$^{212}$Pb-NNV003 as a novel targeted alpha therapy for CD37 positive B-cell CLL and NHL

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Disclosure

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Background
Chronic lymphocytic leukemia (CLL) is the most common leukemia in adults in western countries, accounting for approximately one quarter of all leukemias.

Non-Hodgkin lymphoma (NHL) caused an estimated 200,000 cancer deaths worldwide in 2014.

More than 90,000 cases of chronic lymphocytic leukemia (CLL) and non-Hodgkin lymphoma (NHL) are expected in the US each year.

Front-line therapy: Immuno-chemotherapy using anti-CD20 monoclonal antibodies (mAb) in combination with DNA alkylating agents.

Relapses after repeated administration of immuno-chemotherapy are frequent and relapsed/refractory patients show poor prognosis.
CD37 is strongly and selectively expressed on the surface of mature B lymphocytes and B-cell malignancies.

Development of new therapies targeting CD37 expressing cells may prove useful for relapsed or refractory patients.
$^{212}\text{Pb}$, parent of the $^{212}\text{Bi}$ alpha-emitter

$^{232}\text{Th}$ (Thorium-232)
Decay Chain
02
Preclinical Studies
**212**Pb-NNV003 biodistribution study design

10x10^6 DAUDI s.c.
Or
2.5x10^6 MEC2 s.c.

250-300mm^3

200µg IgG2a I.P.

10µCi 212Pb-NNV003

2h and 24h

Necropsy, tissue collection & weighing

Auto-gamma-counter
\[ ^{212}\text{Pb-NNV003} \text{ Biodistribution in xenograft tumor-bearing mice} \]

- No red flags
- Up to 25\% tumor uptake in Daudi tumors and up to 20\% in MEC-2 tumors
**212Pb-NNV003 acute toxicity study design**

- CB17-SCID or R2G2
- Predosing 200µg IgG2a I.P.
- Escalating 212Pb-NNV003 doses
- Daily observation 3x per week weighing
- Euthanize at 4 weeks or when termination criteria are met

**Day 0**

**Day 1**

**Day 2**
CB17-SCID bear a systemic Prkdc mutation that renders mice radiosensitive
R2G2 are severely immunodeficient but present no radiosensitivity
No acute hematological toxicity was observed, only a slight initial reduction in platelets (PLT) counts which was recovered and stabilized 4-weeks after injection.
**212Pb-NNV003 efficacy study design**

1. **Day 0**
   - 10x10⁶ DAUDI i.v.
   - Or
   - 2.5x10⁶ MEC2 i.v.
   - CB17-SCID
   - Or
   - R2G2

2. **Day 1**
   - 200µg IgG2a I.P.
   - 212Pb-Cetuximab
   - Cold NNV003
   - 212Pb-NNV003
   - Saline

3. **Day 2**
   - Daily observation
   - 3x per week weighing
   - Hematology (every 2 weeks)

4. **Termination**
   - Euthanize when termination criteria are met
• Median survival was not reached at 28 weeks after a single intravenous dose of 2.5, 5 and 7.5 µCi $^{212}$Pb-NNV003. Control animals that received saline, cold antibody or $^{212}$Pb-cetuximab presented a median survival of 7, 7.9 and 7.7 weeks, respectively.
Median survival was not reached at 28 weeks after a single intravenous dose of 10, 15 or 20 µCi of \(\text{^{212}Pb-NNV003}\). Saline, cold antibody or \(\text{^{212}Pb-cetuximab}\) presented a median survival of 4.9, 5.4 and 8.9 weeks, respectively.
Summary

- $^{212}\text{Pb-NNV003}$ displays a favorable toxicity profile at therapeutic doses after a single intravenous injection in tumor-free mice.

- $^{212}\text{Pb-NNV003}$ lead to a significantly increased survival in CLL and NHL tumor-bearing mice.

- The results of preclinical studies suggest that TAT using $^{212}\text{Pb-NNV003}$ may have positive clinical implication for the treatment of CD37 positive CLL and NHL.
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$^{212}\text{Pb}$ for Targeted Alpha Therapy