Hyperthermia and Immunology

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ESIO-Congress, Gottlieb Duttweiler Institut

Immunotherapy and integrative Oncology

April 3, 2025. Rüschlikon/Zurich

Clinically established hyperthermia devices

Radiofrequency-based and recirculation instruments for different entities

Local RF-HT

- Head and neck
- Breast

Deep RF-HT

Allowance of deep regional heating

- Abdominal
- Pelvic
- Extremity malignancies

➔ In use for **STS treatment**

Pyrexar MEDICAL

ALBA precision hyperthermia

Bladder HT

- RF-HT
- Recirculation devices

SYNERGO®

COMBAT MEDICAL

Head & neck HT

- under development

Sensius balanced treatment

High-intensity focused ultrasound (HIFU)

HIFU-based HT

PROFOUND MEDICAL ⊕ PHILIPS

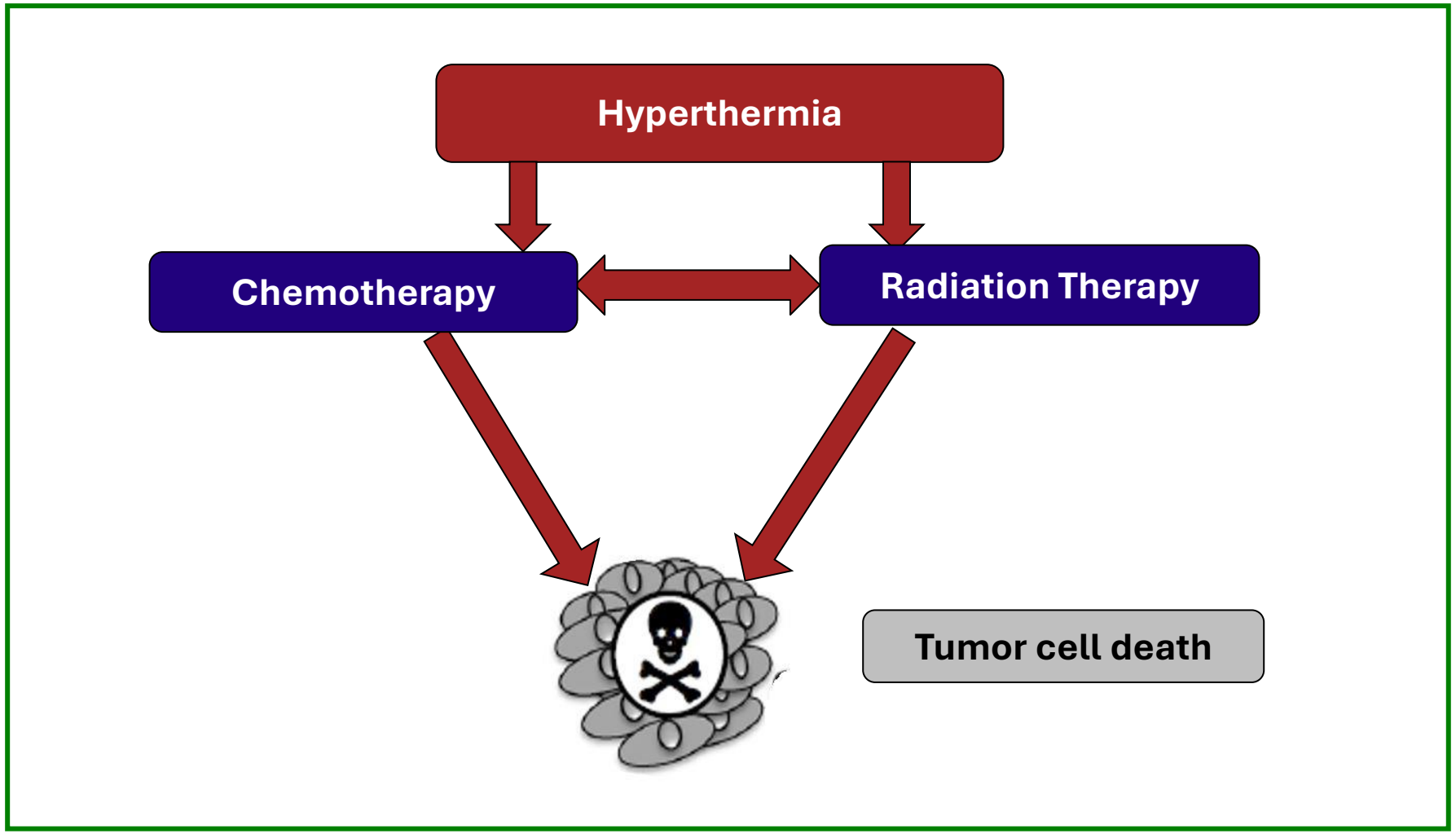
INSIGHTEC ⊕ GE

Haifu

RF: radiofrequency; HT: hyperthermia

“The old story”

Hyperthermia complements standard cancer treatment such as chemotherapy and radiation therapy in destroying tumor cell



Achievements in the clinical application of regional hyperthermia

LMU KLINIKUM

01	**Melanoma[1]:** Improved local tumor control for RT + HT	THE LANCET
02	**Cervical Cancer[2]:** Improved survival for RT + HT	THE LANCET
03	**Chest wall recurrence of breast cancer[3]:** Improved local tumor control for RT + HT	JOURNAL OF CLINICAL ONCOLOGY
04	**Soft Tissue Sarcoma[4,5,6]:** Improved survival for anthracycline-based CTX + HT, Improved immune infiltrate	THE LANCET Oncology; JAMA Oncology; EJC EUROPEAN JOURNAL OF CANCER
05	**Non-testicular malignant germ-cell tumours[7]:** Platinum-based CTX + HT leads to long-term cure	THE LANCET Oncology

[1]Overgaard et al. Lancet. 1995; [2]van der Zee et al. Lancet. 2000; [3]Jones et al. J Clin Oncol 2005;
[4,5,6] Issels et al. Lancet Oncology 2010, JAMA Oncology 2018, Eur J Cancer 2021; Eur J Cancer [4]Wessalowski et al. Lancet Oncol. 2013

The Evidenz:

High-Risk Soft Tissue Sarcoma

Median: 3-year follow-up

Neo-adjuvant chemotherapy alone or with regional hyperthermia for localised high-risk soft-tissue sarcoma: a randomised phase 3 multicentre study

Rolf D Issels, Lars H Lindner*, Jaap Verweij, Peter Wust, Peter Reichardt, Baard-Christian Schem, Sultan Abdel-Rahman, Soeren Daugaard, Christoph Salat, Clemens-Martin Wendtner, Zeljko Vujaskovic, Rüdiger Wessalowski, Karl-Walter Jauch, Hans Roland Dürr, Ferdinand Ploner, Andrea Baur-Melnyk, Ulrich Mansmann, Wolfgang Hiddemann, Jean-Yves Blay, Peter Hohenberger, for the European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group (EORTC-STBSG) and the European Society for Hyperthermic Oncology (ESHO)*

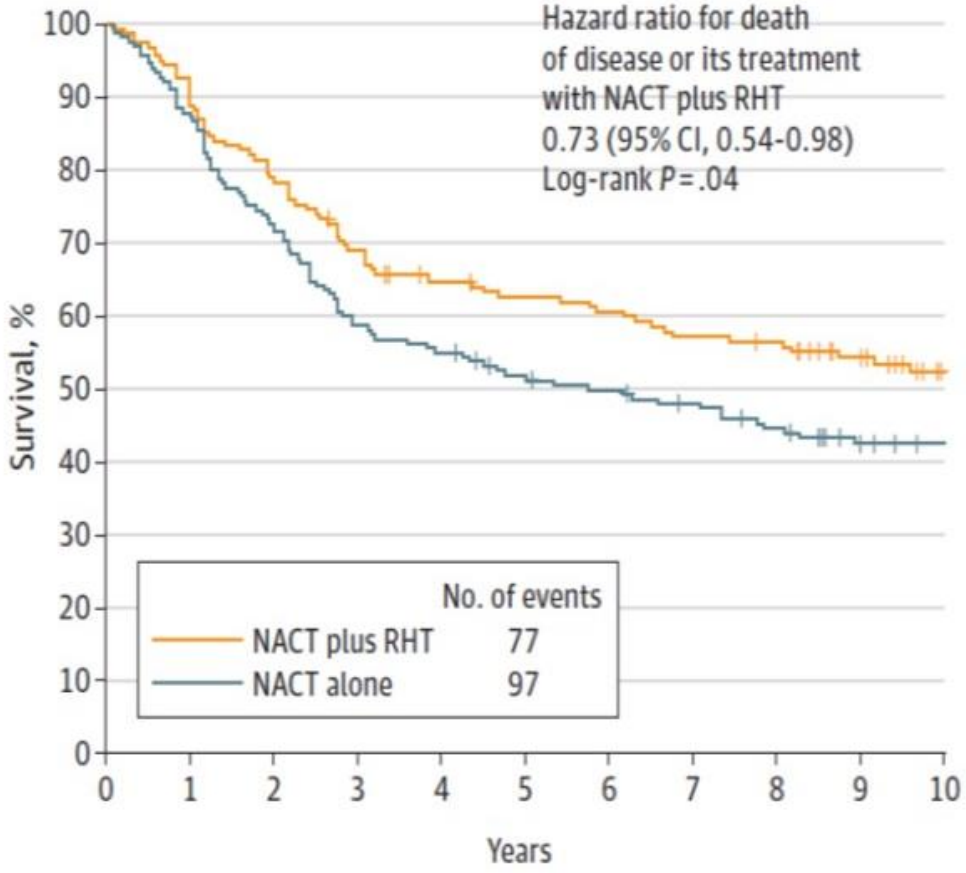
Median: 11.3-year follow-up

Neoadjuvant Chemotherapy Plus Regional Hyperthermia and Long-term Outcomes Among Patients With Localized High-Risk Soft Tissue Sarcoma

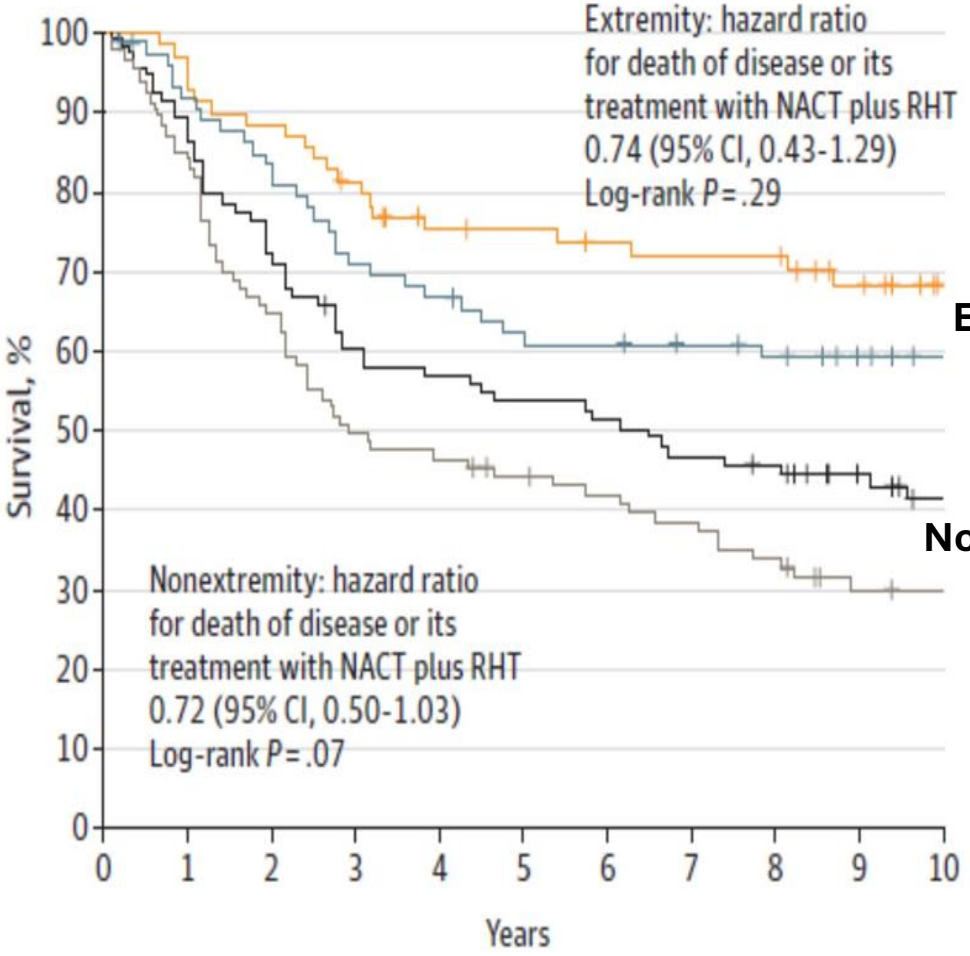
The EORTC 62961-ESHO 95 Randomized Clinical Trial

Rolf D. Issels, MD, PhD; Lars H. Lindner, MD; Jaap Verweij, MD; Rüdiger Wessalowski, MD; Peter Reichardt, MD; Peter Wust, MD; Pirus Ghadjar, MD; Peter Hohenberger, MD; Martin Angele, MD; Christoph Salat, MD; Zeljko Vujaskovic, MD; Soeren Daugaard, MD; Olav Mella, MD; Ulrich Mansmann, MD; Hans Roland Dürr, MD; Thomas Knösel, MD; Sultan Abdel-Rahman, PhSc; Michael Schmidt, MD; Wolfgang Hiddemann, MD; Karl-Walter Jauch, MD; Claus Belka, MD; Alessandro Gronchi, MD;
For the European Organization for the Research and Treatment of Cancer-Soft Tissue and Bone Sarcoma Group and the European Society for Hyperthermic Oncology

High-Risk Soft Tissue Sarcoma



No. at risk											
NACT plus RHT	162	150	128	110	98	94	89	84	82	68	54
NACT alone	167	145	118	96	90	82	78	73	67	56	51



Extremity

Non-Extremity

Adult Soft Tissue Sarcoma

Consensus recommendation

S3-Guideline: June 2022

5.79.	Evidenzbasierte Empfehlung
Empfehlungsgrad **A**	*Neoadjuvant chemotherapy for patients with soft tissue sarcomas of the pelvis, abdomen and extremities should/can be combined with deep hyperthermia*

Question:

How can the addition of regional hyperthermia to systemic chemotherapy lead in responding patients to a long-term survival of a disease that usually causes lethality by distant metastases?

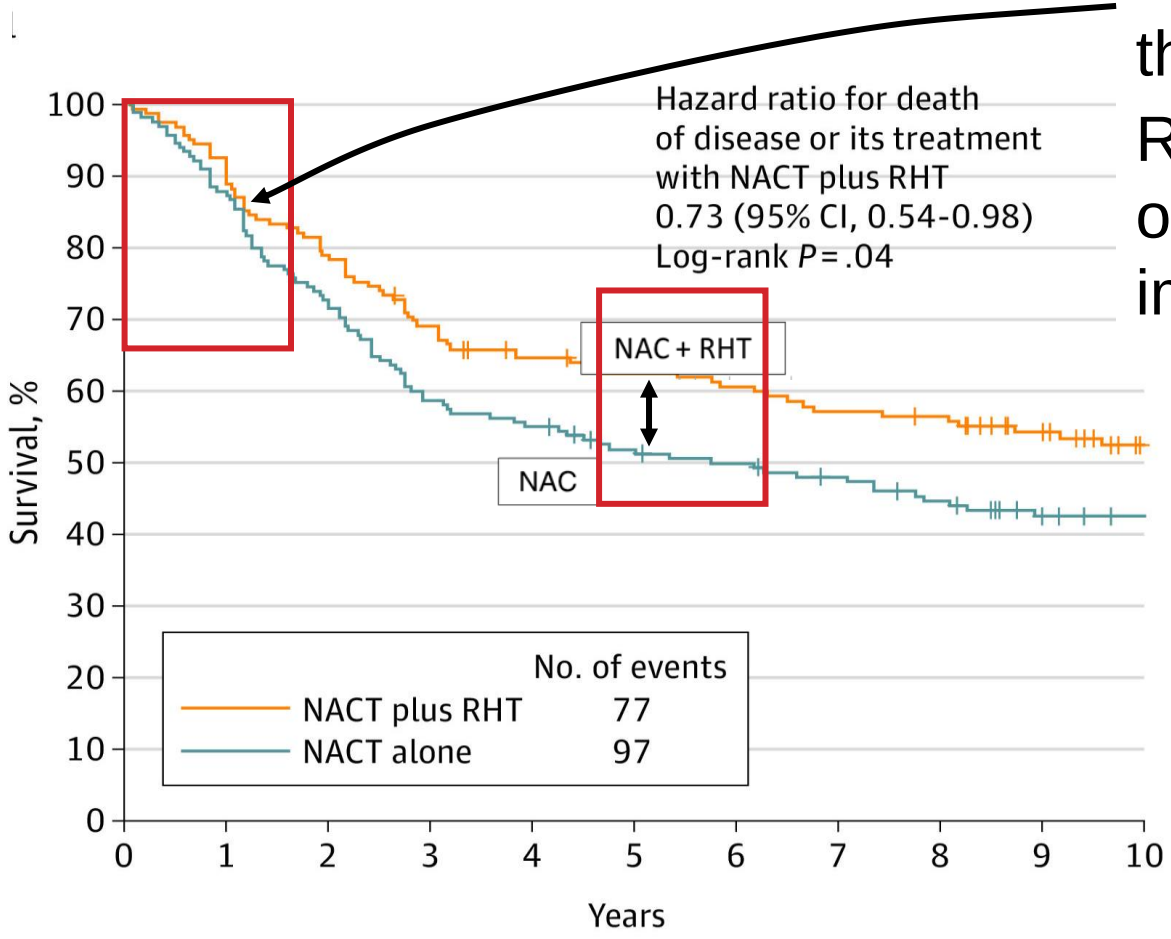
Hypothesis:

Identify features associated with long-term survival achieved through the addition of regional hyperthermia to neo-adjuvant chemotherapy.

Neo-adjuvant Chemotherapy plus Regional Hyperthermia for Localized High-risk Soft-tissue Sarcoma (EORTC 62961)

Late divergence of the survival curves:

Resembling observations in immunotherapy trials

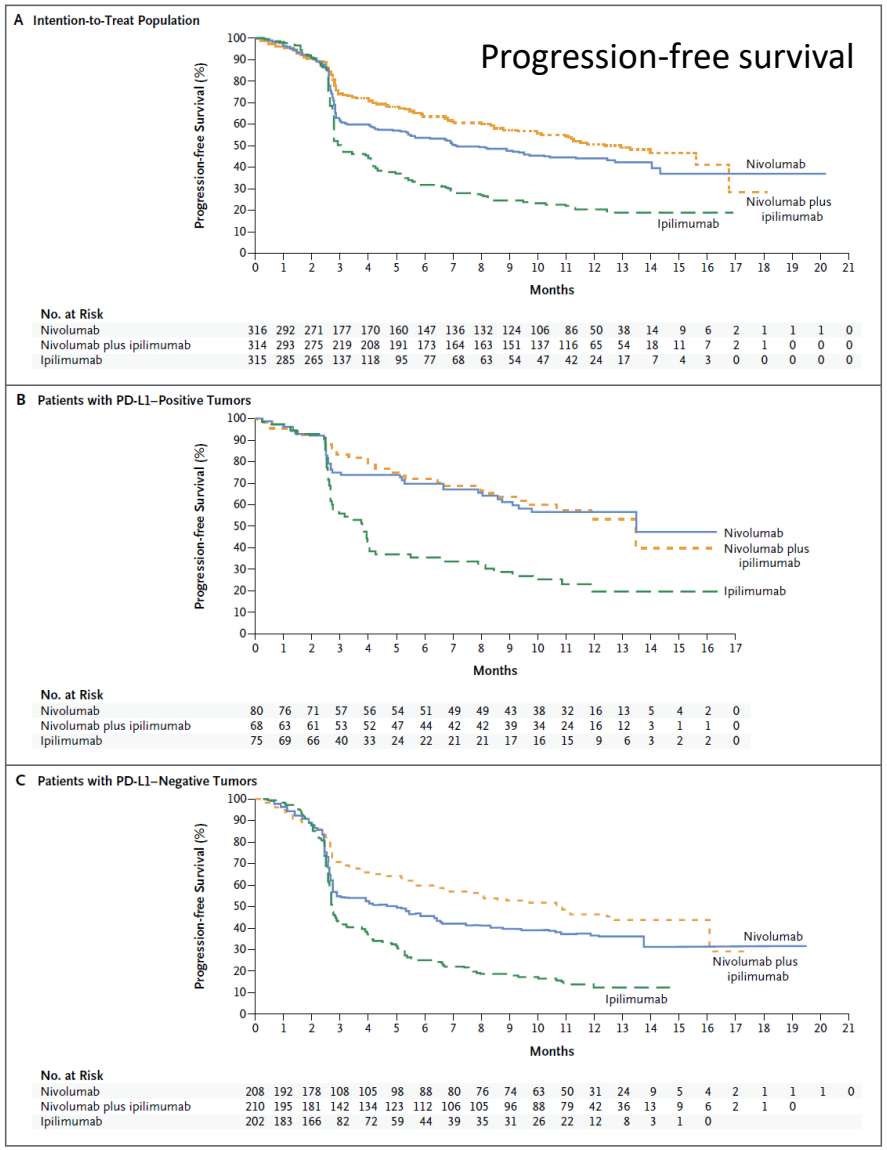


No. at risk

NACT plus RHT	162	150	128	110	98	94	89	84	82	68	54
NACT alone	167	145	118	96	90	82	78	73	67	56	51

Checkpoint inhibitors: Nivolumab and Ipilimumab vs Ipilimumab

Late divergence of survival curves



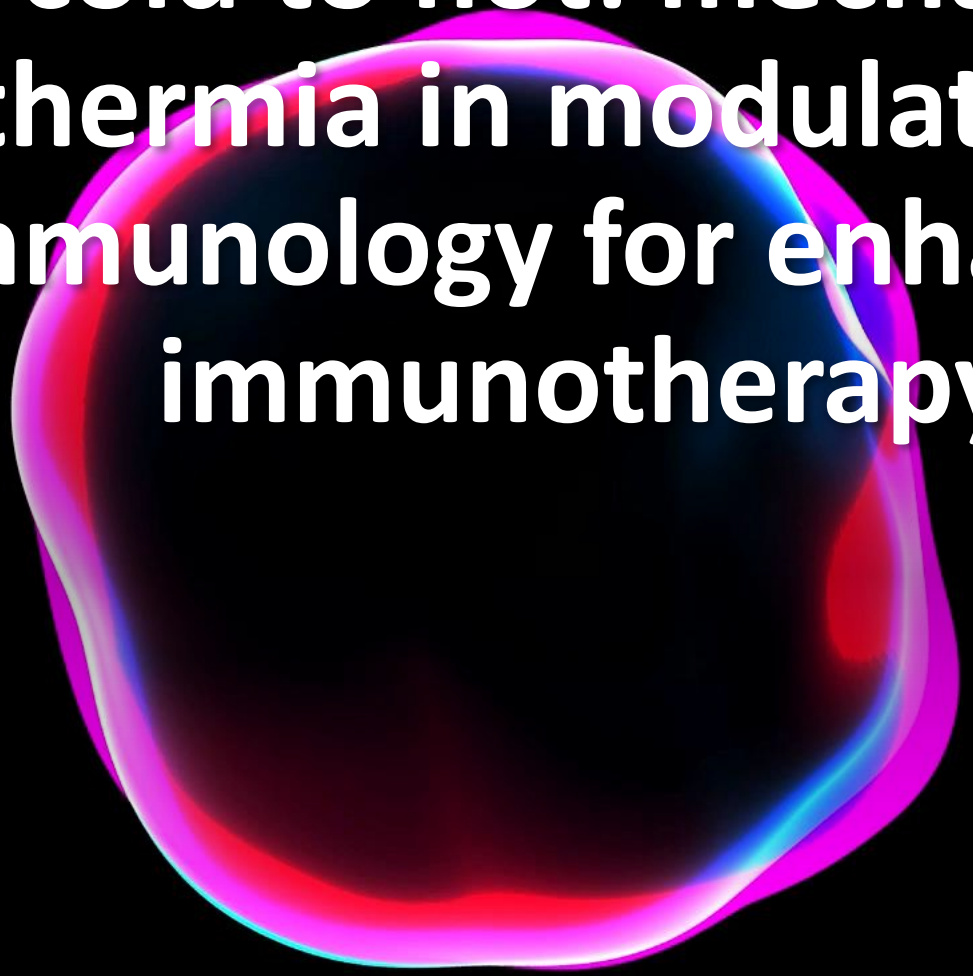
ORIGINAL ARTICLE

Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma

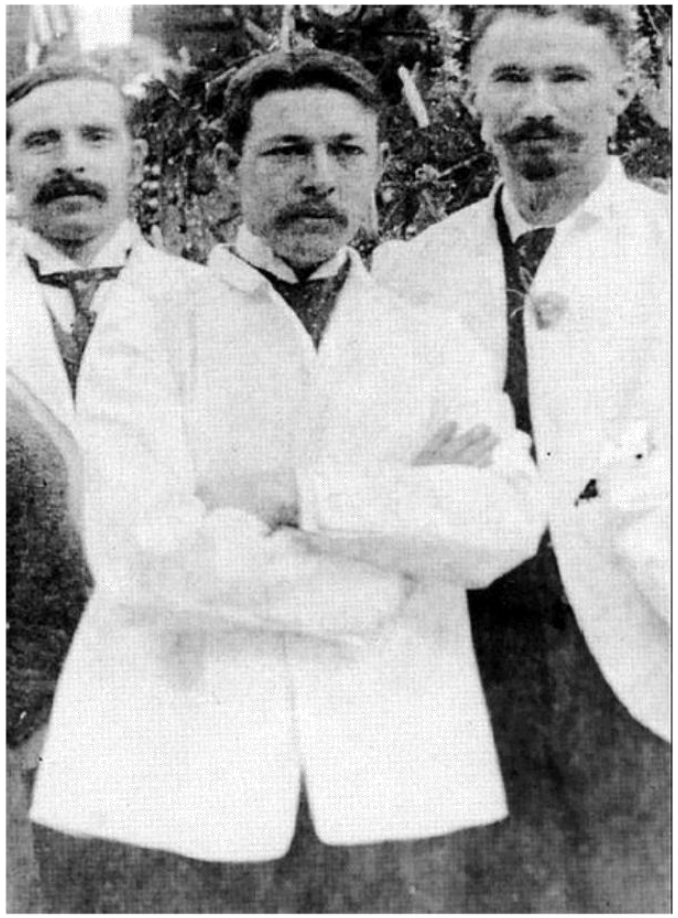
J. Larkin, V. Chiarion-Sileni, R. Gonzalez, J.J. Grob, C.L. Cowey, C.D. Lao, D. Schadendorf, R. Dummer, M. Smylie, P. Rutkowski, P.F. Ferrucci, A. Hill, J. Wagstaff, M.S. Carlino, J.B. Haanen, M. Maio, I. Marquez-Rodas, G.A. McArthur, P.A. Ascierto, G.V. Long, M.K. Callahan, M.A. Postow, K. Grossmann, M. Sznol, B. Dreno, L. Bastholt, A. Yang, L.M. Rollin, C. Horak, F.S. Hodi, and J.D. Wolchok

N.E.J.M. (2015)

From cold to hot: mechanisms of hyperthermia in modulating tumor immunology for enhanced immunotherapy



Bacterial immunotherapy for the treatment of cancer – William Coley and the birth of cancer immunotherapy



New York Times - July 29, 1908

ERYSIPELAS GERMS AS CURE FOR CANCER

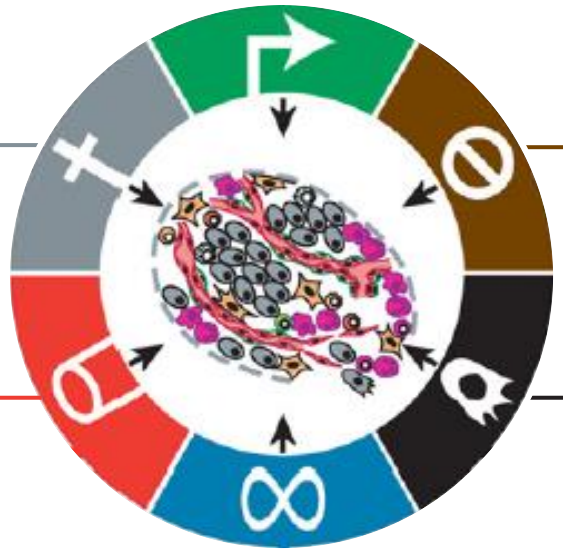
Dr. Coley's Remedy of Mixed Toxins Makes One Disease Cast Out the Other.

MANY CASES CURED HERE

Physician Has Used the Cure for 15 Years and Treated 430 Cases— Probably 150 Sure Cures.

Following news from St. Louis that two men have been cured of cancer in the City Hospital there by the use of a fluid discovered by Dr. William B. Coley of New York, it came out yester-

Hallmarks of Hyperthermia (40°C - 43°C)



01 **Sensitization to chemotherapy**

02 Changing tumor microenvironment

03 Evading DNA repair

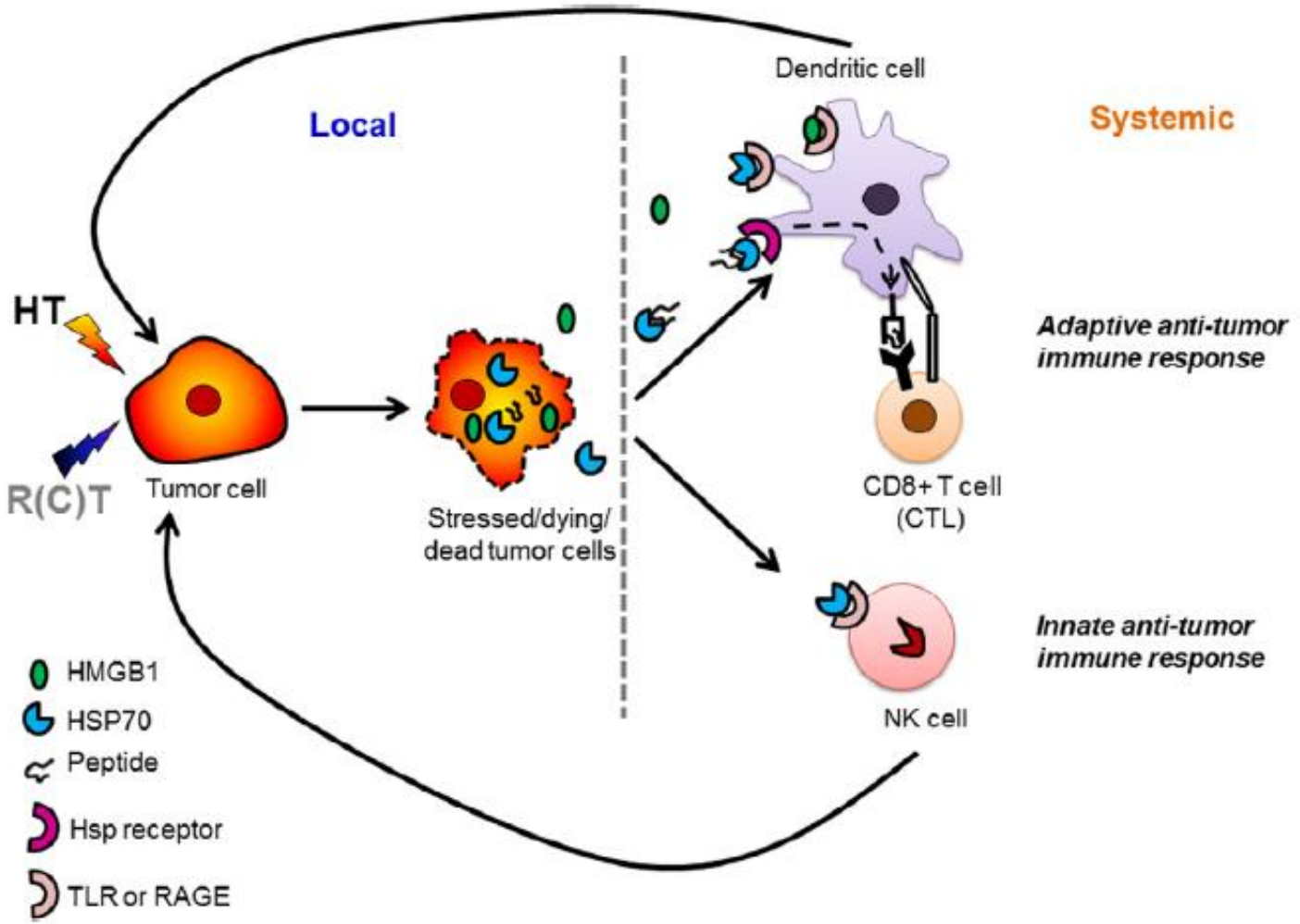
04 Modulating immune response

05 Inducing cellular stress response

06 Blocking cell survival

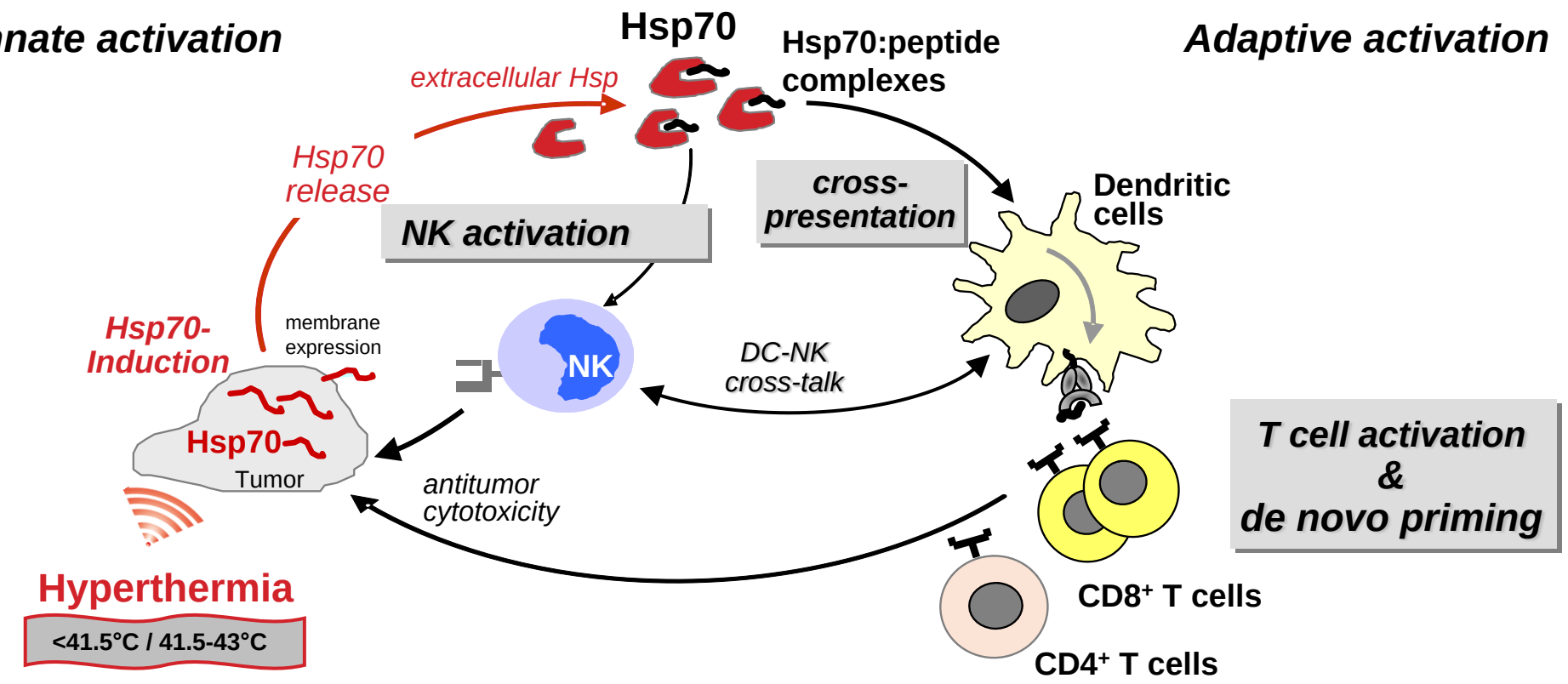
Issels R et al. Int J Hyperthermia 2016

“The new story”
Immunological anti-tumor modes of action



N.R. Datta et al./ Cancer Treatment Reviews 41 (2015)

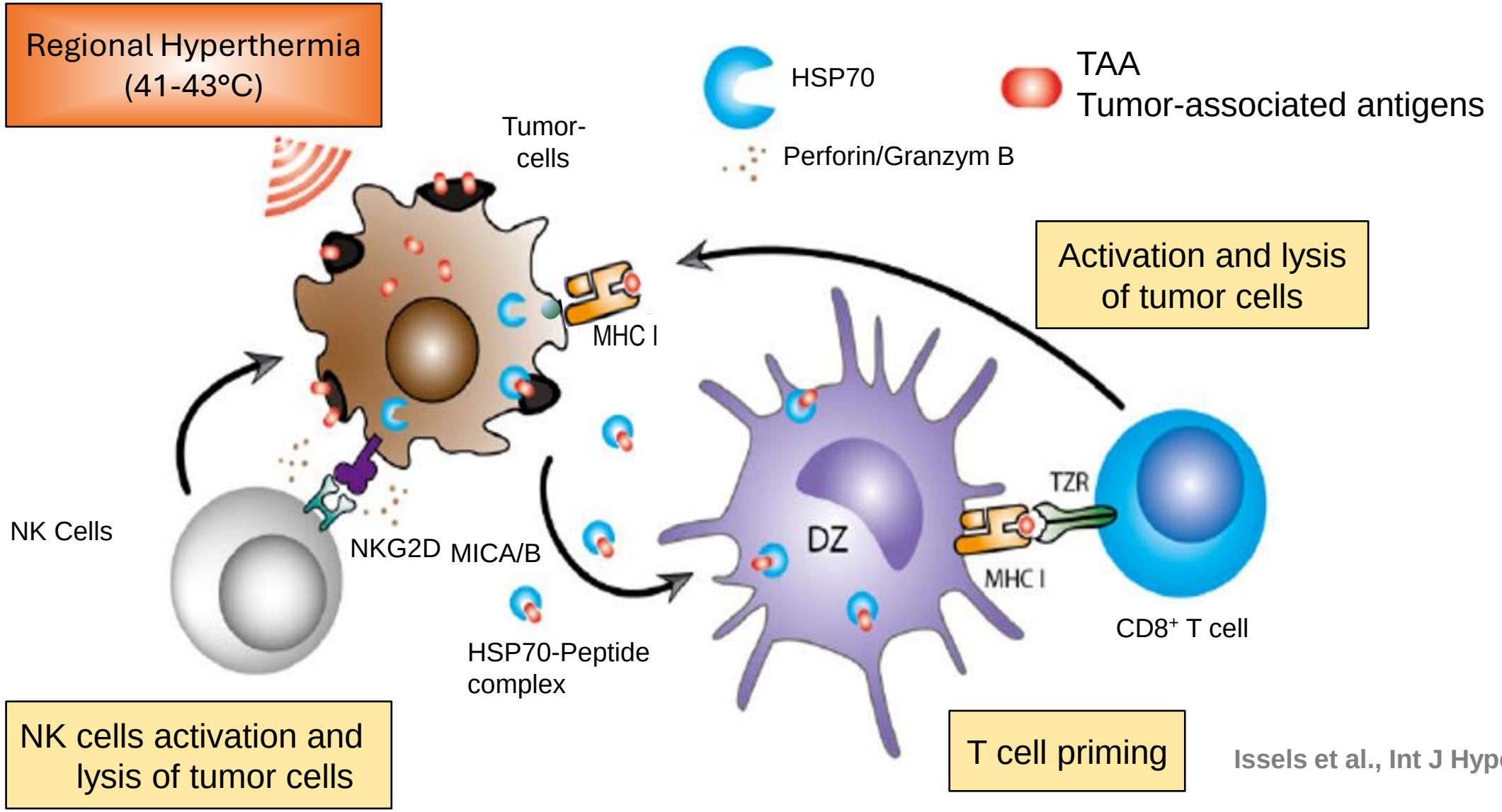
Evidence from preclinical models



Multhoff et al., J Immunol. 1997
Gross et al., Biol Chem 2003
Gastpar et al., J Immunol. 2004

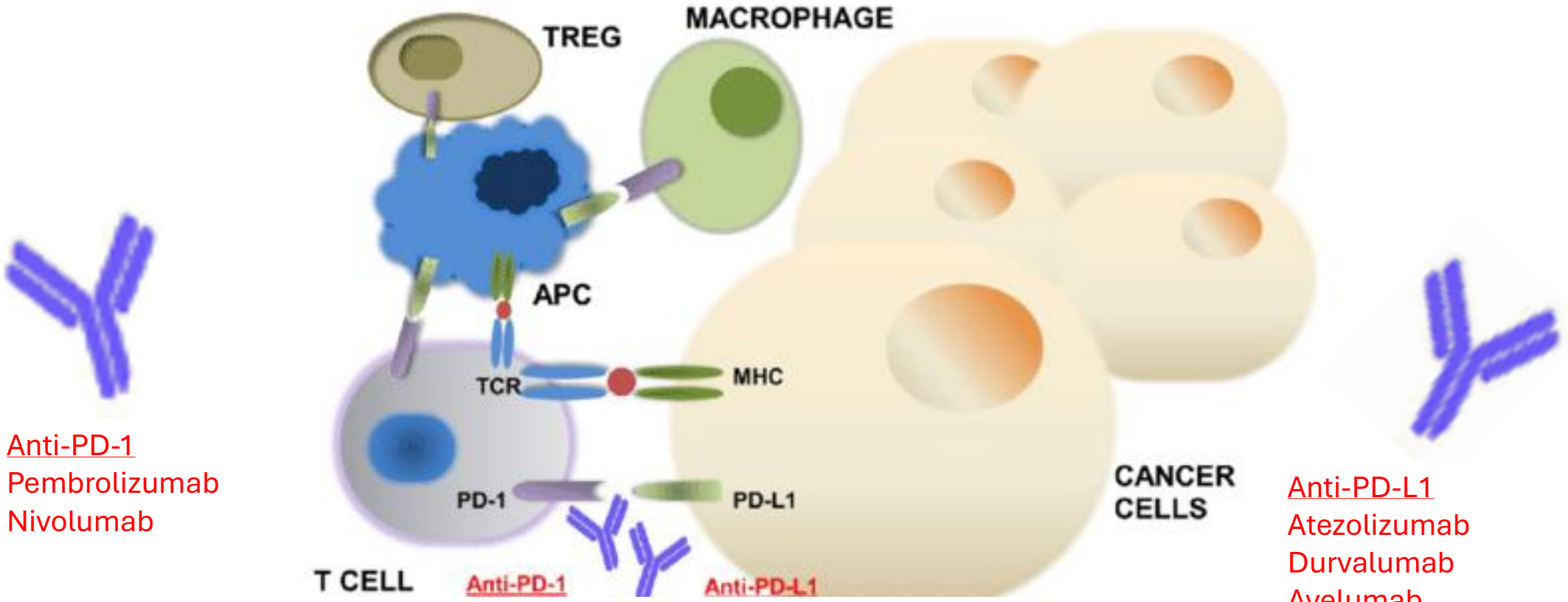
Bendz et al., J Biol Chem. 2007
Pandya et al., Biol. Chem 2009
Jolesch et al., Eur. J Cell Biol 2012
Noessner et al., J Immunol. 2002

Hyperthermia induced activation of Natural Killer (NK) and cytotoxic T cells (CD8)



Issels et al., Int J Hyperthermia 2020

Checkpoint blockade at the tumor site depends on the infiltration of immune cells



Anti-PD-1
Pembrolizumab
Nivolumab

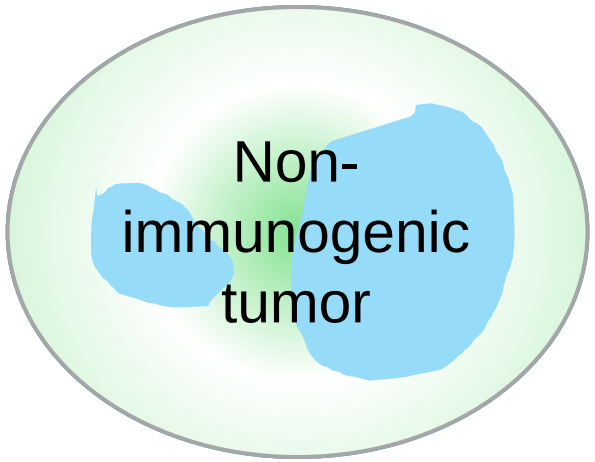
Anti-PD-L1
Atezolizumab
Durvalumab
Avelumab

PD-L1: Programmed death receptor ligand
PD-1: Programmed death receptor
TREG: FOXP3 regulatory T cells
APC: Antigen presenting cells

Question: *Does regional hyperthermia in addition to standard chemotherapy change tumor immune infiltrate ?*

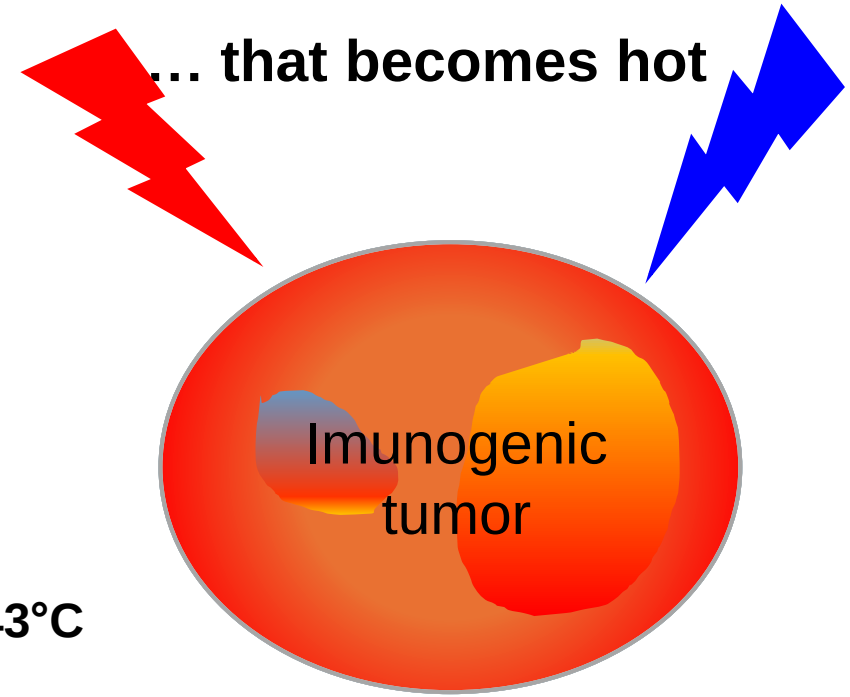
Combination therapy applied to

a cold tumor …



37°C

… that becomes hot



40 – 43°C

Immune infiltrates: translational research program of the EORTC 62961/ESHO RHT 95 randomised clinical trial

Induction treatment

European Journal of Cancer 158 (2021) 123–132

Available online at www.sciencedirect.com

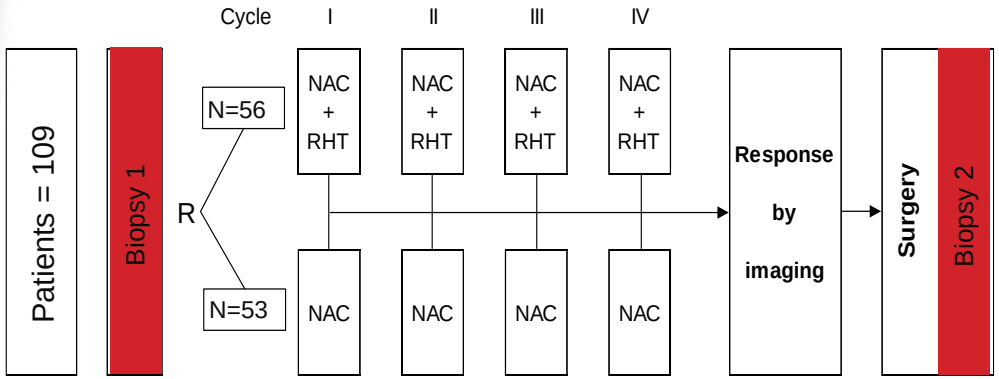
ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Immune infiltrates in patients with localised high-risk soft tissue sarcoma treated with neoadjuvant chemotherapy without or with regional hyperthermia: A translational research program of the EORTC 62961-ESHO 95 randomised clinical trial

Rolf D. Issels [a,*,1], Elfriede Noessner [b,1], Lars H. Lindner [a], Michael Schmidt [c], Markus Albertsmeier [d], Jean-Yves Blay [e], Emanuel Stutz [f], Yujun Xu [g], Veit Buecklein [a], Annelore Altendorf-Hofmann [h], Sultan Abdel-Rahman [a], Ulrich Mansmann [g], Michael von Bergwelt-Baildon [i], Thomas Knoesel [j]



Analysis of immune infiltrates

Subgroup Analysis of the EORTC 62961 - ESHO 95 study

N = 109

- 84 pre-treatment biopsies
- 53 post treatment biopsies
- 28 paired biopsies

TMAs for TILs, CD8, FOXP3, PD-1, PDL-1

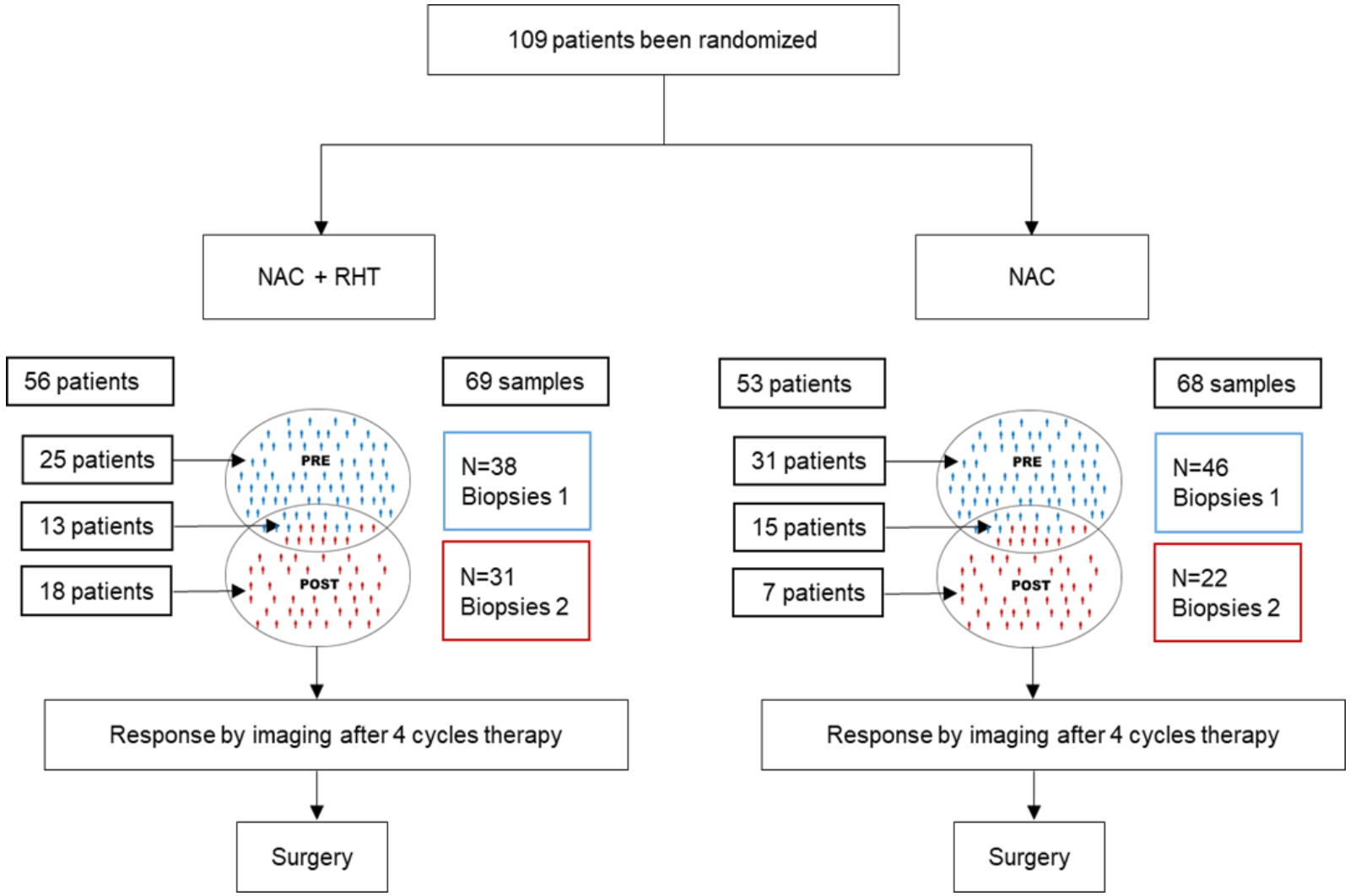
Score:

TILs

- High: > 5 cells / HPF
- Low: ≤ 5 cells / HPF

CD8

- High: ≥ 10 cells / HPF
- Low: < 10 cells / HPF

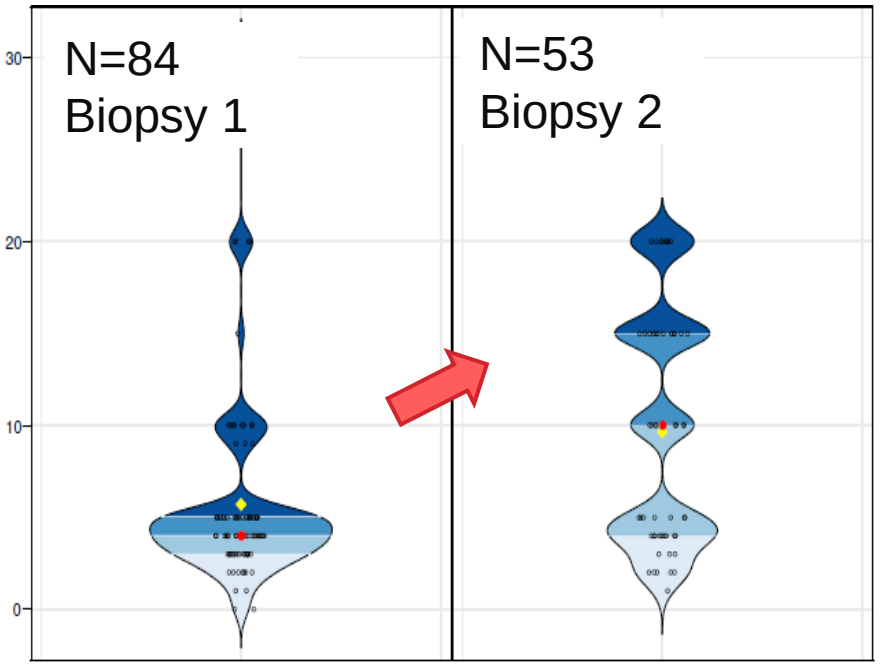


Issels R, Noessner E, Lindner L et al. Eur J Cancer 2021

Change of Immune Infiltrate Pre- to Post-Treatment Biopsies

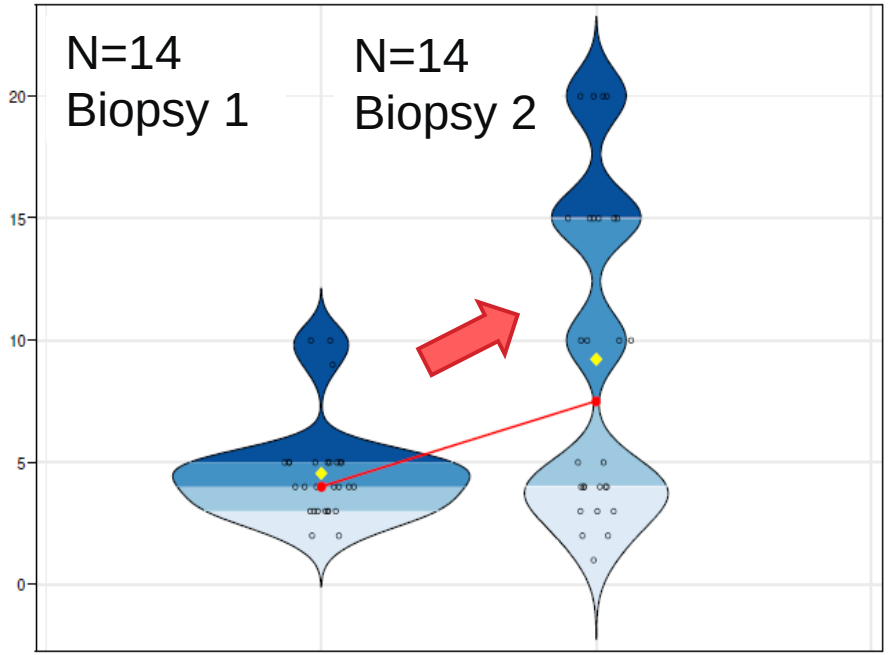
Tumor-infiltrating immune cells (TILs)

Total N=137



paired + unpaired biopsies

Total N=28

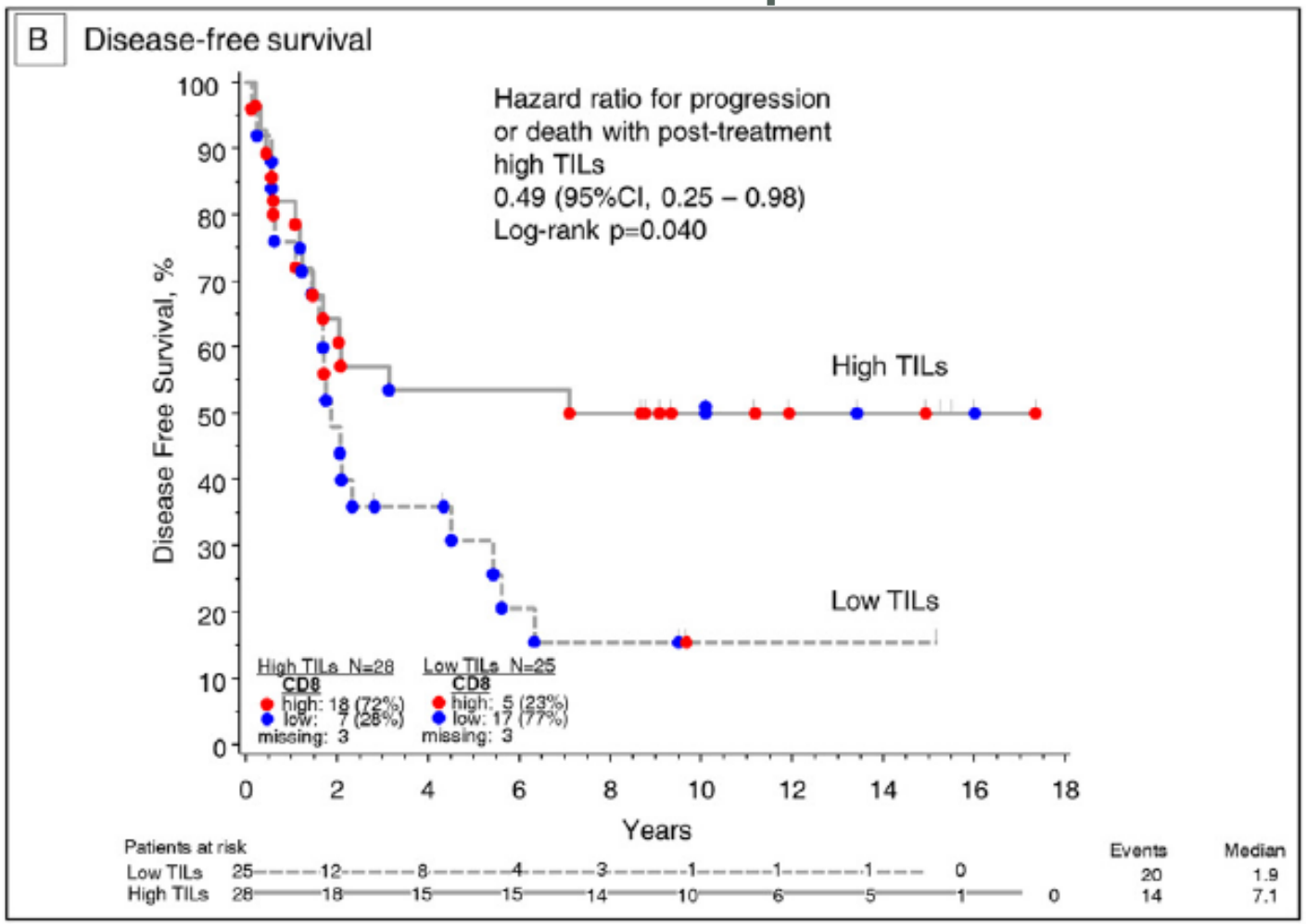


paired biopsies

Role of tumor infiltrating lymphocytes (TILs)

High TILs after treatment correlate with improved outcome

Post-treatment biopsies

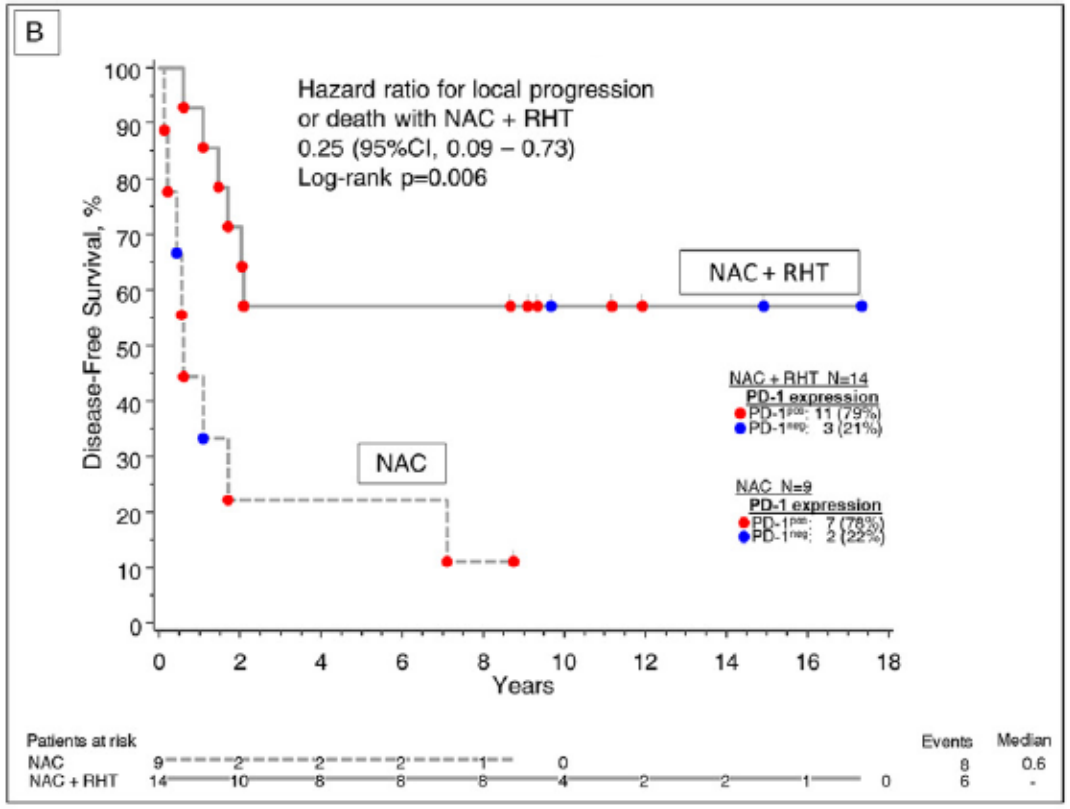


Issels R, Noessner E, Lindner L et al. Eur J Cancer 2021

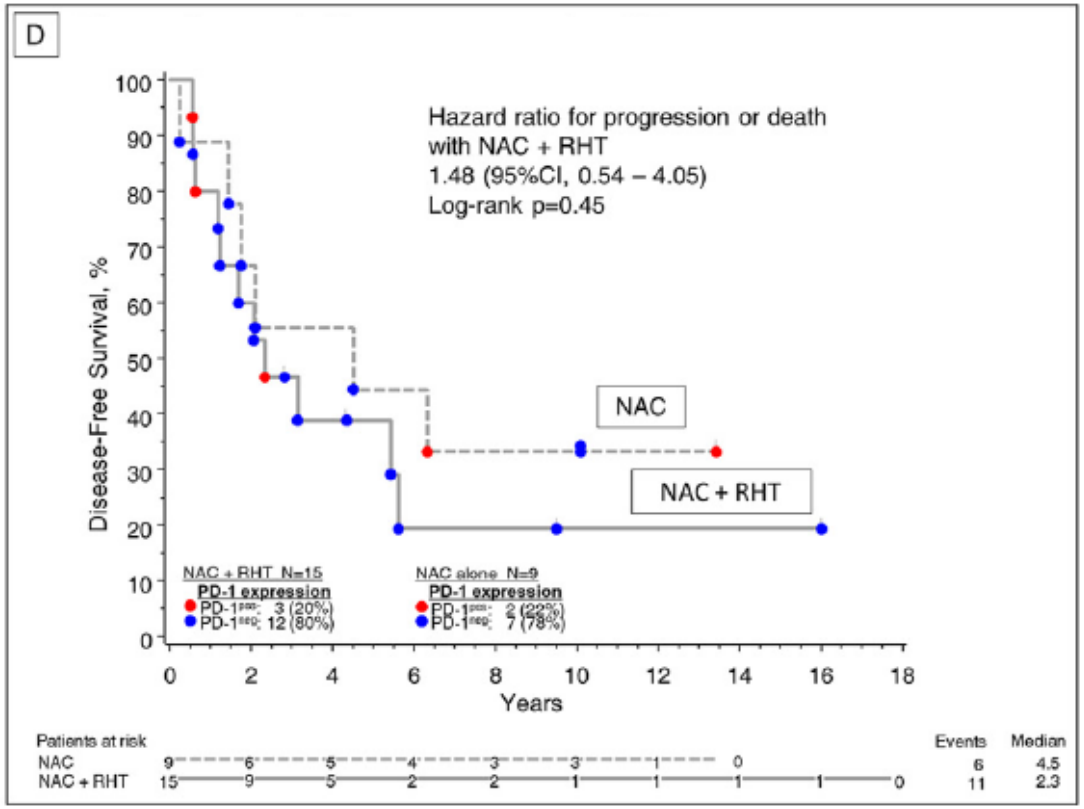
Role of tumor infiltrating CD8 cytotoxic T cells

High CD8 after NAC + RHT correlates with improved DFS

Post-treatment High CD8 NAC +RHT versus NAC



Post-treatment Low CD8 NAC + RHT versus NAC



Issels R, Noessner E, Lindner L et al. Eur J Cancer 2021

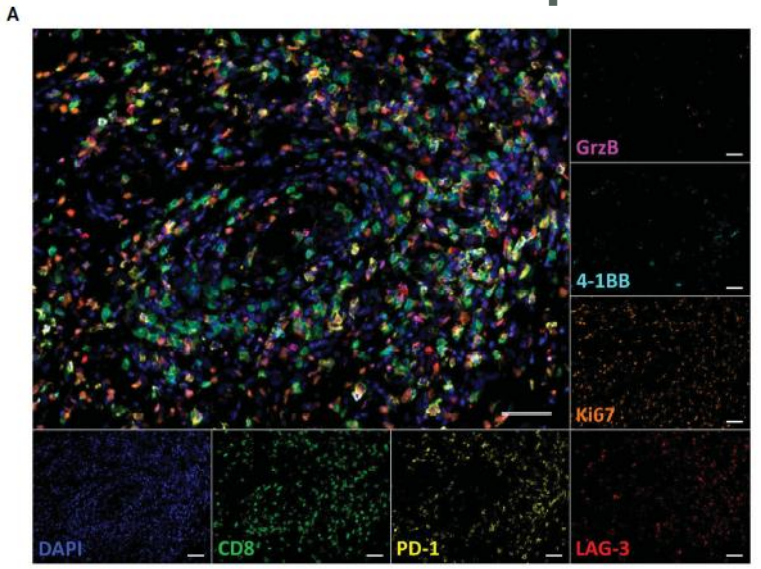
Regional hyperthermia with radio-chemotherapy: prognostic impact of the post-treatment T cell composition and spatial organization in soft tissue sarcoma patients

N = 21

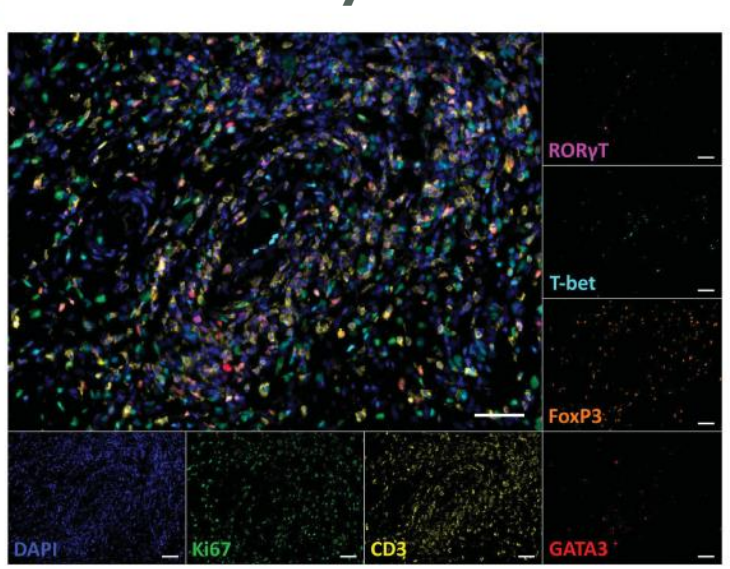
- **Extremity STS**
- **RT 50–50.4 Gy**
- **IFO 6 g/m2**

Paired tissue samples

Multiplex immunohistochemistry



CD8+ T cell panel staining



Th panel staining

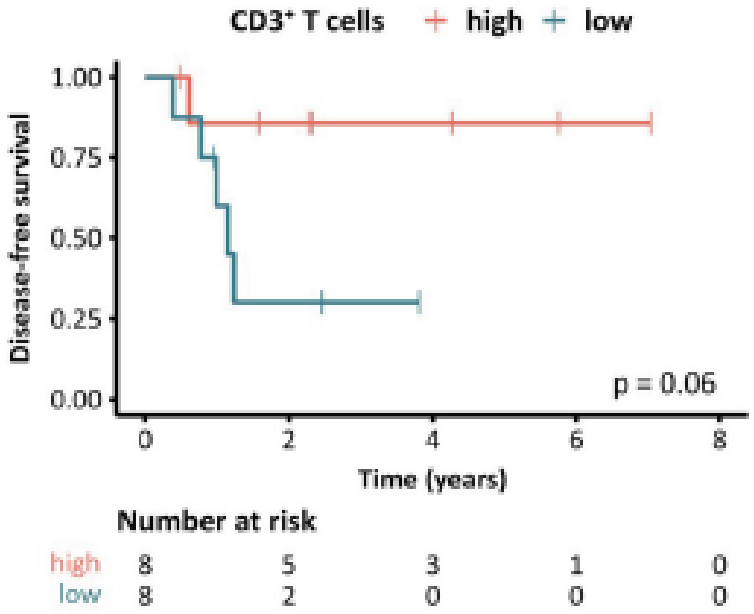
Examination of T cell sub-populations

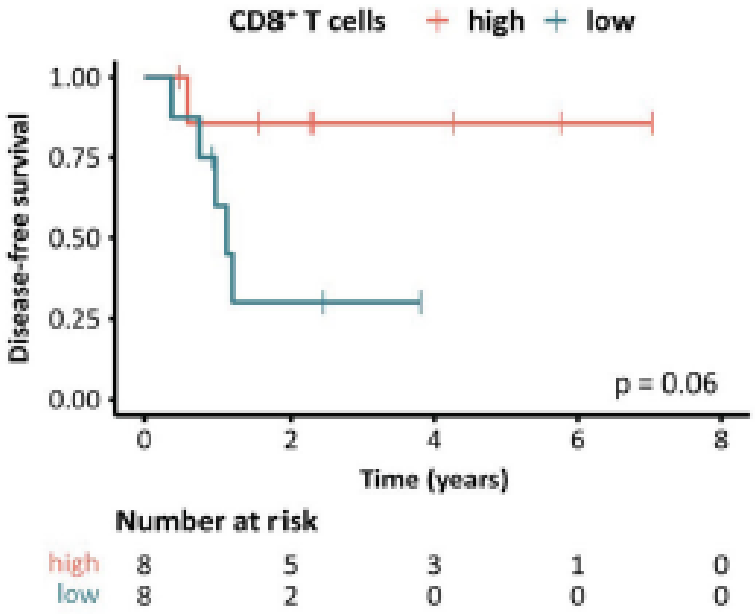
Rupp L et al. Front. Immunol. 2023

Influence on intratumoral T cell densities

High CD3+ and CD8+ T cell infiltration in post-treatment biopsies are associated with improved DFS

Post-treatment:pre-treatment T cell ratio (intratumoral specimens)



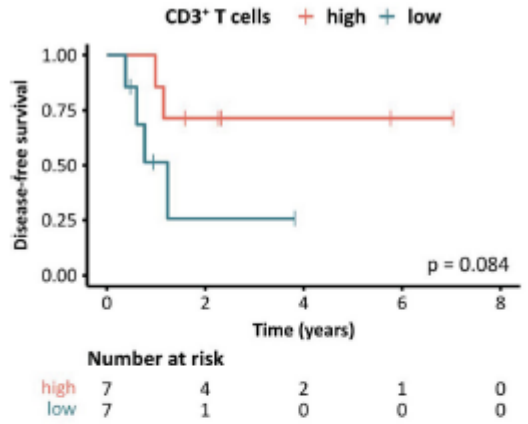


Rupp L et al. Front. Immunol. 2023

Influence on peritumoral T cell densities

Increased ratio of intra- to peritumoral CD8+ cells linked to increased DFS

Intratumoral:peritumoral T cell ratio (post-treatment specimens)



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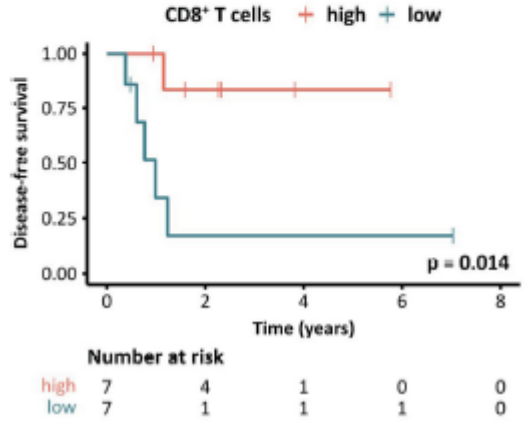
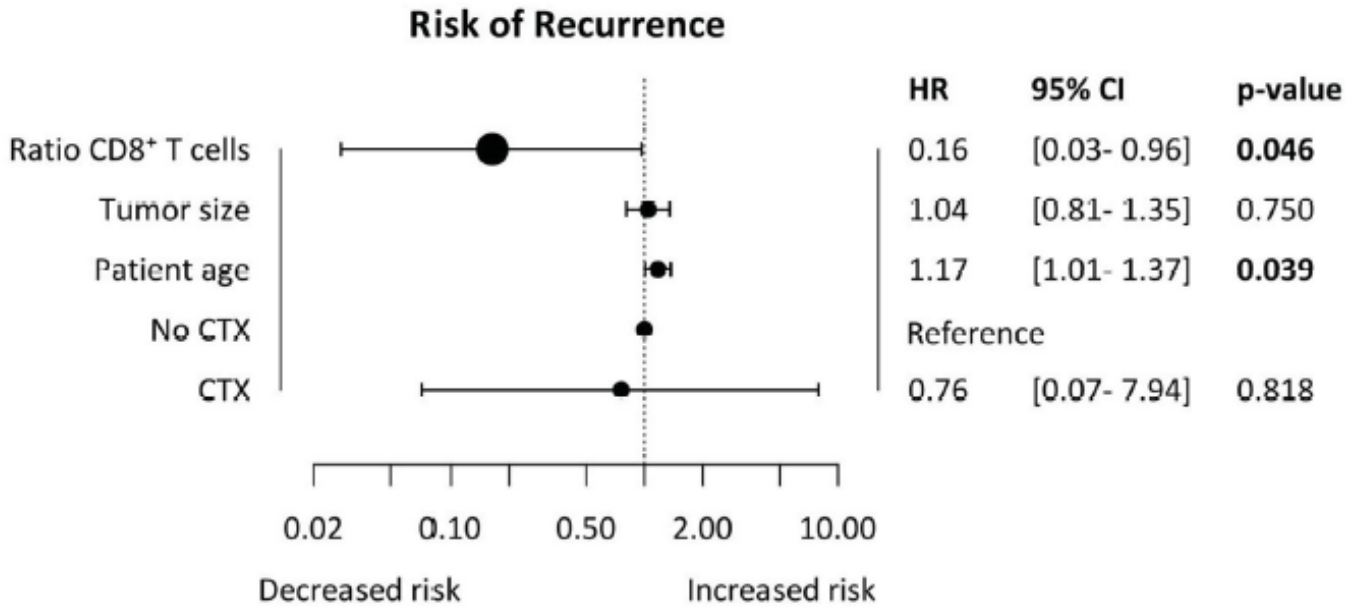
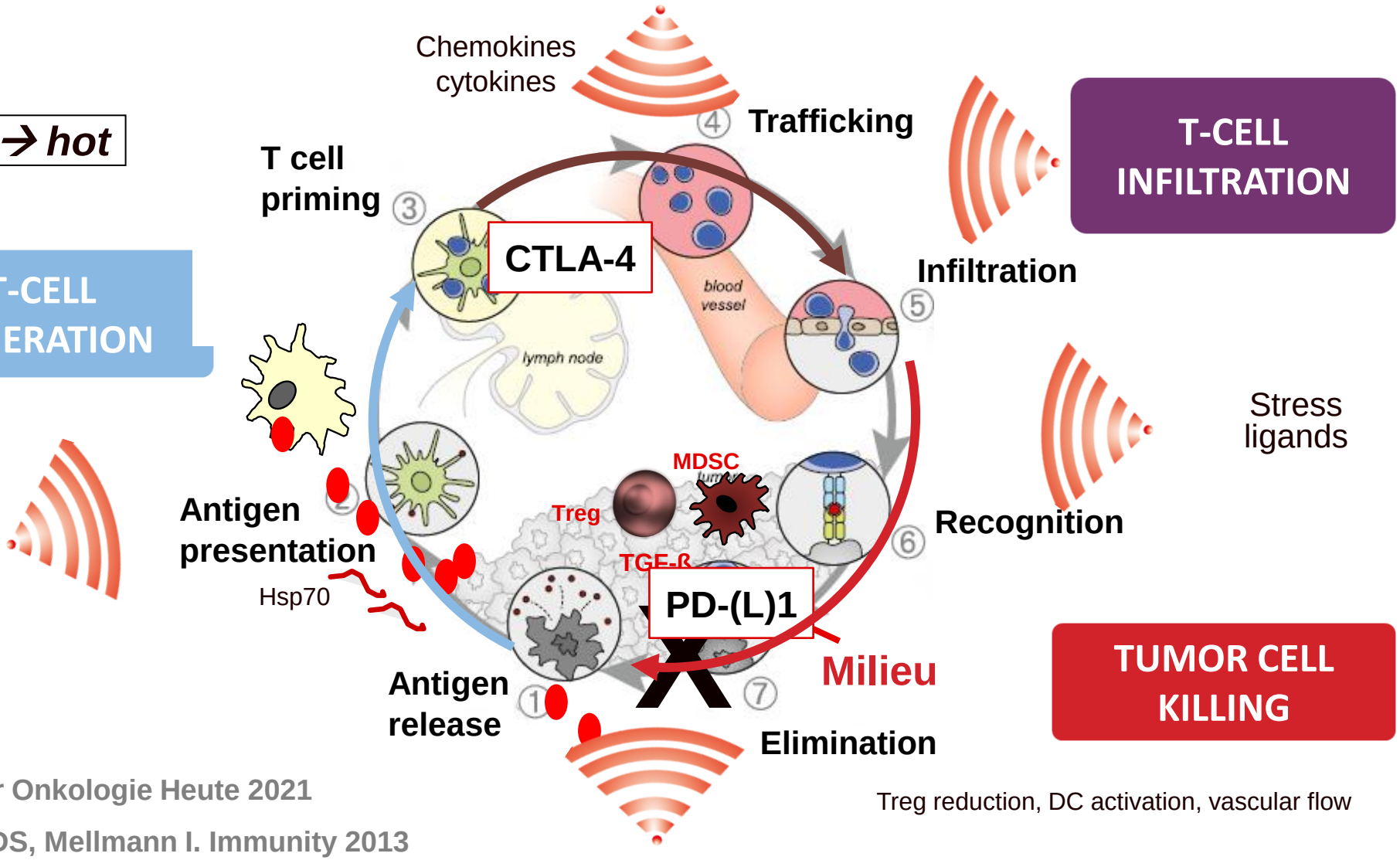




Rupp L et al. Immunol. 2023

Hyperthermia in the context of the cancer immunity cycle

Pleiotropic effects of hyperthermia synergize with checkpoint blockade



Cold tumors → hot

T-CELL GENERATION

T-CELL INFILTRATION

TUMOR CELL KILLING

Hyperthermia

<41.5°C / 41.5-43°C

Treg reduction, DC activation, vascular flow

Noessner & Teschner Onkologie Heute 2021

Modified from Chen DS, Mellmann I. Immunity 2013

I would like to thank

- **Valeria Milani MD**

for her strong interest and knowledge in clinical hyperthermia related immune research.

LMU KLINIKUM
Munich

Thank You
For Your Attention