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Society for Immunotherapy of Cancer

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Low Molecular Weight Heparin Augments the Effectiveness of Immune Checkpoint Inhibitors *in Vitro* and *in Vivo*

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Disclosure

We have no financial disclosure or conflicts of interest with the presented material in this presentation

Parenteral anticoagulants

- Indirect thrombin inhibitors

• Heparins

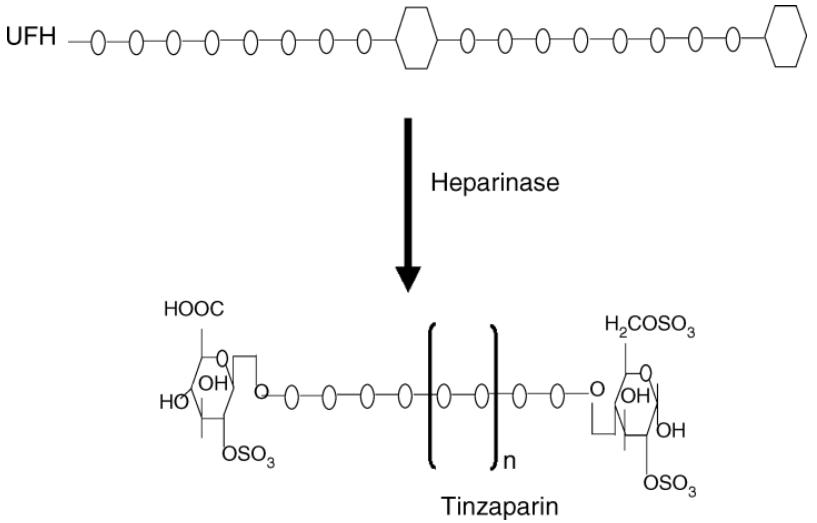
i. High Molecular Weight Heparin - Unfractionated Heparin (UFH)

ii. Low Molecular Weight Heparin (Enoxaparin, Dalteparin, **Tinzaparin**, Reviparin)

iii. Synthetic Heparin Derivatives (Fondaparinux)

- Direct thrombin inhibitors (lepirudin, Bivalirudin, Desirudin, Argatroban, Danaparoid, Rivaroxiban)

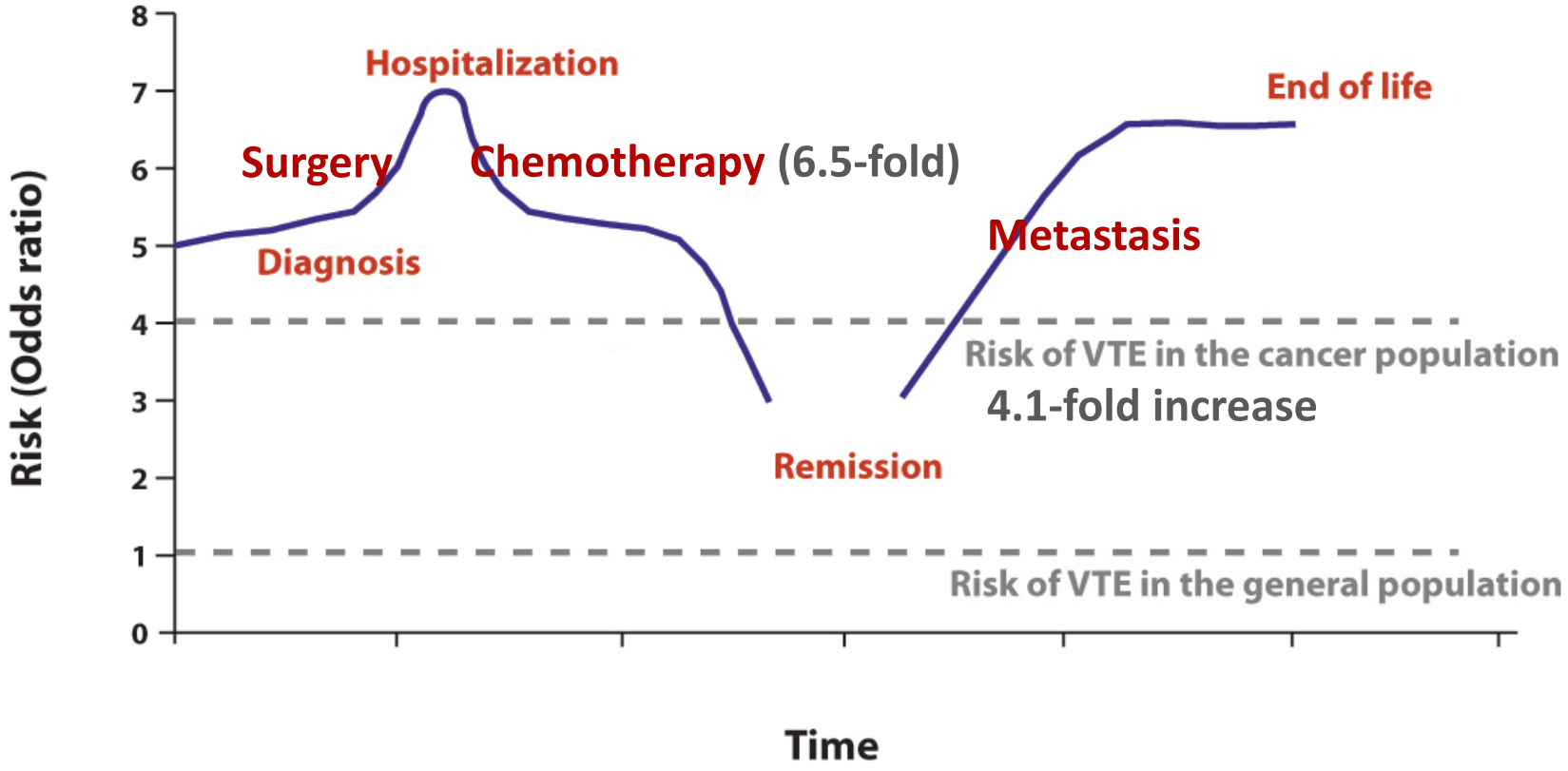
Tinzaparin



- Tinzaparin is a low molecular weight heparin (LMWH)
- Produced by enzymatic depolymerization of unfractionated heparin from porcine intestinal mucosa
- It is a heterogeneous mixture of with an average molecular weight between 5500 and 7500 daltons
- Tinzaparin is composed of molecules with and without a special site for high affinity binding to antithrombin III (ATIII). This complex greatly accelerates the inhibition of factor Xa

Changes in risk for VTE in a typical cancer patient

Risk factor assessment is an ongoing process



JAMA 293: 715–722, 2005
Arch Intern Med 162: 1245–1248, 2002
Arch Intern Med 160:809-815, 2000

Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update

Gary H. Lyman, Alok A. Khorana, Nicole M. Kuderer, Agnes Y. Lee, Juan Ignacio Arcelus, Edward P. Balaban, Jeffrey M. Clarke, Christopher R. Flowers, Charles W. Francis, Leigh E. Gates, Ajay K. Kakkar, Nigel S. Key, Mark N. Levine, Howard A. Liebman, Margaret A. Tempero, Sandra L. Wong, Ann Alexis Prestrud, and Anna Falanga

- LMWH is preferred over UFH for the initial 5 to 10 days of anticoagulation for the pt with cancer with newly diagnosed VTE who does not have severe renal impairment
- For long-term anticoagulation, LMWH for at least 6 mo is preferred because of improved efficacy over VKAs
- Anticoagulation with LMWH or VKA beyond the initial 6 months may be considered for select patients with active cancer, such as those with metastatic disease or those receiving chemotherapy
- Use of novel oral anticoagulants for either prevention or treatment of VTE in patients with cancer is not recommended at this time

Not only for VTE treatment…

Clinical Cancer Research

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Cancer Therapy: Preclinical

Inhibition of CXCR4-Mediated Breast Cancer Metastasis: A Potential Role for Heparinoids?

James R. Harvey, Paul Mellor, Hesham Eldaly, Thomas W.J. Lennard, John A. Kirby, and Simi Ali

DOI: 10.1158/1078-0432.CCR-06-1987 Published March 2007

Anti-angiogenic mechanisms and efficacy of the low molecular weight heparin, tinzaparin: Anti-cancer efficacy

Authors: Shaker A. Mousa, Seema Mohamed

View Affiliations

Published online on: October 1, 2004 https://doi.org/10.3892/or.12.4.683

Pages: 683-688

October 2004
Volume 12 Issue 4
Print ISSN: 1021-335X
Online ISSN:1791-2431

ELSEVIER

Biochemical Pharmacology
Volume 97, Issue 2, 15 September 2015, Pages 147-157

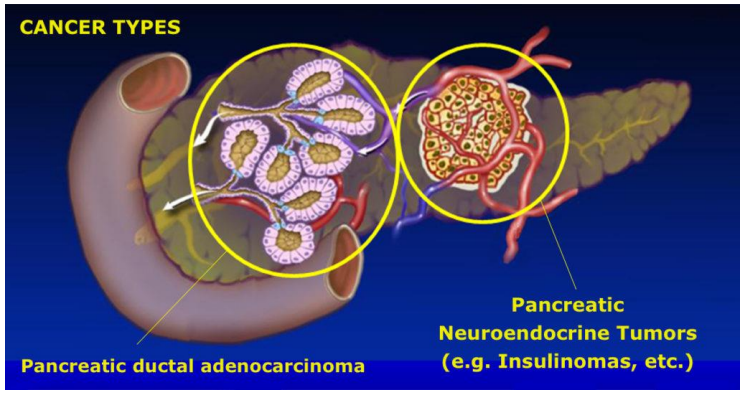
Low molecular weight heparin tinzaparin antagonizes cisplatin resistance of ovarian cancer cells

Daniel Bastian Pfankuchen [a, 1] ✉, Daniel Philipp Stölting [a, 1] ✉, Martin Schlesinger [a] ✉, Hans-Dieter Royer [b] ✉, Gerd Bendas [a] ✉

- Inhibition of metastasis
- Reversal of chemoresistance
- Anti-angiogenic ability

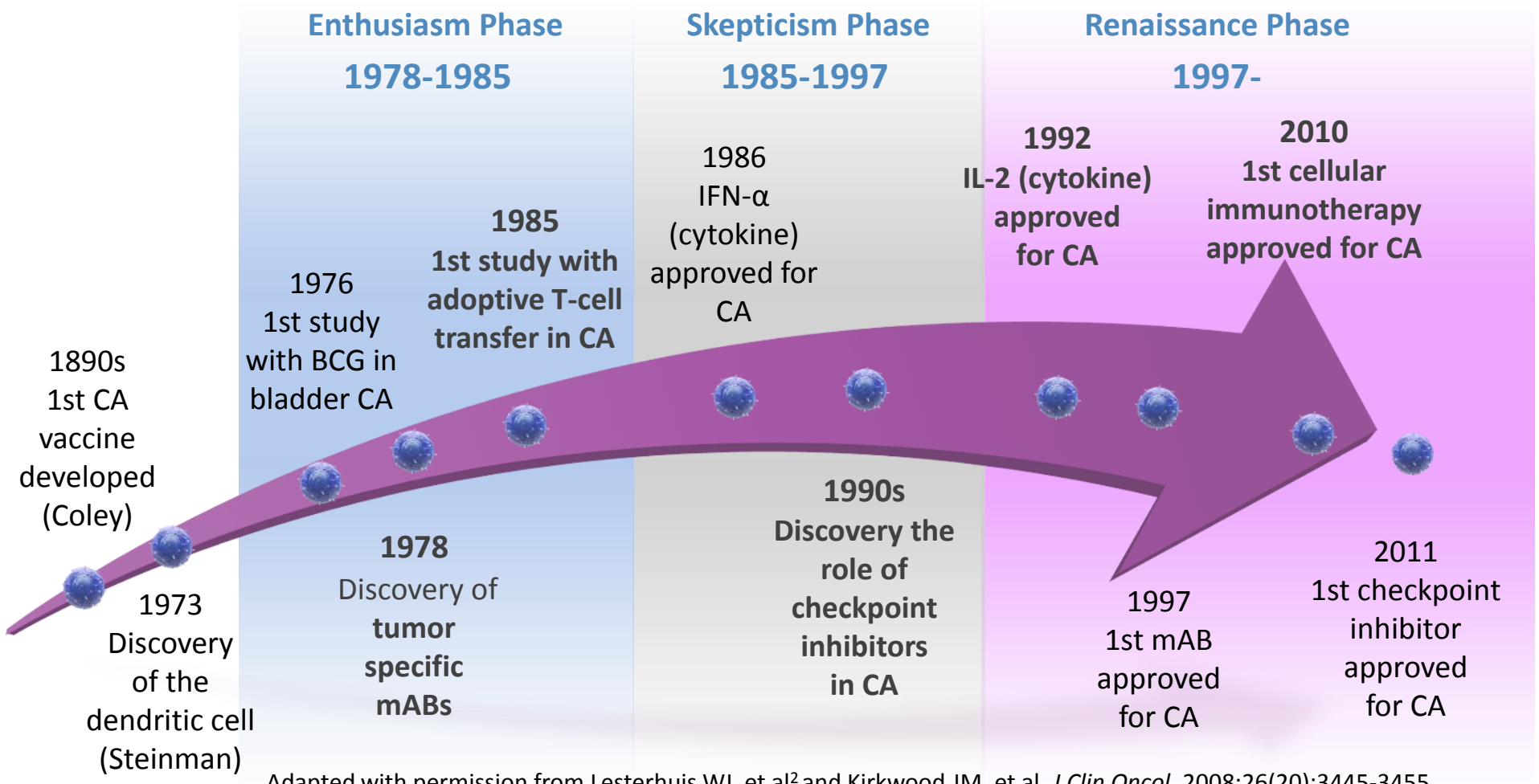
Pancreatic Cancer

- Has an average 5-year survival rate of less than 10%
- Is anticipated to become the second leading cause of cancer–related mortality by 2020
- Classical treatments such as chemotherapy, surgery and radiation have been widely used but they have not exhibited any significant improvements in clinical outcomes



Science, Dec 2013

The Renaissance of Immunotherapy



BCG, Bacille Calmette-Guerin; mABs, monoclonal antibodies; CA, cancer; IFN-α, interferon alpha; IL-2, interleukin-2

Adapted with permission from Lesterhuis WJ, et al[2] and Kirkwood JM, et al. *J Clin Oncol*. 2008;26(20):3445-3455.

May 3, 2019

Estimation of the Percentage of US Patients With Cancer Who Are Eligible for and Respond to Checkpoint Inhibitor Immunotherapy Drugs

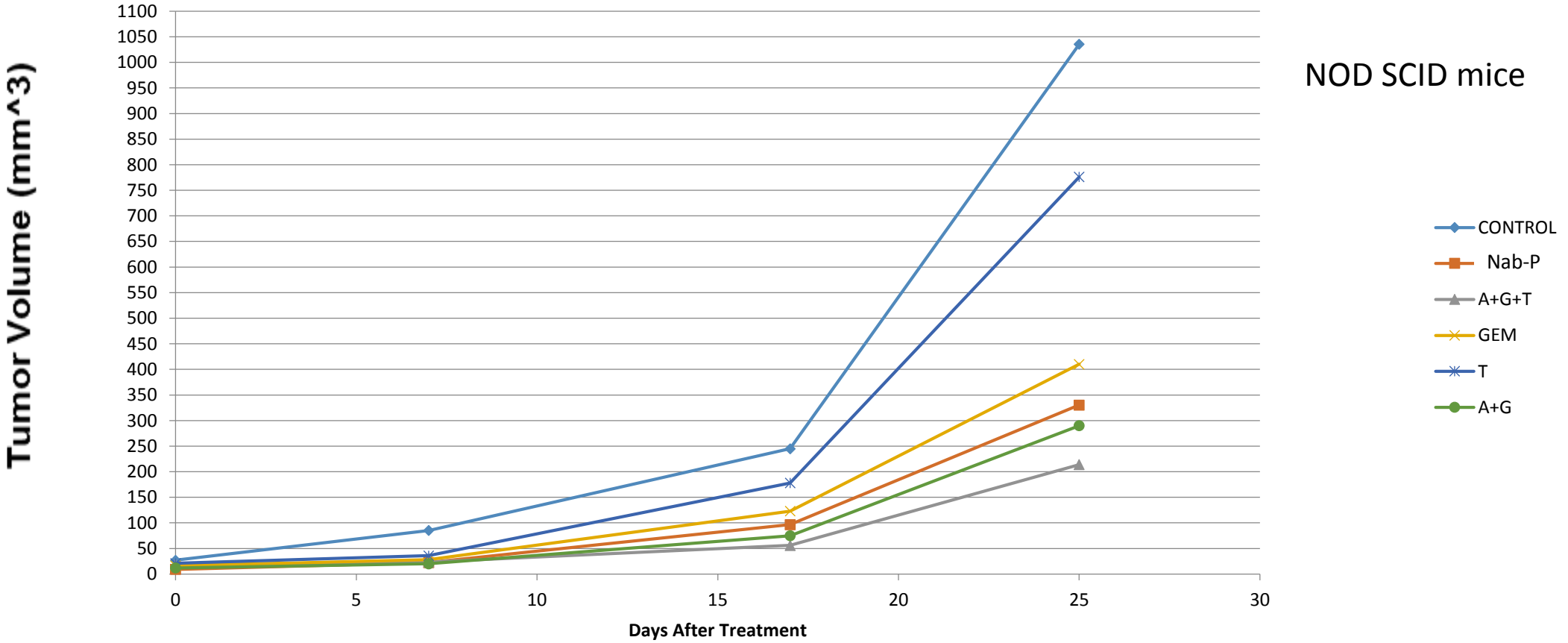
Alyson Haslam, PhD[1]; Vinay Prasad, MD, MPH[2,3,4,5]

» Author Affiliations | Article Information

JAMA Netw Open. 2019;2(5):e192535. doi:10.1001/jamanetworkopen.2019.2535

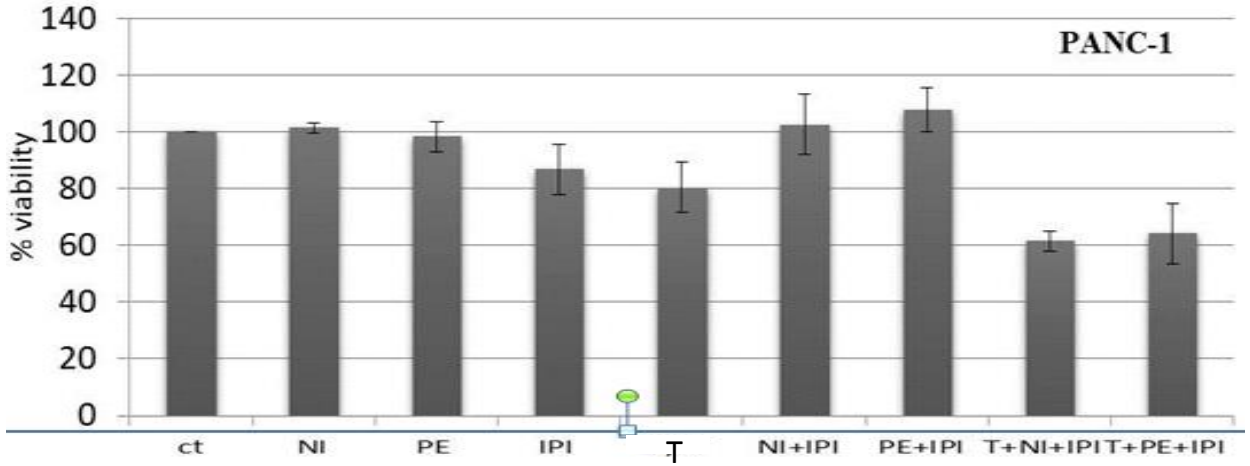
- **Cancer patients eligible for checkpoint inhibitors increased from 1.54% in 2011 to 43.63% in 2018.**
- **Patients who respond to checkpoint inhibitors increased from 0.14% in 2011 to 12.46% in 2018.**

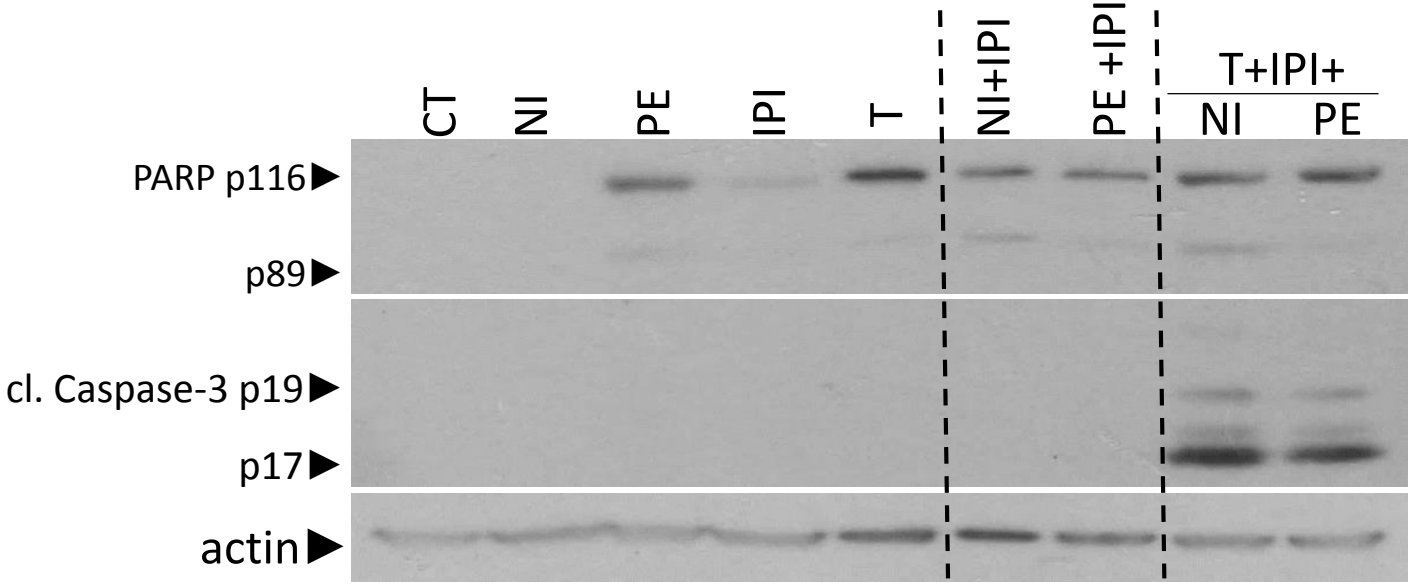
Triple combination of Gemcitabine + Nab-paclitaxel + Tinzaparin leads to a decrease in tumor size relative to control by 480% and relative to Nab-P + G by 27%



NOD SCID mice

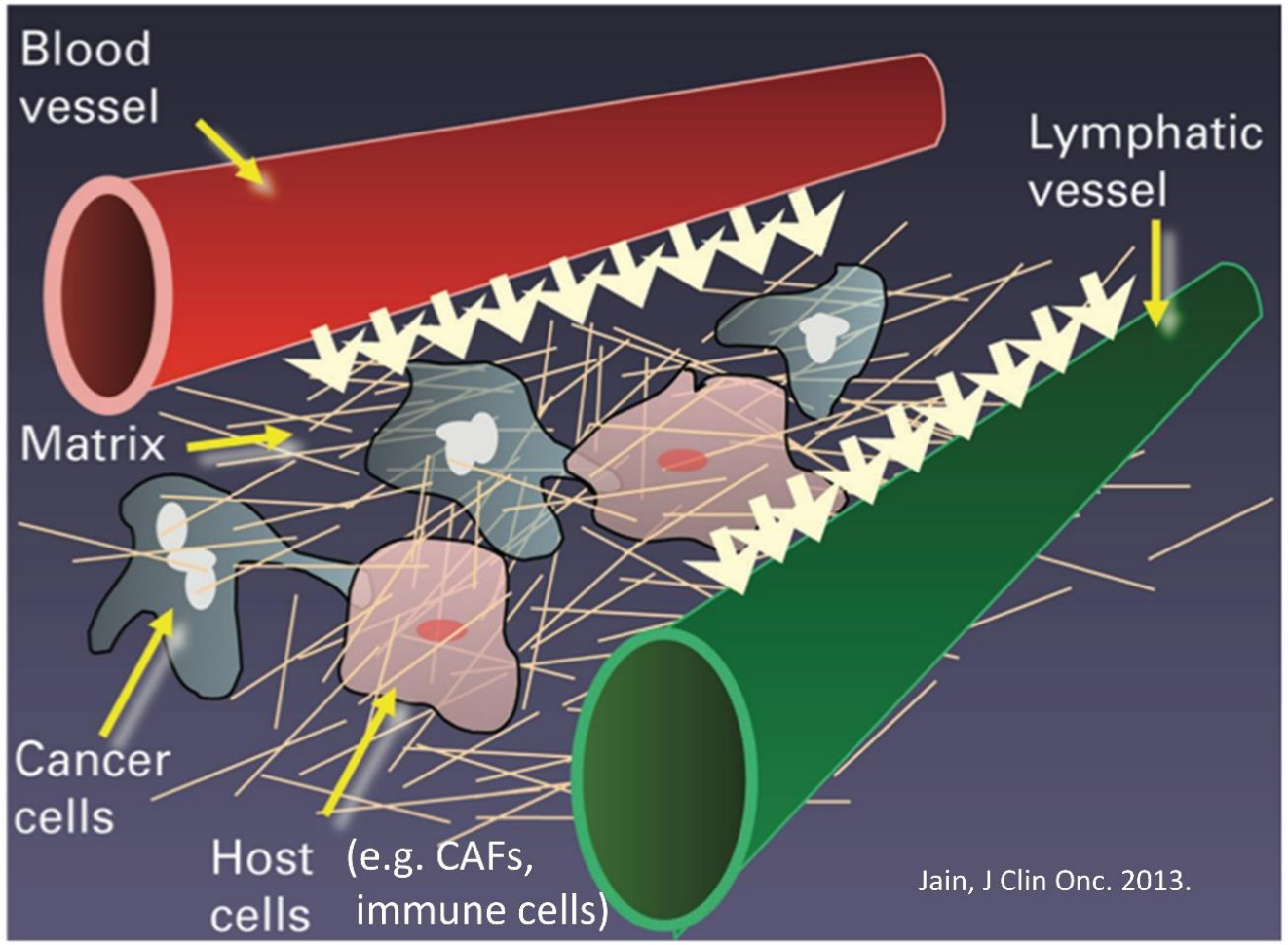
Triple combination of Tinzaparin with 1µM of NIVO / PEMBRO and IPILIMUMAB decreases by around 35-40% cell viability, of pancreatic cancer cell lines, harboring mutant KRAS, through apoptosis





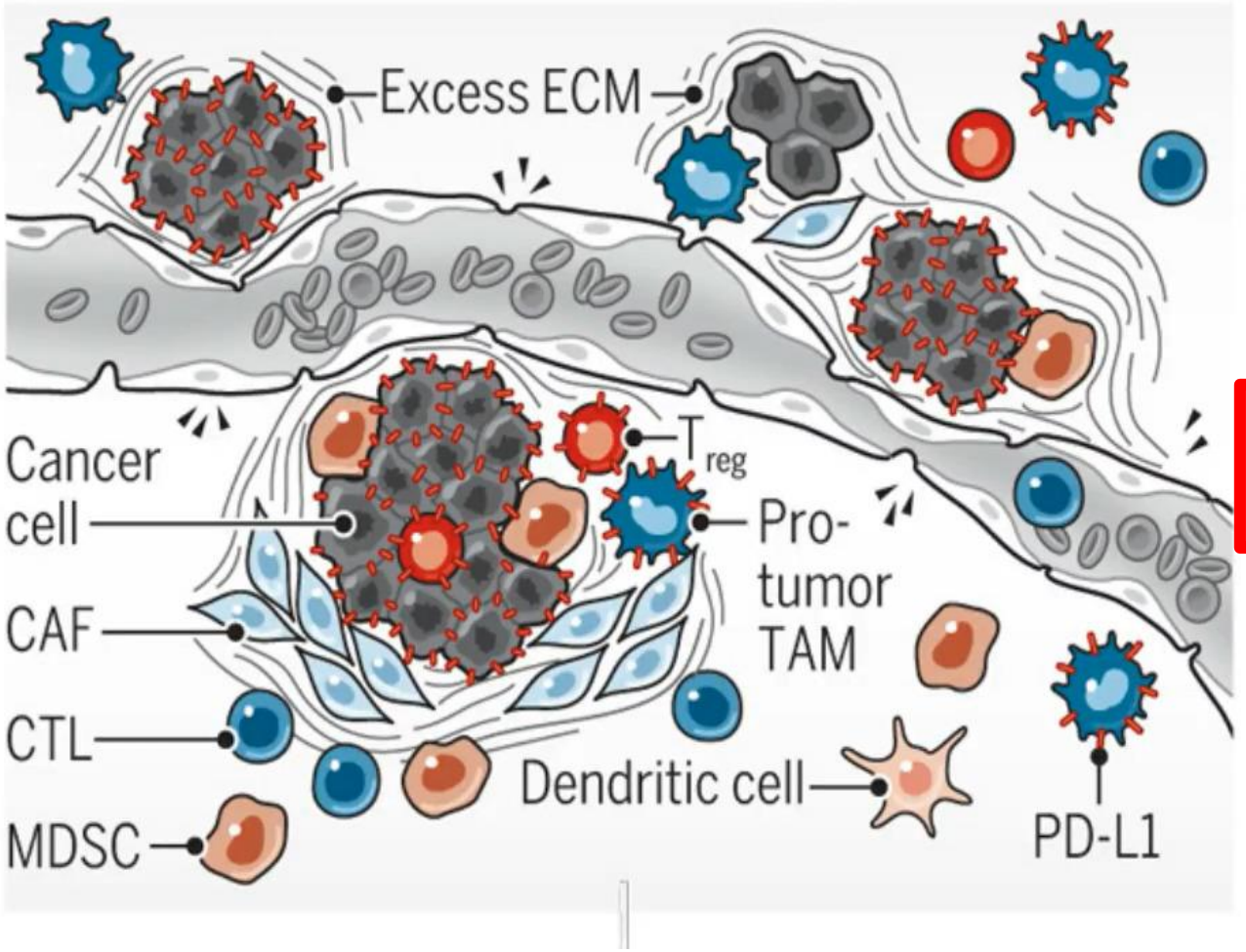
Cell lines lack TME

Tumor Microenvironment



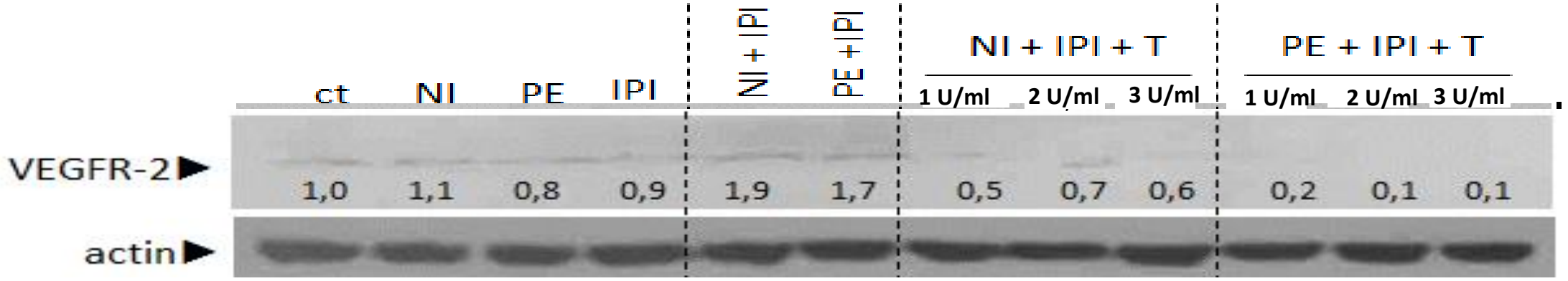
✓ PC microenvironment is characterized by increased desmoplasia, several non-cellular components such as hyaluronic acid and various cells types such as cancer-associated fibroblasts (CAFs), pancreatic stellate cells (PSCs), muscle fibroblasts and immune cells

Due to the TME the penetrance of therapeutic regimes for the elimination of cancer cells is hindered

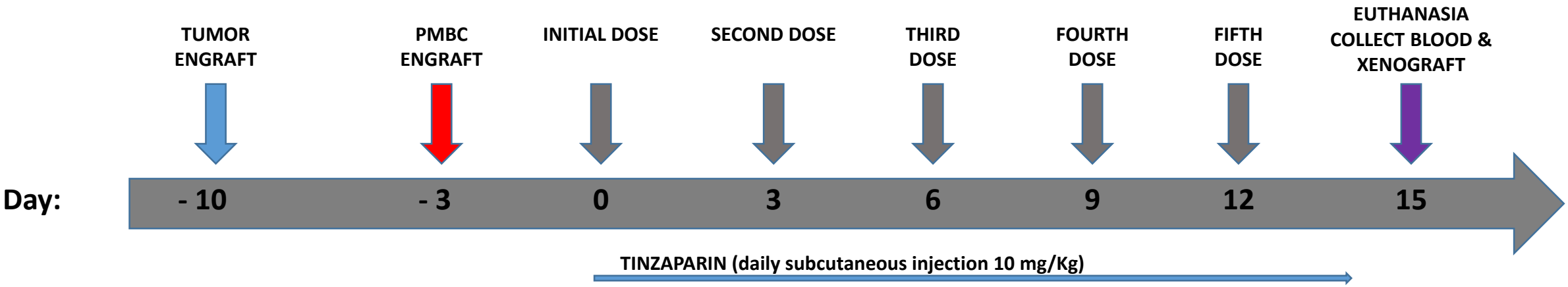


Lance L. Munn and Rakesh K. Jain, Science (365) 544-545

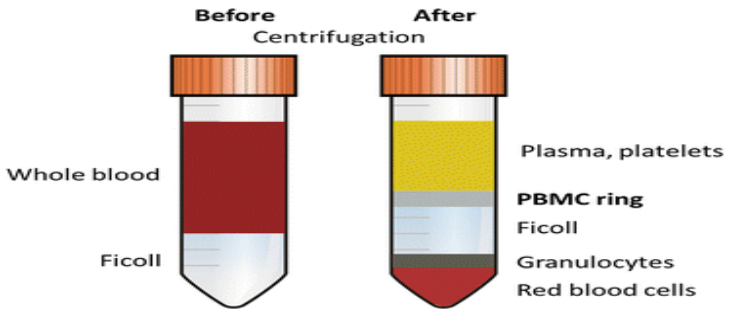
In triple combinatorial scheme PE+IPI+T, the protein levels of VEGFR2 were decreased in mtKRAS PC cell line (PANC1)



IMMUNOTHERAPY PROTOCOL WITH NSG HUMANIZED MICE

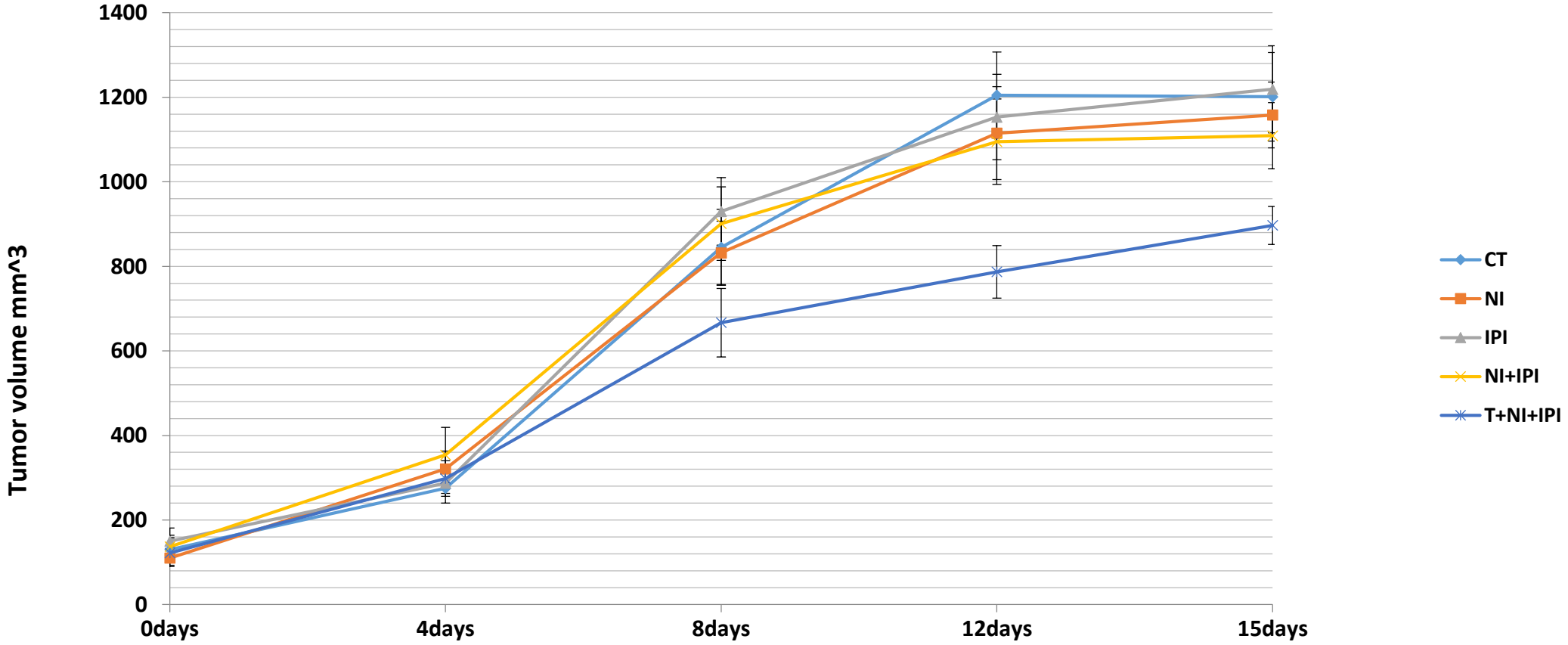


DOSES : SIMPLE OR COMBINED
NAB-PACLITAXEL : 25 mg/kg
GEMCITABINE : 160 mg/Kg
NIVOLUMAB : 10 mg/Kg
PEMBROLIZUMAB : 10 mg/Kg
IPILIMUMAB : 10mg/Kg



10^7 cells

Triple combination of PE + IPI + Tinzaparin leads to a decrease in tumor size relative to control by 26%. No decrease is observed when Tinzaparin is absent



Next steps…

- Check whether Tinzaparin interacts with chemokines
- Test if there is an increase in Tregs levels
- Investigate the effect of different concentrations and dosage regimens in order to increase immunotherapy efficacy

Take Home Message

- ✓ Tinzaparin is efficient for tumor growth inhibition alone or in combination with chemotherapy
- ✓ A potential mechanism of action is through attenuation of VEGF signaling pathway
- ✓Other mechanisms of action can not be excluded but is seems that Tinzaparin affects TME, enhancing the efficiency of immunotherapy results in pancreatic cancer


Thank you for your attention!
University of Athens