INTRAPERITONEAL RADIOIMMUNOTHERAPY FOR DESMOPLASTIC ROUND CELL TUMOR: RESULTS OF A PHASE I STUDY (Clinicaltrials.gov identifier NCT01099644)

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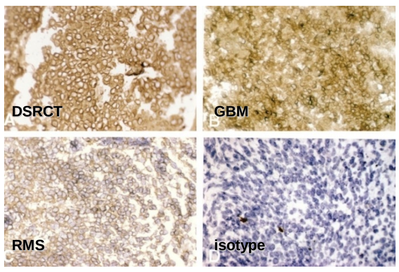
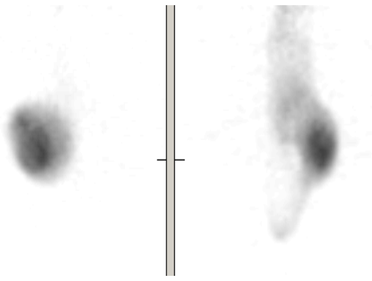
BACKGROUND

- DSRCT, a rare sarcoma of adolescents and young adults, has a long-term survival of <20% despite aggressive multimodality therapy, warranting a search for novel treatments.
- DSRCT recurrences often present as multifocal peritoneal implants.



The murine monoclonal IgG1 antibody omburtamab (previously termed 8H9) recognizes cell surface antigen B7H3 and binds to 96% of DSRCTs with restricted normal tissue reactivity.

^{124}I-omburtamab can image DSRCT xenografts in mice and ^{131}I-omburtamab can suppress tumor growth of B7-H3 tumors



- ^{124}I-omburtamab and ^{131}I-omburtamab being investigated in phase II trial for leptomeningeal metastases (NCT00089245; Kramer PI)
- ^{124}I-omburtamab being investigated in phase II trial for theranostics of DIPG (NCT0102917; Souweidane PI)
- ^{131}I-omburtamab was sequestered in the liver when injected IV (Unpublished data); therefore only compartmental use considered

HYPOTHESIS and OBJECTIVES

Intraperitoneal (IP) radioimmunotherapy with 131I-omburtamab is safe and effective for patients with DSRCT

- To define the toxicity and maximal tolerated dose (MTD) of IP ^{131}I-omburtamab
- Assess tumor targeting, dosimetry and biodistribution of IP ^{124}I-omburtamab
- Assess pharmacokinetics of IP ^{131}I-omburtamab
- Assess response of DSRCT to IP ^{131}I-omburtamab

METHODS: Phase I study (NCT01099644)

Key inclusion criteria

- DSRCT with peritoneal involvement.
- Patients with omburtamab-positive peritoneal tumors other than DSRCT
- Patients with DSCRT not required to have measurable or evaluable disease.
- **Stem cells:** Minimum of 2 x10^6 CD34+ cells/kg should be available.

Key Exclusion criteria

- Severe major organ toxicity; should all be grade 2 or less
- Patients with dense IP adhesions preventing adequate IP distribution.

Dose escalation

- Standard 3+3 design
- ^{124}I-omburtamab dose for imaging kept constant
- ^{131}I-omburtamab dose escalated starting at 30mCi/m^2

Day	Treatment/Intervention
-7- +35	Oral liothyronine and potassium iodide (for thyroid protection)
0	Dosimetric dose of ^{124}I-omburtamab IP. Blood draw for ^{124}I-omburtamab pharmacokinetics. PET scan for ^{124}I-omburtamab dosimetry
1-4	Blood draw for ^{124}I-8H9 pharmacokinetics. PET scan for ^{124}I-omburtamab dosimetry.
3	Therapeutic dose of ^{131}I-omburtamab IP given out-patient
3-7	Blood draw for ^{131}I-omburtamab pharmacokinetics. Gamma camera scan for ^{131}I-omburtamab distribution.
24-38	Extent of disease evaluation
28-35	CBC; decision regarding stem cell rescue
35*	Observations period ends; can continue further therapy

TOXICITY

- Outpatient therapy
- Transient grade 2 pain related to large volume of saline flush
- No hypothyroidism
- Human anti-mouse antibody (HAMA) in 2/40 (5%)
- ASCR not indicated in any patient

RESULTS

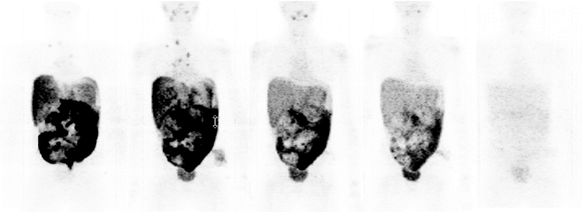
- 52 patients (41 male; 11 female)
- 48 DSRCT; 1 RMS; 1 Ewing sarcoma
- Median age 18.5 (range 2.9-38) years
- Median time from catheter insertion 18 (9-35) days

^{131}I-omburtamab dose (mCi/m^2)	Planned number of patients	Actual numbers treated
30	3	3
40	3	3
50	3	3
60	3-6	7*
70	3	3
80 (Phase II dose)	23	27*
90	3-6	5
Total		**52**

^{131}I-omburtamab dose (mCi/m^2)	Grade 3 ANC	Grade 4 ANC	Grade 3/4 plts	Grade 3 AST elevation
30 (n=3)	0	0	0	0
40 (n=3)	0	0	0	0
50 (n=3)	0	0	0	0
60 (n=7)	0	0	0	0
70 (n=3)	0	0	1	0
80 (n=27)	2	2	4	1
90 (n=6)	0	1	0	0
Total (52)	**2 (4%)**	**2 (4%)**	**5 (10%)**	**1 (2%)**

PHARMACOKINETICS and BIODISTRIBUTION

- Blood pharmacokinetics: biphasic pattern
- Initial rising phase with median half-time of 23.1±15.1 hours
- Subsequent falling phase with a median half-time of 55.9 ±34.5 hours
- Mean projected peritoneal self-dose (maximum) was 4.18±1.56 mGy/MBq. Plateaued off at 80mCi/m2
- Mean projected absorbed doses to blood, kidney, liver, lung and spleen were well below tolerable levels:2.0,0.37,0.51, 0.11 and 0.35 mGy/MBq ^{131}I-omburtamab, respectively.



Day 0 (~4h pi) | Day 1 | Day 2 | Day 3 | Day 5

OUTCOMES

- As expected, no responses in patient with measurable disease
- Survival was significantly worse for patients receiving IP-RIT with residual disease compared to those treated after R1-resection: median PFS and OS for the two groups was 8.2±3.8 months versus 15±0.8 months and 22.1±4.9 months versus 53.4±5.2 months respectively (p<0.01 for both).
- Of the 23 patients receiving IP-RIT after R1-resection at the recommended phase II dose or higher, 10 remain alive disease-free at a median follow up of 36 months after RIT, and only 4 (17%) developed their initial relapse in the abdominopelvic compartment.

Conflict of Interest Statement: *MSK has institutional financial interests related to this research in the form of intellectual property rights and equity interests in Y-mAbs, the company licensing the intellectual property from MSK.* N.K. Cheung reports receiving commercial research grants from Y-mAbs Therapeutics, Inc. and Abpro-Labs, Inc., holding ownership interest/equity in Y-mAbs Therapeutics and in Abpro-Labs, and owning stock options in Eureka Therapeutics, Inc. NKC is the inventor of issued patents licensed by MSK to Y-mAbs Therapeutics, Biotec Pharmacon, and Abpro Labs. NKC was named as an inventor on several issued and pending patents filed by MSK. NKC is a scientific advisory board member of Abpro Labs and Eureka Therapeutics. S. Modak reports consulting for Y-mAbs Therapeutics.

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