CLR1404

Potential for both imaging diagnosis and therapeutic = “diapeutic” agent
• Prolonged tumor-selective retention in >60 in vivo rodent and human cancer models & cancer stem cell models ("universal")
• No retention w/in benign or inflamed tissue
• Significant tumor growth reduction and survival benefit from a single injection of $^{131}$I-CLR1404 in a wide range of human tumor xenograft models

Purpose

Report our initial experience with CLR1404 for localization and imaging of a broad spectrum of cancer in early human trials

- **PET/CT imaging with** $^{124}$I-CLR1404
  - Oncologic imaging; compare with $^{18}$FDG PET

- **SPECT/CT imaging with** $^{131}$I-CLR1404
  - Therapeutic form of this “diapeutic” agent

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Methods

- IRB-approved prospective imaging protocols
- All patients gave signed informed consent
- Early phase trials with $^{124}$I-CLR1404 PET and subtherapeutic $^{131}$I-CLR1404 SPECT
- **Main inclusion criterion:** biopsy-proven refractory advanced solid malignancy
  - Separate trial of primary brain tumors excluded
Methods

- $^{124}$I-CLR1404 PET/CT scans:
  - 64-detector-row PET/CT scanner (Discovery VCT, GE Healthcare, Waukesha, WI)
  - Serial imaging out to 5-10 days following the injection of up to 5 mCi of $^{124}$I-CLR1404
  - 2D acquisition mode
  - No correction employed for the $^{124}$I cascade gammas
  - Low-dose non-contrast MDCT for attenuation correction and lesion localization using 140 kV$_p$ and tube current modulation (70 mA average)

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Methods

- $^{131}$I-CLR1404 SPECT/CT scans:
  - Serial imaging (Infinia/Hawkeye, GE Healthcare) out 21 days
  - Phase I dosimetry trial not designed to show therapeutic benefit
  - Non-contrast low-dose CT was performed using 140 $kV_p$ and 2.5 mA

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Methods

- Review of imaging studies:
  - All PET/CT and SPECT/CT studies were reviewed on PACS workstation (McKesson) with fusion software (Mirada XD3)
  - Correlation with concurrent $^{18}$FDG PET/CT in most cases
  - Additional relevant cross-sectional imaging studies were also reviewed
Results

Study Cohort: 22 patients with metastatic cancer

- Mean age, 60.4 years; 12M, 10F
- Complex prior treatment histories
- **Tumor types:** bronchogenic carcinoma (n=7), colorectal cancer (n=4), prostate cancer (n=3), triple-negative breast cancer (n=2), esophageal cancer (n=2), head & neck squamous cell carcinoma (n=2), pancreatic cancer (n=1), and melanoma (n=1)
Results

\(^{124}\text{I}\)-CLR1404 PET/CT in 14 patients and \(^{131}\text{I}\)-CLR1404 SPECT/CT in 9 patients

- Preferential uptake of \(^{124}\text{I}\)- and \(^{131}\text{I}\)-CLR1404 within metastatic foci with all cancer subtypes

- Persistent retention within metastatic sites, coupled with progressive washout of background activity, favored delayed imaging (6-21 days after single injection).

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Results

$^{124}$I-CLR1404 PET/CT in 14 patients and $^{131}$I-CLR1404 SPECT/CT in 9 patients

- CLR1404 uptake was evident in pulmonary, nodal, skeletal, hepatic, CNS, and other sites of active metastatic disease
- Potential advantages in oncologic imaging over FDG PET included both fewer false-negatives and fewer post-treatment false-positives

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70M with bronchogenic carcinoma
60F with recurrent malignant melanoma

124I-CLR1404 PET

18F-FDG PET

Post-Contrast MR

Follow-up MR

PRESENTED AT: 50th ANNUAL MEETING  SCIENCE & SOCIETY
48M with colorectal carcinoma

Post-Contrast CT

$^{131}$I-CLR1404 SPECT/CT
57F with colorectal carcinoma
58F with triple-negative breast carcinoma
65M with bronchogenic carcinoma
46M with BOT squamous cell carcinoma

$^{124}$I-CLR1404 PET/CT
53F with triple-negative breast carcinoma
Limitations

• Early phase investigation in humans
  – Imaging protocols not standardized or optimized, precluding quantitative analysis
  – $^{131}$I-CLR1404 doses subtherapeutic
  – Wide variety of cancer types (proof of concept)
• No iodine correction
• 2D mode of acquisition for PET studies
Conclusions

• Selective tumor uptake of CLR1404 with prolonged retention within a broad spectrum of historically difficult-to-treat metastatic cancers
  – Regardless of the site of metastatic disease

• Distinct advantages over FDG PET observed:
  – Detection in cases of FDG false-negatives
  – Lack of uptake in cases of FDG false-positives
  – $^{124}$I-CLR1404 may improve accuracy for oncologic PET imaging
Conclusions

• Combined diagnosis and therapy ("diapeutic") using the same molecule (CLR1404) may allow for truly personalized cancer care:
  – Ensuring pre-treatment tumor-specific uptake
  – Providing patient-specific dose planning
  – Enabling treatment-specific imaging surveillance
Diapeutic Treatment Paradigm

$^{124}\text{I-CLR404}$ PET/CT

Distribution, Quantification, & Personal Dose Calculation

$^{131}\text{I-CLR1404}$ Therapy Dose Injection

Monitor Response w/ $^{124}\text{I-CLR404}$ PET/CT

\[ D_{\text{Tumor}} = D_{\text{Surf/Thick}} + \frac{k_{21}}{k_{G}} \left( \frac{1}{w_1 + w_2} \frac{\lambda \cdot k_{34}}{k_{G}} \left( (k_{20} - k_{31})(w_1 k_{21} + w_2 k_{12}) - w_1 k_{31} \right) \right) \]
Thank You