Lu-177 OPS-201 (satareotide) Trial for Metastatic Neuroendocrine Tumour

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Disclosures

Founding Director:

- Theranostics Australia P/L
- Oceanic Molecular P/L
- Principal Investigator (Hollywood Private Hospital): Ipsen Lu-177 OPS-201 Trial
Introduction

• *The times they are a changin’* ..... 

• 2005:
  – Indium octreotide imaging 
  – Somatostatin receptor agonist treatment 

• 2016:
  – Ga-68 octreotate: state of the art imaging for NET (not Medicare) 
  – Lu-177 octreotate: most efficacious therapy for NET 

• 2020:
  – "Ga-68 OPS 202 (satareotide) for NET imaging 
  – "Lu-177 OPS 201 (satareotide) for NET therapy
Background

SOMATOSTATIN RECEPTOR AGONISTS VS ANTAGONISTS

• Somatostatin receptor (SSTR) targeting for imaging has been common for over 20 yrs and for therapy for over 10 yrs

• Conventional wisdom
  – binding of a SSTR agonist (e.g. octreotide) to G-protein activated receptor with subsequent internalisation into cell
  – More robust for imaging
  – Safety for therapy
Somatostatin Receptor Agonists Vs Antagonists
Somatostatin Receptor Agonists Vs Antagonists

- Ginz et al PNAS 2006 found a new class of antagonistic peptides
- Independent to receptor activation status therefore many more potential binding sites
- Despite lack of internalization did not show increased clearance – in fact appeared to be the opposite (Cescato 2011, Fani 2012, Wild 2014)
Somatostatin Receptor Antagonist

- Higher Bmax\textsuperscript{1}
- Higher Tumor Uptake\textsuperscript{2}
- Longer Tumor Retention Time\textsuperscript{3}
- Higher renal uptake

177\textsuperscript{Lu}-DOTA-TATE Agonist 177\textsuperscript{Lu}-DOTA-BASS Antagonist \textsuperscript{4}

Somatostatin Receptor Agonists Vs Antagonists
Further Development: Radiolabeled SST2 “Antagonist” for PET

$^{68}\text{Ga-DOTATATE}$  $^{68}\text{Ga-OPS202}$

**Fig.1**
Micro-PET imaging of $^{68}\text{Ga-OPS202}$ in HEK-sst$_2$ mice xenografts, compared to $^{68}\text{Ga-DOTATATE}$

In comparison to the agonist the antagonist:
- Higher number of binding site (Bmax)
- Higher tumour uptake

$^{68}\text{Ga-OPS202} = \text{sst\ antagonist}$

Gallium-68 Satoreotide in NET
Patient 3: 32-year old male with Ileum NET (G2, Ki67 2-5%) who has known liver and lymph-node metastases. ? Restaging

Octreoscan®
scintigraphy 24h p.i.
sst₂ receptor agonist

02.09.14

past

6⁸Ga-DOTATOC
PET 1h p.i.
sst₂ receptor agonist

14.11.14

present

6⁸Ga-OPS202
PET 1h p.i.
sst₂ receptor antagonist

18.11.14

future?
Somatostatin Receptor Antagonists in the Clinic

\[ ^{177}\text{Lu-OPS201} \]

\[ ^{177}\text{Lu-DOTA-TATE} \]

Pilot Study: SPECT imaging illustrating an increased tumor uptake of $^{177}$Lu with antagonist (OPS-201), implying potential for greater therapeutic efficacy.

PET scan demonstrates pelvic metastases. SPECT imaging post-$^{177}$Lu-agonist and antagonist, demonstrating increased (x4) tumour uptake of $^{177}$Lu with antagonist, implying potential for greater therapeutic efficacy; higher tumour / kidney ratio implies wider safety window.
68Ga-DOTATATE PET images of patient 2 before (A) and 3 mo after (B) treatment with 15.2 GBq of 177Lu-DOTA-JR11 and 68Ga-DOTATATE PET images of patient 3 before (C) and 12 mo after (D) treatment with 5.9 GBq of 177Lu-DOTA-JR11.

New agent trials

- Ipsen commenced phase III trial of In-111 octreotide vs Ga-68 OPS-202 Satareotide (USA)
- Ipsen in recruitment/early phase I Lu-177 OPS-201 in NET (USA – New York) – dose finding/toxicity
- Ipsen chosen sites for phase II/III Lu-177 OPS-201 in metastatic NET:
  - 7 sites around the world - 1 in USA, 1 in UK, 4 in Europe,
  Theranostics Australia Hollywood Hospital Perth and Peter MacCallum Cancer Institute, VCCC Melbourne are Australian sites.
Phase II/III Lu-177 OPS 201 Trial

- Metastatic GPNET; low ki-67; No previous Lu-177 therapy; No significant renal disease; Progressive disease (imaging)
- Lutetium therapy alone - not with chemotherapy; 4 cycles 8 weeks apart
- Initial Gallium- octreotate scan
- 45 patients to be recruited worldwide
- Extensive follow up: clinical, imaging and blood tests over 2 years
- Initial application approved by Hollywood Ethics June 2016; awaiting revision of protocol (Ipsen); for recruitment likely October/November 2016
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