Immunotherapy with Salvage Surgery and IORT for Treatment of Persistent/Recurrent Head and Neck Cancers

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Background

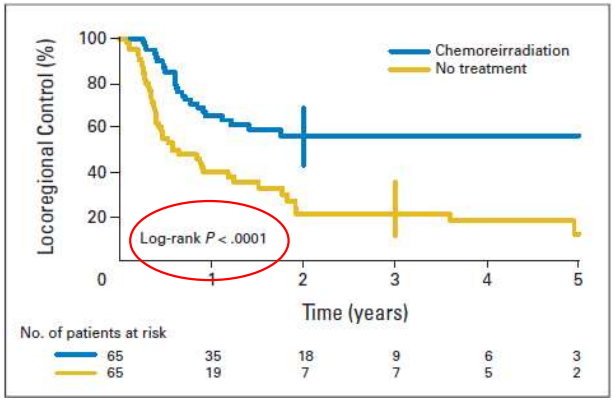
- Standard of care for locoregionally recurrent head/neck cancer is surgical resection with adjuvant therapy.
- Local control after surgery alone is unacceptably low. Post-op chemoradiation has been shown to improve LC and PFS.
- Local failure remains the primary site of recurrence and overall prognosis is very poor.
- IORT may play a role in improving local control and decreasing toxicity for these patients.

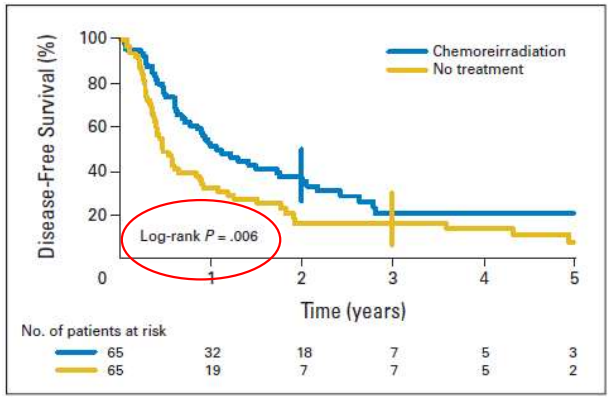
Randomized Trial of Postoperative Reirradiation Combined With Chemotherapy After Salvage Surgery Compared With Salvage Surgery Alone in Head and Neck Carcinoma

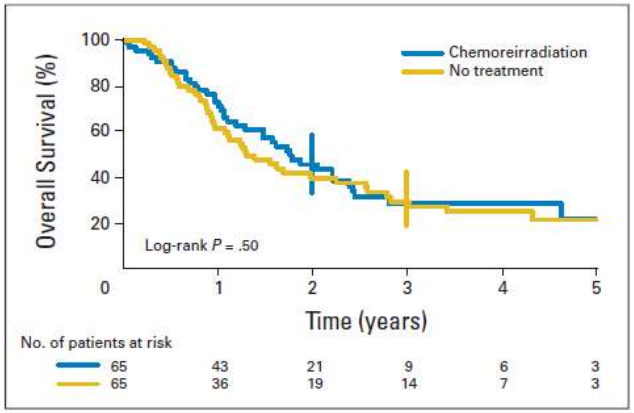
François Janot, Dominique de Raucourt, Ellen Benhamou, Christophe Ferron, Gilles Dolivet, René-Jean Bensadoun, Marc Hamoir, Bernard Géry, Morbize Julieron, Marine Castaing, Etienne Bardet, Vincent Grégoire, and Jean Bourhis

- 130 previously radiated patients with recurrent head/neck cancer
- Randomized to surgery followed by:
  - Observation
  - Chemoradiation
    - 60 Gy with concurrent 5-FU and Hydroxyurea

Results


Locoregional Control (%)
100
80
60
40
20
0
Chemoreirradiation
No treatment
Log-rank P < .0001
1
2
3
4
5
Time (years)
No. of patients at risk
65 35 18 9 6 3
65 19 7 7 5 2


Disease-Free Survival (%)
100
80
60
40
20
0
Chemoreirradiation
No treatment
Log-rank P = .006
1
2
3
4
5
Time (years)
No. of patients at risk
65 32 18 7 5 3
65 19 7 7 5 2


Overall Survival (%)
100
80
60
40
20
0
Chemoreirradiation
No treatment
Log-rank P = .50
1
2
3
4
5
Time (years)
No. of patients at risk
65 43 21 9 6 3
65 36 19 14 7 3

Toxicity

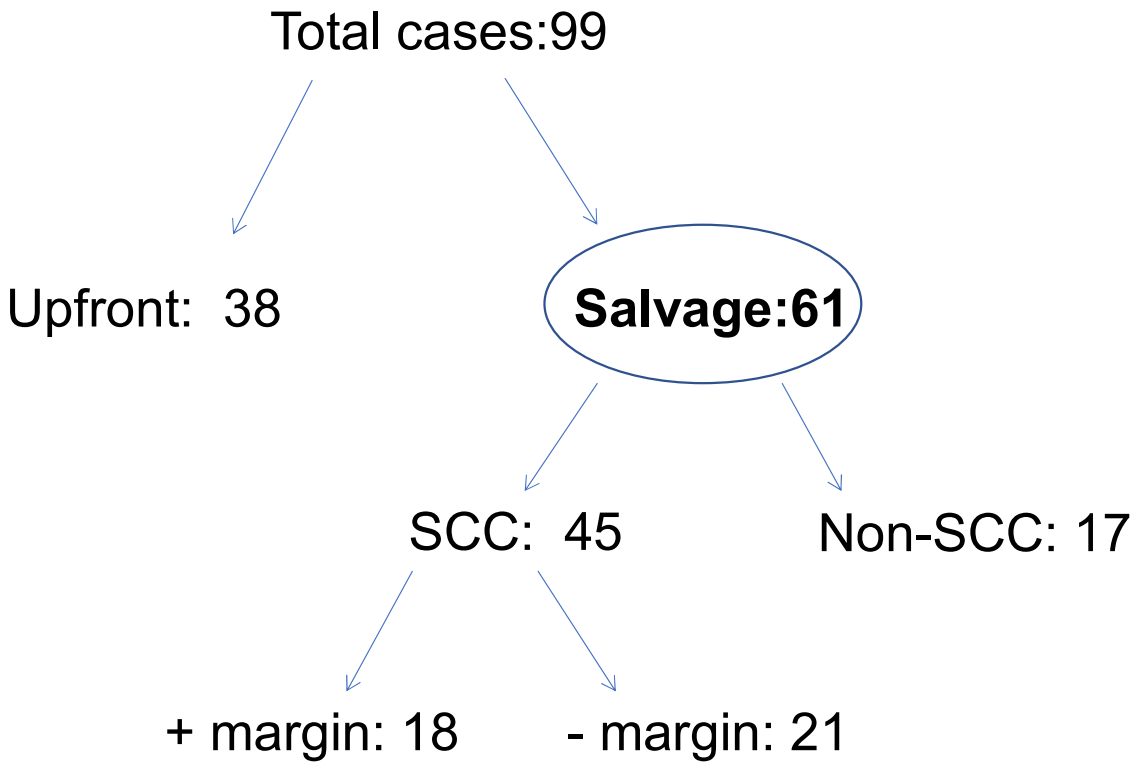
Table 3. Late Toxicity at 1 and 2 Years After Random Assignment

Toxicity	RT Arm (n = 42; 1 missing) No.	RT Arm (n = 42; 1 missing) %	WS Arm (n = 33; 3 missing) No.	WS Arm (n = 33; 3 missing) %
Toxicity at 12 and 12.5 months after random assignment, RTOG grade ≥ 3				
Mucositis	4	10	1	3
Skin	0	0	0	0
Subcutaneous tissues	6	14	3	9
Larynx	0	0	0	0
Osteoradionecrosis	1	2		
Trismus	3	7	2	6
Pharyngeal stenosis	1	2	0	0
No. of patients	11	26	3	9
Toxicity at 24 months after random assignment, RTOG grade ≥ 3*				
Mucositis	1	6	0	0
Skin	1	6	0	0
Subcutaneous tissues	4	22	1	5
Larynx	1	6	0	0
Trismus	5	28	2	10
Osteoradionecrosis	3	17	0	0
Pharyngeal stenosis	1	5.5	0	0
No. of patients	7	39	2	11

Purposes of study

1. Conduct a retrospective review of our clinical outcomes using IORT for recurrent head/neck cancer.
2. Compare our outcomes to historical controls.
3. Determine if surgical margin status, ENE, and other variables have a significant impact on LRC, PFS, and OS.

Case Breakdown at The Ohio State University from 2004-2015



Patient Characteristics

- 55 (90%) had recurrence, 6 (10%) had persistent disease

Age	Median 58 (range 26 – 86)
Gender	
Male	39 (64)
Female	22 (36)
Primary disease site	
Oropharynx	15 (25)
Oral cavity	10 (16)
Sinonasal	10 (16)
Larynx	9 (15)
Salivary	7 (11)
Unknown primary	5 (8)
Skin	3 (5)
Hypopharynx	1 (2)
Neck	1 (2)
IORT treatment site	
Primary	41 (67)
Neck	20 (33)

	n (%)
Histology	
Squamous	45 (74)
Adenoid Cystic	5 (8)
Carcinoma	4 (7)
Sarcoma	3 (5)
Mucoepidermoid	2 (3)
Ex pleomorphic adenoma	1 (2)
Adenocarcinoma	1 (2)
Margins	
Positive	28 (46)
Negative	27 (44)
Unknown	6 (10)
Perineural invasion	
Present	32 (52)
Not present	7 (11)
Unknown	22 (36)
Lymphovascular invasion	
Present	13 (21)
Not present	13 (21)
Unknown	35 (58)

Prior therapy

	n	Details
Surgery	44	Median # of surgeries: 1 Average # of surgeries: 1.8 Range: 1 – 7
EBRT (one course)	54	Median: 66 Gy Range: 25 – 70.2 Gy
EBRT (two courses)	2	72 Gy + 66 Gy 40 Gy + 52 Gy
EBRT + IOERT	2	60 Gy + 15 Gy 50.4 Gy + 10 Gy

IORT Prescriptions

- Median dose was 12.5 Gy (range 10 – 17.5 Gy)

	n (%)
Dose (Gy)	
10	29 (48)
12.5	12 (20)
15	17 (28)
17.5	3 (5)
Energy (MeV)	
6	58 (95)
9	2 (3)
12	1 (2)
Isodose level (%)	
90	59 (97)
100	2 (3)
Bevel diameter (cm)	
3	3 (5)
4	7 (11)
5	20 (33)
6	17 (28)
7	6 (10
8	5 (8)
9	2 (3)
10	1 (2)

Additional treatment

	n	Regimen
No post-op EBRT Post-op EBRT	38 23	N/A Median 45 Gy; Range 25 –56 Gy
No post-op chemo Post-op chemo	52 9	N/A Carboplatin/Paclitaxel (4) Cisplatin (4) Carboplatin (1)

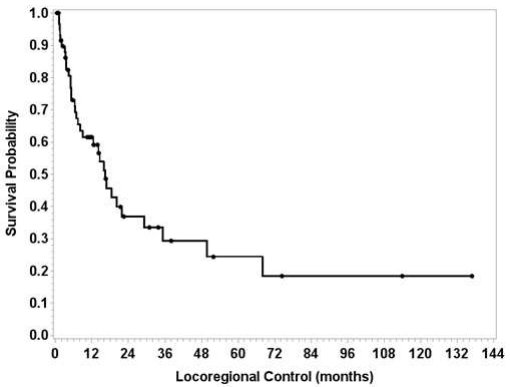
~62 % of patients only had surgery and IORT

Results

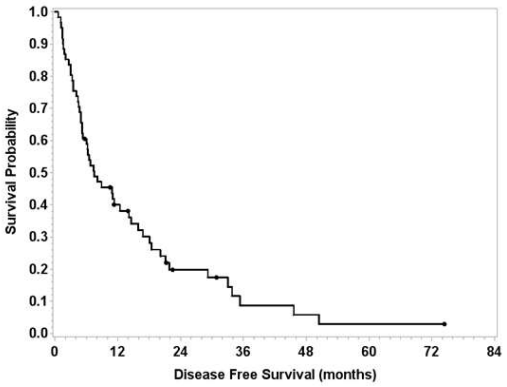
	N	Median LRC (months)	1 yr LRC	Median PFS (months)	1 yr PFS	Median OS (months)	1 yr OS	2 yr OS
All histologies	61	16.6	59%	9.8	39%	19.1	62%	42%
Squamous cell Non-squamous cell	45 16	14.5 18.4 p = 0.30	55%	6.2 18.1 p = 0.09	28%	15.0 37.7 p = 0.03	60%	32%
SCC - Positive margin SCC - Negative margin	18 21	5.2 14.5 p = 0.31	42% 60%	4.5 7.4 p = 0.09	17% 40%	9.6 16.1 p = 0.06	44% 75%	27% 42%
Post-op EBRT No post-op EBRT	23 38	16.8 15.9 p = 0.68		6.5 8.9 p = 0.38		13.1 26.3 p = 0.26		

Salvage – All histologies

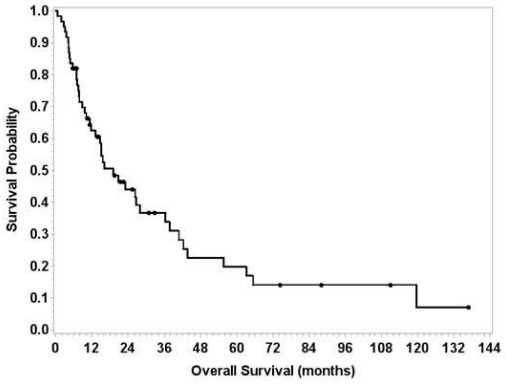
1 y LC 59%



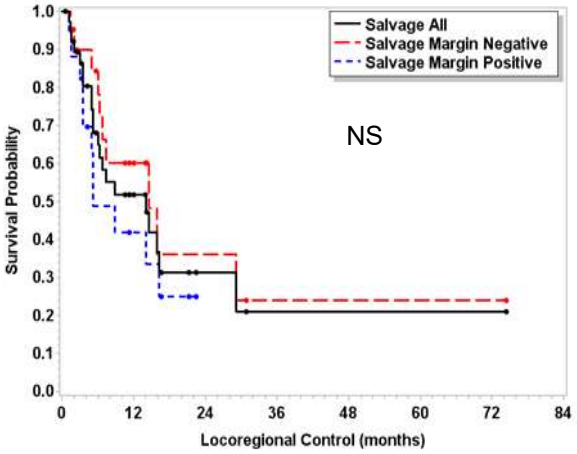
1 y DFS 39%

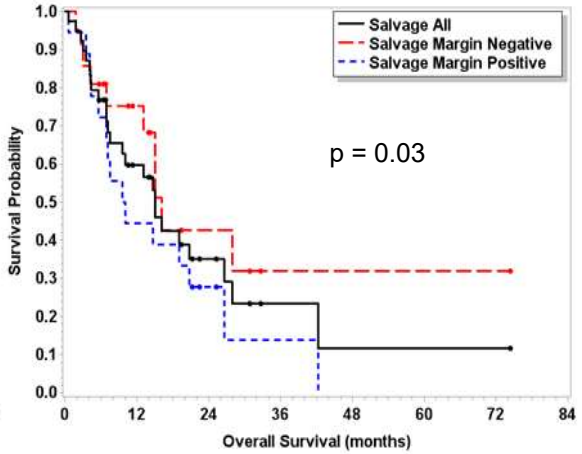


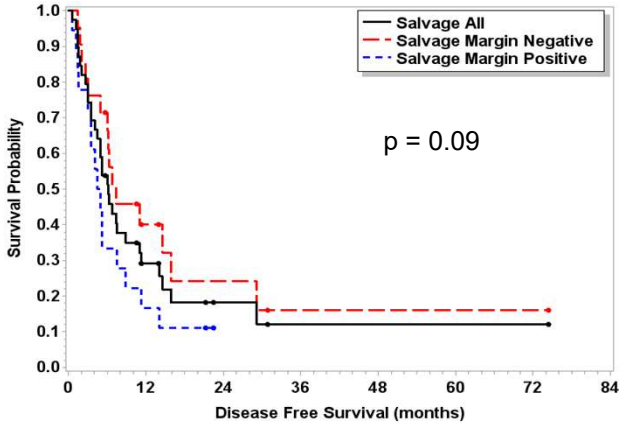
1 y OS 62%
2 y OS 42%



Salvage - SCC


Salvage All
Salvage Margin Negative
Salvage Margin Positive
NS
Survival Probability
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
12
24
36
48
60
72
84
Locoregional Control (months)


Salvage All
Salvage Margin Negative
Salvage Margin Positive
p = 0.03
Survival Probability
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
12
24
36
48
60
72
84
Overall Survival (months)


Salvage All
Salvage Margin Negative
Salvage Margin Positive
p = 0.09
Survival Probability
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
12
24
36
48
60
72
84
Disease Free Survival (months)

Grade 5 toxicity

- Carotid blowout
  - 18 days after surgery
  - Within IORT treatment field
  - Patient had split thickness skin graft placed over carotid at time of surgery

Other significant toxicities

- ORN (2)
- Wound dehiscence (1)
- PC fistula (1)
- TE fistula (1)
- Grade ≥ 3 ~10% ***

Conclusions

- In a population of previously radiated recurrent H&N cancer patients, IORT achieved 1 and 2-year OS rates comparable to the French trial, despite only 38% receiving post-operative RT and 10% receiving post-op chemoRT.
- Advantages of IORT may include decreased toxicity, decrease duration of post-op treatment.

ORIGINAL ARTICLE

Intraoperative electron beam radiotherapy for locoregionally persistent or recurrent head and neck cancer

Patrick Wald MD[1] | John Grecula MD[1] | Steve Walston DO[1] | Lai Wei PhD[2] | Aashish Bhatt MD[3] | Douglas Martin MD[1] | Marcelo Bonomi MD[4] | James Rocco MD[5] | Matthew Old MD[5] | Theodoros Teknos MD[3] | Dukagjin Blakaj MD, PhD[1]

Head & Neck. 2019;1–6. wileyonlinelibrary.com/journal/hed

- Future Directions

- Emerging data is revealing that HNSCC display an enriched immune landscape with key immunological implications.
- Both HPV+ and HPV– HNSCC tumors are found to display among the most prominent immune-infiltrate, with highest levels of CD8+ T cells and activated NK cells, paralleled by a marked expression of regulatory pathways in-cluding regulatory T cells (Treg) and related immune checkpoints like CTLA-4, GITR, ICOS, IDO, KIR, TIGIT, 4-1BB and VEGFA, in addition to PD-1.
- HNSCC has strong immunogenic features needing comparable immunosuppressive pressure to be nullified in most progressing patients.
- Can we provide new antigens with radiation therapy or 'jump start' the immune system in the recurrent/persistent H&N cancer patients?
- Radiation therapy may increase the capability of the immune system to exert its function through an increase in tumor neoantigens, due to the mutagenic activity of radiation, boost in antigen presentation, enhanced killing by CD8+ T-cells and improved cytokines production triggering a acute proinflamatory cascade. Irradiation induces upregulation of PD-L1,which could reduce the immune response of effector T-cells but at the same time potentiate the activity of PD-1 blockers.

Mandal R, et al. The head and neck cancer immune landscape and its immunotherapeutic implications. JCI Insight 1(17).
Cavaleri S, et al. Immuno-Oncology in head and neck squamous cell cancers: News from clinical trials, emerging predictive factors and unmet needs. Cancer treatment reviews 2018

Oral Oncology 110 (2020) 104900

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

A predictive survival model for patients with head and neck squamous cell carcinoma treated with immune check point inhibitors

M. Bonomi[a,*,1], P. Bhateja[a,1], M. Issa[a], B. Klamer[b], X. Pan[b], A. Blakaj[c], V. Karivedu[a], L. Mousa[a], D. Mitchell[e], M Gamez[e], S. Kang[d], N. Siem[d], M. Old[d], R. Carrau[d], J. Rocco[d], D. Blakaj[e]

Issa et al. BMC Cancer (2022) 22:767
https://doi.org/10.1186/s12885-022-09809-5

BMC Cancer

RESEARCH Open Access

Update of a prognostic survival model in head and neck squamous cell carcinoma patients treated with immune checkpoint inhibitors using an expansion cohort

Majd Issa[1*], Brett G. Klamer[2], Nikol Mladkova[3], Georgios I. Laliotis[4], Vidhya Karivedu[1], Priyanka Bhateja[1], Chase Byington[1], Khaled Dibs[3], Xueliang Pan[2], Arnab Chakravarti[3], John Grecula[3], Sachin R. Jhawar[3], Darrion Mitchell[3], Sujith Baliga[3], Matthew Old[5], Ricardo L. Carrau[5], James W. Rocco[5], Dukagjin M. Blakaj[3†] and Marcelo Bonomi[1†]

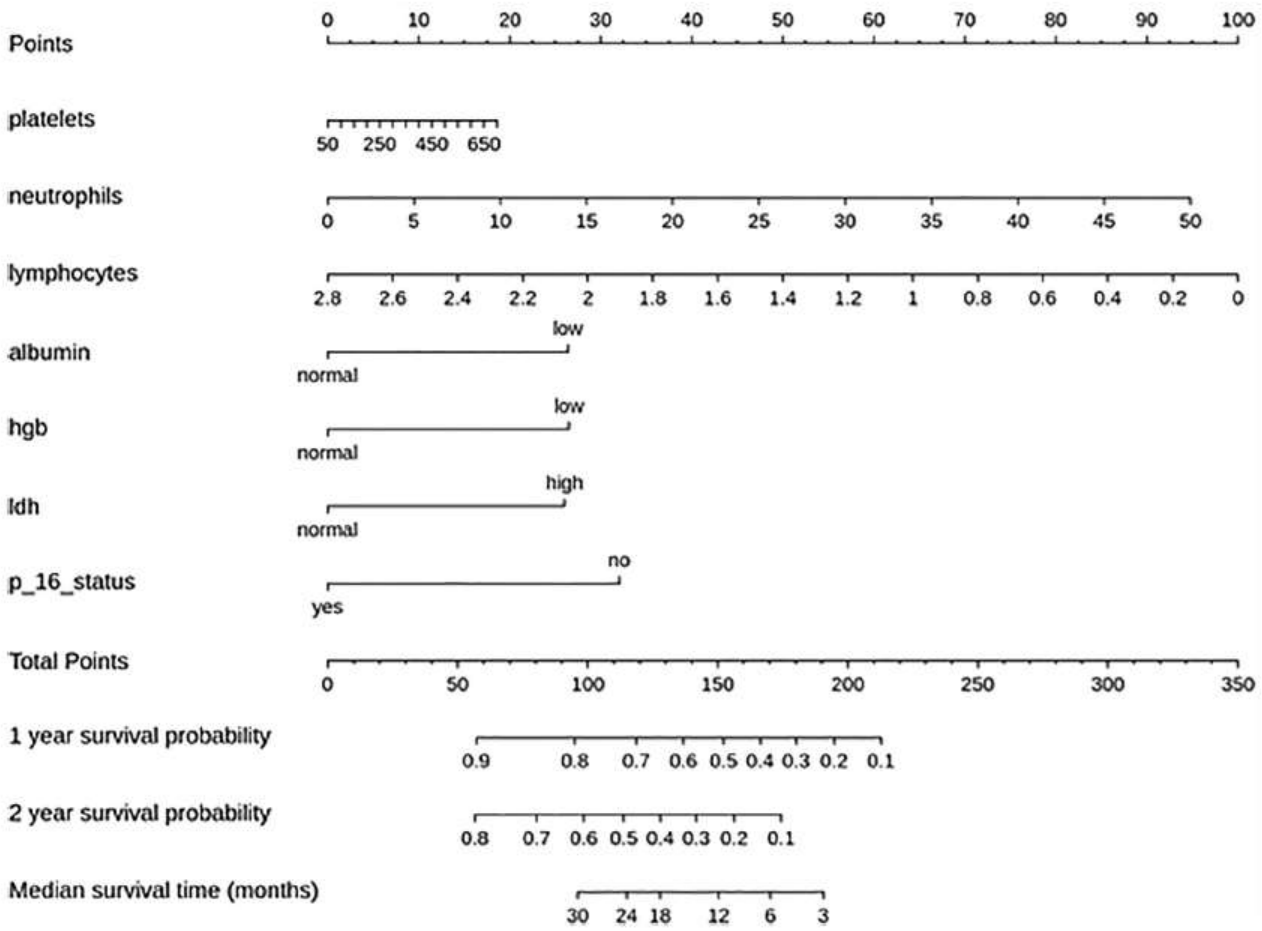
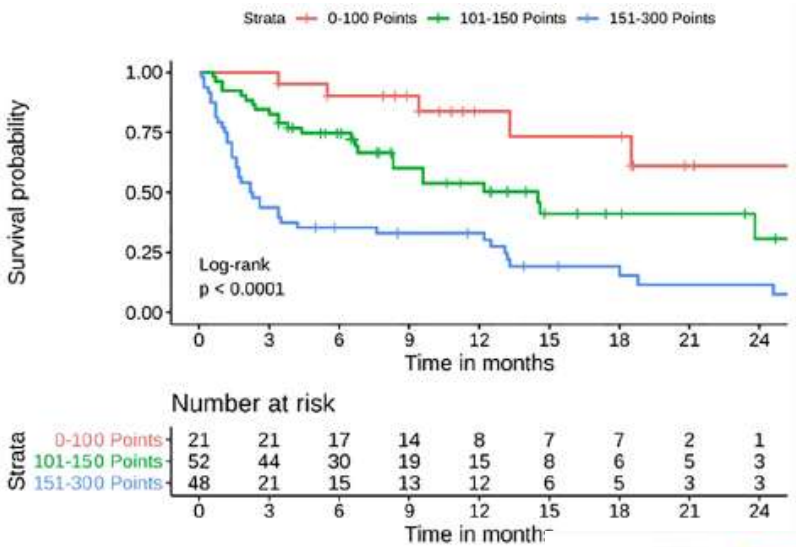
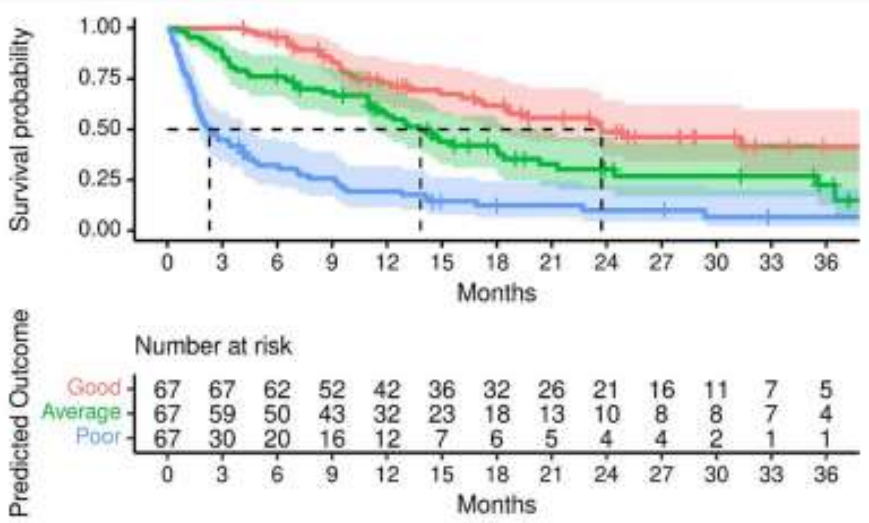


Fig. 1. Nomogram of overall survival. Age and Sex were removed with no effect on interpretation.



- IO Toxicity prediction Nomogram coming
- 350K grant from Tempus for WES/RNAseq samples
- Goal - Update Nomogram with molecular information

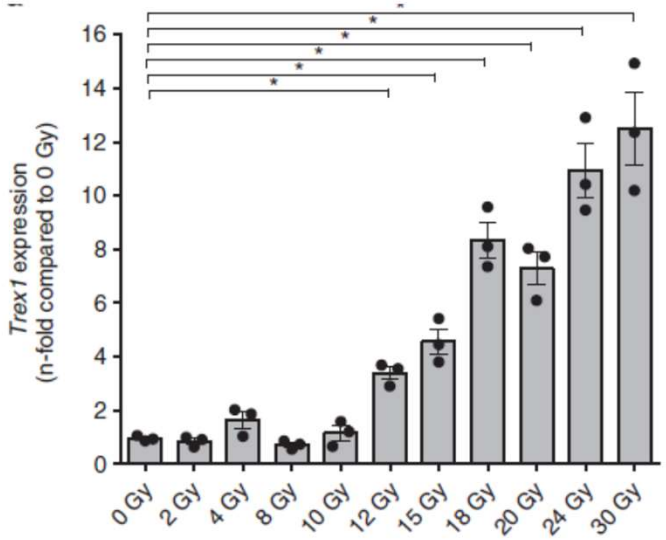


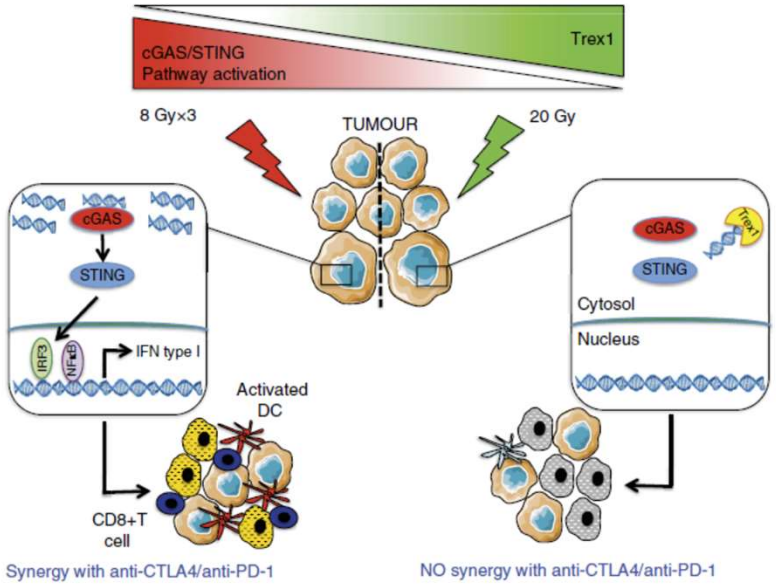
Received 27 Mar 2017 | Accepted 12 Apr 2017 | Published 9 Jun 2017

DOI: 10.1038/ncomms15618 OPEN

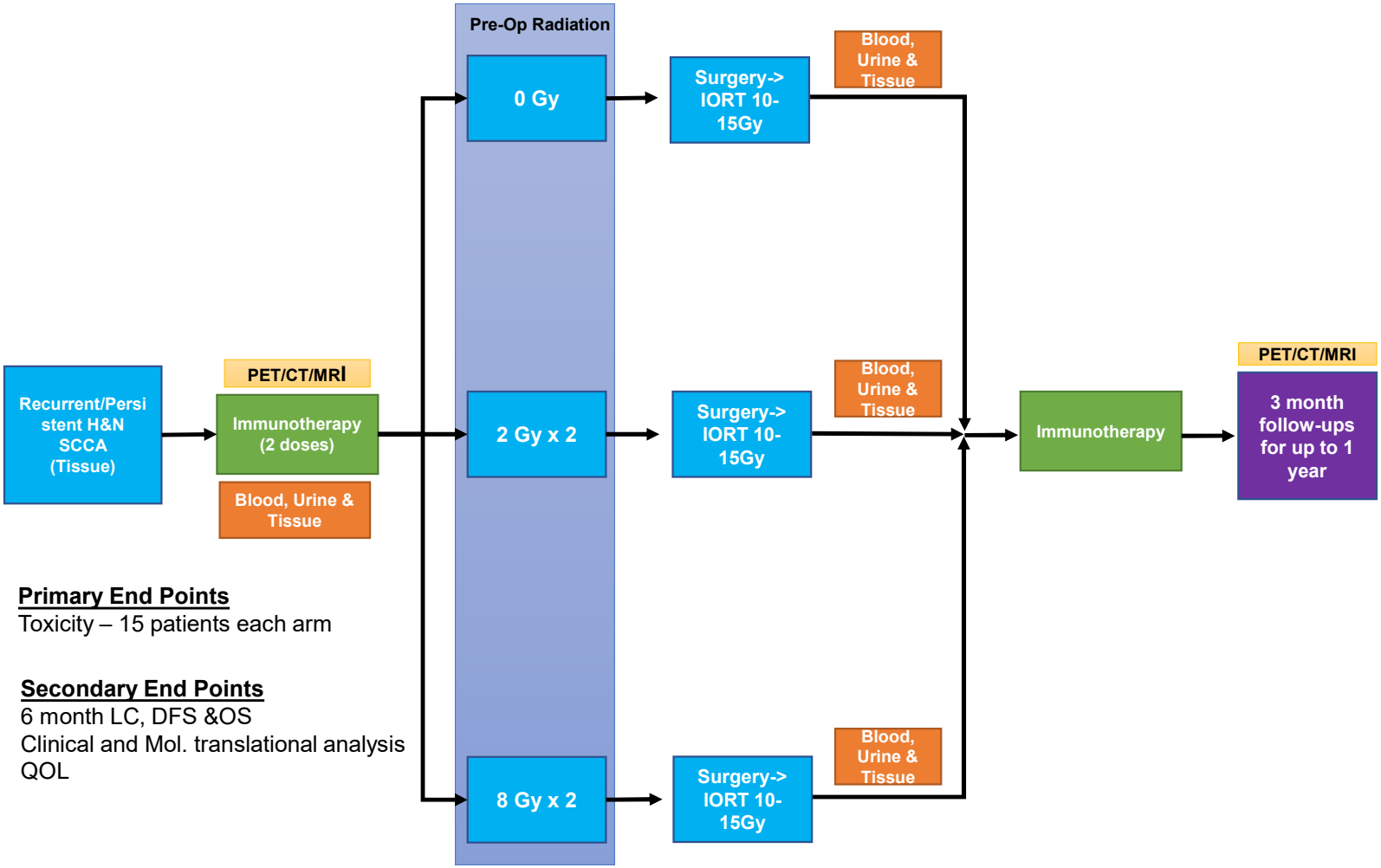
DNA exonuclease Trex1 regulates radiotherapy-induced tumour immunogenicity

Claire Vanpouille-Box[1], Amandine Alard[2,†], Molykutty J. Aryankalayil[3], Yasmeen Sarfraz[1], Julie M. Diamond[1], Robert J. Schneider[2], Giorgio Inghirami[4], C. Norman Coleman[3], Silvia C. Formenti[1] & Sandra Demaria[1,4]





HNSALV Trial



Primary End Points

Toxicity – 15 patients each arm

Secondary End Points

6 month LC, DFS &OS

Clinical and Mol. translational analysis

QOL

Some descriptive data till now

- 18 patients recruited…3 in 2022, 4 in 2023, and 11 in 2024.
- 5 arm A, 5 arm B, 5 arm C, and 3 pending randomization.
- OPC, OC, Lx.
- 3 completed the 1-year IO, and FU: NED. 3 Expired with OS Range 9-14 months for these 3 patients
- Aim is to recruit 45 patients.

Acknowledgments

- Arnab Chakravarti MD
- John Grecula MD
- Mauricio Gamez MD
- Patrick Wald MD
- Nikol Mladkova MD PhD
- Marcelo Bonomi MD
- James Rocco MD PhD
- Matt Old MD
- Enver Ozer MD
- Amit Agrawal MD
- Steven Kang MD
- Ricardo Carrau MD
- Nolan Seim MD
- Kyle VanKoevering MD

THANK YOU!