Modélisation du microenvironnement tumoral: le paradigme des cancers MSI-H

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Pattern of response in MSI-H

B Radiographic Response

- Mismatch repair–proficient colorectal cancer
- Mismatch repair–deficient colorectal cancer
- Mismatch repair–deficient noncolorectal cancer

Change from Baseline in the Sum of Longest Diameters (%)

- 20% increase (progressive disease)
- 30% decrease (partial response)

PD-1 Blockade in Tumors with Mismatch-Repair Deficiency D.T. Le, NEJM, June 2016
Deciphering tumor and micro-environment

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- Genomic analyses
- Immunogenomic analyses
- Integrative analyses

- Molecular mechanisms
- Predictive biomarkers
- Drug targets
- Therapeutic strategies

A problem: mutational load & immune infiltration

Spranger S, et al. Density of immunogenic antigens does not explain the presence or absence of the T-cell-inflamed tumor microenvironment in melanoma. PNAS; 2016;113:E7759–68.

Lynch and POLE syndromes: some are immuno depleted

Are all MSI Equals?

EL-DAKDOUKI Y, VERLINGUE L et al. Poster #1171P ESMO 2017
CD8+ T-cells > MSI status

Identifying cancer infiltrating immune cells: a new gold standard?

Prognosis impact associated with tumor infiltration by various hematopoietic populations (IHC mainly)

Immune Contexture, Immunoscore, and Malignant Cell Molecular Subgroups for Prognostic and Theranostic Classifications of Cancers, Etienne Becht, Advances in Immunology, Volume 130, 2016
How to integrate such information?

Artificial neural network

Hidden

Input

Output

Ok for face recognition, car driving, finance...

Molecular interaction network

VS

Ok for face recognition, car driving, finance...

...but biology already has regulation networks!

Verlingue L, et al. A. A comprehensive approach to the molecular determinants of lifespan using a Boolean model of geroconversion. Aging Cell. 2016 Sep
Dynamic regulation networks

IL1/IL6

T CD4

Cancer cells

Macrophages

Dendritic cells
Merci pour votre attention