Society for Immunotherapy of Cancer

Welcome to The 2019 Cancer Immune Responsiveness Workshop

Organizers:

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Alessandra Cesano - disclosure

- I am a full time employee of ESSA Pharmaceuticals
- I am a consultant of Nanostring Inc. and Refuge Biotechnologies Inc.

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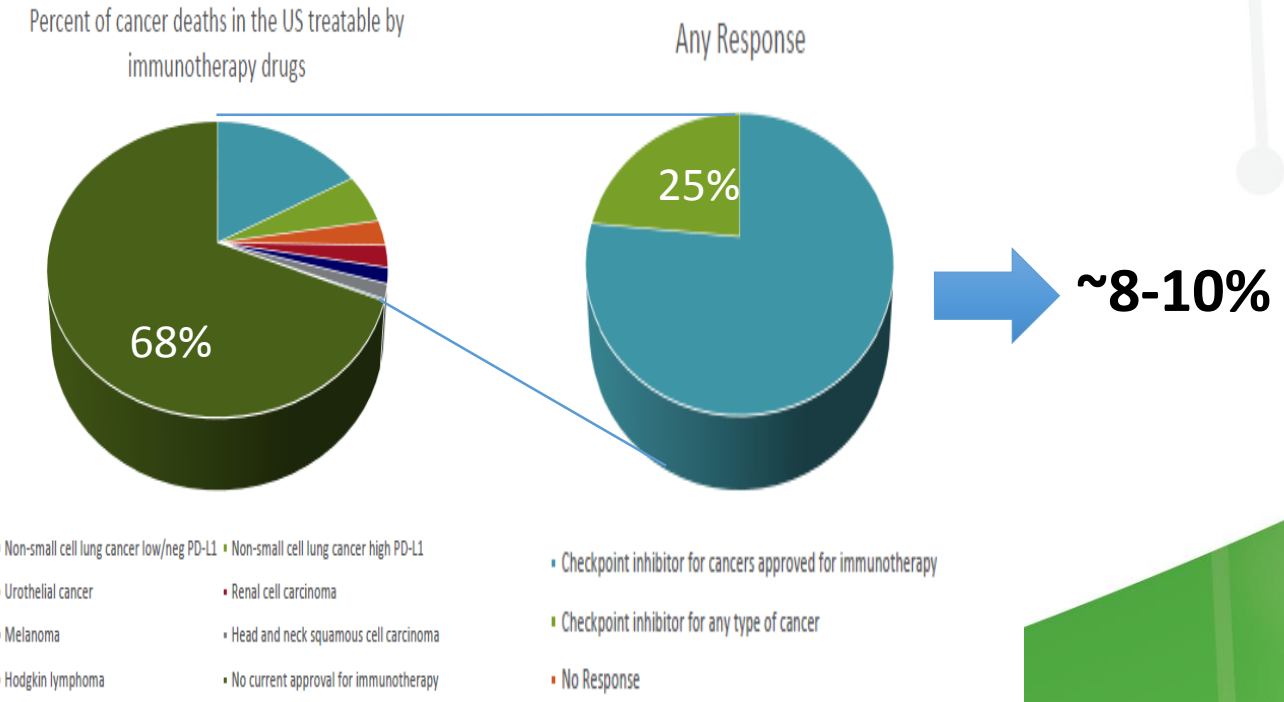
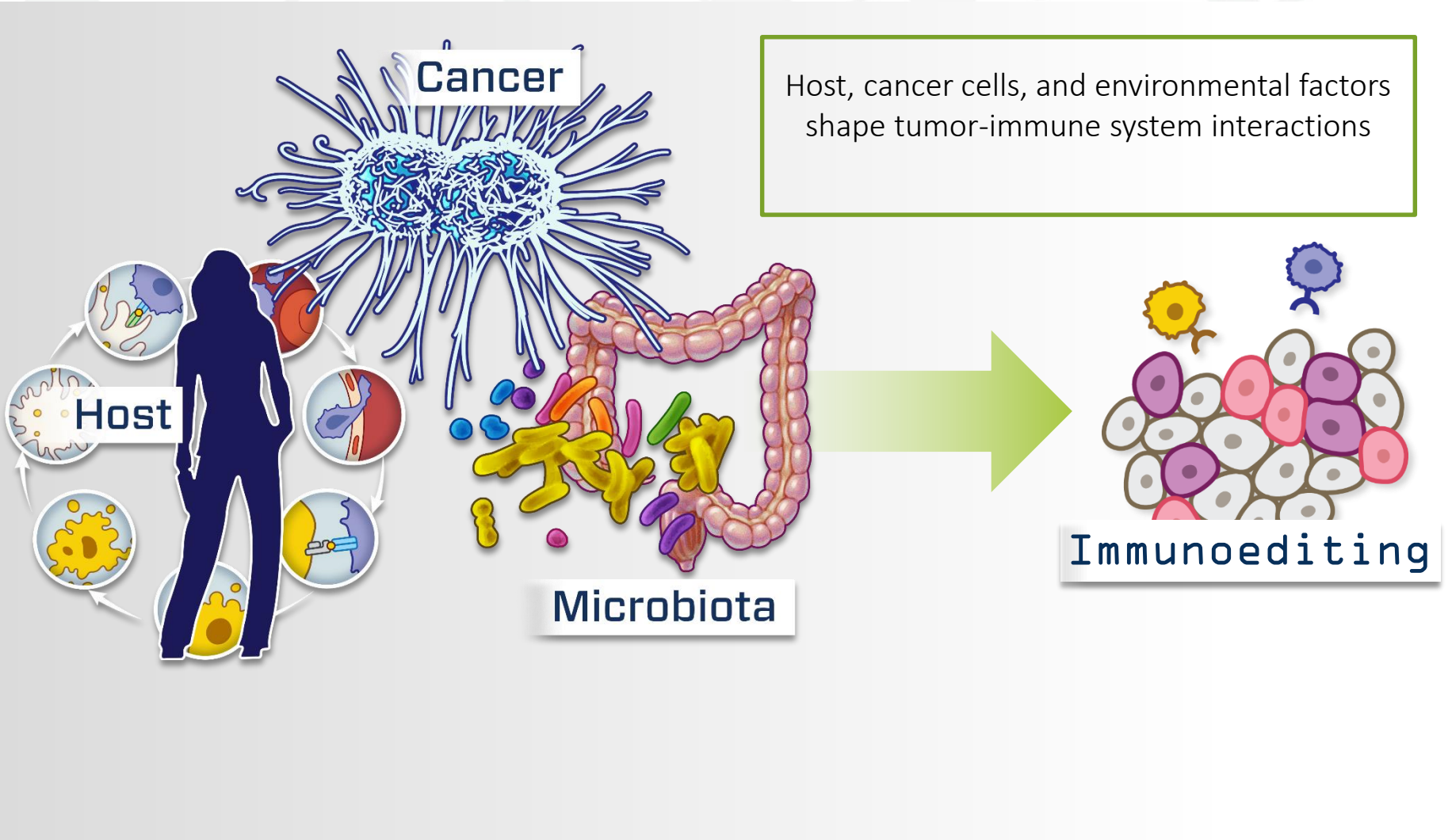
Despite the “IO-hype” Few Patients Actually Benefit from Currently Approved IO Drugs

- **Checkpoint blockade immuno-therapy elicits durable anti-tumor response in a subset of patients with advance cancers…**
- **… however the majority of advance cancer patients do not benefit from these drugs**
  - Except for mNSCLC most major cancer types are **primary resistant** to single agent checkpoint inhibition
  - Depending on tumor type **secondary resistance** occurs in 30 to 50% of (partial) responders



Source: Adapted from Abola and Prasad, JAMA, 2016

Immuno-Oncology: Systems Biology at Work



Host, cancer cells, and environmental factors shape tumor-immune system interactions

A short history of the CIR Task Force and Workshops (1)

- Premise:
  - CIR remains a major limitation to cancer immunotherapy approaches in the clinic
  - The determinants of CIR are multifactorial including:
    - Genetic makeup of the patient
    - Tumor genomic instability
    - External modifiers (e.g. microbiome, comorbidity, concomitant medications etc.)
- In 2018 the SITC convened a Task Force of experts from various disciplines to address the complexity of CIR from an holistic view
- Two main goals:
  - Identify the fundamental questions related to CIR
  - Create an interactive community of experts to guide scientific and research priorities to uncover mechanisms of CIR

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A short history of the CIR Task Force and Workshops (2)

- Five working groups were created that include:
  1. Genetic Germline contributions to CIR – *Chair: David Bedognetti*
  2. Genetic-Somatic contributions to CIR – *Chair: Josue Samayoa*
  3. Genomic-Transcriptional contributions to CIR – *Chair: Stefani Spranger*
  4. Determinant(s) of Immunogenic Cell Death that modulate CIR – *Chair: Sarah Warren*
  5. Experimental Models that best represent CIR and its conversion to an immune responsive state – *Chair: Rongze Lu*

- A manuscript summarizing the contributions of each group was published in JITC in July 2019

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Bedognetti et al. Journal for ImmunoTherapy of Cancer (2019) 7:131
https://doi.org/10.1186/s40425-019-0602-4

Journal for ImmunoTherapy of Cancer

REVIEW Open Access

Toward a comprehensive view of cancer immune responsiveness: a synopsis from the SITC workshop

Davide Bedognetti[1†], Michele Ceccarelli[2], Lorenzo Galluzzi[3,4,5], Rongze Lu[2†], Karolina Palucka[6], Josue Samayoa[2†], Stefani Spranger[7†], Sarah Warren[8†], Kwok-Kin Wong[9], Elad Ziv[10], Diego Chowell[11], Lisa M. Coussens[12], Daniel D. De Carvalho[13], David G. DeNardo[14], Jérôme Galon[15], Howard L. Kaufman[16], Tomas Kirchhoff[17], Michael T. Lotze[18], Jason J. Luke[19], Andy J. Minn[20], Katerina Politi[21], Leonard D. Shultz[22], Richard Simon[23], Vésteinn Thórsson[24], Joanne B. Weidhaas[25], Maria Libera Ascierto[26], Paolo Antonio Ascierto[27], James M. Barnes[2], Valentin Barsan[28], Praveen K. Bommareddy[29], Adrian Bot[30], Sarah E. Church[8], Gennaro Ciliberto[31], Andrea De Maria[32], Dobrin Draganov[33], Winson S. Ho[34], Heather M. McGee[35], Anne Monette[36], Joseph F. Murphy[37], Paola Nisticò[31], Wungki Park[11], Maulik Patel[2], Michael Quigley[38], Laszlo Radvanyi[39], Harry Raftopoulos[40], Nils-Petter Rudqvist[3], Alexandra Snyder[41], Randy F. Sweis[19], Sara Valpione[42], Roberta Zappasodi[47,48], Lisa H. Butterfield[43], Mary L. Disis[44], Bernard A. Fox[45], Alessandra Cesano[8], Francesco M. Marincola[46*] and Society for Immunotherapy of Cancer (SITC) Cancer Immune Responsiveness Task Force and Working Groups

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Table 1 Main unanswered questions identified by each working group

WORKING GROUP	Main Questions
I. Germline GENETIC Contributions TO Cancer Immune Responsiveness	1. Which are the key molecular mechanisms involved in anti-tumor immunity that might be modulated by germline genetic variants? 2. Are common genetic polymorphisms associated with a differential spontaneous or treatment-induced anti-tumor immune response? 3. How can we implement the study of host genetic diversity to identify novel biomarkers of responsiveness or toxicity to cancer immunotherapy?
II. Somatic GENETIC Contributions TO Cancer Immune Responsiveness	1. Can our knowledge of how cancer-intrinsic features influence the tumor microenvironment help us optimize immunotherapy combinations? 2. How do we harmonize biomarkers derived from different technologies in order to specifically tailor IO therapy for a patient and increase the likelihood of response? 3. Will understanding the role of epigenetic re-programming downstream of molecular alterations in tumor cells reveal new opportunities to combat cancer immune-evasion strategies?
III. Transcriptional Changes Related to CIR	1. Can we generate transcriptional signature with high predictive value for a specific tumor-immune microenvironment? 2. Can transcriptional profiling be developed as a biomarker for the CIR? 3. What technological advances do we need to dissect the tumor-immune microenvironment in space and time?
IV. Immunogenic Cell Death and Cancer Immune Responsiveness	1. What are the key molecular events that occur during immunogenic cell death that prime a robust immune response and promote immunological memory? 2. Which therapeutic strategies will more effectively promote ICD while minimizing off target inhibition of immune responses? 3. How can detection of immunogenic cell death be routinely incorporated into clinical trials?
V. Experimental Models of the Immune Landscape of Cancer	1. What are the current limitations of humanized PDX mouse models? 2. What approaches can be undertaken towards more faithful models of human cancer-human myeloid cells interface? 3. How to develop models that better model to reproduce tumor mutational load?

Additional SITC CIR workshop 1.0 outcomes

- Preparation of a manuscript entitled: *"Consensus guidelines for the definition, detection and interpretation of immunogenic cell death"* – Lorenzo Galluzzi and Sarah Warren
- Organization of a second workshop to be held in 2019 to further the suggestions and recommendations derived from the Workshop held in 2018:
  - Scientific presentations addressing individual questions
  - Definition of specific actions to be pursued by individual working groups to address specific questions including:
    - Collaborative initiatives
    - Access to public available databases to address systematically questions relevant to CIR
    - Development of question-driven strategic partnerships
  - Suggestion to consolidate the genetic-focused working groups and the ICD and experimental models working groups
  - Inclusion of an External Factors related to CIR working group

SITC 2019 CIR Workshop – Day 1

- Three working groups:
  - Germline, Somatic Genetics and Epigenetics of Immune Landscape
    - Co-chairs:
      - Davide Bedognetti, MD, PhD – Sidra Medicine
      - Josue Samayoa, PhD – Abbvie
  - Transcriptional Patterns of Distinct Immune Landscapes
    - Co-chairs:
      - Yana G. Najjar, MD – University of Pittsburgh
      - Hua E. Yu, PhD – City of Hope
  - Therapeutic Interventions to Modify the TME and Related Experimental Systems for Validation
    - Co-chairs:
      - Sarah Warren, PhD – Nanostring Inc.
      - Rongze O. Lu, PhD – University of Texas at Austin

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SITC 2019 CIR Work – Day 2

(in common with the SITC 2019 Adoptive Cell Therapy Workshop)

- One session with panel discussion dedicated to External Circumstantial Factors
  - Co-chairs:
    - Christine Spencer, PhD – PICI
    - Alessandra Cesano, MD PhD – ESSA Pharma
- One session focusing on Emerging Ideas and New Concepts
  - Co-chairs:
    - Kyung-Ho Roh, PhD – The University of Alabama in Huntsville
    - Francesco M. Marincola, MD – Refuge Biotechnologies

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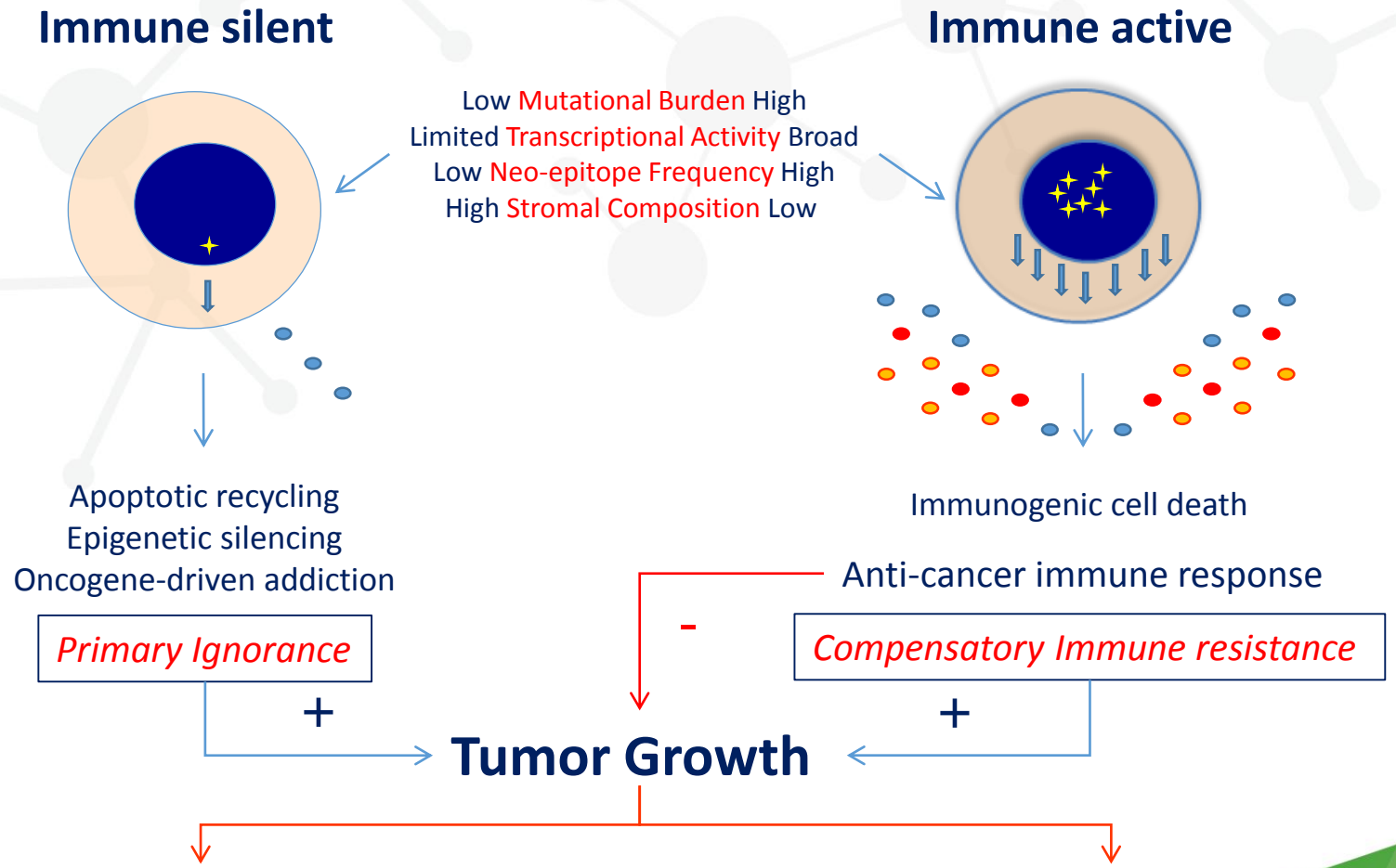
The “Two-Option Choice” (TOC) determinism in the natural history of cancer: A conserved evolutionary crossroad for cancer survival



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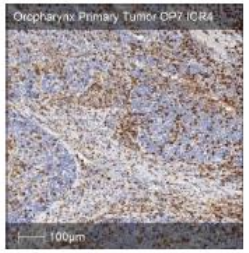
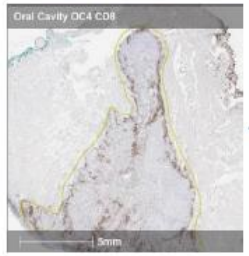
Relevance of TME in the context of CAR-T effectiveness

What are the TME conditions that incite chemo-attraction (or lack thereof) of adoptively transferred T cells to the tumor site?

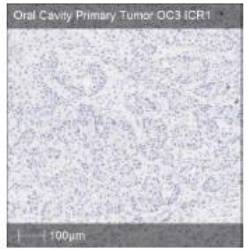
Inflamed

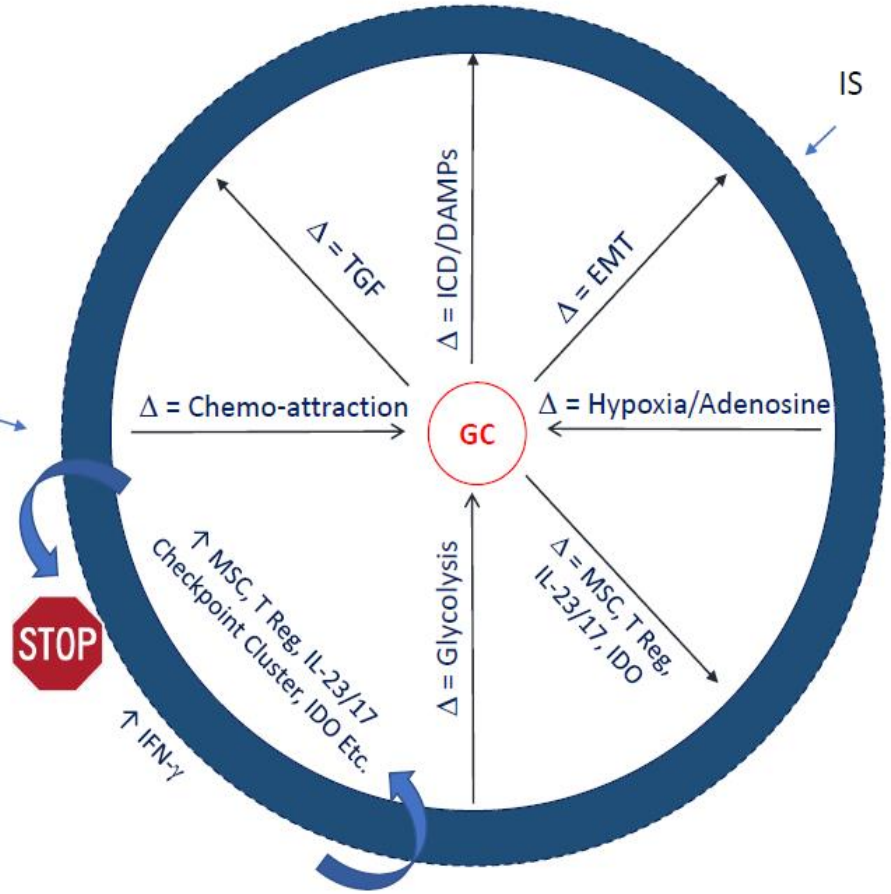


Stromal Excluded



Immune Desert





DAMPs = Damage Associated Molecular Patterns
GC = Germinal Center
ICD = Immun. Cell Death
IS = Immune Siege
MSC – Myeloid Suppressor Cells

Need for tools for *quantitative* and *spatial* analysis of different putative mechanisms relevant to immune-resistance in solid tumors