Whole Abdominopelvic Radiotherapy and Radioimmunotherapy after Complete Resection of Desmoplastic Small Round Cell Tumor: Significant Impact on Survival

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DISCLOSURES

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.

S. Modak reports consulting for Y-mAbs Therapeutics and Progenics

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DSRCT: Current Status of Therapy

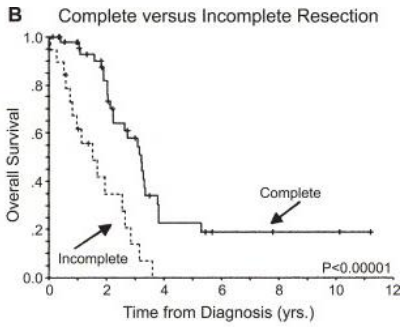
- **Moderately chemosensitive and radiosensitive : High-dose chemotherapy P6 protocol**

  Kushner etal JCO 1996

- **"Gross total resection" required for favorable outcome: 5yr OS 20%**

  Lal etal Pediatr Surg 2005

  Subbiah etal CCR 2018

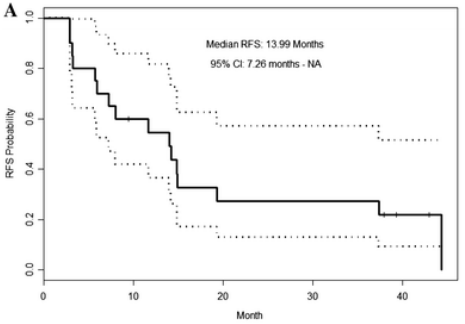


  - **HIPEC: Median EFS: 14.9 mo; Median OS: 44mo**

    Hayes -Jordan Ann Surg Oncol 2018

- **Myeloablative autologous transplant ineffective: longterm OS 20%**

  Forlenza etal 2015



  - **Whole abdominal IMRT better tolerated and possibly effective**

    Pinnix etal Pediatr IJROBP 2012

    Casey etal IJROBP 2013

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Pre-2009 Approach @MSKCC

P6 chemotherapy regimen* (*or other induction***) x 5-6 cycles

Surgery

Chemotherapy x 1-2 cycles

Second look surgery to achieve “Gross total resection”

Whole Abdominopelvic IMRT (WAP-IMRT) 3000cGy***

Maintenance chemo

Kushner* etal JCO 1996
Magnan** etal (Unpublished)
Desai, Wolden et al Int J Radiat Oncol Biol Phys 2013***

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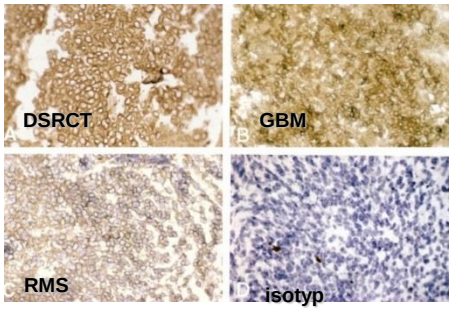
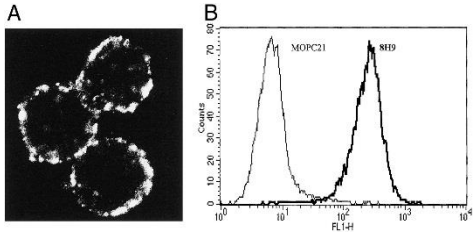
Development of omburtamab (8H9) : murine IgG1 MoAb that targets B7H3

Binds to range of pediatric solid tumors; restricted against normal tissues; Not immunomodulated off cell surface; Expressed on >95% DSRCT

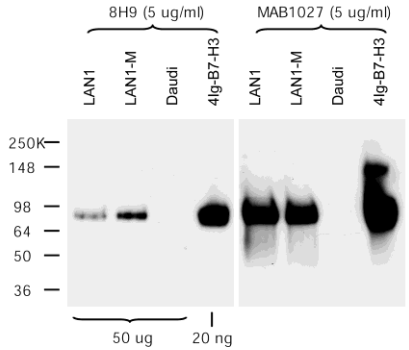
(Modak etal, Cancer Res 2001; Modak etal Med Ped Onc 2001)



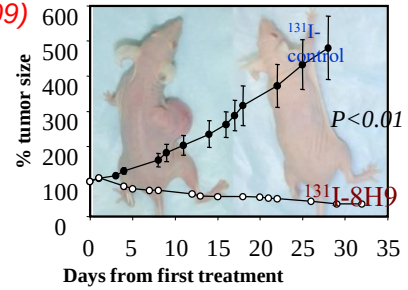


Binds to immunomodulatory molecule B7H3

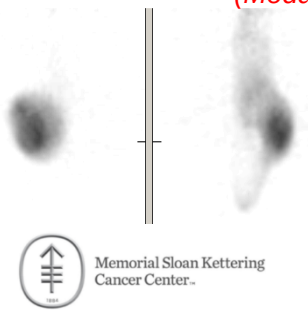
(Xu etal Cancer Res 2009)



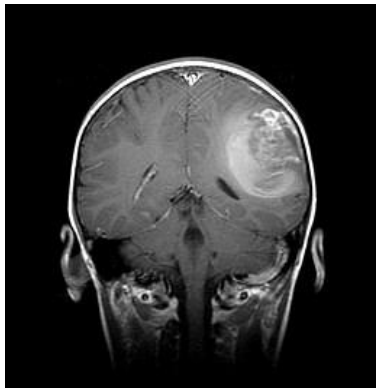
Radioiodinated 8H9 *targets JN-DSCRT-1 SQ* xenografts and has therapeutic effect on RMS xenografts

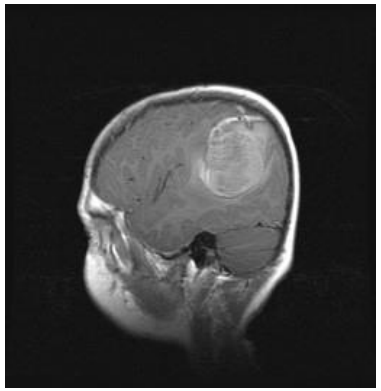


(Modak etal Cancer Biother 2005)

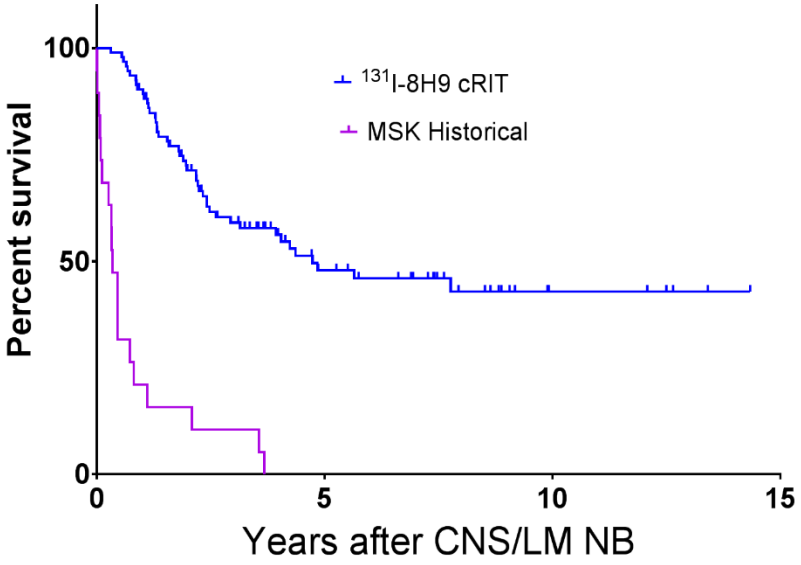


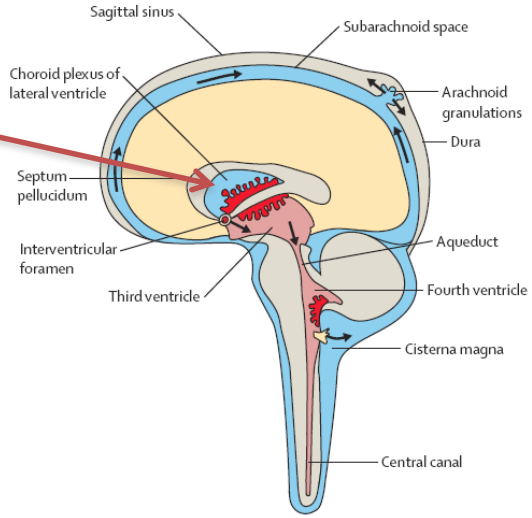
Compartmental radioimmunotherapy (cRIT) using intrathecal (intra-Ommaya) ^{131}I-mAb (outpatient):





^{131}I-8H9 (anti-B7H3)





Kramer et al. J Neurooncology 97:409, 2010
Croog et al. Int J Radiat Biol Oncol 78:849, 2010
Kramer et al. 2017, SIOP, SNO

^{131}I-8H9 (omburtamab): FDA Breakthrough Therapy Designation
International trial is underway (NCT00089245), PI: Kim Kramer

Rationale for Intraperitoneal Radioimmunotherapy (IP-RIT) of DSRCT

- Relapses are often within the peritoneum
- Enhance local control by targeting micrometastases
- Non-cross resistant modality
- Targets disease sites that may not be accessible to chemotherapy
- Potential to safely deliver very high doses of radiation to micrometastases
- Availability of antibody omburtamab suitable for compartmental RIT

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Treatment schema for phase I study (poster #97)

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

For expansion cohort, observation period reduced to 14 days

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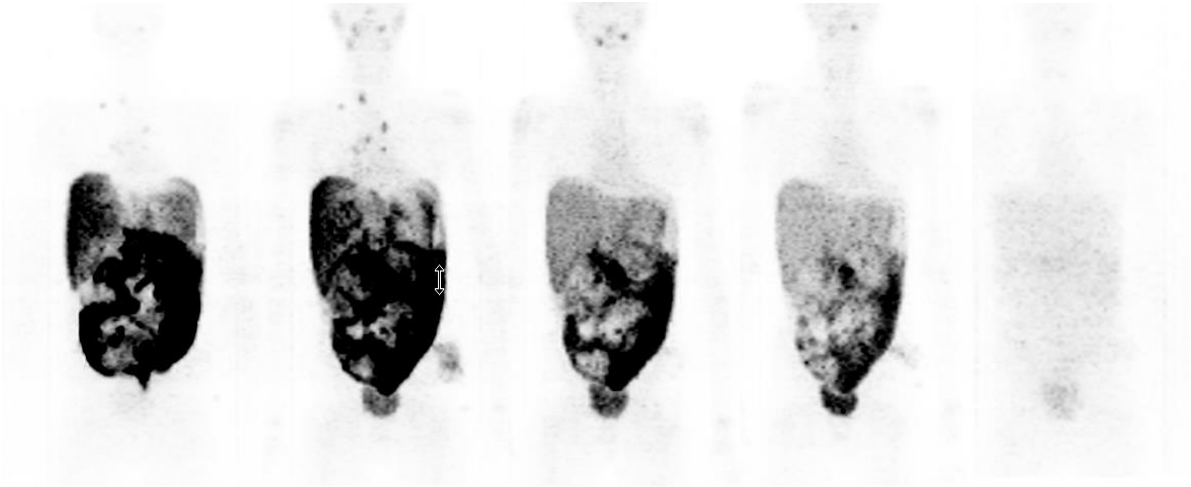
IP RIT : Toxicities on phase I study: Poster #97

- Well tolerated at all dose levels
- Out-patient treatment (after first 3 patients)
- Main toxicity was transient abdominal pain and discomfort for <60 minutes after IP injection
- No DLTs; MTD not reached
- No hypothyroidism
- No significant myelosuppression; Stem cell rescue not required

^{131}I-omburtamab dose (mCi/m^2)	Grade 3 neutropenia	Grade 4 neutropenia	Grade 3 thrombocyto-penia	Grade 3 AST elevation	Grade 2 abdominal pain
30 (n=3)	0	0	0	0	2
40 (n=3)	0	0	0	0	1
50 (n=3)	0	0	0	0	1
60 (n=7)	1	0	0	0	0
70 (n=3)	0	0	0	0	0
80 (n=27)	2	2	5	1	0
90 (n=6)	0	1	1	0	0
Total	**3**	**3**	**6**	**1**	**4**

Phase I study: Representative whole body ^{124}I-8H9 PET scans (Poster 97)



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

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Post 2009 @MSKCC

P6* (*or other induction***) x 5-6 cycles

↓

Surgery

↓

P6 (*or other induction*) x 1-2* cycles

↓

Second look surgery

↓

Gross total resection

↓

Phase I: IP-RIT with ^{131}I-omburtamab 80mCi/m^2

↓

Whole Abdominopelvic IMRT (WAP-IMRT) 3000cGy

↓

Maintenance chemo/Biological therapy

Objectives and Methods

- To determine the effect of WA-IMRT after GTR on survival
- To determine the effect of IP-RIT after GTR on survival

- Retrospective: 2000-2018
- Included prospective data from phase I trial
- GTR defined from surgery notes
- Survival analyzed **from time of surgery**

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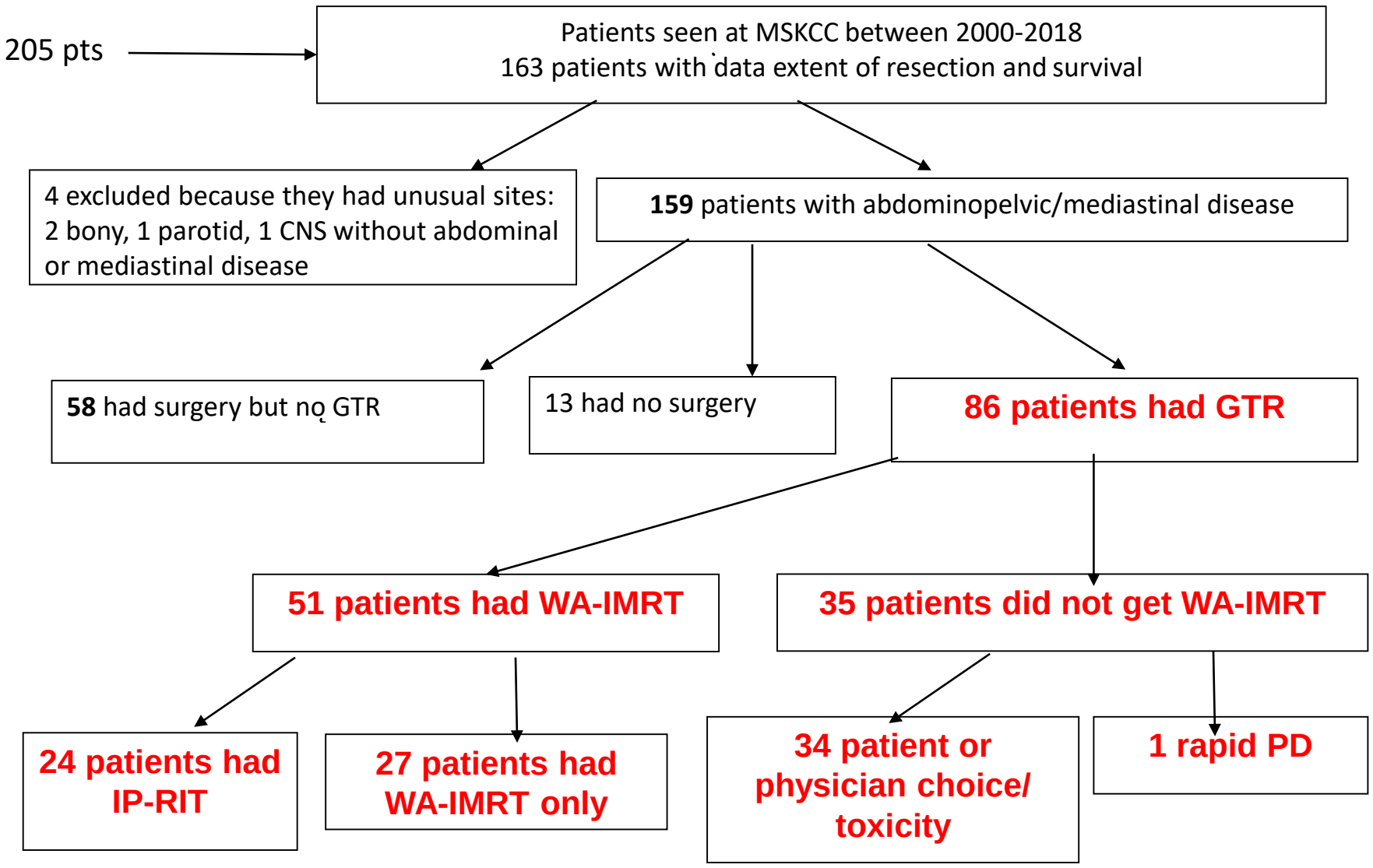
DATABASE ANALYZED

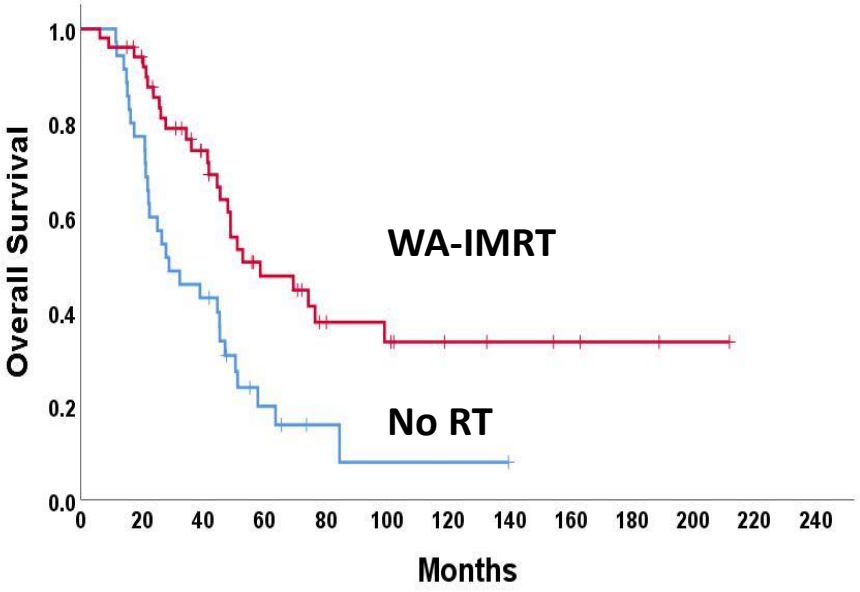


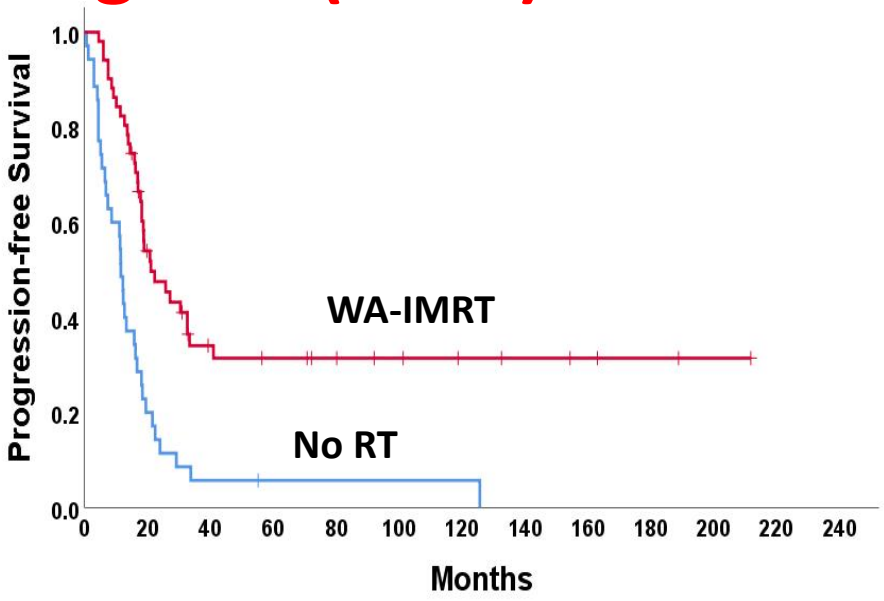
Patients undergoing GTR (n=86)

	N	Alive (N)	Alive PF (N)	Median PFS* (mo)	Median OS* (mo)
Received WA-IMRT	51	28	18	21.1±4.7	58.6±12.7
Did not receive WA-IMRT	35	6	1	11.5±0.7	28.8±8.2
Received IP RIT+ WA-IMRT	24	15	9	22.3±5	58.6±7.7

*Survival calculated from time of surgery

Patients undergoing GTR (n=86)





	PFS	OS
WA-IMRT vs no WA-IMRT (51 vs 35)	< 0.001	0.001
IP-RIT+WA-IMRT vs others (24 vs 62)	0.02	0.06

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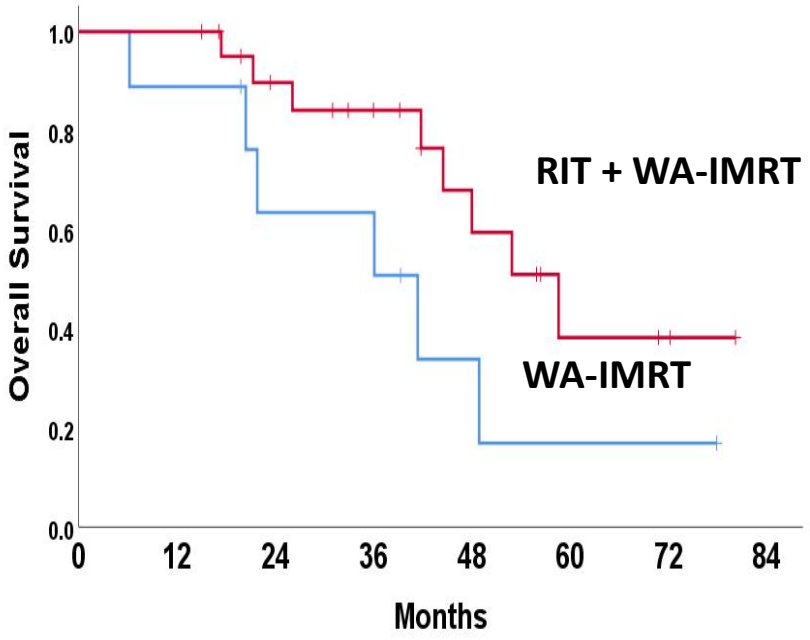
33 GTR +WA-IMRT patients from 2009-17
(Phase I IP-RIT with omburtamab commenced in 2009)

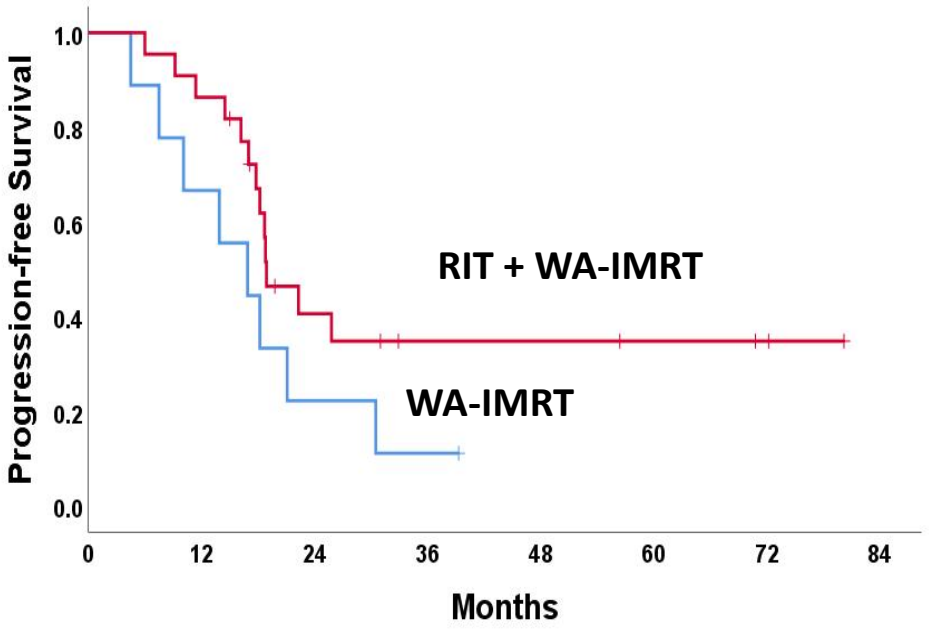
	N	Alive (N)	Alive PF (N)	Median PFS (mo)	Median OS (mo)
Received WA-IMRT only*	9	3	1	16.9±4.5	41.4±12
Received IP-RIT +WA-IMRT	24	15	9	22.3±5	58.6±7.7

*due to unavailability (phase I) (n=4) or catheter blockade (n=5)

*Survival calculated from time of surgery

33 GTR +WA-IMRT patients from 2009-17





	PFS	OS
IP-RIT+WA-IMRT vs WA-IMRT	0.1	0.07

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CONCLUSIONS

- WA-IMRT should be considered for all patients whose tumor can be resected
- IP-RIT with omburtamab is safe and shows promise when added to WA-IMRT

LIMITATIONS

- These approaches may not help all patients who do not achieve GTR of DSRCT
- Lack of evaluable disease means that survival is the only read out (similar situation to HIPEC)
- Multicenter prospective studies indicated

Treatment schema for Phase II (NCT04022213)**

Day	Treatment/Intervention
-7 to+28	Oral liothyronine and potassium iodide commenced (for thyroid protection).
0	Therapeutic dose of ^{131}I-8H9 IP given out-patient
3-7	Blood draw for ^{131}I-8H9 pharmacokinetics. Gamma camera scan for ^{131}I-8H9 distribution.
14	Whole abdominopelvic IMRT 3000cGy
~44	Autologous stem cell boost if necessary
>44	*Maintenance chemotherapy*

Primary Aim:

- Achieve a favorable PFS of 20 months

Secondary Aims:

- Biomarker: DSRCT cfDNA in blood and peritoneal fluid*
- Further safety data on early WAP-IMRT

*Shukla et al JCO Precision Onc 2017

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**Potential for multi-center evaluation

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Acknowledgements

The Taylor Matthews Foundation
A TAY-BANDZ ORGANIZATION

-mAbs

STEVEN VANOVER FOUNDATION

SARCOMA SPORE GRANT MSKCC

MSK Nursing, radiochemistry, physics, radiation safety

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