
IMIM
Parc de Salut MAR
Barcelona
Institut Hospital del Mar d'Investigacions Mèdiques
20th October 2017
Optimizing Immunotherapy
New Approaches, Biomarkers, Sequences and Combinations
PRBB Auditorium, Barcelona

08:30–09:00 Registration

09:00–09:05 Welcome and opening
JOAQUIM BELLMUNT

09:05–09:30 Where we stand in Immunotherapy: IO+IO Combinations
IGNACIO MELERO

09:30 Table 1 — Immunotherapy in the clinic

Moderator – JOAQUIM BELLMUNT

09:30–09:45 Melanoma
JOSE LUIS MANZANO

09:50–10:05 Lung
MARGA MAJEM

10:10–10:25 Genitourinary
ENRIQUE GALLARDO

10:30 Discussion

10:50–11:20 BREAK (COFFEE)

11:20 Table 2 — Biomarkers in immunotherapy

Moderator – JOAN ALBANELL

11:20–11:35 PDL1 as a predictive biomarker: pros and cons
EDURNE ARRIOLA

11:40–11:55 HLA expression: implications for immunotherapy
AURA MUNTASELL

12:00–12:15 Predictive value of the Mutational load, neoantigens and clonal antigens. Somatic and germline genomic alterations
BEATRIZ BELLOSILLO

12:20–12:35 RNA Signatures as predictive biomarker
JOAN CARLES

12:40–12:55 Microbiome as predictor of benefit and toxicity
GIULIANA MAGRI

13:00–13:15 Commercially available tests and their predictive role
TERESA RAMOS

13:20–13:35 The role of tumor-infiltrating lymphocytes in immunotherapy
FEDERICO ROJO

13:40 Discussion

14:00–15:00 Lunch

15:00 Table 3 — What the future holds

Moderator – EDURNE ARRIOLA

15:00–15:15 Combination and sequencing: with radiation therapy, with chemotherapy and with targeted therapies
JOSEP MA PIULATS

15:20–15:35 Other immunotherapeutic approaches: new check point inhibitors and antibody drug conjugates
MARIA MARTINEZ

15:40–15:55 Vaccines
BEGOÑA MELLADO

16:00–16:15 CARTs: Driving T-lymphocytes as a cell immunotherapy
MANEL JUAN

16:20 Discussion

16:40 Closing remarks
JOAQUIM BELLMUNT

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IMIM Director

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Optimizing Immunotherapy
New approached, biomarkers, sequences and combinations

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Associate Professor of Medicine

Harvard Medical School/Dana-Farber Cancer Institute

Barcelona, Oct 20th 2017

Disclosures

- Advisory role:
  - Genentech, Merck, Pfizer, GSK, BMS, Pierre-Fabre, Sanofi Aventis, Astellas, OncoGenex, Janssen
- Speaker role:
  - Pfizer, Merck, GSK, Novartis, Pierre-Fabre, Astellas
- Research funding:
  - Takeda, Pfizer, Novartis, Sanofi Aventis

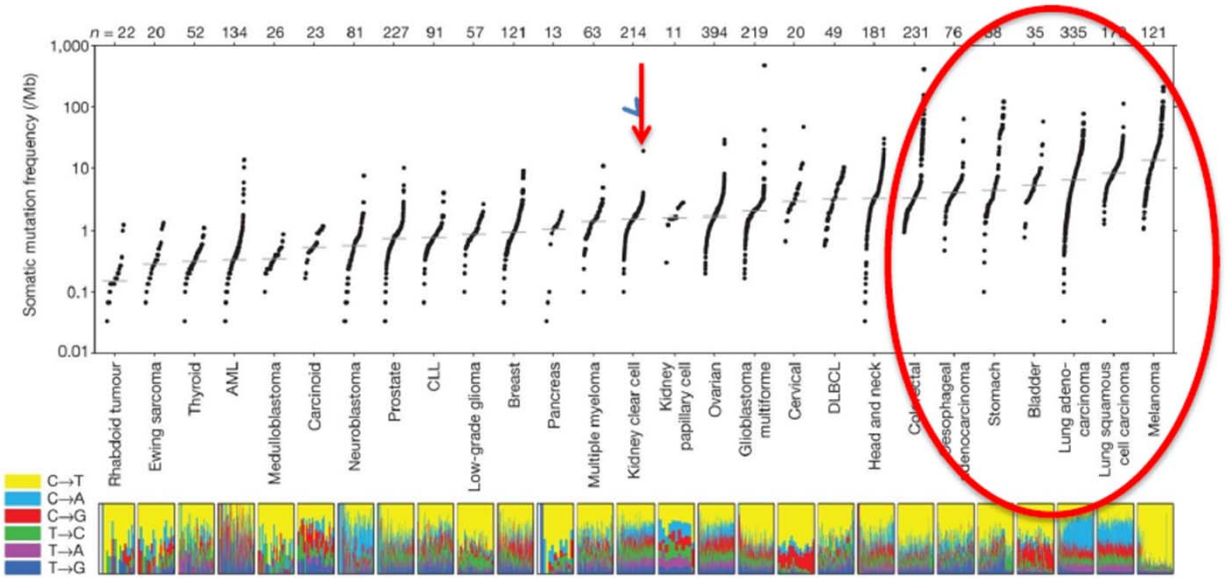
A Brief History of Immuno-Oncology

- 1796 First use of immunotherapy to control disease – smallpox vaccine
- 1975 First production of monoclonal antibodies for therapeutic use
- 1986 **IFN-alpha**: First immuno-oncology treatment approved for cancer (hairy cell leukemia)
- 1990 Bacillus Calmette-Guerin (**BCG**) (bladder cancer)
- 2010 **Sipuleucel-T** (prostate cancer)
- 2011 CTLA-4 inhibitor **ipilimumab** (metastatic melanoma)
- 2014 **Blinatumomab** (acute lymphoblastic leukemia)
- 2014 Anti-PD-1 monoclonal antibodies **pembrolizumab and nivolumab** (unresectable or metastatic melanoma)
- 2015 Adjuvant **ipilimumab** (melanoma)
- 2015-16 **Nivolumab, pembrolizumab** (NSCLC, RCC)
- *2016-17 Nivolumab, atezolizumab, durvalumab,Avelumab, pembrolizumab approved in several tumor types*
- 2017- CAR-T cells approved for ALL and refractory adult large B-cell lymphoma

Genetic Basis For Clinical Response

- Is there a role for mutational frequency in tumor selection for PD1/PD-L1 pathway inhibition?

Somatic mutation frequencies observed in exomes from 3,083 tumour–normal pairs.



MS Lawrence *et al. Nature* **000**, 1-5 (2013) doi:10.1038/nature12213

Many tumors that respond to PD1 pathway inhibition: Melanoma, NSCLC, and Bladder Cancer have a high mutation rate

Current US/EU Approval Status of Immune Checkpoint Inhibitors

	PD-1						PD-L1					CTLA-4	Combo
	Pembrolizumab			Nivolumab			Atezolizumab		Durvalumab	Avelumab		Ipilimumab	Nivo + ipi
Line	1L+	2L+	3L+	1L+	2L+	3L+	1L+**	2L+	2L+	1L+	2L+	1L+	1L+
mMelanoma	US EU	US EU		US EU	US EU							US EU	US EU
Lung	US EU	US EU		US	US EU			US					
Hodgkin			US EU			US EU							
aRCC					US EU								
mHNSCC		US			US								
mUC	US EU	US EU			US EU		US EU	US EU	US		US		
Merkel cell											US		
NEW													

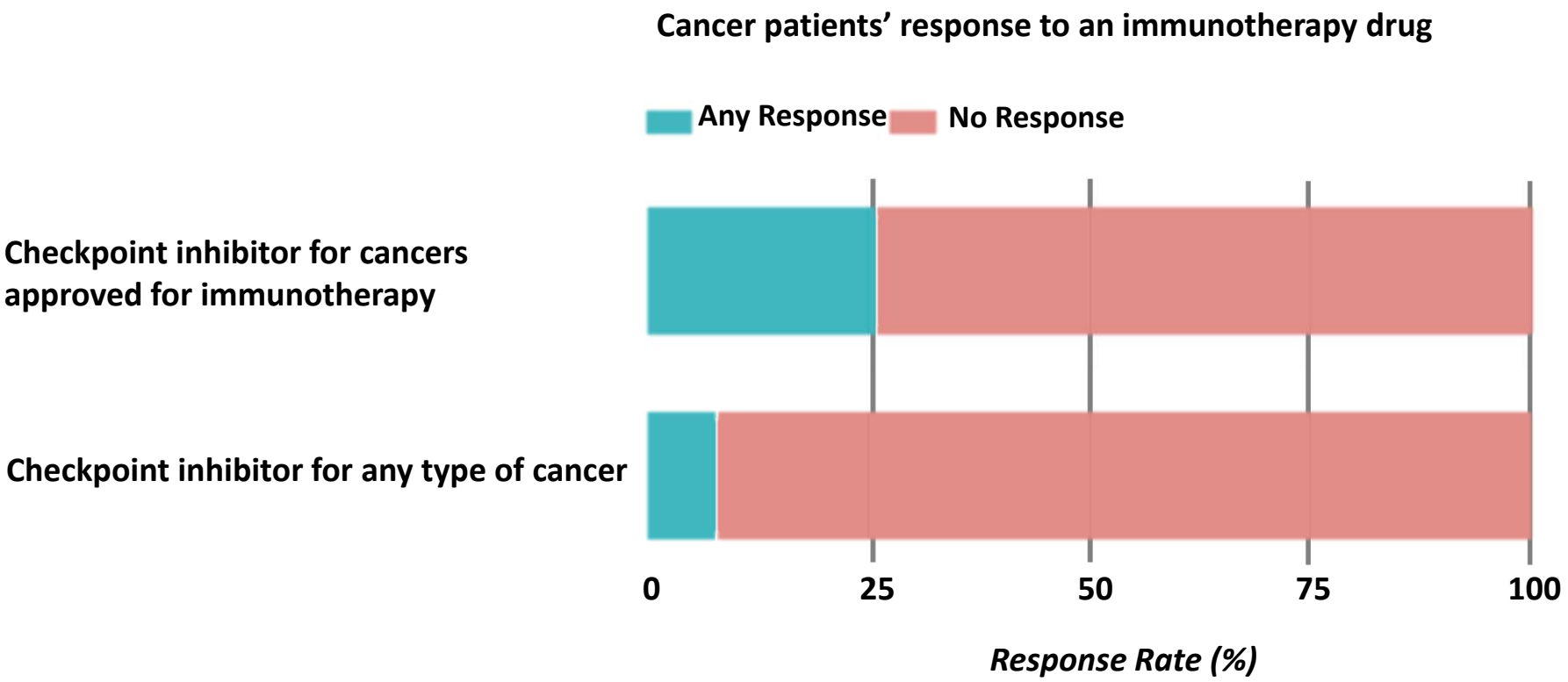
US ■ EU ■

EU, European Union; HNSCC, head and neck squamous cell carcinoma; ipi, ipilimumab; m, metastatic; nivo, nivolumab; PD-1, programmed cell death protein-1; PD-L1, programmed death-ligand 1; RCC, renal cell carcinoma; UC, urothelial carcinoma; US, United States.
Product Prescribing Information.

Pembrolizumab indicated for treatment of patients with unresectable / metastatic solid tumors that are microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR)

FDA, May 23rd , 2017

Cancer Patients' Response to an IO Drug



Gay N, Prasad V. STAT. March 8, 2017. https://www.statnews.com/2017/03/08/immunotherapy-cancer-breakthrough/..

Potential Biomarkers for PD-1/PD-L1 therapy

- PD-L1 by IHQ. CD8 infiltrate.
- RNA immune signatures
- Neoantigen and mutational burden (MSI,defects in DNA repair)
- T cell clonality. genetically amplified PD=L1 and PD-L2 (Hodgkin),Viral antigens (HPV, Head and neck, Merkel)
- Other mutations and CNV

Understanding immunology and genetics has identified groups that respond well to PD-1/PD-L1 therapy

- PD-L1: the antibody, cut off points, disease and timing matters
- RNA immune signatures and T cell clonality emerging. RNA subtypes to be confirmed
- Highly mutated tumors (MSI, defects in DNA repair -DDR genes-)
- Neoantigen and mutational burden to be confirmed in select tumors

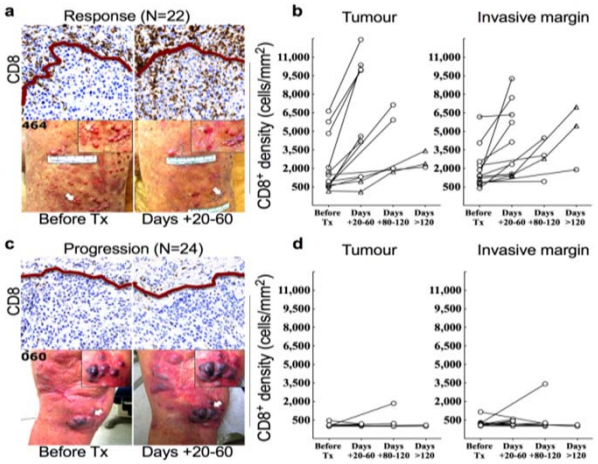
Response enrichment with all these biomarkers

  - Dynamic markers, recent tissue better
  - Different in combination trials

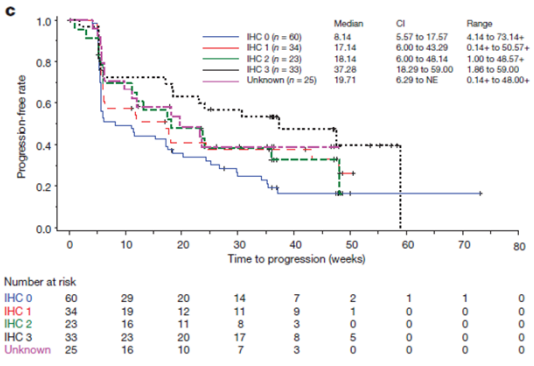
- Genetically amplified PD=L1 and PD-L2 (Hodgkin),Viral antigens (HPV, Head and neck, Merkel)
- More biomarkers to come …….!!!!!

Can We Select Patients More Likely to Respond to PD-1/L1 Blockade?

1. Pre-existing T cell infiltration and adaptive PD-L1 expression

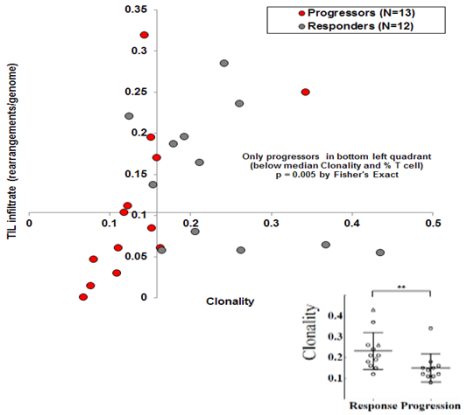


Tumeh, et al. *Nature.* 2014.



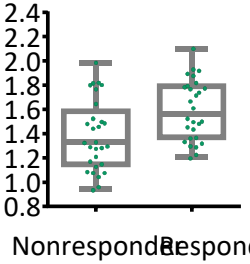
Herbst, et al. *Nature.* 2014.

2. TCR clonality



Tumeh, et al. *Nature.* 2014.

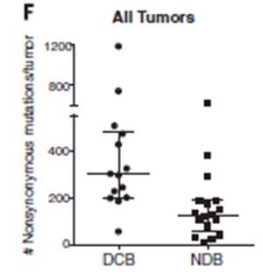
3. IFN signature by expression profiling



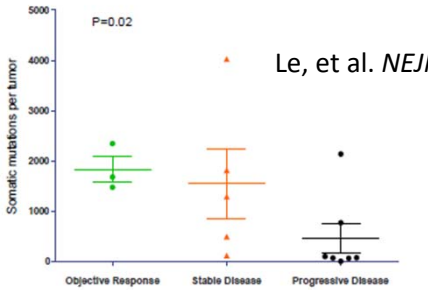
Ribas, et al. ASCO. 2015.

Best Overall Response, RECISTv1.1

4. Mutational load

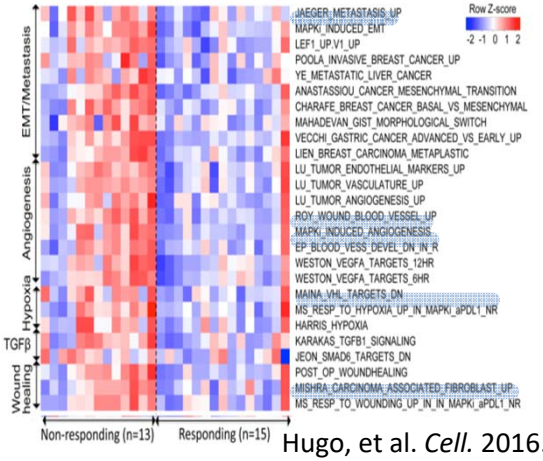


Rizvi, et al. *Science.* 2015.



Le, et al. *NEJM.* 2015.

5. Transcriptome



Hugo, et al. *Cell.* 2016.

Immunotherapy Today

- ***Exciting times in the treatment of cancer***
- Immunotherapy is a well tolerated and active treatment for our patients
- Many open questions remain with regards to understanding predicting factors
- Several other novel immunotherapies are in clinical development
  - New Checkpoint inhibitors
  - Combinations (IO/Chemo)
  - Antibody drug conjugates
  - Targeted agents

- Chemotherapy is here to stay

Immunotherapy in UC

- **Exciting times in the treatment of cancer**

- Immunotherapy is a well tolerated and active treatment for our patients
- → **But only 15-20% of patients derive benefit** and many open questions remain with regards to understanding predicting factors

- The future is combination (or sequential ?)
  - Check-point inhibitors
  - Immune based therapies (vaccines, ADC, Bispecific antibodies, CAR-T cells…)
  - + Targeted agents (cabozantinib, FGFr3 inh..)
  - Combination/ Sequential use of chemo and XRT
  - Customized: Genomically based