La medicina di precisione nel tumore del polmone

dalla mutazione al singolo Paziente

Paolo Marchetti

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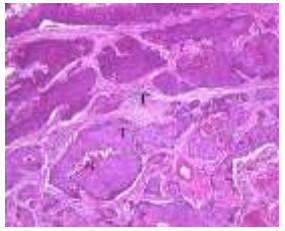
NEW TREATMENT ALGORITHM FOR ADVANCED SQUAMOUS NSCLC



Squamous

TEST PD-L1 : PD-L1 ≥ 50% PEMBRO (30% of NSCLC)

1st Line

CBDCA+Tax+Pembro all comers
CT+Nivo PD-L1 < 1%
Nivo+IPI in high TMB (not yet approved)

TEST PD-L1 : PD-L1 < 50%

PLATIN + GEM/TXT/TAX/ VNR/ABR

Nivolumab

Atezolizumab

Pembrolizumab (PD-L1 ≥ 1%)

2nd Line

Docetaxel ± Ramucirumab

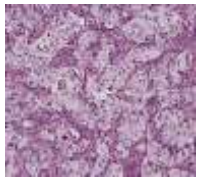
3rd Line

Erlotinib

4rd Line

NEW TREATMENT ALGORITHM FOR A-NONSQUAMOUS WT NSCLC

EGFR,ALK,ROS-1 + in about 20% of cases → Targeted Therapies



Non Sq WT

1st Line

TEST PD-L1 : PD-L1 ≥ 50% PEMBRO (30% of NSCLC)

DDP+Pem+Pembro all comers (FDA/EMA+)
CBDCA+Tax+Bev+Ate all comers
CT+Nivo PD-L1 < 1%
Nivo+IPI in high TMB (not yet approved)

TEST PD-L1 : PD-L1 < 50%

DDP/Pem

P-based CTx + BEVA

Pem Maintenance

BEVA until PD

Nivolumab

Atezolizumab

Pembrolizumab PD-L1 ≥ 1%

2nd Line

Docetaxel ± Nindetanib

Docetaxel ± Ramucirumab

3rd Line

Erlotinib

Pemetrexed

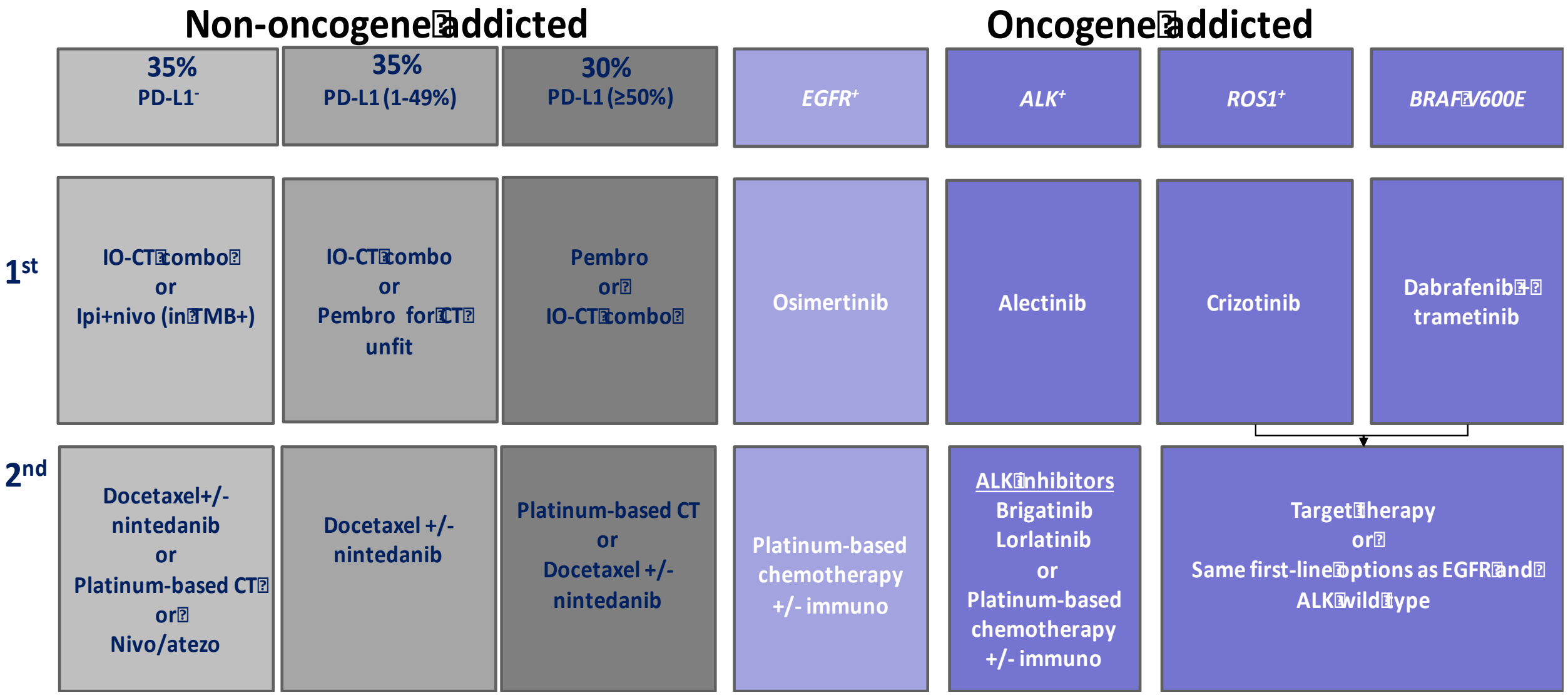
4rd Line

Erlotinib

5rd Line

Courtesy of C. Gridelli, 2018

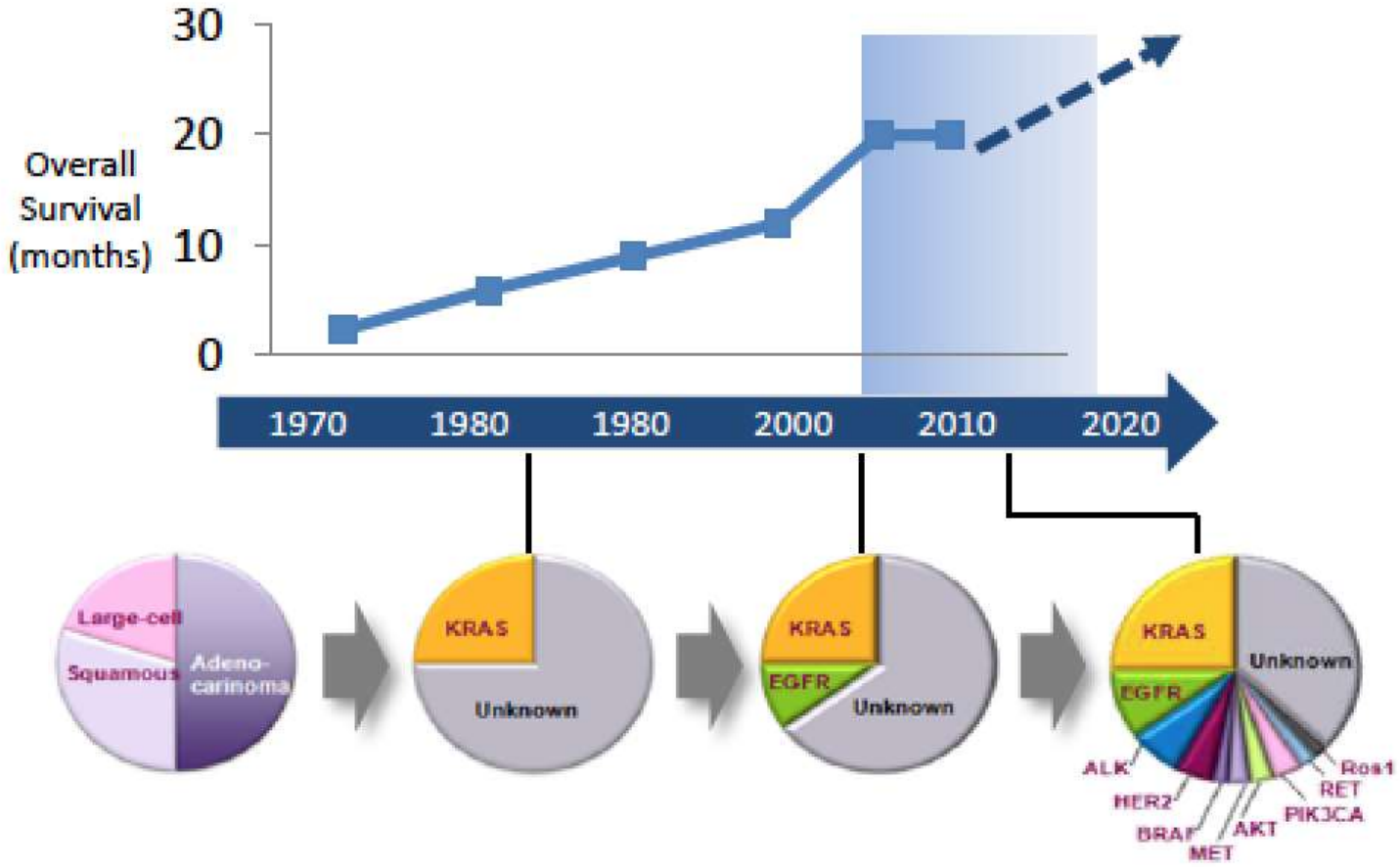
New options for NSCLC therapy in 2019



Courtesy Federico Cappuzzo, 2018

Targeted therapeutics are improving survival…

Example: NSCLC is an evolving landscape



The rise of omics…or the search for biomarkers?

- **Diagnostic biomarkers**
  - High specificity – detection of specific disease
- **Prognostic biomarkers**
  - Differential expression – correlation with patient outcome
  - Stratification of high vs. low risk patients
  - Guide for patient information and monitoring
- **Predictive biomarkers**
  - Differential expression – correlation with treatment response
  - Stratifictation to responders and non-responders
  - Guide to determine selection of therapeutic regimens

Cancer Biomarkers Market Worth 20.48 Billion USD by 2022

According to a new market research "*Cancer Biomarkers Market by Type (Protein Biomarker, Genetic Biomarker), Cancer Type (Breast, Melanoma, Leukemia, Lung), Profiling Technology (Omics, Imaging, Immunoassay, Bioinformatics), Application (Diagnosis, Prognostics, R&D) - Global Forecast to 2022*", Published by MarketsandMarkets™, **the market is projected to reach USD 20.48 Billion by 2022 from USD 11.53 Billion in 2017**.

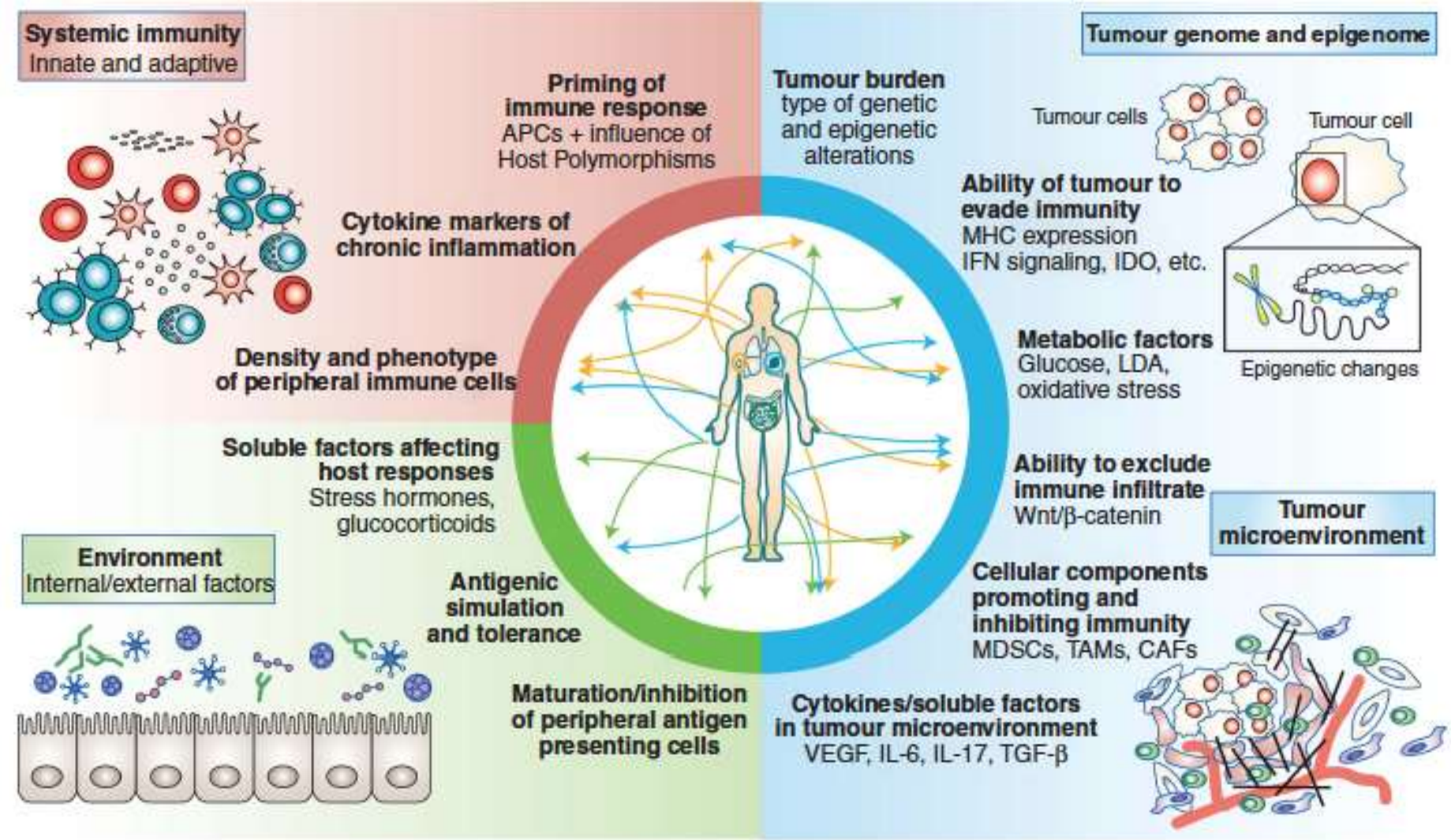
Biomarkers in the Age of Omics

Predicting response to checkpoint inhibitors beyond PD-L1 (or mutational burden and MSI)

- Limitations to biomarker discovery are not only technical or bioinformatic but conceptual as well:
  - First, the confusion stemming from the imposition of a ***pathology-type immunohistochemical marker*** (IHCM) concept on omics data without fully understanding the characteristics and limitations of IHCMs as applied in clinical pathology.
  - Second, the lack of serious consideration for the scope of ***disease heterogeneity***.
  - Third, the refusal of the biomedical community to borrow from ***other biological disciplines*** their well established methods for dealing with heterogeneity.

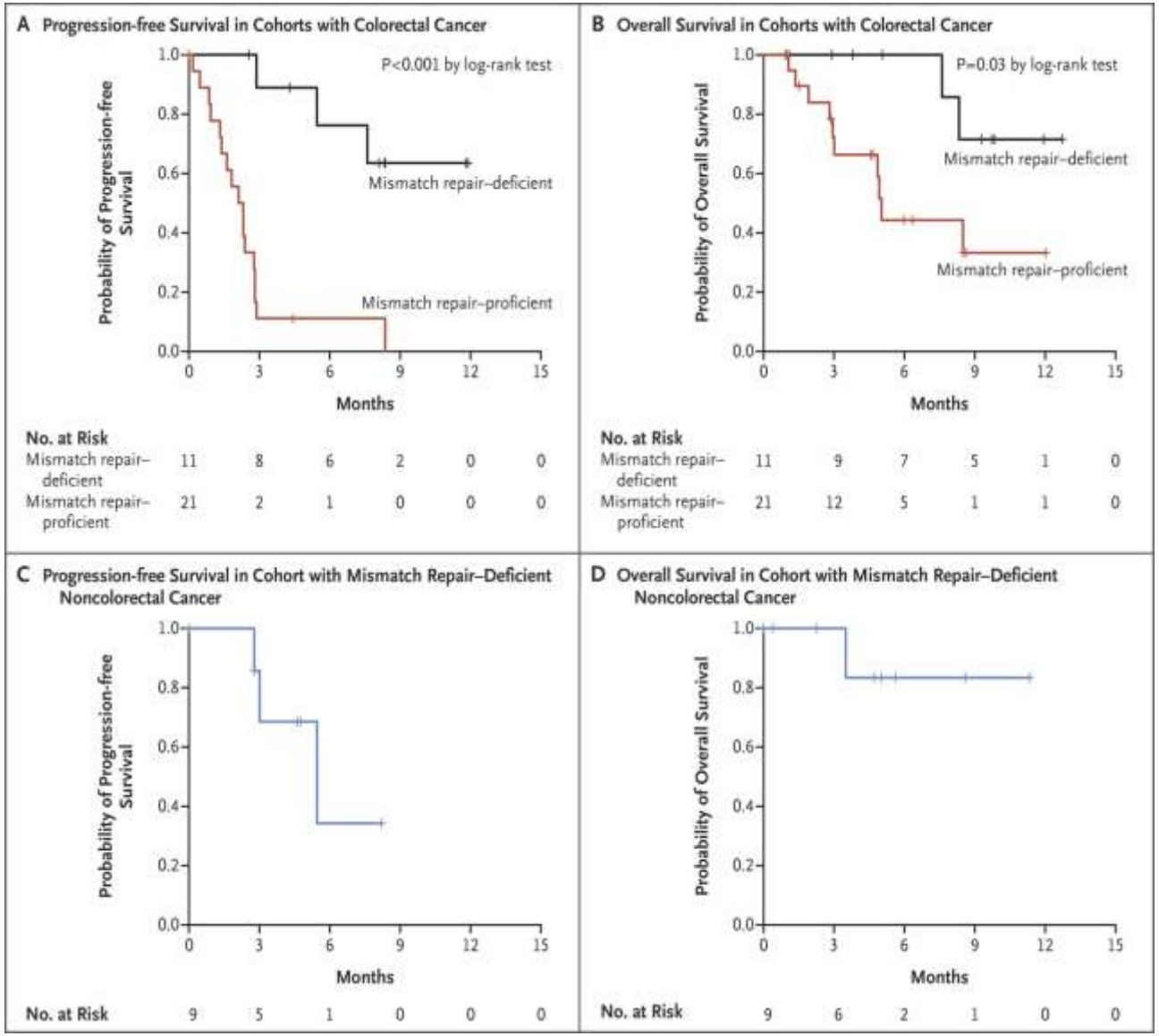
Mones S. Abu-Asab et al., OMICS 15, 105-112, 2011

Immune parameters influencing response to immunotherapy



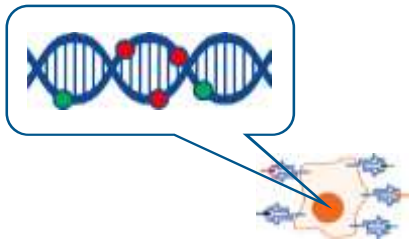
Cogdill A, Brit J Cancer 2017

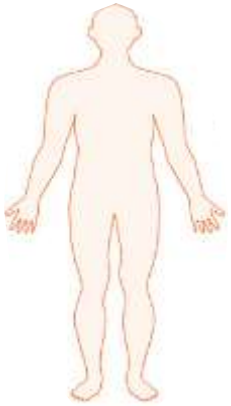
Clinical Benefit of Pembrolizumab Treatment According to Mismatch-Repair Status



Le DT et al. N Engl J Med 2015; 372:2509-2520.

TMB & ICIs therapy





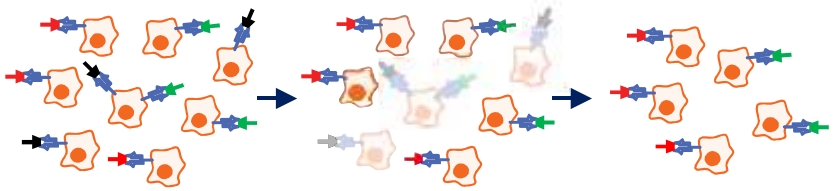
Immune checkpoint blockade therapy

e.g., anti-PD-1, anti-CTLA-4

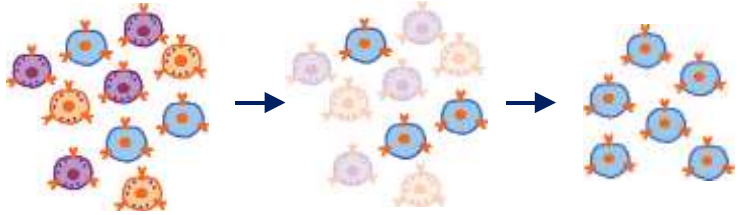
High tumor mutation load/burden correlates with increased neoantigens

Response to therapy

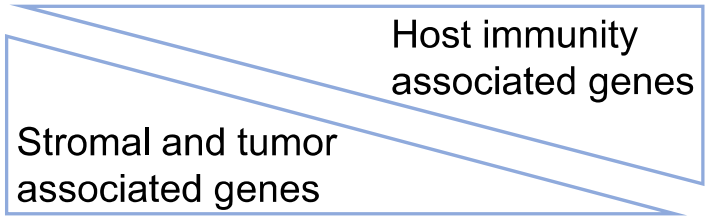
Tumor cells expressing certain neoantigens are lost



Clonal T-cell populations expand in proportion to the number of neoantigens lost



Changes occur in the microenvironment and gene expression programs



Riaz et al., Cell 2017

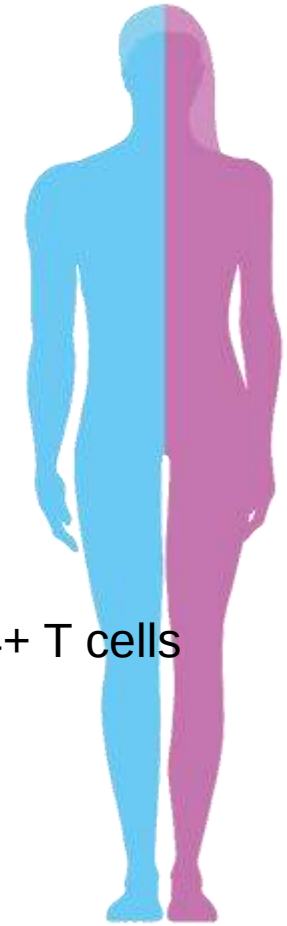
Sexual Dimorphism of Immune Responses: A New Perspective in Cancer Immunotherapy

♂ *Innate immunity*

↑ NK counts
↑ neutrophils mobility and inflammatory activity

♀ *Innate immunity*

↑ DC antigen presentation
↑ DC production of IFNγ
↑ macrophages phagocytic activity
↑ neutrophils phagocytic activity
↑ MDSCs suppressive function
↑ frequency of ILCs



♂ *Adaptive immunity*

↑ CD8+ T cell counts
↑ IL-17 production by CD4+ T cells
↑ Treg cell counts
↑ Th1 cell functions
↓ B cell counts
↓ basal Ig
↓ antibody responses

♀ *Adaptive immunity*

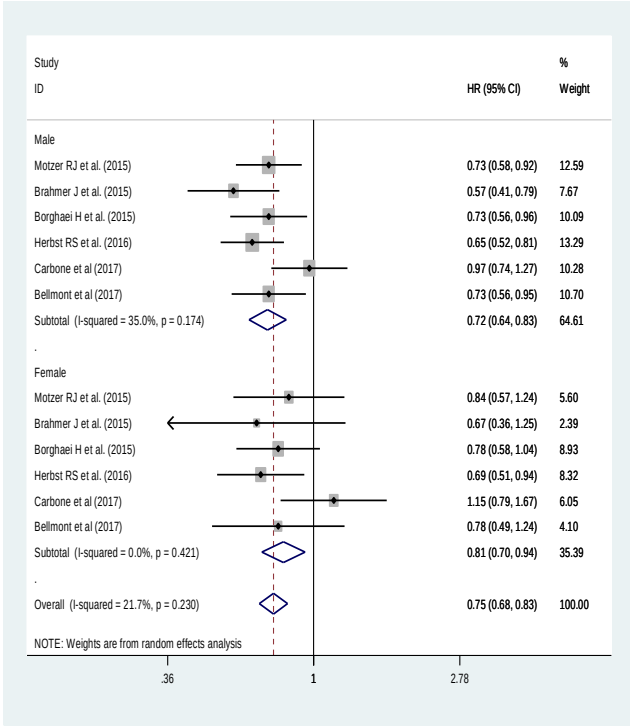
↑ CD4+ T cell counts
↑ activated and proliferating CD4+ T cells
↑ IFNγ production by CD4+ T cells
↑ activated and proliferating CD8+ T cells
↑ CD8+ T cell cytotoxic activity
↑ CD4+/CD8+ T cell ratio
↑ Th2 cell functions

I Capone, P. Marchetti, P.A. Ascierto et al, Frontiers in Immunology. 2018;9:552.

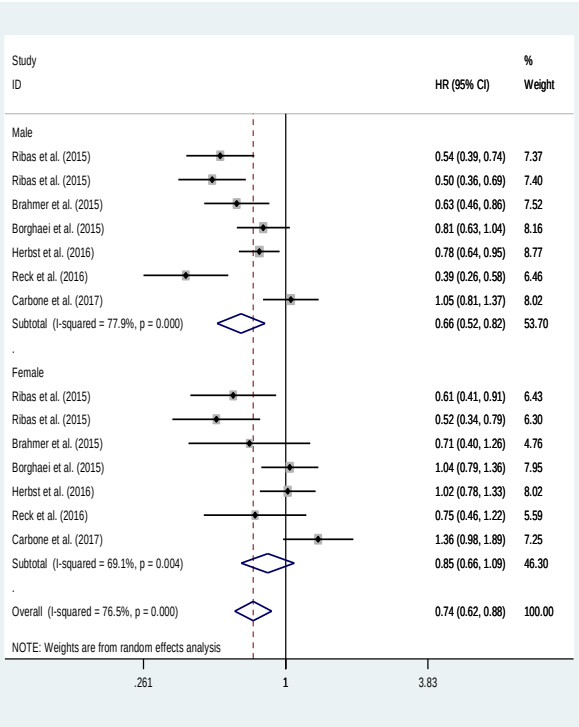
The sexist behaviour of immune checkpoint inhibitors in cancer therapy?

Andrea Botticelli[1,2], Concetta Elisa Onesti[1,2], Ilaria Zizzari[3], Bruna Cerbelli[4], Paolo Sciattella[5], Mario Occhipinti[1], Michela Roberto[1,2], Francesca Di Pietro[1,2], Adriana Bonifacino[6], Michele Ghidini[7], Patrizia Vici[8], Laura Pizzuti[8], Chiara Napoletano[3], Lidia Strigari[9], Giulia D'Amati[4], Federica Mazzuca[1,2], Marianna Nuti[3] and Paolo Marchetti[1,2]

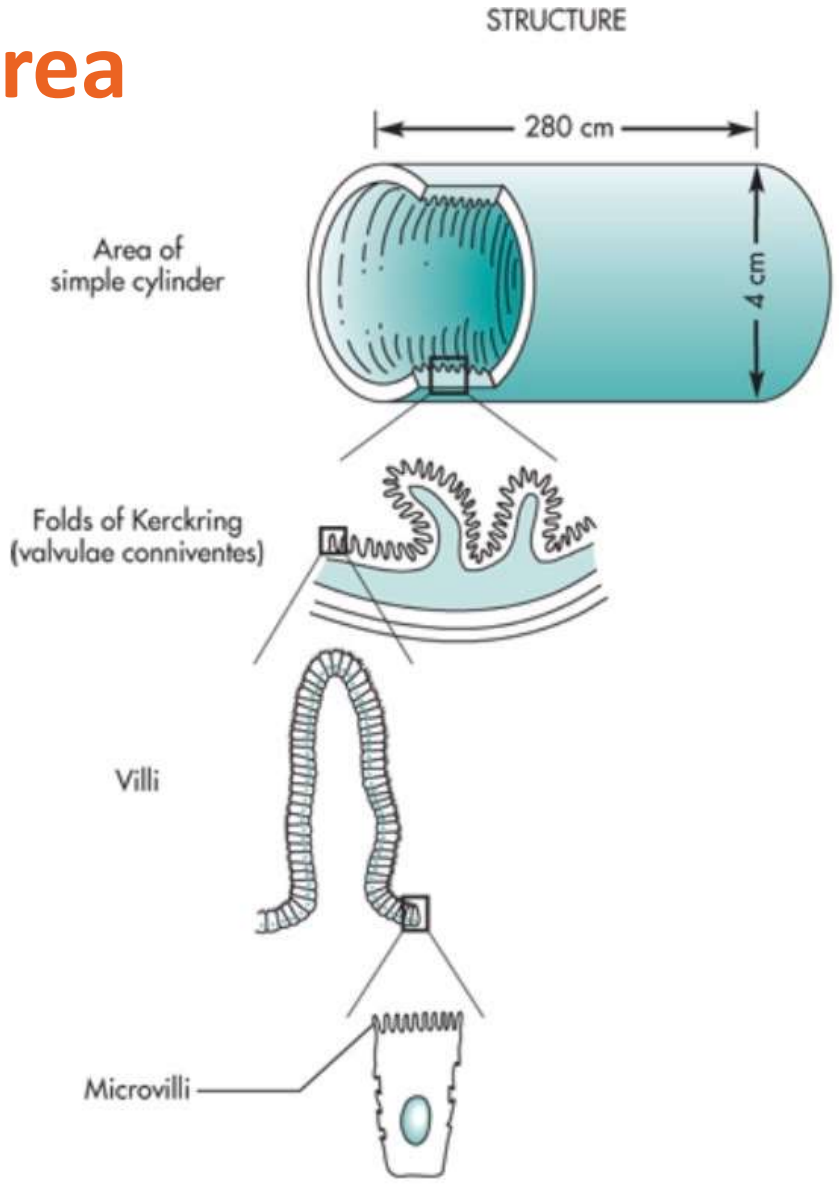
Anti-PD-1: OS



Anti-PD-1: PFS



Intestinal surface area



Source: Leon Shargel, Andrew B.C. Yu: Applied Biopharmaceutics & Pharmacokinetics, 7th Ed.
www.accesspharmacy.com
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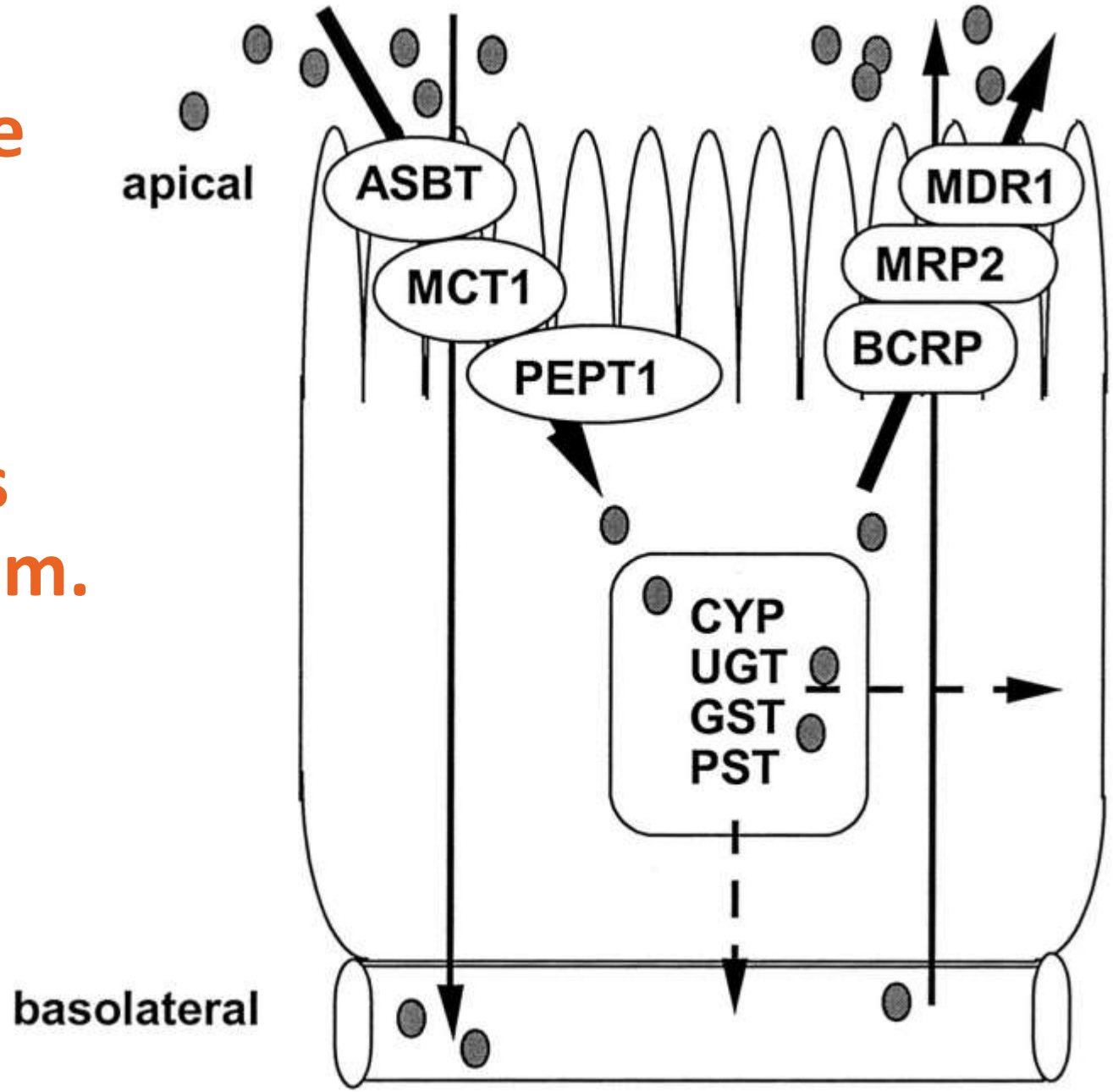
Schematic diagram of the enterocyte of the intestine showing absorptive and efflux transporters at the apical and basolateral membranes, and enzymes for intracellular metabolism.



Cross-talk between microbiota and immune fitness to steer and control response to anti PD-1/PDL-1 treatment

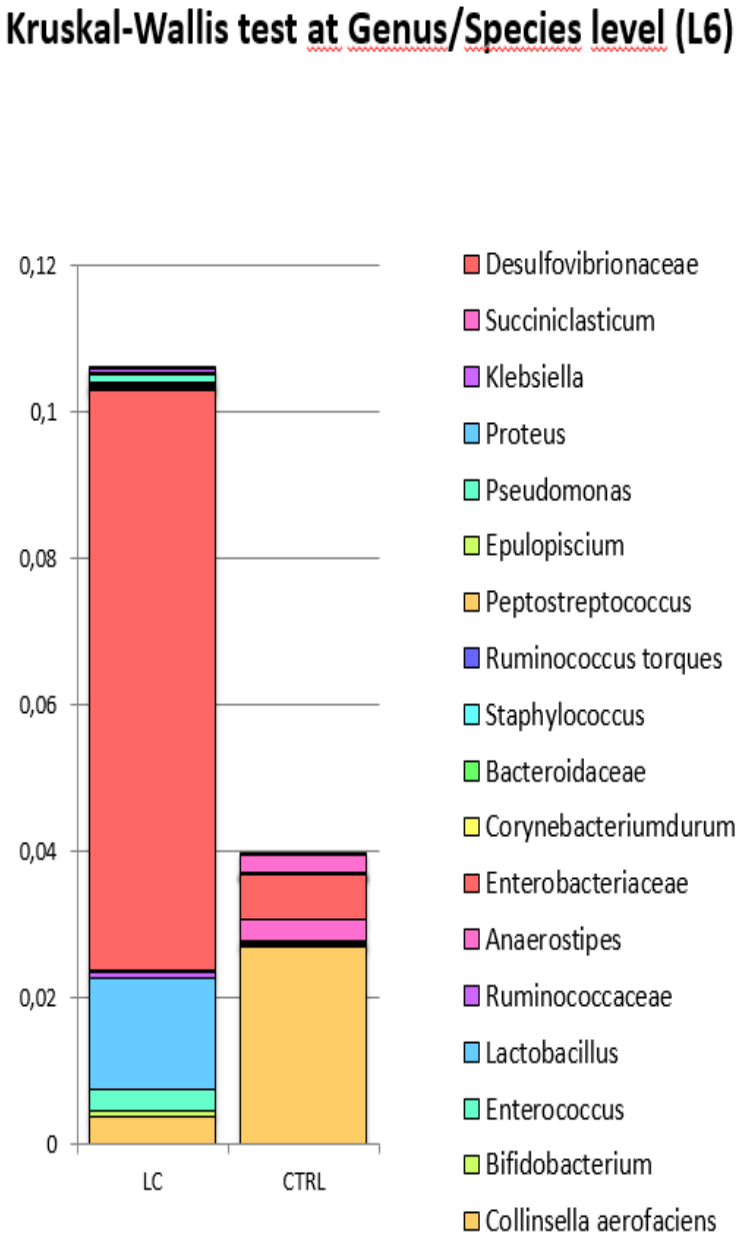
...The loss of the protective function of intestinal barriers that interacts with the environment measured as increased intestinal permeability and the changes occurring in the microbiota composition have been proposed as a mechanism potentially explaining the pathogenesis of immune related toxicity. ...

A Botticelli, …, M Nuti, P Marchetti. Oncotarget, 2017, Vol. 8, (No. 5), pp: 8890-8899

CHANGES OF MICROBIOME PROFILE DURING NIVOLUMAB TREATMENT (very preliminary data)

Healthy controls/cancer patients

In NSCLC patients Rikenellaceae, Prevotella, Streptococcus, Lactobacillus ($p < 0.05$), Bacteroides plebeius, Oscillospira, Enterobacteriaceae ($p < 0.05$) appeared increased compared to CTRLs.



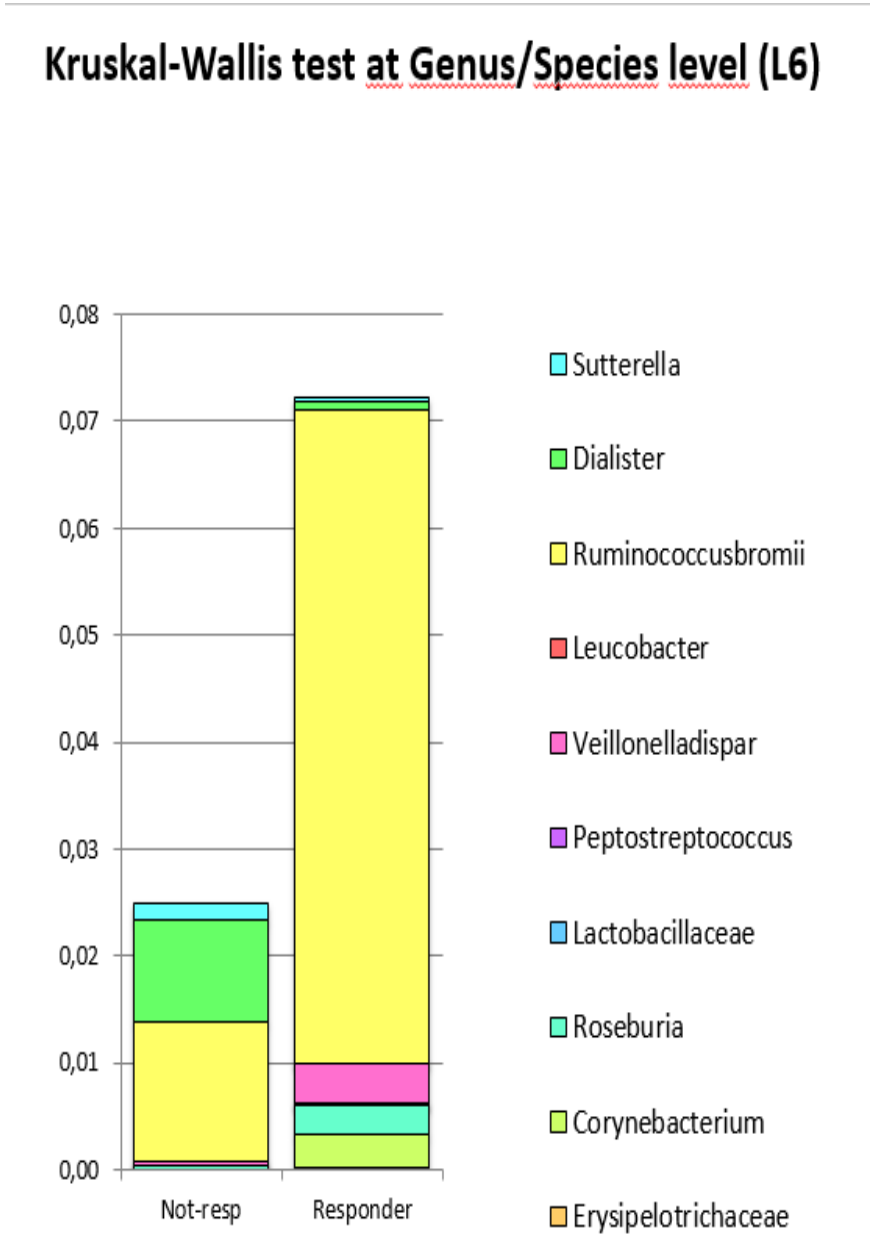
A Botticelli, …, P Marchetti, ASCO 2018

CHANGES OF MICROBIOME PROFILE DURING NIVOLUMAB TREATMENT (very preliminary data)

RESPONDERS VS NON RESPONDERS

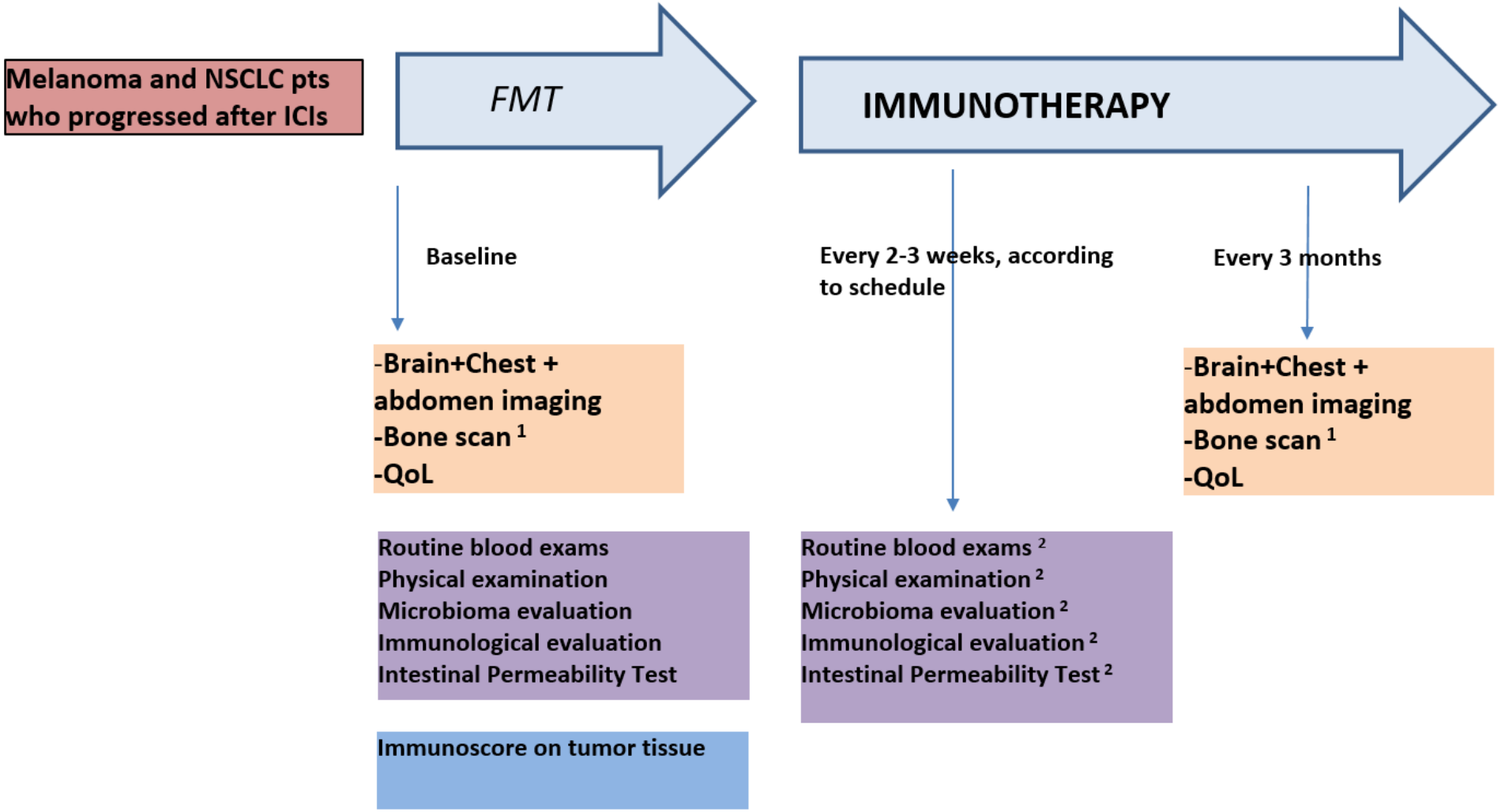
Not responders had Ruminococcus bromii, Dialister, Sutterella more abundant than responder patients to therapy ($p < 0.05$).

Slightly increased in responders appeared Akkermansia muciniphila, Bifidobacterium longum and Faecalibacterium prausnitzii ($p < 0.05$). Propionibacterium acnes, Veillonella, Staphylococcus aureus, Peptostreptococcus appeared significantly over-expressed.



A Botticelli, …, P Marchetti, ASCO 2018

Faecal Transplantation



[1] If clinically indicated

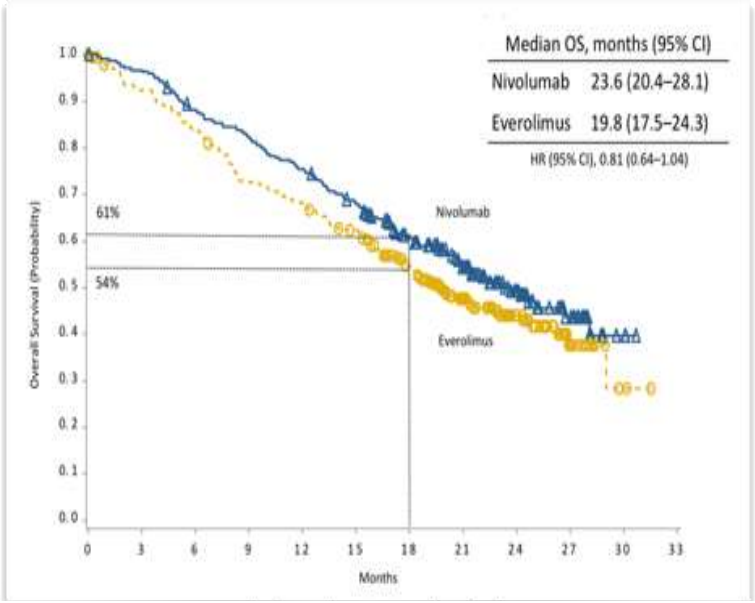
[2] in the case of serious adverse events additional evaluation will be perfmormed

Pazopanib immunopriming effect.

What was our starting point?

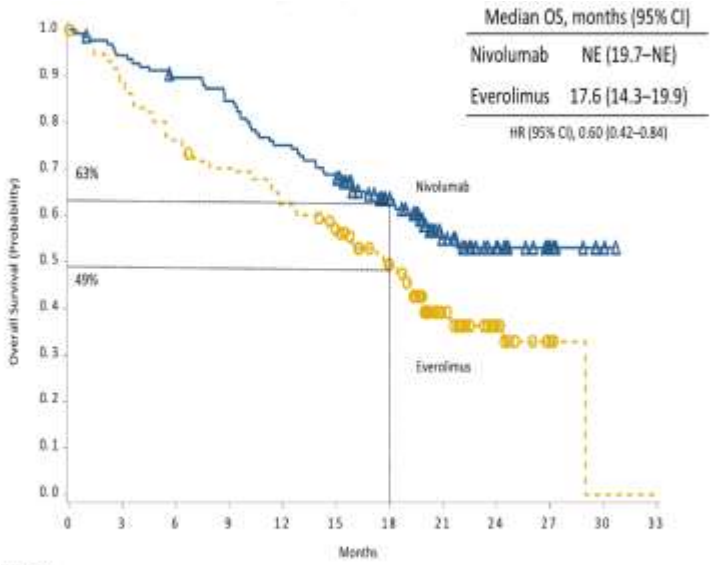
Nivolumab

OS: Prior sunitinib



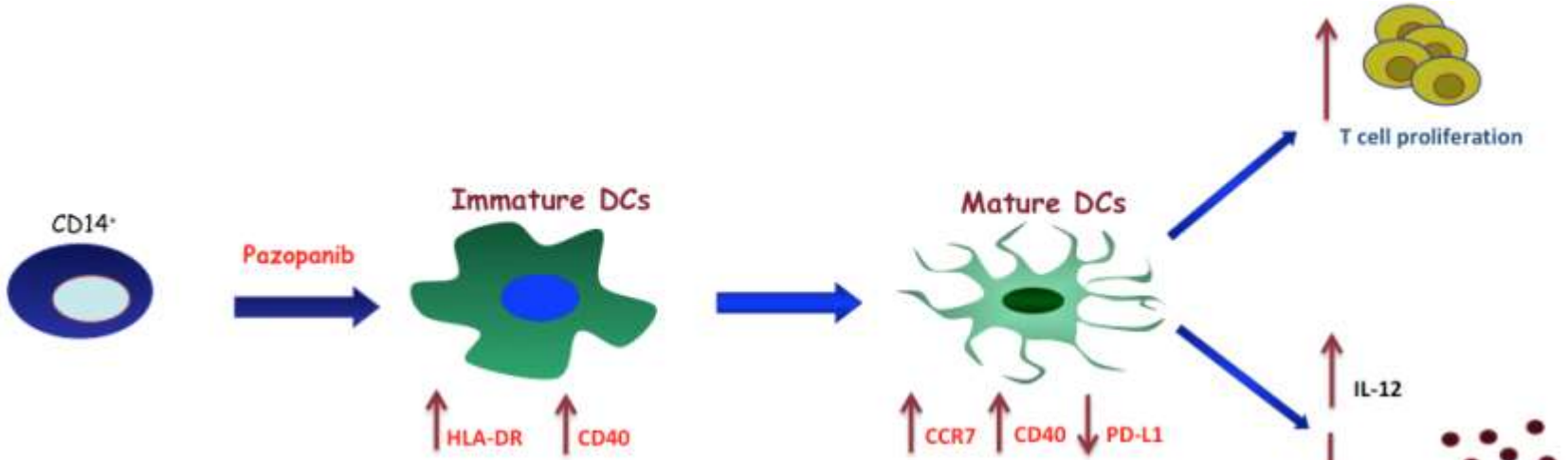
Nivolumab

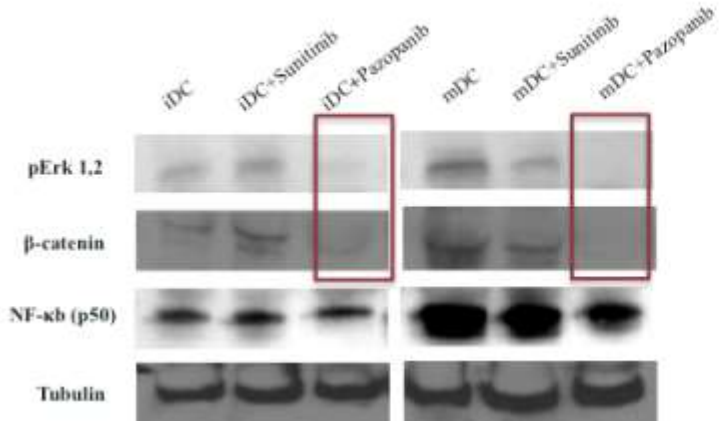
OS: Prior pazopanib



Motzer RJ, ASCO 2016

The example of TKI Pazopanib anti VEGF-R: immunopriming effect on DC downregulating Erk/β-catenin





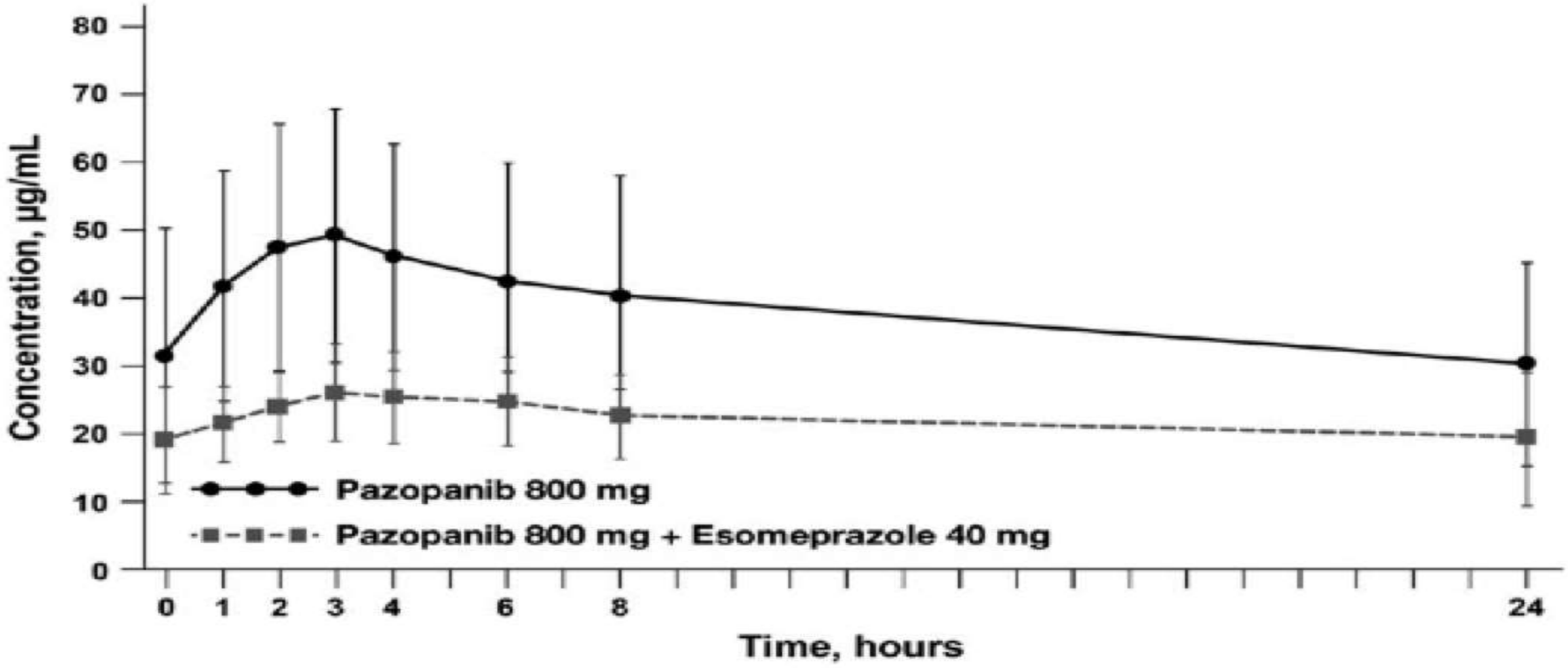
Erk/β-catenin signaling :

- **Induction of inflammatory cytokine IL-10 and IL 27**
- **Induction of IDO, Treg and TGF-β**
- **Involved in tumor progression**
- **Involved in lymphocyte trafficking**

I G Zizzari, C Napoletano, A Botticelli … P Marchetti, M Nuti Cancer Immunol Res April 26 2018

When Pharmacological interactions are detrimental for efficacy

Metastatic renal cancer, intermediate risk according to Moetzer Criteria.
Pazopanib as first line of therapy. Self-administration of esomeprazole.



Courtesy of D. Santini, 2017

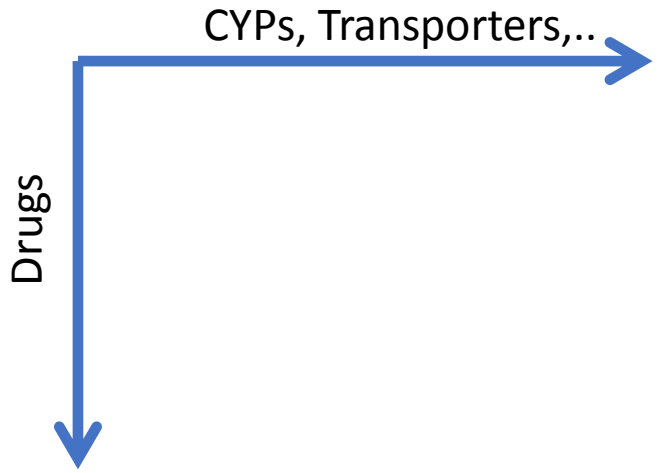
Tan AR et al. Cancer Chemother Pharmacol (2013) 71:1635–1643

Polypharmacy, Drug Metabolism / Interactions

- ~ 45% above 50 years take more than 5 drugs per day+

- Free Online Database: Transformer*
  - 2.800 Drugs
  - 60.000 Combination conflicts
  - 5.500 Interactions
    - 4.000 Phase I (CYPs)
    - 400 Phase II enzymes
    - 1.100 Transporter
    - 350 Food interactions
  - >100.000 Scientific references

  (from text mining + manual curation)

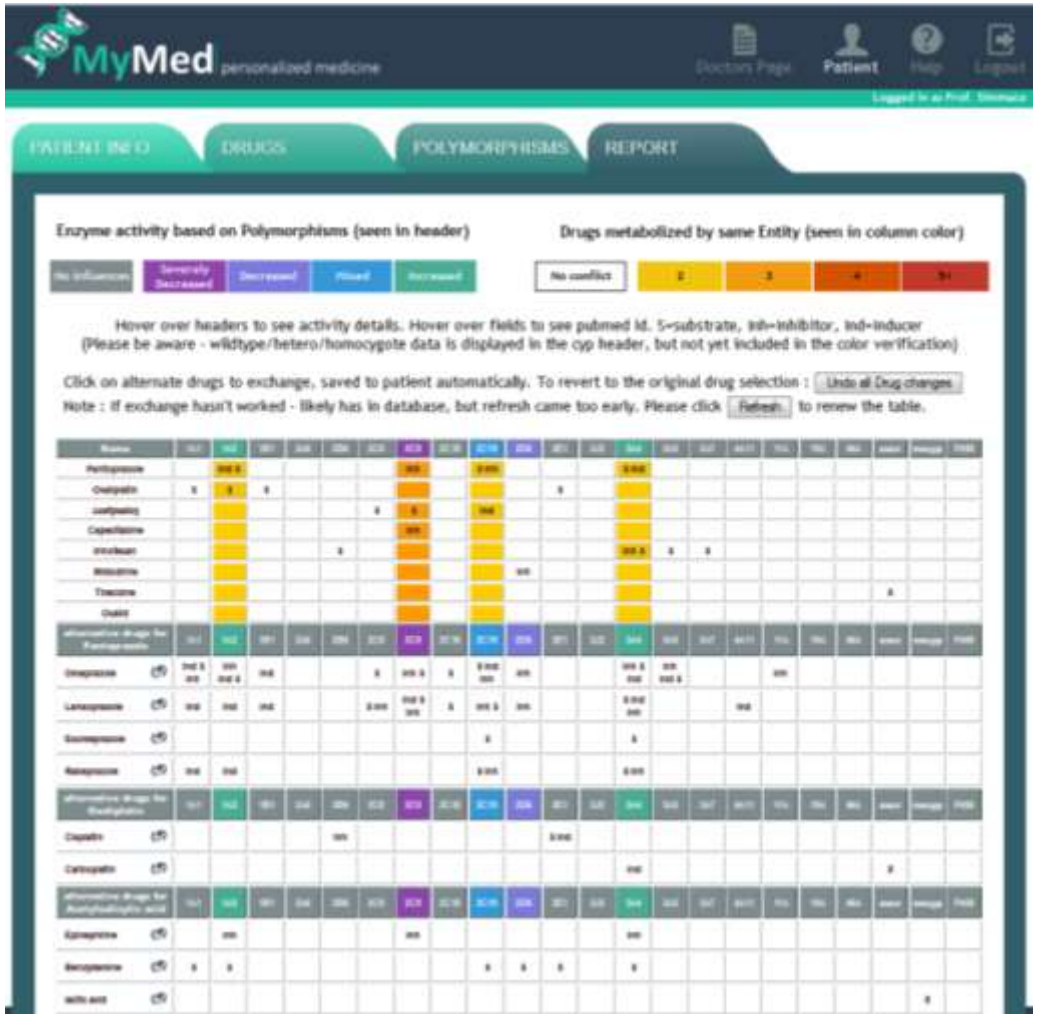


- Free Online Database: Withdrawn**

http://bioinformatics.charite.de/transformer

+ Morgan, T.K., et al. (2012) A national census of medicines use: a 24-hour snapshot of Australians aged 50 years and older. *Med J Aust*, **196**, 50-53.
* Hoffmann, M.F., Preissner, S.C., Nickel, J., Dunkel, M., Preissner, R. and **Preissner, S.** (2014) The Transformer database: biotransformation of xenobiotics. *Nucleic Acids Res*, 42, D1113-1117.
** WITHDRAWN: a resource for withdrawn and discontinued drugs. Siramshetty VB, Nickel J, Omieczynski C, Gohlke BO, Drwal MN, Preissner R. Nucleic Acids Res. 2016; 44(D1): D1080-6.

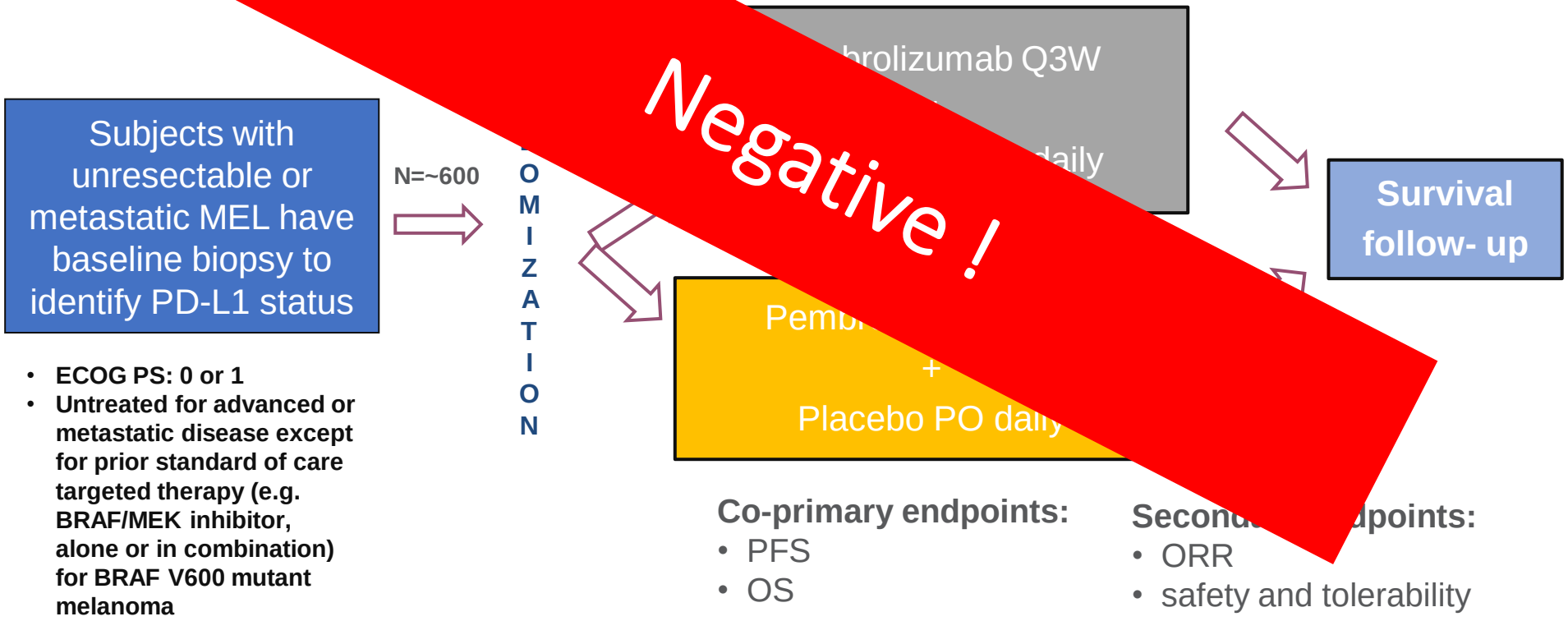
Charité University partnership: the MyMed tool



Robert Preissner, Charité, Berlin

ECHO-301 (Keynote-252): Phase 3 study of pembrolizumab + epacadostat or placebo in patients with unresectable or metastatic melanoma

- Randomized Phase 3, double-bl… …ntrolled study of pembrolizumab in combination with the IDO1 inhibitor, epacadostat or placebo in subjects with unres… …melanoma



- **ECOG PS: 0 or 1**
- **Untreated for advanced or metastatic disease except for prior standard of care targeted therapy (e.g. BRAF/MEK inhibitor, alone or in combination) for BRAF V600 mutant melanoma**

Negative !

ORR, overall response rate; OS, overall survival; PFS, progression-free survival; ECOG-PS, Eastern Cooperative Oncology Group performance status; Q3W, every 3 weeks; BID, twice daily

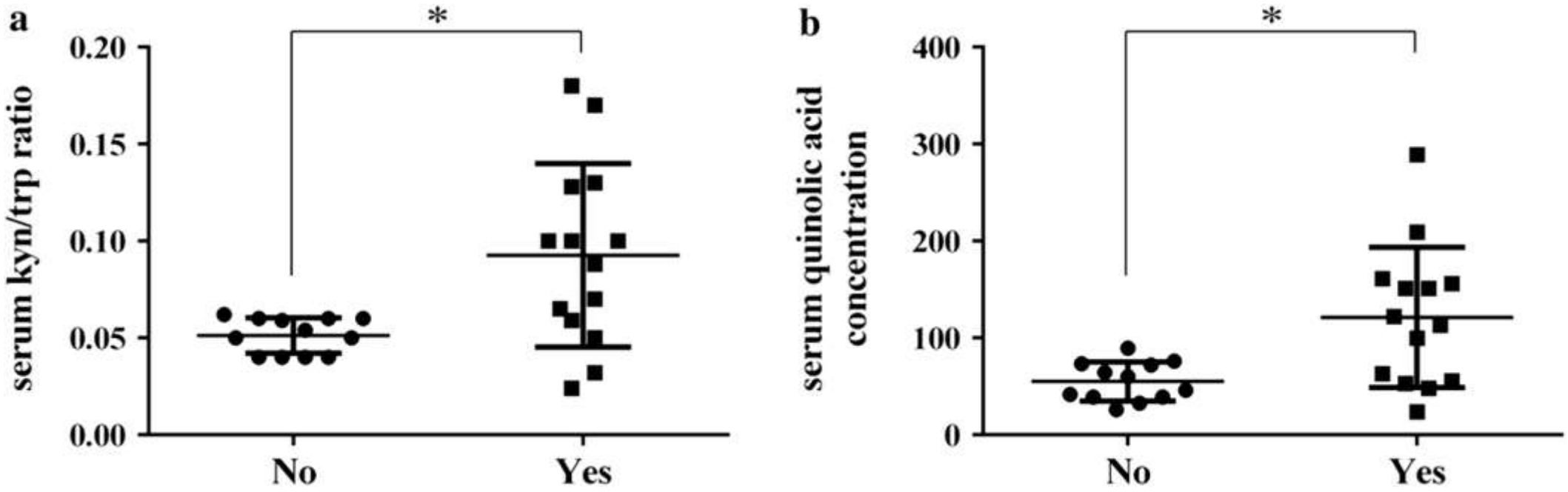
Clinicaltrials.gov: NCT02752074

Presented by Paolo A. Ascierto at ASCO 2018

Can IDO activity predict primary resistance to anti-PD-1 treatment in NSCLC?

Correlation of serum kyn/trp ratio and serum quinolic acid concentration with immunotherapy response.

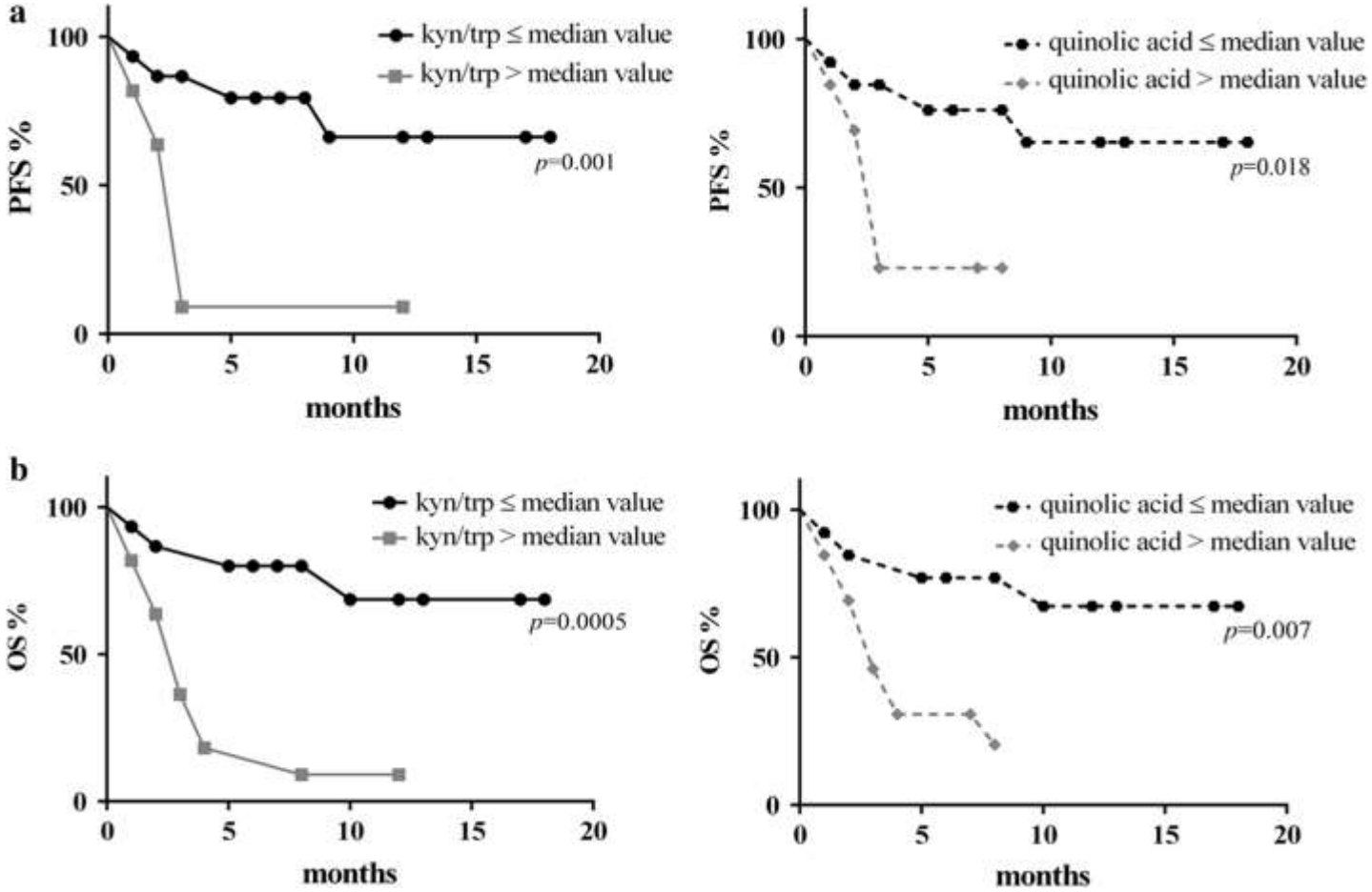
Patients who showed an early progression (YES, n = 14) present a significantly higher concentration of kyn/trp ratio (a) and quinolic acid concentration (b) compared to patients who do not have an early progression (NO, n = 12). #p < 0.05 (Mann–Whitney test)



A Botticelli, …, P Marchetti, et al. J Transl Med (2018) 16:219

Can IDO activity predict primary resistance to anti-PD-1 treatment in NSCLC?

Correlation of serum kyn/trp ratio and quinolonic acid concentration with survival. Progression free survival (PFS, a) and overall survival (OS, b) were addressed by the Kaplan–Meier method and log-rank test

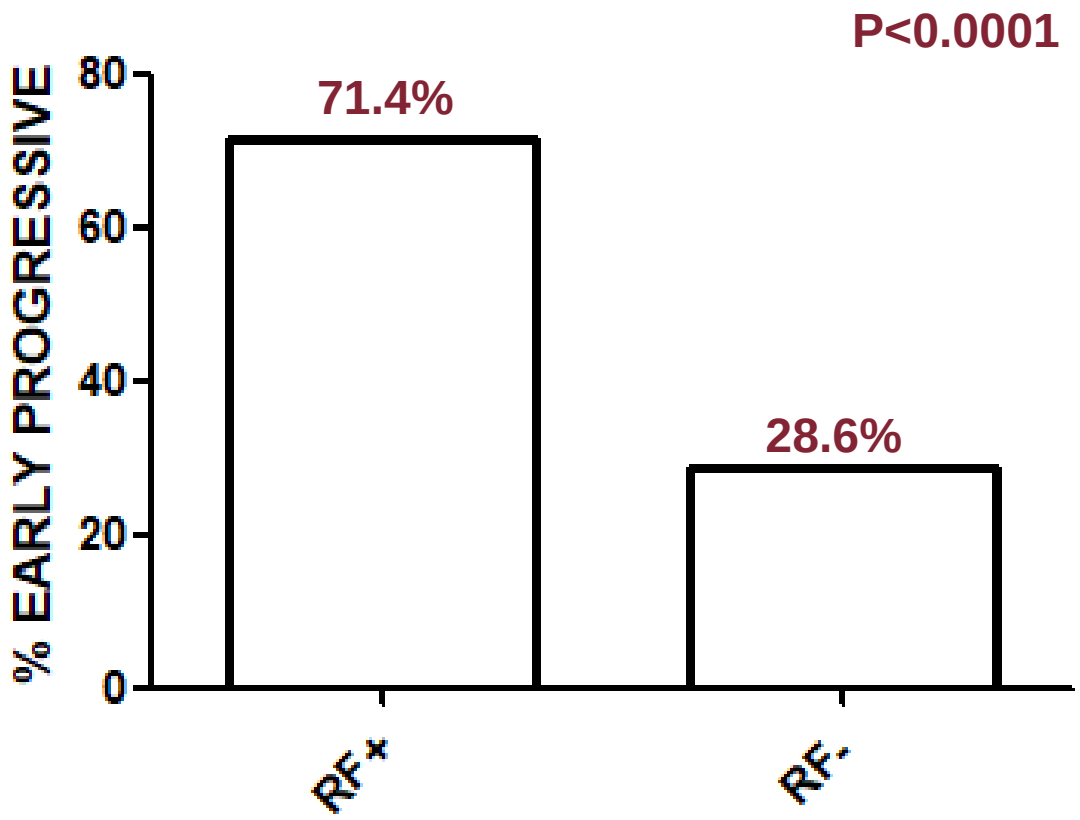


A Botticelli, …, P Marchetti, et al. J Transl Med (2018) 16:219

The rheumathoid factor (RF) story….

- The reumatoid factor is an Ig-M with affinity with IgG2 and to less extent with IgG1, totally unspecific.
- Is present in serum of 70% of pts with reumathoid arthritis.
- Is present in 5-10% normal subjects – increased in the elderly.

The rheumathoid factor (RF) story….
7/35 NSCLC pts treated with nivolumab show high levels of RF
71.4% are progressive at the first evaluation



M Nuti, A. Botticelli, P. Marchetti, et al., Unpublished results

Anatomic site of metastases can influence response to nivolumab in NSCLC patients.

- Sixty-five patients, affected by stage IV NSCLC, treated with Nivolumab
- Twenty-three patients (32%) presented early progression, while 16 patients presented PFS longer than 12 months (24%).
- We found a significant association between the presence of liver metastases and early progression both at univariate analysis (p = 0,001) and multivariate analysis (p = 0,005), and between PFS > 12 months and presence of only lung and/or lymph node metastases at univariate analysis (p = 0,03).
- No statistical associations were demonstrated between disease progression and PS, age, sex and site of metastases.
- **Conclusions**: Our results suggest that liver metastases could predict resistance to immunotherapy. Otherwise lung or lymph node metastases could select patients with long term benefit.

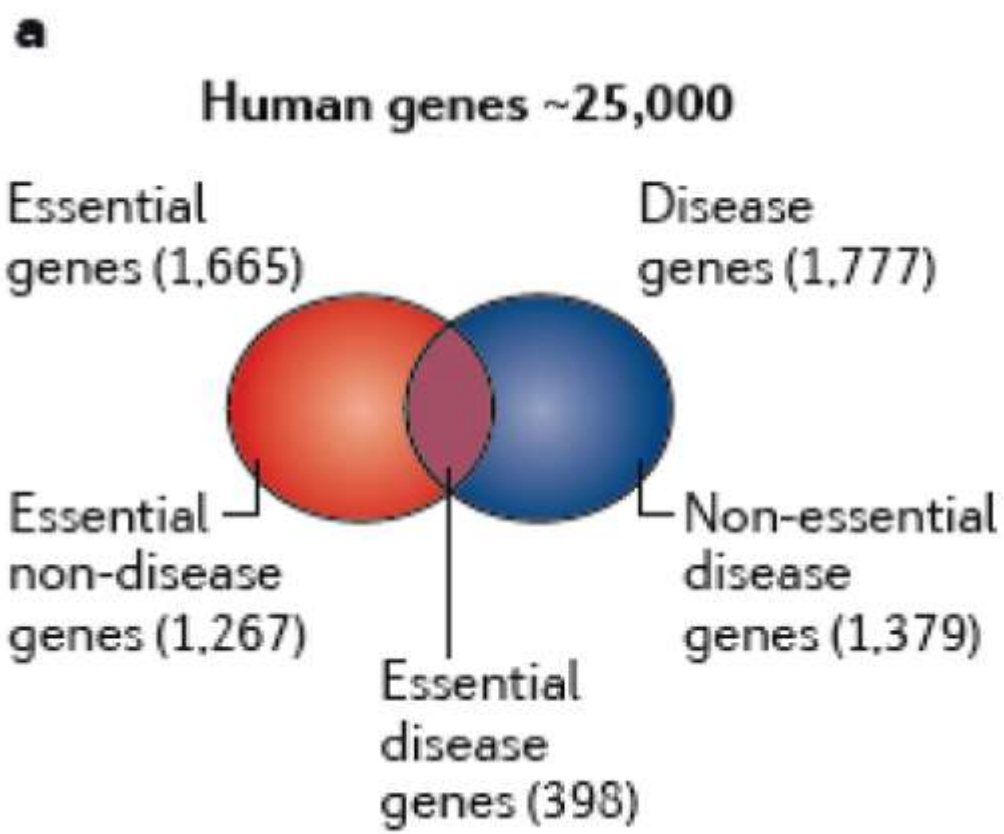
A Botticelli, …, P Marchetti, ASCO 2018

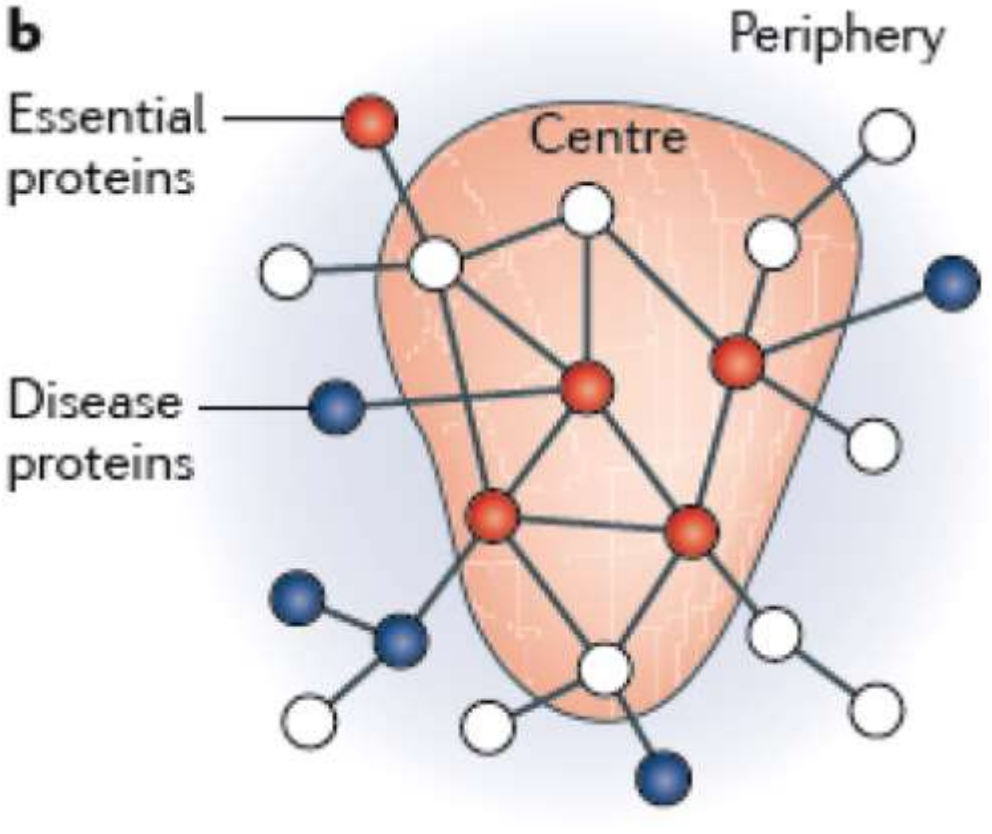
What is “Network Medicine”?

- The study of cellular, disease, and social networks which aim to quantify the complex interlinked factors contributing to individual diseases […] by integrating genetic, genomic, biochemical, cellular, physiological, and clinical data to create a network that can be used to model predictively disease expression and response to therapy.
- ***It will, no doubt, revolutionize the science and practice of medicine.***

AL Barabási, N Gulbahce, J Loscalzo Nature Reviews, Genetics Volume 12; 2011: 65

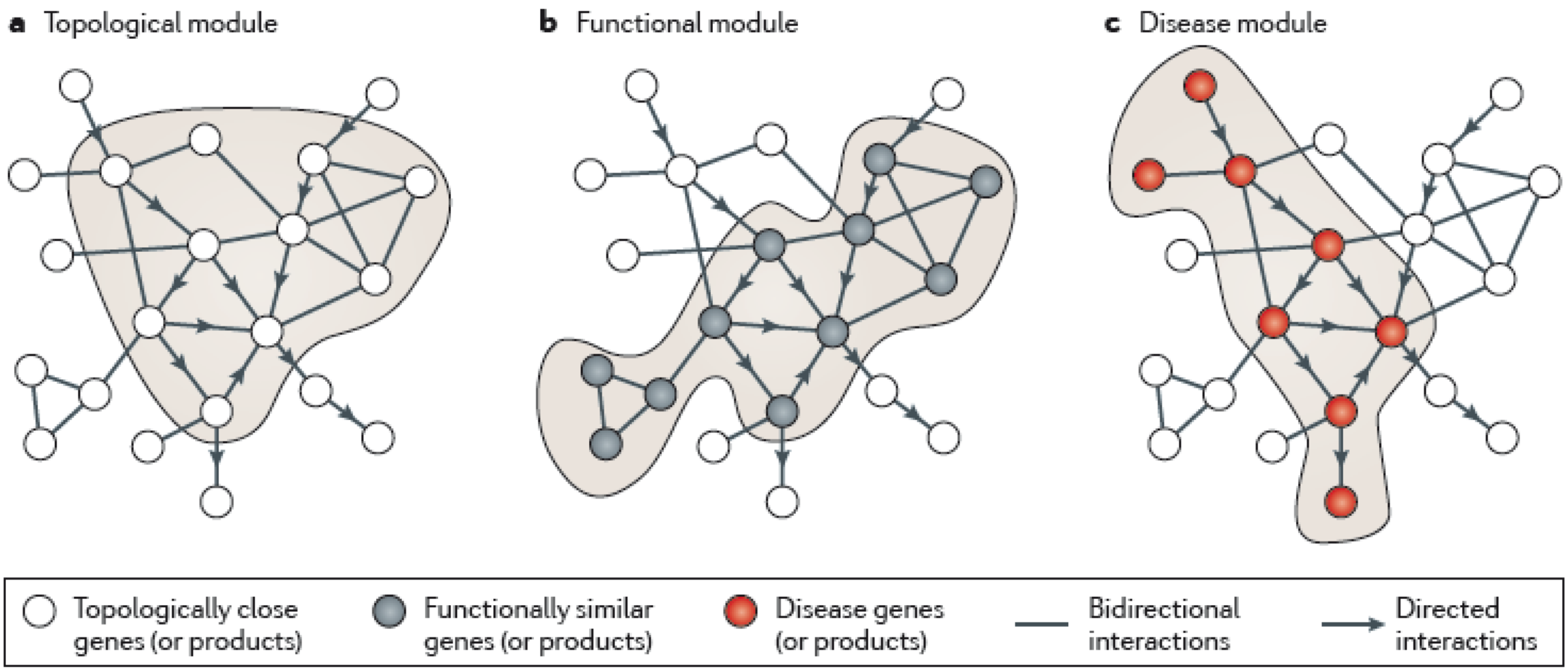
Disease and essential genes in the interactome





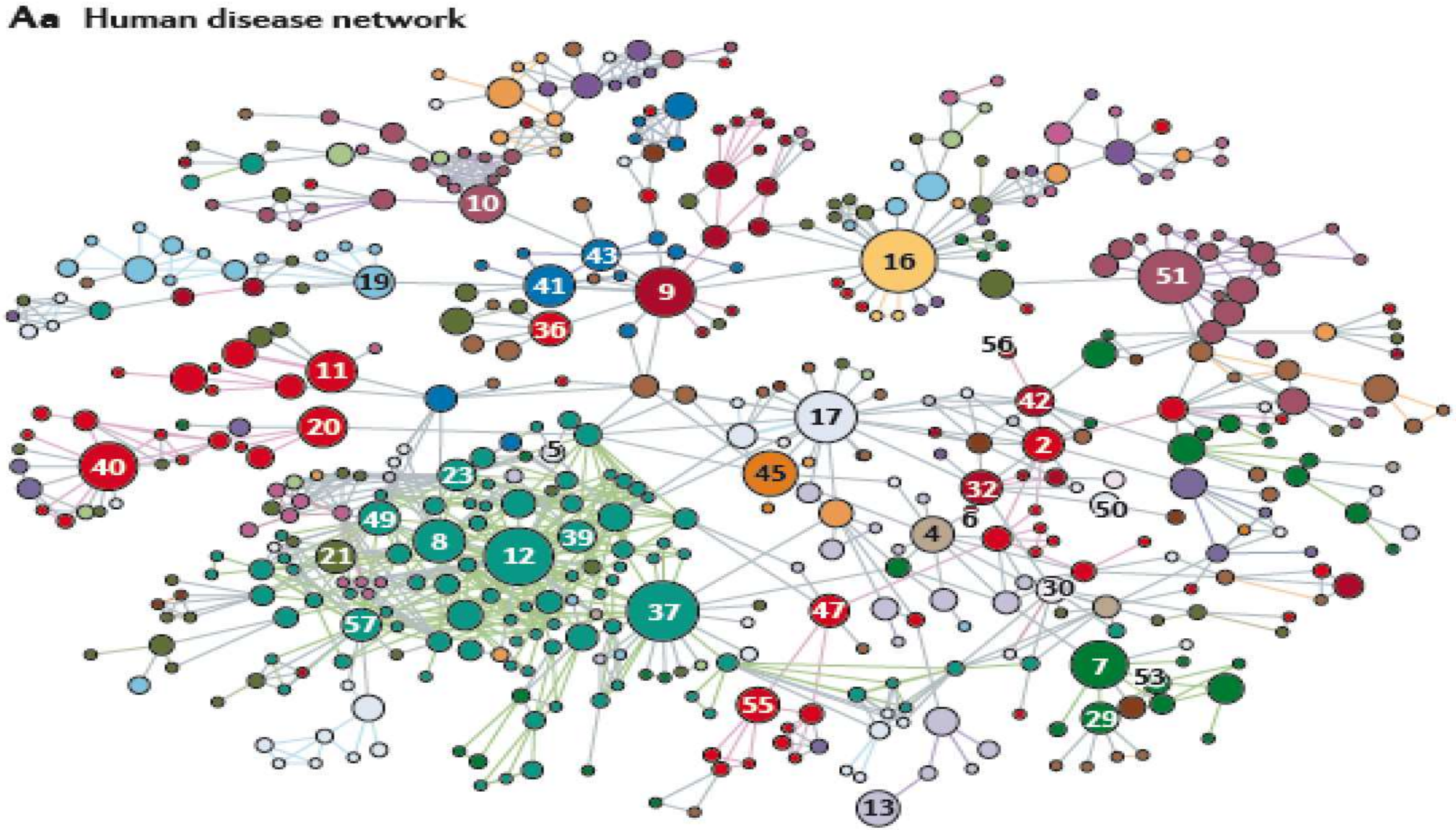
AL Barabási, N Gulbahce, J Loscalzo Nature Reviews, Genetics Volume 12; 2011: 65

Disease modules



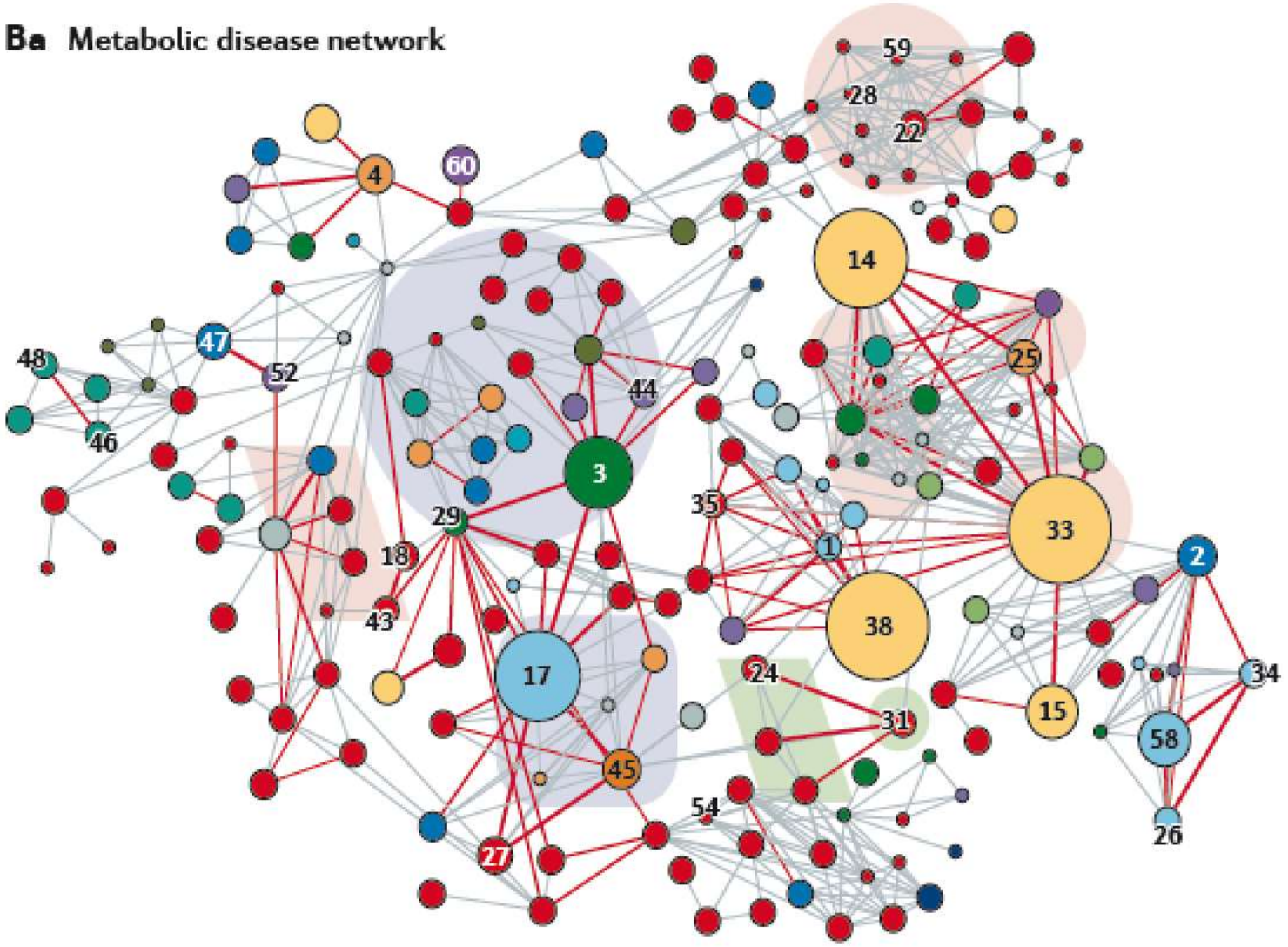
AL Barabási, N Gulbahce, J Loscalzo Nature Reviews, Genetics Volume 12; 2011: 65

Disease networks



AL Barabási, N Gulbahce, J Loscalzo Nature Reviews, Genetics Volume 12; 2011: 65

Disease and essential genes in the interactome



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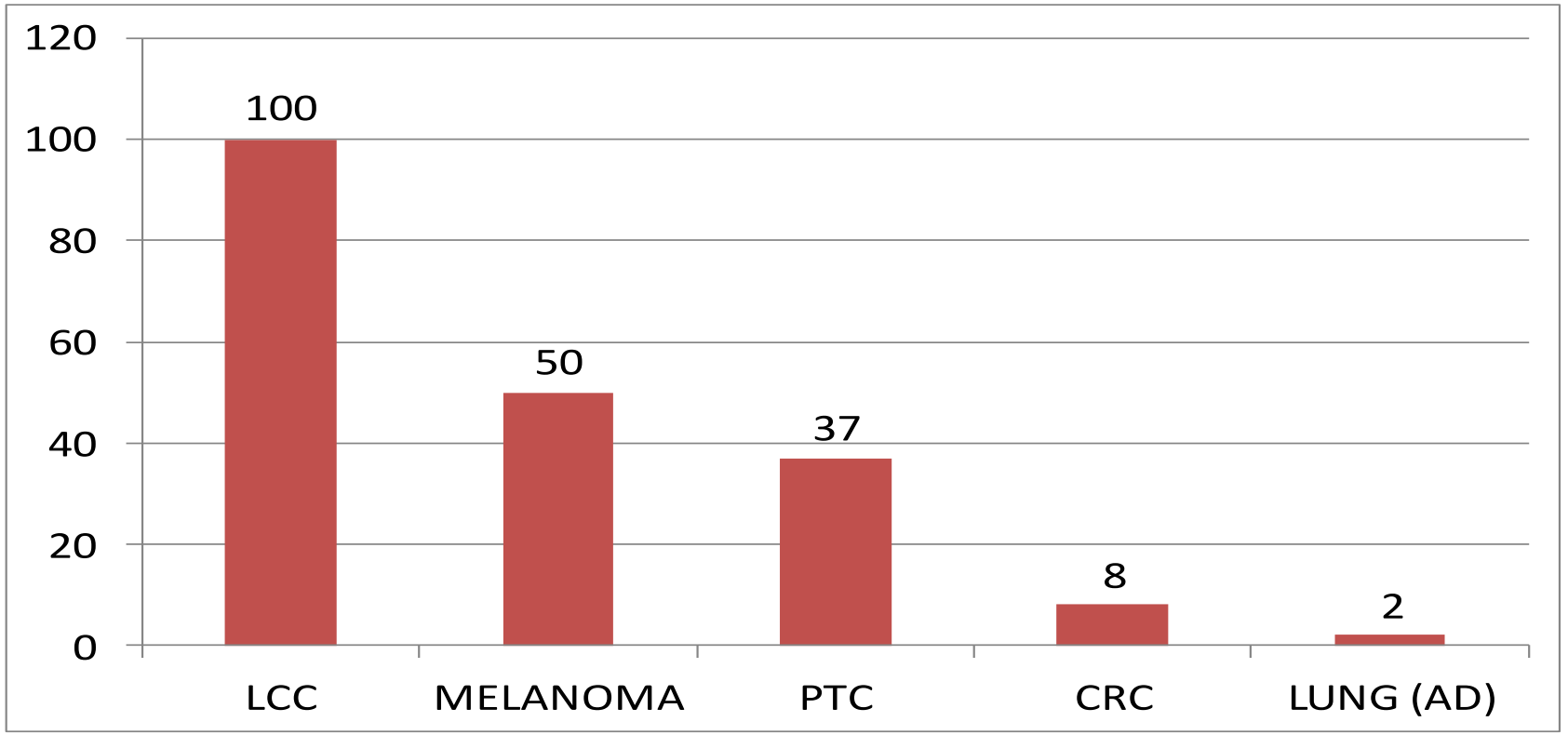
Frequenza mutazione BRAF V600E in vari tumori

Tumori con mutazione BRAF V600E:
- Melanoma
- Leucemia cellule capellute (LCC)
- PTC (tiroide)
- Adenoca polmonare
- Adenoca colon-retto (CRC)
- Ca sieroso ovaio
- Mieloma multiplo
- Glioblastoma
- Ca endometrio
- Ca mammella



Rosa Falcone, Farina, Paci, Sebastiano Filetti

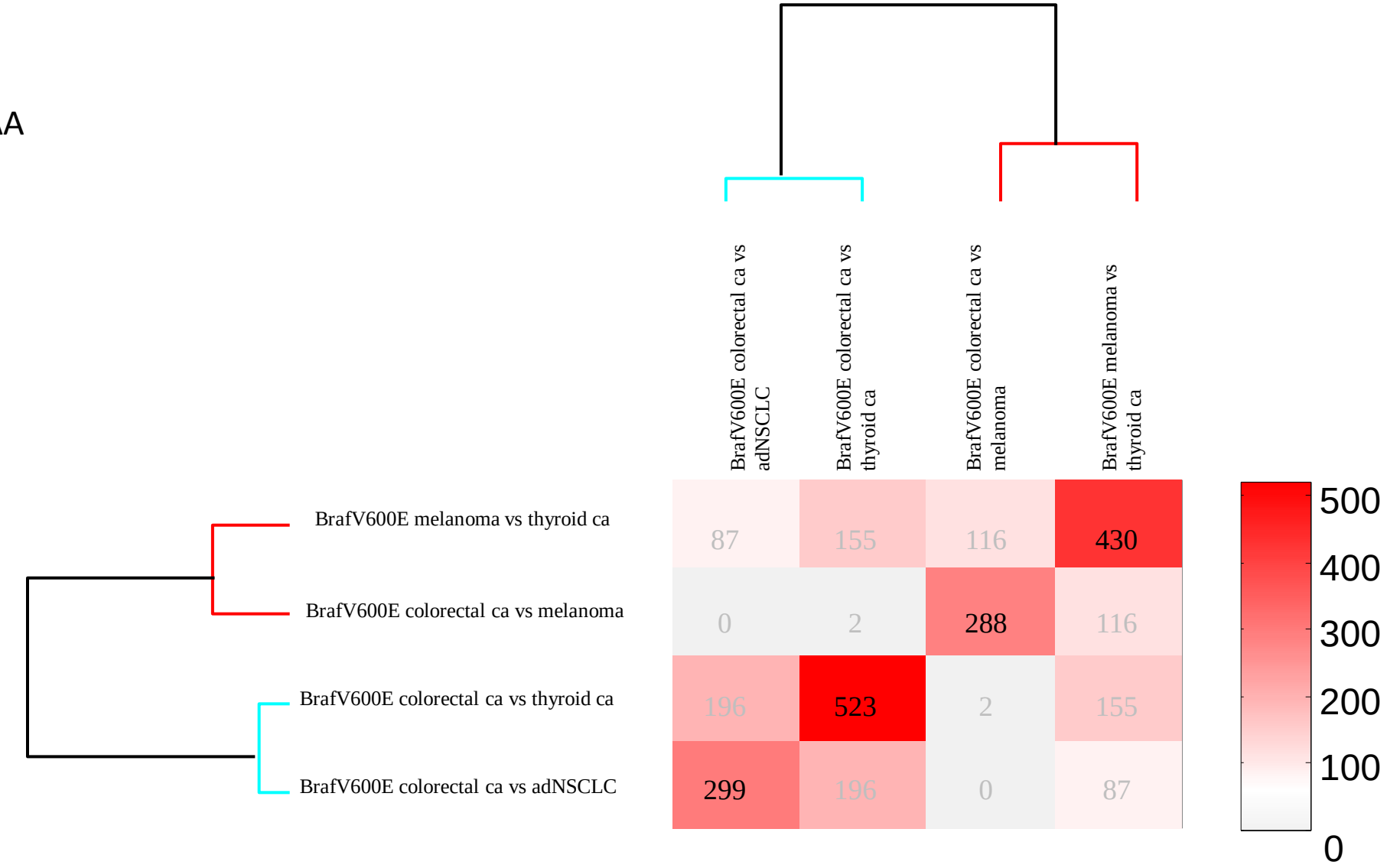
Variabilità della risposta al vemurafenib nei tumori con mutazione BRAF V600E

CANCRO	ORR (%)
LCC	96-100
Melanoma	51
Tiroide	38.5
NSCLC	33
Colon	4.8

Chapman PB et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. BRIM-3 Study Group. N Engl J Med. 2011
Tiacci E et al. Targeting Mutant BRAF in Relapsed or Refractory Hairy-Cell Leukemia. N Engl J Med. 2015
Kopetz S et al. Phase II Pilot Study of Vemurafenib in Patients With Metastatic BRAF-Mutated Colorectal Cancer. J Clin Oncol. 2015

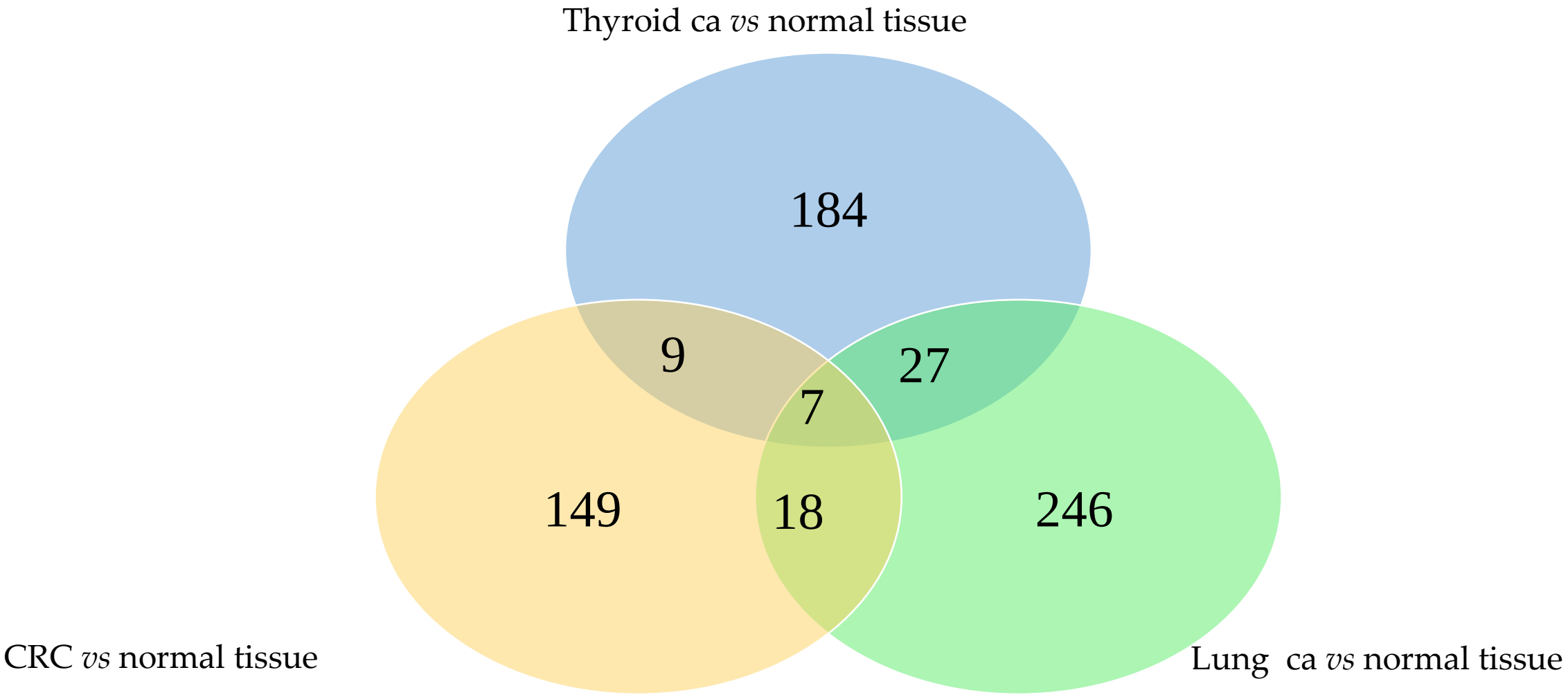
Confronto tra tumori BRAF V600E mutati

AA



R. Falcone, L. Farina, P. Paci, S. Filetti

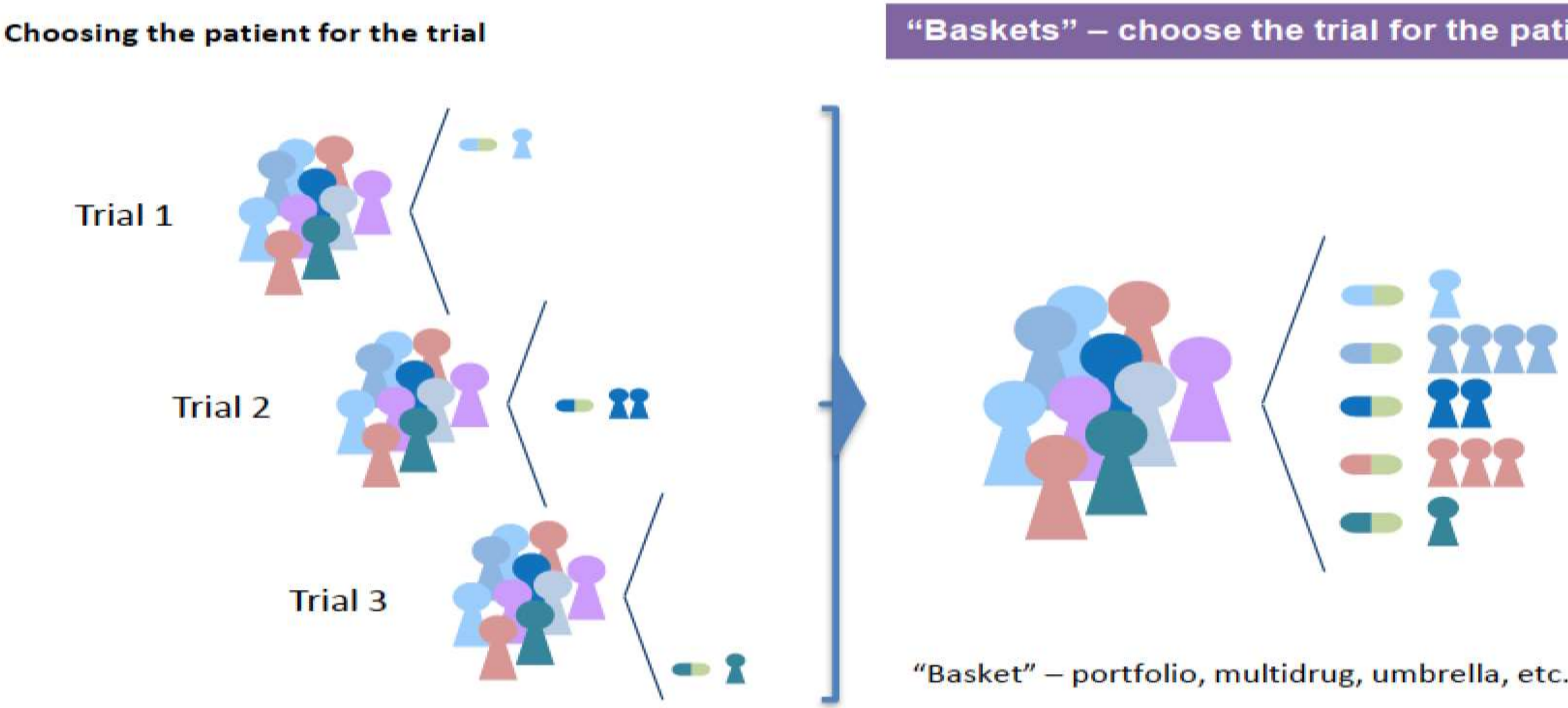
Venn diagram showing shared and non-shared switch genes for each BRAF V600E cancer compared to its normal tissue.



R. Falcone, L. Farina, P. Paci, S. Filetti

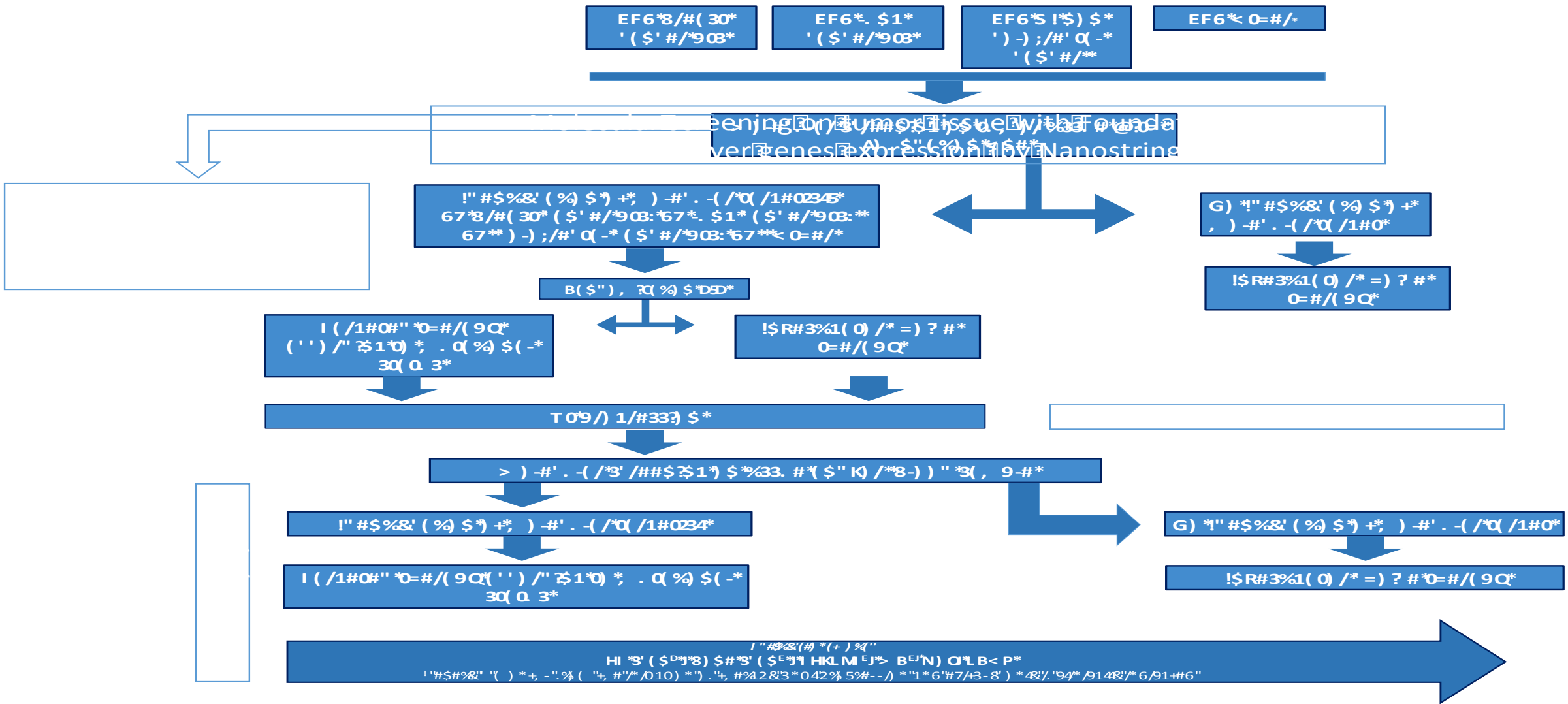
The ROME trial: *from histology to target*

A multi-basket trial

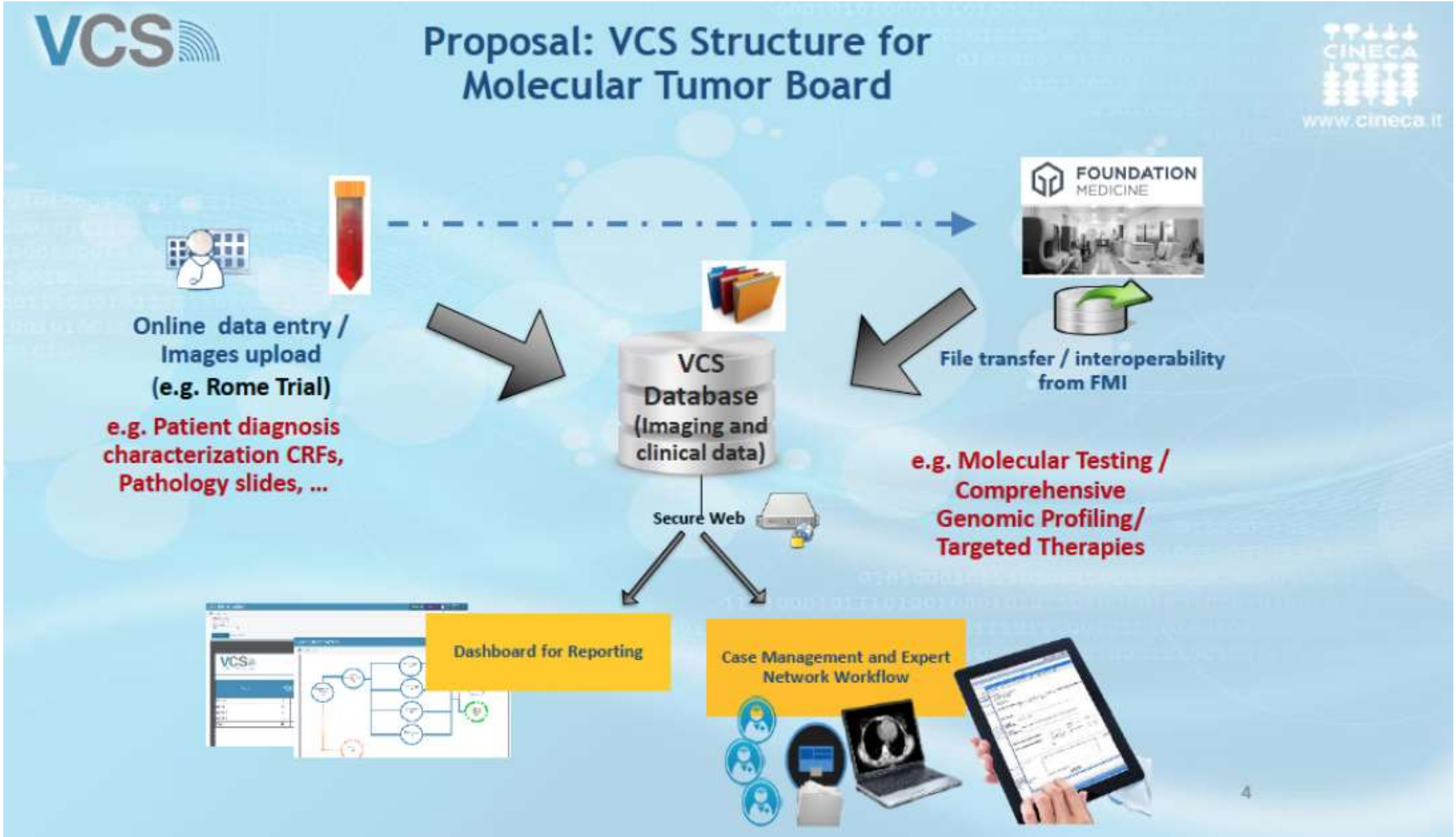


The ROME trial: *from histology to target*

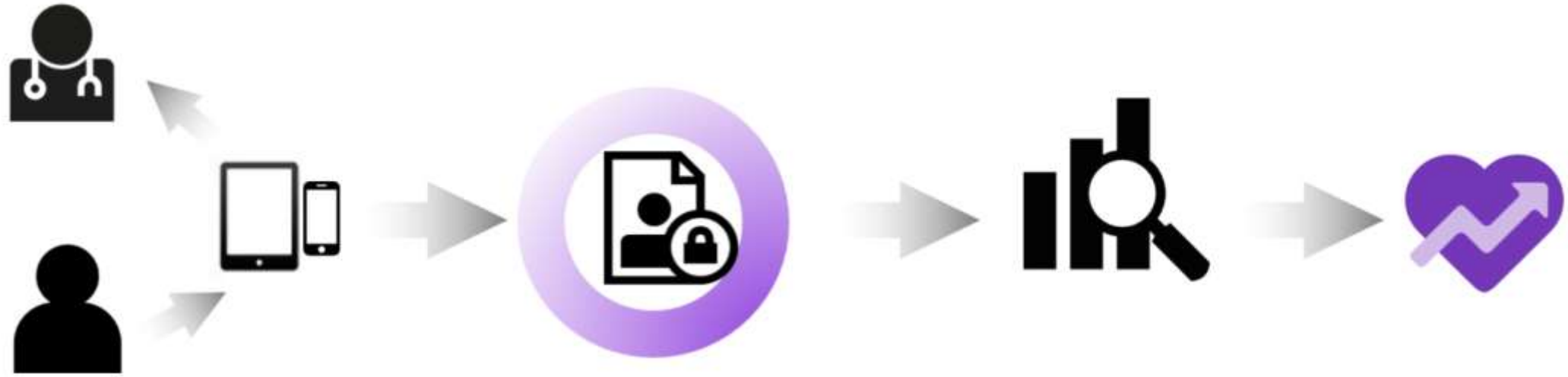
A multi-basket trial



Virtual Consultation System



The combination of Patient-Experience with Advanced Data-Analytics could improve clinical outcomes in oncology



1 **Patient Experience**
to improve patients lives with personalized, medical and mobile support tools

2 **Advanced data-analytics**
to large-scale Patient Reported Outcome data providing insights into the effectiveness of treatments

The combination of Patient-Experience with Advanced Data-Analytics could improve clinical outcomes in oncology

Our proactive approach: Immunosafe

remote monitoring of patients undergoing immunotherapy

Critical issues and the challenges for oncologists today

- Understand the dynamic features of the immune system (plus…redundancy, pleiotropic action, epigenetic influences…) and of the immune-drugs
- Actively contribute to the immunoncology revolution (from clinical practice to laboratory and from laboratory to clinical practice)
- Propose a new vision for collaborative studies with Pharma
- Suggest, demand, dictate new rules for regulatory authorities: ***from personalized medicine to personalized oncology***