Bottlenecks in PCM development
WIN. Paris, 2015

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THE MELANOMA PARADIGM
MUTATION DRIVEN DRUG DEVELOPMENT
INNOVATIVE IMMUNOMODULATION
Molecular profiling
Identification of the molecular alteration
Targeted therapy according to the molecular profile
Tumor Specimen
Molecular profiling

Precision Medicine: identify-hit the target
Rational Genomics: “Molecular Portraits” for targeted therapy allocation

Rapid through Clinical Trials

Logistics – Logistics – Logistics
Focus, time pressure, culture, infrastructure

Examples of Current Clinical Trials
SAFIR01 Molecular Screening in Breast Cancer

Which candidate target?

Biopsy of metastatic sites
Frozen sample
CGH/hot spot mutations
(PIK3CA/AKT)*

eligible for phase I
N= 400

Primary endpoint:
% of patients included
in phase I/II trial according to the profile

Funded by INCA
Sanger 30 genes

FGFR1
FGFR2
FGF4 amp

NOTCH amp

PIK3CA / AKT / PTEN alteration

Genetic instability

VEGFA amplification

PAK1 ampli

Target discovery

Trial A
Trial B
Trial C
Trial D
Trial E
Trial F
Trials X, Y...

Funded by INCA
Sanger 30 genes

André et al ESMO 2012, Lancet Oncol 2014
Recruitment completed between May 2011 and August 2012

High level of expectation

André ESMO 2012
Molecular alterations

Targetable alterations

Rare alterations

% of patients with available genomic result

29% molecular alteration
IN THE END ONLY 12% gets targeted therapy

André et al, Lancet Oncology 2014
MOSCATO: MOlecular Screening for CAncer Treatment Optimization

Biopsy → Histological analysis → Molecular analysis
- CGH, NGS → WES
- Gene-panel sequencing

14 calendar days
CGH+RNAseq+NGS - WES

TARGET IDENTIFIED IN 45-50%
Targeted therapy in 20-25%
850 / 900 PATIENTS IN 2.5 Years
PROBLEMS

• ATTRITION RATE

• 100 pts
• 45-50 pts have target identified
• 25 are actionable
• 20% overall response rate
• So in the end 5/100 patients benefit….

• INNATE RESISTANCE + ORGAN CONTEXT
NEEDS

• Higher Target Identification Rate
• Higher % of Actionable Targets
• Higher number / diversification of new drugs
• Rational intra/interpathway combinations
• Functional assays
• Simplification of models
Problems with Targeted Drugs

• Lack of Durability of responses
  – Improvement with combo’s limited
  – Combo’s of non-active drugs can be active

• Lack of Transversality of impact across tumor types
  – Organ of origin
  – Context
Molecular Alterations in Melanoma

- **FGFR**
  - Amplified in 30%

- **PTEN**
  - Amplified or mutated in 20%-40% acral and mucosal melanoma
  - 50%-65% V600E mutation
  - 15% mutation

- **PI3K**
  - Amplified in 10%-15%

- **Ras GDP**
  - Amplified in 10%-15%

- **N-Ras GTP**
  - Amplified or mutated in 20%-40%

- **Kit**
  - Amplified in 10%-15%

- **GRB2**
  - Amplified in 10%-15%

- **SOS**
  - Amplified or mutated in 20%-40%

- **B-Raf**
  - 50%-65% V600E mutation

- **C-Raf**
  - Amplified or mutated in 20%-40%

- **MEK**
  - Amplified in 30%

- **ERK**
  - Frequent loss

- **ELK**
  - Amplified in 30%

- **MITF**
  - Amplified in 30%

- **CDK2/4**
  - Amplified in 30%

- **Cyclin D**
  - Amplified in 30%

- **p16**
  - Frequent loss

- **Akt**
  - 25%-50% loss

- **TOR**

Vemurafenib and Dabrafenib show similar efficacy

Vemurafenib

Dabrafenib (n=187)

DTIC

Chapman et al., NEJM 2011

Hauschild et al., Lancet 2012
Safety and efficacy of vemurafenib in \textit{BRAF}^{V600E} and \textit{BRAF}^{V600K} mutation-positive melanoma (BRIM-3): extended follow-up of a phase 3, randomised, open-label study


OS 9.7-13.6 mts
Gain: 3.9 mts
HR 0.70

V600E (91%): 13.3-10.0  HR = 0.75
V600K:(9%)  14.5– 7.6  HR = 0.43

PFS  1.6- 6.9 mts
Gain 5.3 mts*
HR 0.38
Molecular Alterations in Melanoma

BRAF + MEK Inhibitors

FGFR

Amplified or mutated in 20%-40% acral and mucosal melanoma

KIT

15% mutation

GRB2

SOS

N-Ras GTP

C-Raf

B-Raf

50%-65% V600E mutation

Ras GDP

PI3K

Amplified in 10%-15%

Akt

TOR

ERK

MITF

ELK

CDK2/4

Cyclin D

Amplified in 30%

Amplified in 10%-15%

25%-50% loss

PTEN

Amplified or mutated in 20%-40% acral and mucosal melanoma

15% mutation

50%-65% V600E mutation

Frequent loss

25%-50% loss

Adapted from Sosman, Curr. Oncol. Rep. 11, 405 (2009)
Median Follow-up: D + T = 11 months and Vem = 10 months

≈ 8 weeks

- Why translates 4 months additional PFS only into 2 months OS benefit?
- What kind of pricing will this OS benefit justify?

A SOBERING END RESULT

- Early events driven by bad prognosis patients?
- Single BRAFi patients subsequently treated in D+T NNP?
- D+T faster PD, thus less 2nd line therapy?
CONTEXT

Organ of origin determines role of molecular alteration

Organ of origin and organ hosting metastases determine environment and interactions
Drug Development Challenges

• Tumor by evolution is “moving target”
  • Heterogeneity and Innate resistance
  • Acquired resistance/Additional mutations
  • We still suffer from Mono-Dimensional thinking about pathways

We need to address:
• Cross Talk Complexity between pathways
• Nodes of Convergence of Pathways
Differential response of BRAF inhibition in *BRAF* mutant melanoma vs colon cancer

CONTEXT and CROSS TALK

Kopetz et al., ASCO 2010
CROSS TALK and RESISTANCE

CONTEXT and CROSS TALK

Human colon cancer growth in mice

No drug
EGFR inhibitor
BRAF inhibitor
BRAF+EGFR inhibitor

Prahallad et al, Nature 2012
Drug Development Challenges

• Tumor by evolution is “moving target”
  • Heterogeneity and Innate resistance
  • Acquired resistance/Additional mutations
  • We still suffer from Mono-Dimensional thinking about pathways

We need to address:
• Cross Talk Complexity between pathways
• Nodes of Convergence of Pathways
eIF4F Node of Convergence
Ras/Raf – PI3K- Caspase cascade

Nexus: eIF4F

Amplified or mutated in 20%-40% acral and mucosal melanoma

15% mutation

50%-65% V600E mutation

25%-50% loss

Frequent loss

Amplified in 30%

Amplified in 10%-15%

Amplified in 10%

eIF4F is a nexus of resistance to anti–BRAF and anti–MEK cancer therapies

Lise Boussemart1,2,3*, Hélène Malka-Mahieu1,2,4*, Isabelle Girault1,4, Delphine Allard1, Oskar Hemmingsson1†, Gorana Tomasic4, Marina Thomas3, Christine Basmadjian5, Nigel Ribeiro7, Frédéric Thuaud6, Christina Mateus3, Emilie Routier3, Nyam Kamsu-Kom6, Sandrine Agoussi1, Alexander M. Eggermont2,3, Laurent Désaunay5, Caroline Robert1,2,3 & Stéphan Vagner1,2,3†

In BRAF(V600)-mutant tumours, most mechanisms of resistance to drugs that target the BRAF and/or MEK kinases rely on reactivation of the RAS–RAF–MEK–ERK mitogen-activated protein kinase (MAPK) signal transduction pathway, on activation of the alternative PI3K–AKT–mTOR pathway (which is ERK independent) or on modulation of the caspase-dependent apoptotic cascade1–3. All three pathways converge to regulate the formation of the eIF4F eukaryotic translation initiation complex, which binds to the 5′-methylguanylate cap of messenger RNA, thereby modulating the translation of specific mRNAs4–5. Here we show that the persistent formation of the eIF4F complex, comprising the eIF4E cap-binding protein, the eIF4G scaffolding protein and the eIF4A RNA helicase, is associated with resistance to anti–BRAF, anti–MEK and anti–BRAF plus anti–MEK drug combinations in BRAF(V600)-mutant melanoma, colon and thyroid cancer cell lines. Resistance to treatment and maintenance of eIF4F complex formation is associated with one of three mechanisms: reactivation of MAPK signalling, persistent ERK-independent phosphorylation of the inhibitory eIF4E-binding protein 4EBP1 or increased pro-apoptotic BCL-2-modifying factor (BMF)-dependent degradation of eIF4G. The development of an in situ method to detect the eIF4E–eIF4G interactions shows that eIF4F complex formation is decreased in tumours that respond to anti–BRAF therapy and increased in resistant metastases compared to tumours before treatment. Strikingly, inhibiting the eIF4F complex, either by blocking the eIF4E–eIF4G interaction or by targeting eIF4A, synergizes with inhibiting BRAF(V600) to kill the cancer cells. eIF4F not only appears to be an indicator of both innate and acquired resistance but also is a promising therapeutic target. Combinations of drugs targeting BRAF (and/or MEK) and eIF4F may overcome most of the resistance mechanisms arising in BRAF(V600)-mutant cancers.
• Targeted Agents will be effective across different tumor types with that target
  – importance of organ of origin
  – Answer is NO

• For combination therapies one must demonstrate the antitumor effects for each individual agent
  – Answer is NO
Phase 3 Trials testing general concepts of PCM

Ready for prime time?
Biopsy metastatic site:
- NGS Array CGH

Molecular alteration
- Excluding EGFR mut and ALK trl

Chemotherapy 4 cycles

No PD

Targeted therapy According to Molecular alteration
- Pemetrexed if Non-SCC
- EGFR TKI if SCC

Followed up but not included

metastatic NSCLC first line chemotherapy

All histologies
Biopsy metastatic site: NGS CGH: 51 alterations

Molecular alteration Excluding HER2

Chemotherapy 6-8 cycles

No PD

Targeted therapy According to Molecular alteration

Chemotherapy continuation

No alteration

Followed up but not included
RISKS with phase 3 Trials

• Attrition rate problem not solved
• Short-lived impact with many targeted agents
• Combo’s not explored
• Field evolving and in no way mature
• Too early for the phase 3 question?

• Communicate to the public that it is RESEARCH and not a “done deal”
OUR MONO-DIMENSIONAL THINKING ABOUT PATHWAYS

Cross Talk (Rene Bernards)
Master Regulators (Andrea Califano)
A map of human cancer signaling

Qinghua Cui, Yun Ma, Maria Jaramillo, Hamza Bari, Arit Awan, Song Yang, Simo Zhang, Lixue Liu, Meng Lu, Maureen O'Connor-McCourt, Enrico O'Purisima, and Edwin Wang.

Figure 3. Human oncogene-signaling map. The human cancer-signaling map was extracted from the human signaling network, which was mapped with cancer genes.
BREAKTHROUGH ACTIVITY IN STAGE IV MELANOMA

Percent Change From Baseline in Longest Diameter of Target Lesion

BREAKTHROUGH
CTLA-4 and PD1/PDL1

Mostly CENTRAL in LNN

 Activation (cytokines, lysis, proliferation, migration to tumor)

CTLA-4 Blockade (ipilimumab, tremelimumab)

PD-1 Blockade (nivolumab, lambrolizumab)

Mostly PERIPHERAL Tumor Microenvironment
20% long term survival
3 mg/kg = 10 mg/kg (more naïve pts 10mg/kg)
BRAFinh in BRAFmutant compared to anti-PD1 in Wildtype Advanced Melanoma

OS 9.7-13.6 mts
Gain: 3.9 mts
HR 0.70

PFS 1.6-6.9 mts
Gain 5.3 mts*
HR 0.38
Single agent Pembrolizumab (anti-PD1) or nivolumab + ipilimumab

Nivolumab + Ipilimumab

Pembrolizumab Alone

Individual Patients Treated with Pembrolizumab

Percent Change from Baseline in Target Lesion

(2-Dimension Measurement)

Prior ipilimumab treatment
No prior ipilimumab treatment

Individual Patients Treated with Pembrolizumab
Overall Survival for Concurrent Therapy Ipilimumab + Nivolumab by Dose Cohort

Survival at 1 yr from 25% to 90%
Survival at 2 yr from 12% to 80%
Survival at 3 yr from 8% to 74%
Survival at 5 yr from 3% to > 50%?

(Sznol et al, NYC 2015)
PFS by PD-L1 Expression Level (5%)

PD-L1 ≥5%*

Proportion alive and progression-free

No. at Risk

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Proportion alive and progression-free

Months

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*Per validated PD-L1 immunohistochemical assay based on PD-L1 staining of tumor cells in a section of at least 100 evaluable tumor cells.

PD-L1 <5%*

Proportion alive and progression-free

No. at Risk

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Proportion alive and progression-free

Months

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mPFS

HR

NIVO + IPI

NIVO

IPI

( Wolchok, ASCO 2015)
TRANSVERSAL IMPACT
Nivolumab vs Docetaxel in NSCLC Overall Survival (FDA et al. 2015)

Figure 1: Overall Survival - Trial 2

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<th>OPDIVO</th>
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Overall Survival (Months)
Pembrolizumab in Gastric Cancer:

39 pts, median FU: 8.8 months. 2/3 of pts had ≥ two prior therapies, 30% achieved PR. 50% of pts some degree of tumor shrinkage. Median duration of response: 24 weeks (range 8+ to 33+ wks.

Analysis cut-off date: November 10, 2014.

Presented by: Kei Muro
Nivolumab for Metastatic Renal Cell Carcinoma: Results of a Randomized Phase II Trial


Results
A total of 168 patients were randomly assigned to the nivolumab 0.3- (n = 60), 2- (n = 54), and 10-mg/kg (n = 54) cohorts. One hundred eighteen patients (70%) had received more than one prior systemic regimen. Median PFS was 2.7, 4.0, and 4.2 months, respectively (P = .9). Respective ORRs were 20%, 22%, and 20%. Median OS was 18.2 months (80% CI, 16.2 to 24.0 months), 25.5 months (80% CI, 19.8 to 28.8 months), and 24.7 months (80% CI, 15.3 to 26.0 months), respectively. The most common treatment-related adverse event (AE) was fatigue (24%, 22%, and 35%, respectively). Nineteen patients (11%) experienced grade 3 to 4 treatment-related AEs.
Nivolumab in Refractory Renal Cell Cancer: No Dose Effect; Durability +
According to Moskowitz (MSKCC), it is believed that classic Hodgkin’s lymphoma may represent a uniquely vulnerable target for PD-1 blockade. Specifically, amplification of 9p24.1 is frequent in the disease and results in the overexpression of PD-L1 and PD-L2.

<table>
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<th>ORR</th>
<th>86%</th>
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<td>CR</td>
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<td>PR</td>
<td>45%</td>
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<tr>
<td>SD</td>
<td>21%</td>
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**DURABILITY:** Seventeen of the 19 responses were ongoing
No more blockbusters?
TRANSVERSAL IMPACT IMMUNO

• Anti-PD1 (and anti-PDL1): is the most important drug in history of oncology

• IMMUNOTHERAPY: TRANSVERSAL IMPACT

  – Melanoma : approved 2014, will take first place for all, adjuvant started launched March 2015
  – Renal : on its way up the ladder all the way to first place?
  – Bladder (ASCO and ESMO 2014) will take first place

  – Lung: Approved 2015 , will take first place, adjuvant started (PD1 and PDL1)
  – Head and Neck (ASCO 2015) like lung: major results in 2015
  – Oesophagus and Stomach (ASCO GI 2015) may take first place
  – HCC will potentially take first place (ASCO 2015)
  – MSI tumors (CRC and others): 60% response rate (ASCO 2015)
    • CRC MSI: RR 62% ; CRC RR 0%; Others MSI RR 60% !!!!
  – Hodgkin (ASH 2014) very important future/first place
  – TNBC?
Mutational Load and Sensitivity to anti-CTLA4/PD1

MSI tumors (CRC and others): 60% response rate (ASCO 2015)
CRC MSI: RR 62%; CRC RR 0%; Others MSI RR 60%!!
CONTEXT in IMMUNOTHERAPY
a major challenge

• Organ of origin
• Organ hosting metastatic lesions

• Environment per organ is different
• Monocytic regulatory systems will be different
• Optimal dose anti-CTLA4 and anti-PD1 not known

• OPEN DOOR FOR AGONISTS
  • Cytokines: physiologic dosing?
  • Agonist MoAbs: physiologic dosing

• Organ origin and hosting metastatic lesions

• Neoantigens: signatures?

• Role Microbiota
A SECOND LIFE FOR ALL? ONLY THE BEGINNING

Cytokines
- IFN
- IL2
- IL7
- IL21
- GmCSF

Adoptive Tcell therapy
- Activated TCR engineered CARs

Vaccination
- DC
- DNA
- RNA

Immuocyte depletion
- Treg
- MDSC

MoAb-conjugates
Multiple mechanisms of synergy between the different treatment modalities

**Immunogenic Cell Death**

(Zitvogel & Kroemer)

- **Radiation**
  - Adhesion molecules (CAM-1) and death receptors (FAS)
  - Peptide pools
  - Upregulation of MHC-I
  - Uploading of antigen processing machinery

- **Chemotherapy**
  - Effector immune infiltrate
  - Release of tumour antigens (cascade)
  - Translocation of calreticulin
  - CD8 T-cells
  - TAA cross-presentation
  - Dendritic cell

- **Targeted therapies**
  - Vascular normalisation
  - T-cell initiation
  - Cytokine release
  - CD8 T-cells
  - T-cell function

- **MDSC**
  - Treg cells
  - Activation of apoptosis
  - Blockage of cell cycle

**Adapted from**
Mutational Load and response to ipilimumab in advanced melanoma

ORIGINAL ARTICLE

Genetic Basis for Clinical Response to CTLA-4 Blockade in Melanoma

Alexandra Snyder, M.D., Vladimir Makarov, M.D., Taha Merghoub, Ph.D., Jianda Yuan, M.D., Ph.D., Jesse M. Zaretsky, B.S., Alexis Desrichard, Ph.D., Logan A. Walsh, Ph.D., Michael A. Postow, M.D., Phillip Wong, Ph.D., Teresa S. Ho, B.S., Travis J. Hollmann, M.D., Ph.D., Cameron Bruggeman, M.A., Kasthuri Kannan, Ph.D., Yanyun Li, M.D., Ph.D., Ceyhan Elipenahli, B.S., Cailian Liu, M.D., Christopher T. Harbison, Ph.D., Lisu Wang, M.D., Antoni Ribas, M.D., Ph.D., Jedd D. Wolchok, M.D., Ph.D., and Timothy A. Chan, M.D., Ph.D.
Mutational Load and response to ipilimumab in advanced melanoma

Figure 2. Mutational Landscape of Tumors According to Clinical Benefit from Ipilimumab Treatment.
Neo-epitopes and response to ipilimumab in advanced melanoma

A Neoepitopes in Discovery Set

Long-Term Benefit

Minimal or No Benefit

B Neoepitopes in Validation Set

Long-Term Benefit

Minimal or No Benefit

C Survival in Discovery Set

Survival (% of patients)

With signature (N=10)

P<0.001 by log-rank test

Without signature (N=15)

D Survival in Validation Set

Survival (% of patients)

With signature (N=20)

P<0.001 by log-rank test

Without signature (N=19)
• Breaking Tolerance will get Nobel Price

• **Immuno combos will dominate drug development for the next 5-10 years**

• **Breaking tolerance is the key prerequisite**
  – Inhibitor – Agonist combos is next step

• **Multidrug class combos and multimodality combos may be guided by immunogenic cell death prerequisite**

• **Genomics enters Immunotherapy**
  – Neoantigens, signatures, drug discovery
MORE OPPORTUNITIES than BOTTLENECKS!