Marqueurs immunologiques précoces de l'effet des immunothérapies du cancer : vers des critères de substitution ?

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Les immuno-thérapies (1)

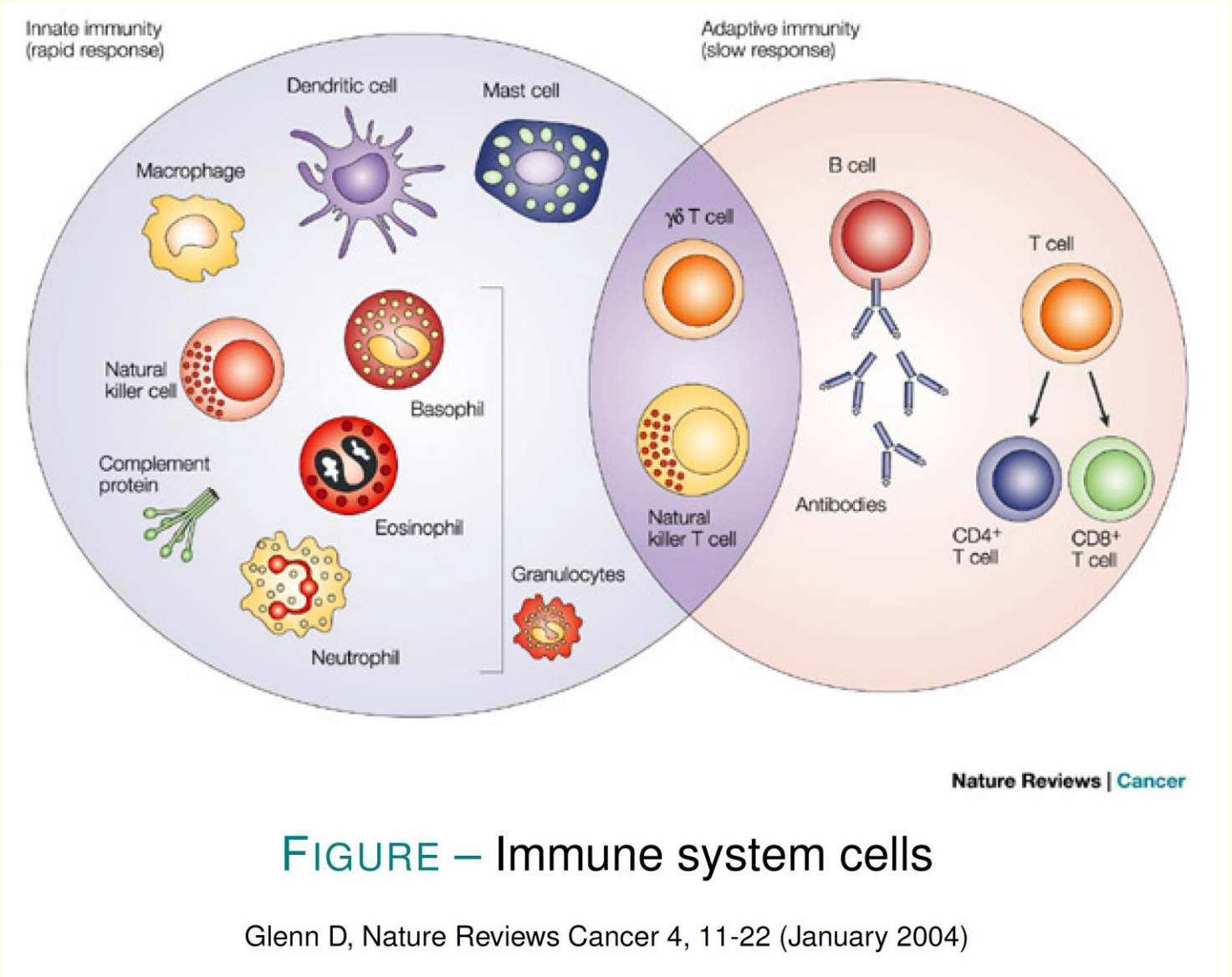
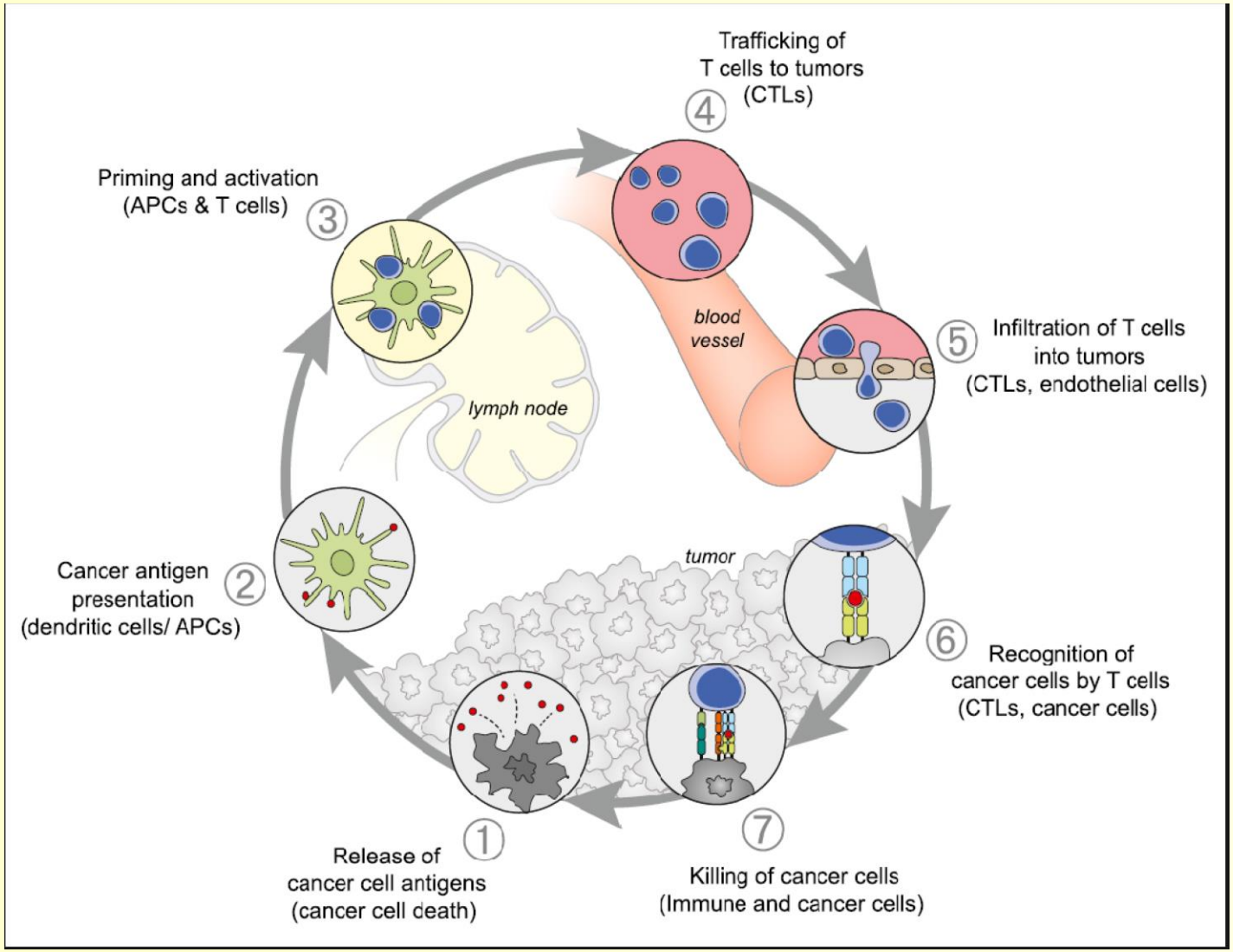


FIGURE – Immune system cells

Glenn D, Nature Reviews Cancer 4, 11-22 (January 2004)

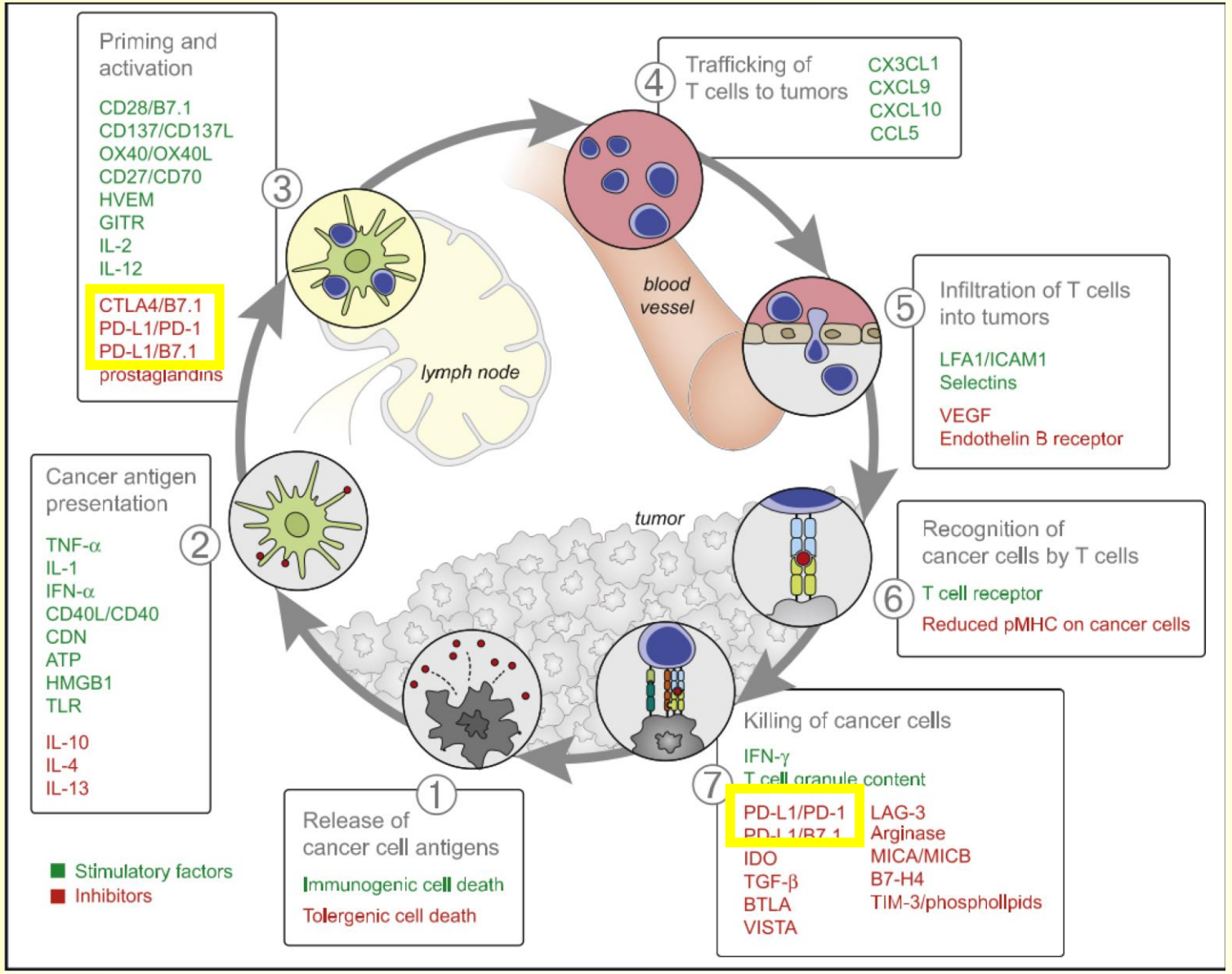
Les immuno-thérapies (2)

Le cycle cancer immunité



Chen, D. S., & Mellman, I. (2013).
Oncology meets immunology : The cancer-immunity cycle.

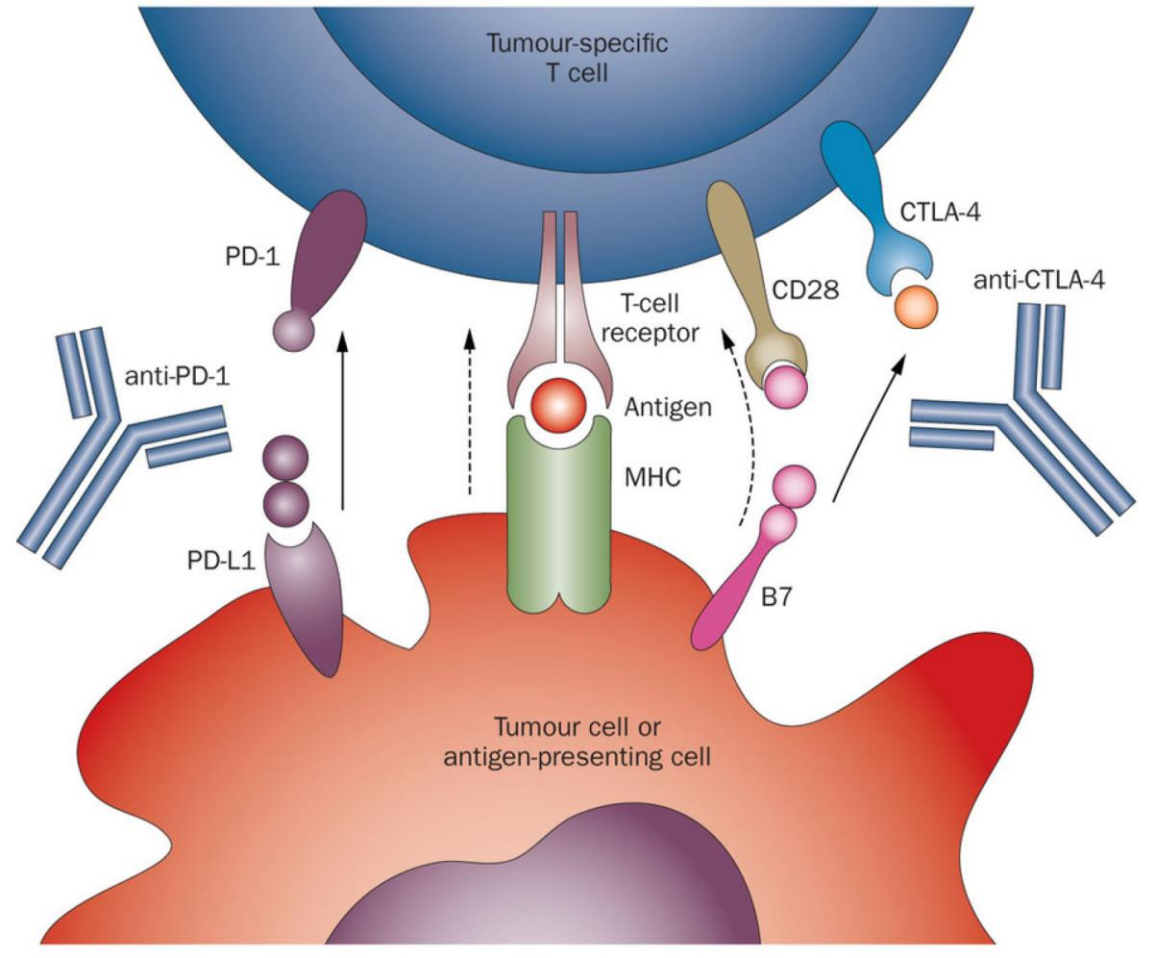
Les immuno-thérapies (3)



Chen, D. S., & Mellman, I. (2013).
Oncology meets immunology : The cancer-immunity cycle.

Les immuno-thérapies (4)

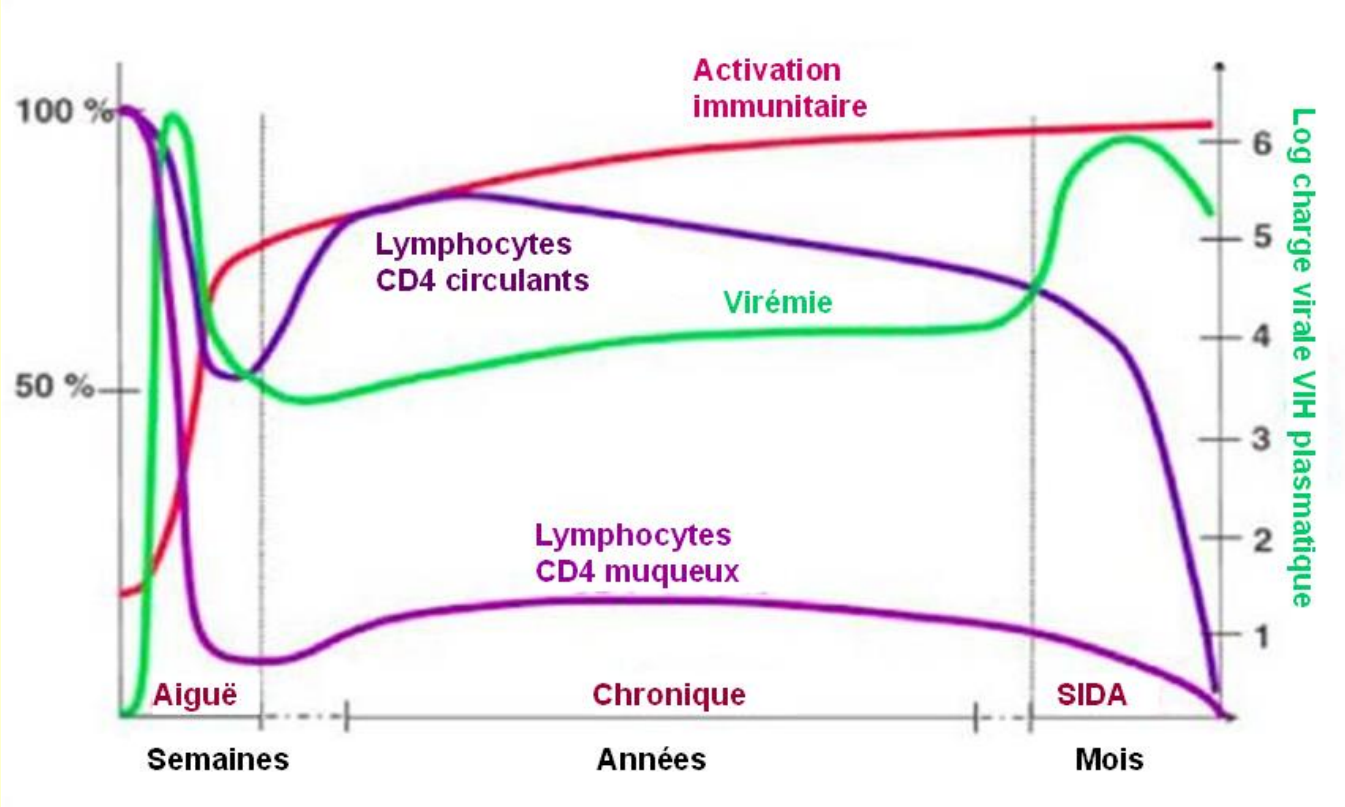
Une cible immunologique : blocage des immune checkpoints



Drake,C.G.et al.Nat.Rev.Clin.Oncol.11,24□
37 (2014)

Infections à VIH : marqueurs précoces (1)

- Le contexte de l'infection à VIH
- Histoire naturelle de l'infection



- Charge virale VIH : marqueur de la réplication virale
- CD4 : marqueurs de l'immunosuppression

Infections à VIH : marqueurs précoces (2)

Critères de jugement, critères d'intérêt

Essais thérapeutiques	Etudes observationnelles
Critère de jugement virologique (essais d'enregistrement) Critère d'efficacité CD4 (ex AUC, essai d'intensification par il2)	Décès et SIDA Morbidité sévère - cardiovasculaire - rénale - cancers - maladies hépatiques Marqueurs d'activation

Infections à VIH : marqueurs précoces (3)

- Effets des CD4 et de la charge virale, à 0, 6 et 36 mois de traitement, sur la survenue de SIDA/décès
- 14 208 patients avec mesures aux 3 points
- Analyse en landmark, baseline =36 mois
- Après 36 mois de traitement, mesures à 36 mois les plus pronostiques de SIDA/décès
- Réponse virologique à 6 mois, reflétée par la charge virale plasmatique, et l'évolution des CD4 entre 6 et 36 mois restant pronostiques de la survenue de SIDA

Lanoy et al., AIDS 2009

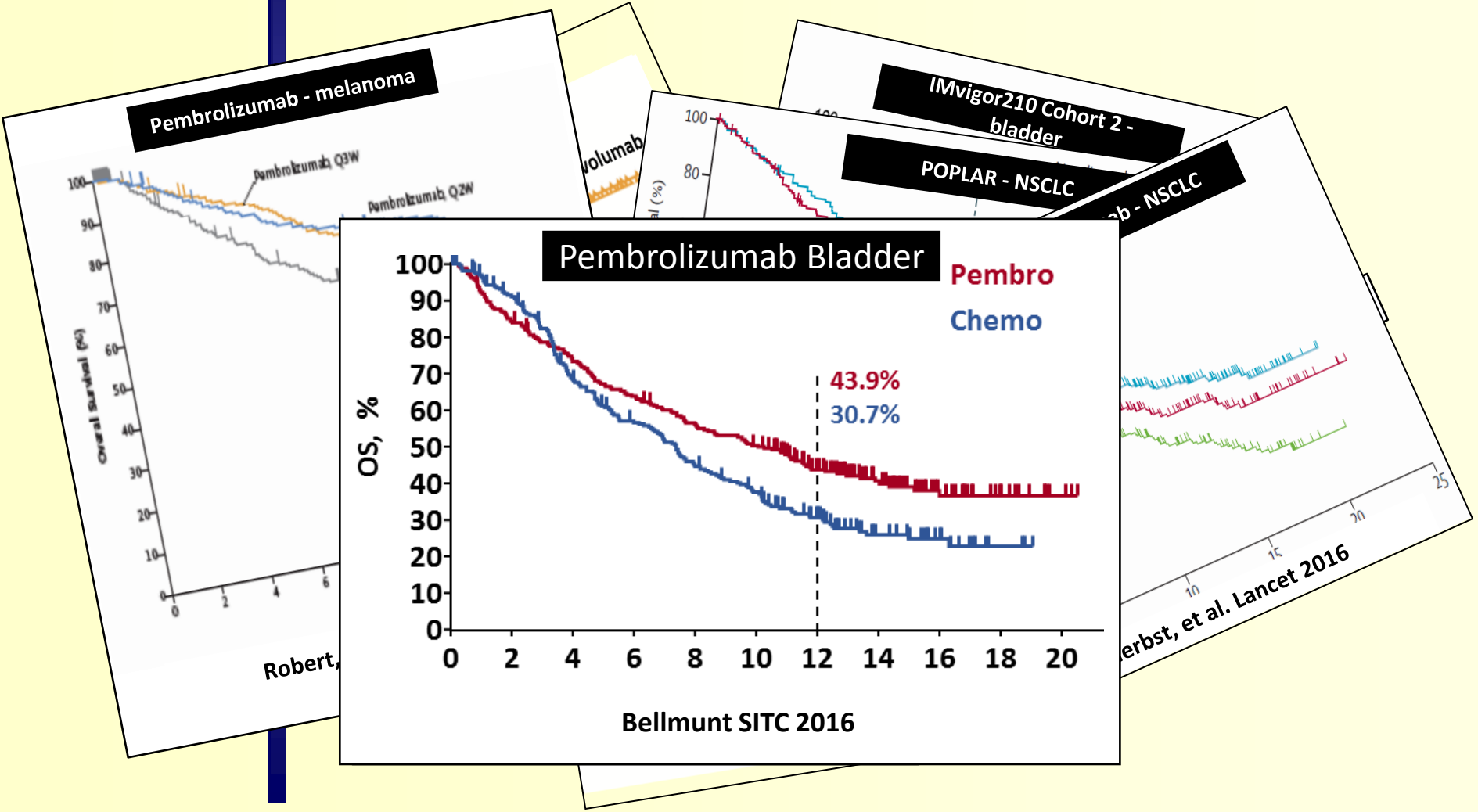
Mesurer l'effet d'un marqueur précoce

- Rappels sur l'analyse en landmark (📄 Hein Putter, SMAC 2013 Bordeaux)
- A l'initiation du traitement, on ne connaît pas le niveau d'expression du marqueur précoce
- En survie, on ne stratifie pas sur une exposition future (!!!)
- 2 alternatives :
  - Covariable dépendante du temps (attention au guaranteed time bias)
  - Analyse en landmark
    - Considérer l'expression du marqueur à différentes landmarks
    - Censurer les patients présentant l'événement avant la landmark

Overall survival: endpoint of interest

- Which efficacy endpoint(s) should be considered?
- One aims to determine if the experimental immunotherapy prolongs patients' survival
- Identifying the treatment effect on overall survival

Which translates into benefits in OS

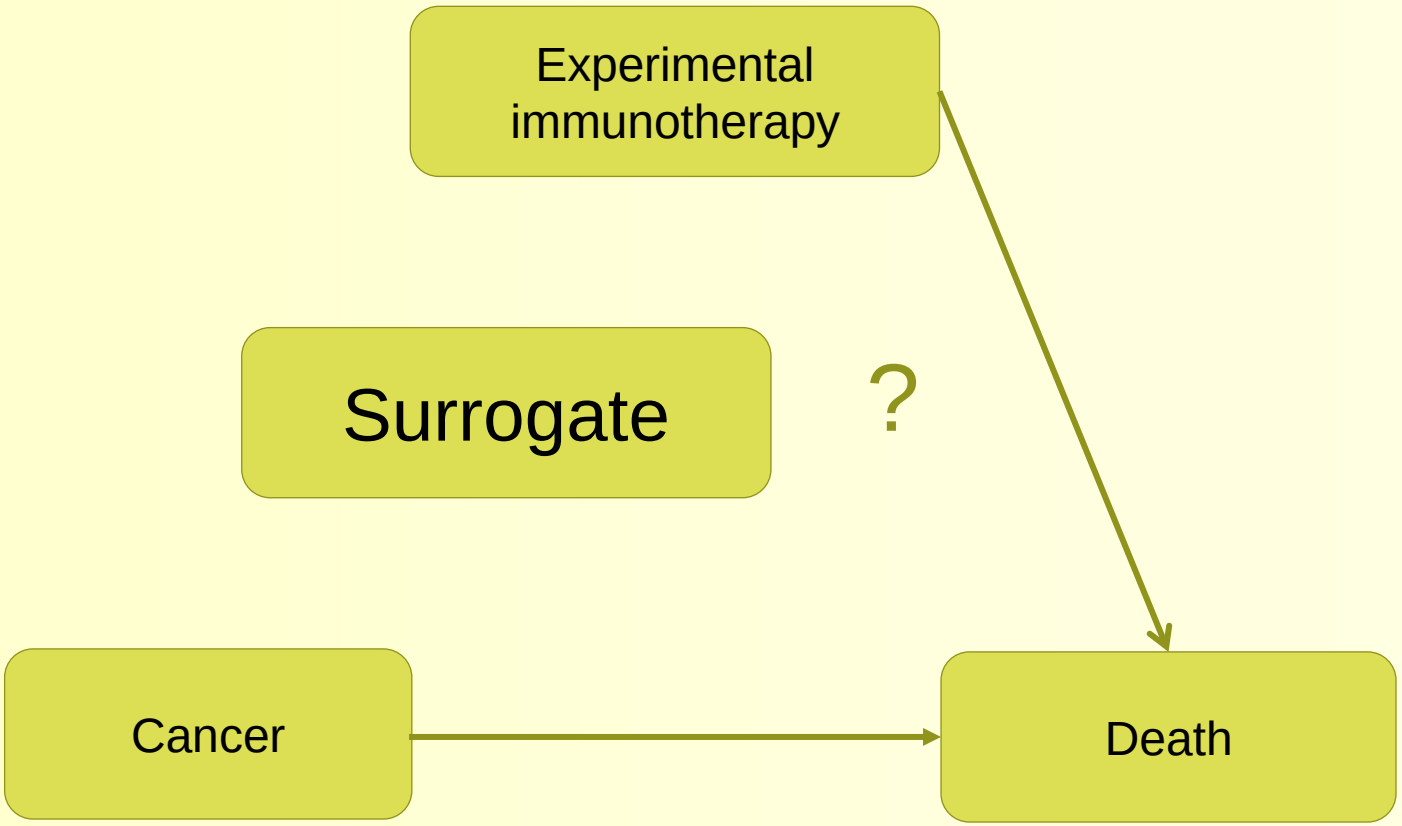


From Aurélien Marabelle

Obstacles for identifying treatment effect on overall survival

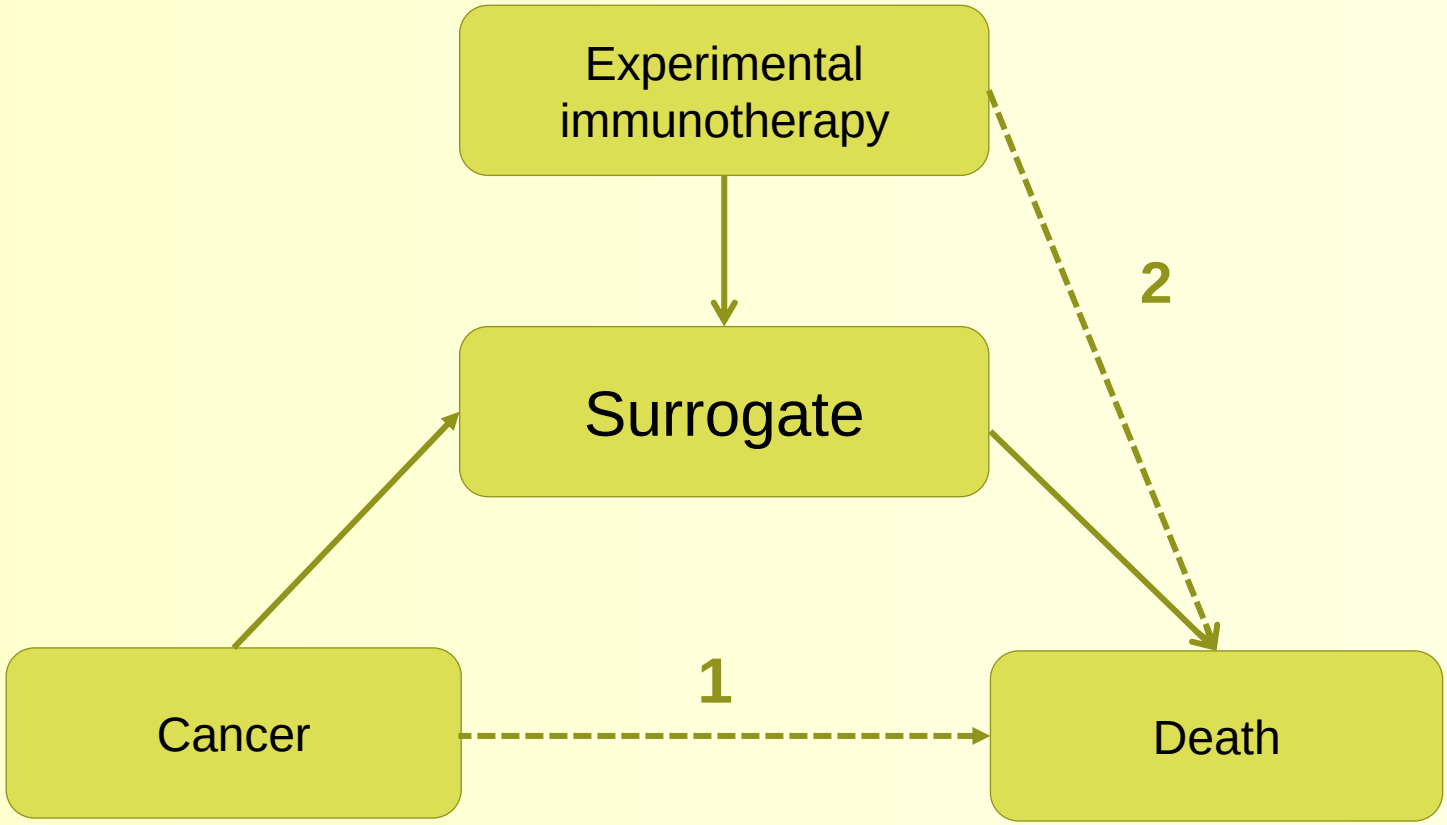
- Occurrence of death after long follow-up
- ⇨ Problems in feasibility, trial duration
- In randomized controlled trial, one aims to allow switch after control treatment failure
- In intent to treat analysis,
- ⇨ Treatment effect is estimated without bias (≠ per protocol analysis leading to selection bias)
- ⇨ experimental treatment effect on overall survival diluted by switch

Candidate surrogate endpoints



After Lavery Mult Scler Int. 2014 et Prenctice Stat Med 1989

Surrogate endpoint validated if:



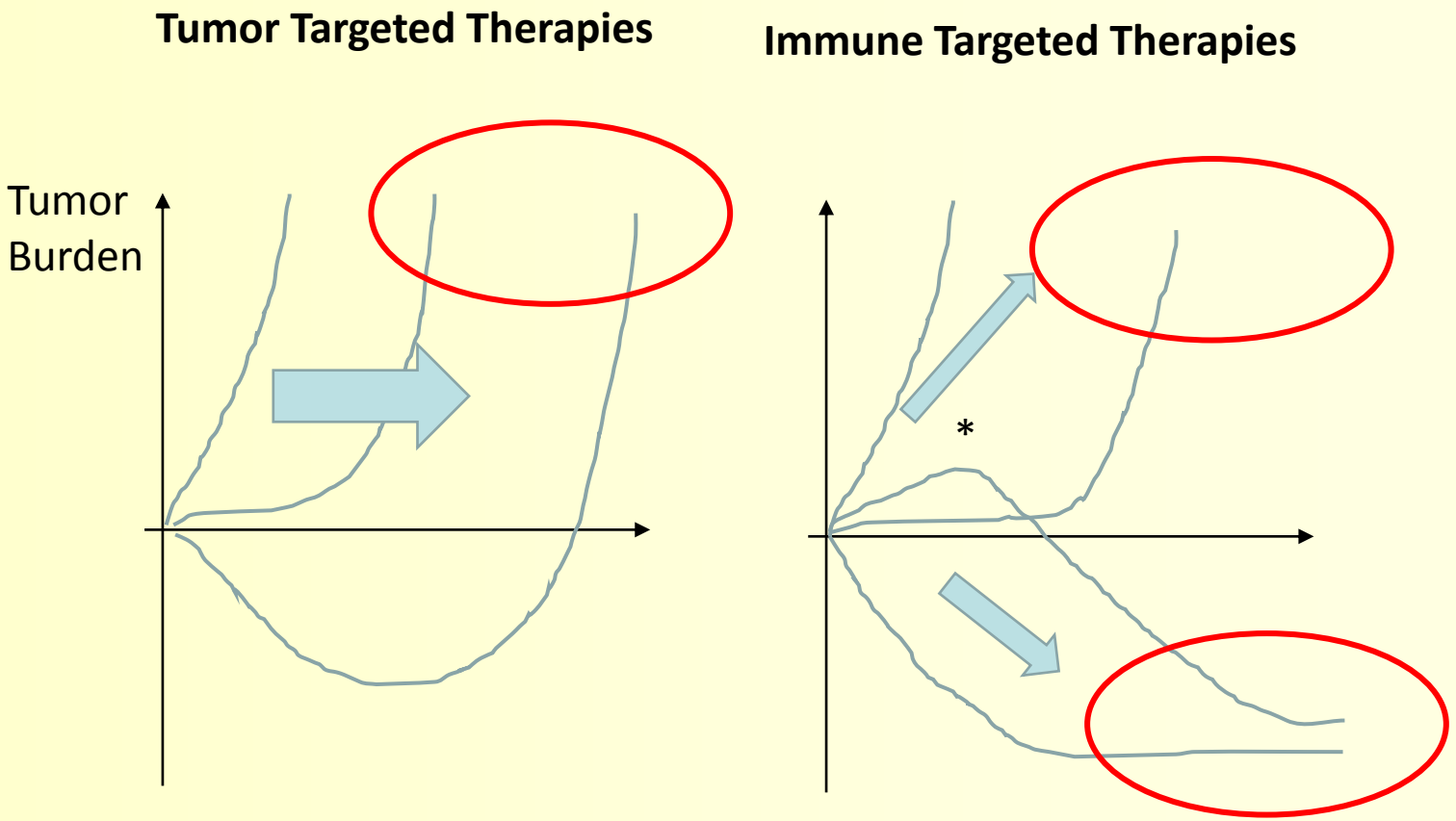
1. All cancer effect on death identified through the surrogate
2. All treatment effect on cancer identified through the surrogate

After Lavery Mult Scler Int. 2014 et Prenctice Stat Med 1989

Progression -free survival

- Progression-free survival validated as surrogate endpoint of overall survival
  - For several cancer locations
  - For several therapies (cytotoxic, targeted therapies)
- Evaluating treatment effect on progression-free survival and allowing cross-over at progression
  - Treatment effect on PFS as primary endpoint, no effect dilution
  - Treatment effect on OS as secondary endpoint, effect dilution
- For immunotherapy, PFS good surrogate endpoint for overall survival ?
- For immunotherapy combination with PFS validated as surrogate endpoint for standard drug, is PFS validated as surrogate endpoint?

Clinical Trial Endpoints



From Aurélien Marabelle

Pseudo-progressions

- How to model disease progression in context of pseudo-progression?
- When a pseudo-progression/progression occurs:
  - ⇨ Therapeutic decision: treatment is maintained or not
  - ⇨ New evaluation(s) will conclude that the observed event was progression or pseudo-progression
- Classical survival analysis could not be adequate
- Use of multi-state models

Identifier tôt les patients susceptibles de répondre au traitement

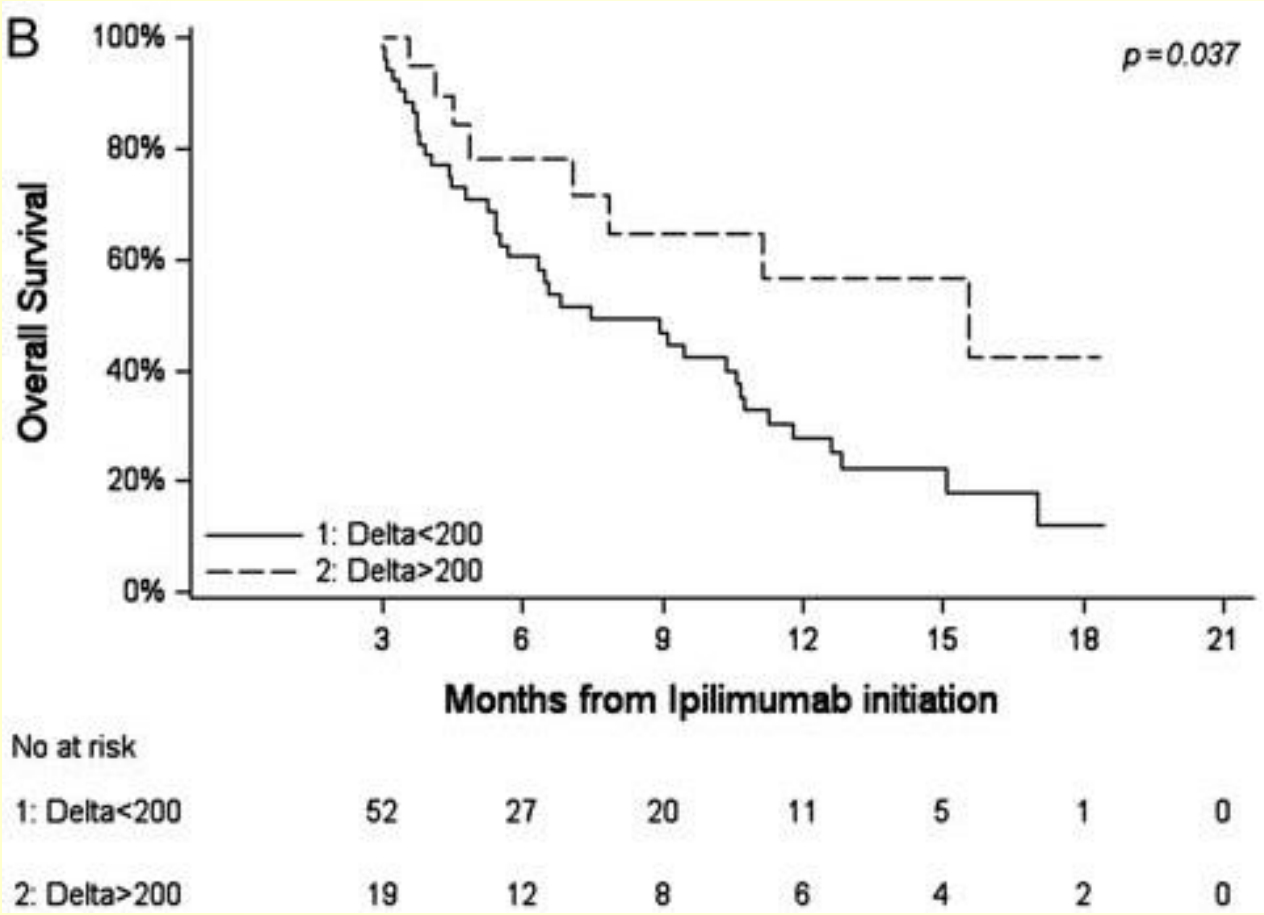
- Early markers (measured at short term after treatment initiation) :
  - Of toxicity (infra-clinical stage)
  - Of treatment response
  - Useful to monitor follow-up of patients under treatments
- Clinical, biological markers
- Repeated measures
- Adequate modeling
  - Longitudinal models
  - Joint models
  - Landmark analyses

Marqueur biologique précoce

Experience in daily practice with ipilimumab for the treatment of patients with metastatic melanoma: an early increase in lymphocyte and eosinophil counts is associated with improved survival

J. Delyon[1*], C. Mateus[1], D. Lefeuvre[2], E. Lanoy[2], L. Zitvogel[3,4,5], N. Chaput[4], S. Roy[1], A. M. M. Eggermont[6], E. Routier[1] & C. Robert[1,7]

Ann Oncol 2013



Différence en lymphocytes sur les deux premiers cycles

AE : marqueurs de l'activation directe du système immunitaire

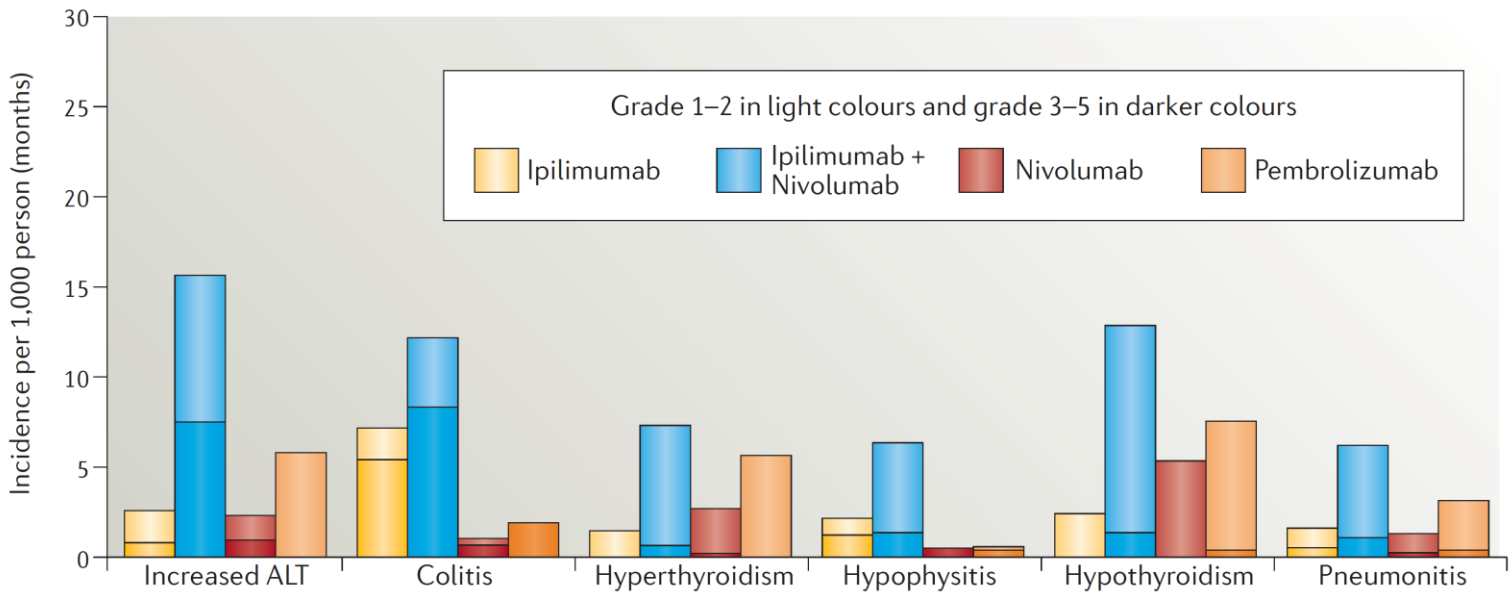


Figure 3 | **Adverse events of special interest noted with immune-checkpoint inhibitors.** These adverse events are a direct result of activation of the immune system, as reported in patients treated with ipilimumab, pembrolizumab, nivolumab or ipilimumab plus nivolumab. Incidence per 1,000 person-months; these incidences include data from the following studies: CA-184-002 (REF. 16), KEYNOTE-001 (REF. 30), KEYNOTE-001 (randomized cohorts[31]), KEYNOTE-002 (REF. 32), KEYNOTE-006 (REF. 33), CheckMate-037 (REF. 100), CheckMate-066 (REF. 29), CheckMate-067 (REF. 45), and CheckMate-069 (REF. 44).

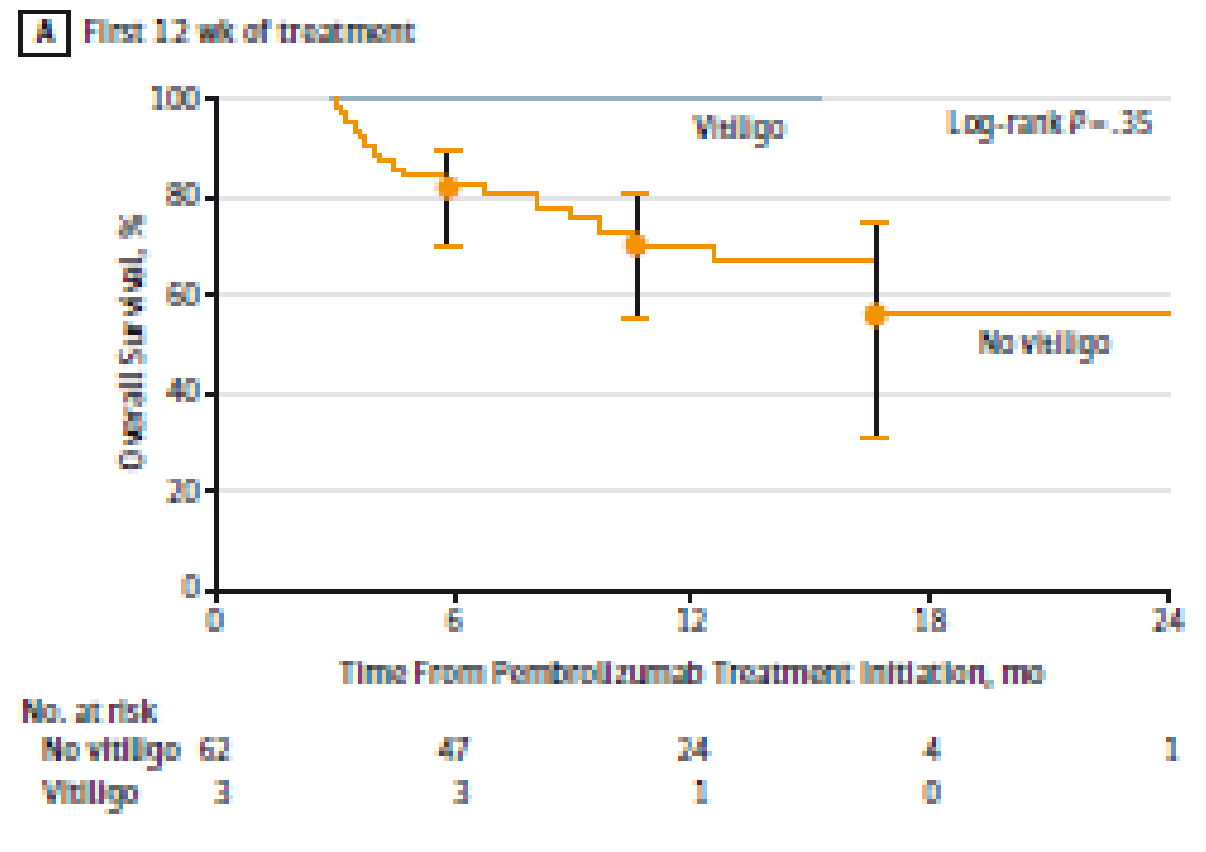
Boutros et al. Nat. Rev. Clin. Oncol. 2016

Marqueur clinique précoce

Original Investigation

Association of Vitiligo With Tumor Response in Patients With Metastatic Melanoma Treated With Pembrolizumab

Camille Hua, MD; Lise Boussemart, MD, PhD; Christine Mateus, MD; Emilie Routier, MD; Céline Boutros, MD; Hugo Cazenave, MD; Roxane Viollet, MD; Marina Thomas, MD; Séverine Roy, CRA; Naïma Benannoune, CRA; Gorana Tomasic, MD; Jean-Charles Soria, MD, PhD; Stéphane Champiat, MD; Matthieu Texier, MSc; Emilie Lanoy, PhD; Caroline Robert, MD, PhD



Microbiote
=
marqueur
pronostique

- Survenue d'entérocolites (semblable à maladie de Crohn) sous ipilimumab
- Profils différents du microbiote intestinal
- Meilleure réponse et plus d'entérocolites chez les patients présentant un profil de microbiote riches en Faecalibacterium et firmicute

- Chaput N et al. Ann. Oncol. 27 mars 2017;

Recherche en cours

- PhD student Vahé Asvatourian: Contribution of causal models in evaluating immunotherapies from observational data
  - Analyzing multidimensional immunologic markers

  collected before and during treatment
  - Outcomes: toxicity/response to treatment/OS
  - Identifying causal effects of markers

- Need in personalized medicine:
  - To understand molecular mechanisms
  - To identify therapeutic targets
  - To evaluate immunomics markers:
    - Prognostic value
    - Predictive value
    - Value as early marker of treatment response

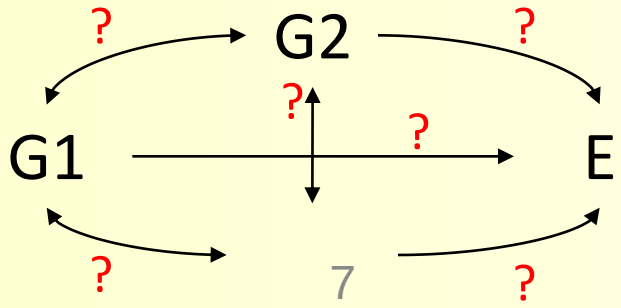
Statistical challenges

- High dimensional : $\boldsymbol{p} >> \boldsymbol{n}$
  - $Markers\ (p) \approx 1000 - 10000$
  - $Samples\ (n)\ 50 - 100$
- Multi-collinearity
- Selection bias occurring in observational settings
- DAGs and causal models could be used in a comprehensive approach to determine among immunomics markers those

How to establish causal DAGs in immunomics context since

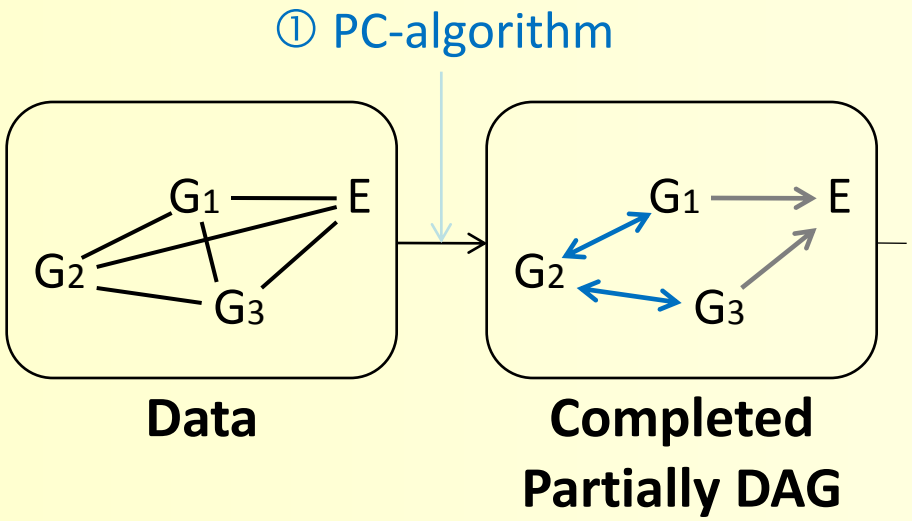
- no a priori knowledge of ordered relationships between immunomics markers
- High number of markers

Example



IDA : Intervention calculus when the DAG is absent (*Maathuis, The annals of statistics 2009*)

1. PC-algorithm to search for the underlying DAG

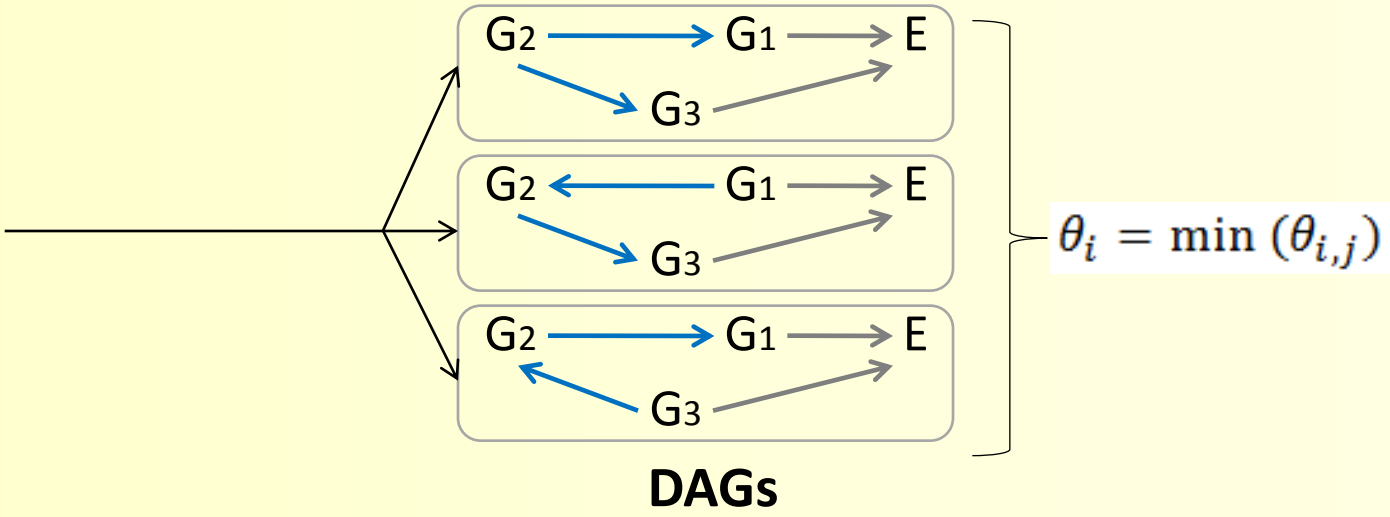


PC-algorithm Peter Spirtes and Clark Glymour, 2000

IDA : Intervention calculus when the DAG is absent

(*Maathuis, The annals of statistics 2009*)

2. Do-calculus : Estimation of causal effects



Causality in omics context requires (1):

- Expert knowledge: the collect of confounders has to be exhaustive
- Access to raw data: filtering or normalization could induce potential selection bias
- Use of pipeline describing all steps of data treatment processing

Current work

- PhD student Vahé Asvatourian: Contribution of causal models in evaluating immunotherapies from observational data
  - Causal inference in analyzing immunologic markers
  - Markers collected before and during treatment
  - Outcomes: toxicity/response to treatment/OS

1. extending the IDA to repeated measures
2. Framework for simulating DAGs
3. Integration prior knowledge in DAGs

En conclusion

- Immunothérapies ciblent le système immunitaire
- Nombreux marqueurs de l'effet des immunothérapies
  - Biologiques
  - Cliniques
- Identification de marqueurs précoces de l'effet des traitements pour :
  - Identifier à un stade infra-clinique les patients susceptibles de présenter des toxicités/des réponses au traitement
  - Monitorer les patients sous traitements
  - Identifier des médiateurs de l'effet des traitements, critères de substitution potentiels ?

Cliniciens

- Céline Boutros
- Julie Delyon
- Eric Deutsch
- Camille Hua
- Aurélien Marabelle
- Sophie Postel-Vinay
- Caroline Robert

Statisticiens

- Vahé Asvatourian
- Matthieu Texier
- Delphine Lefeuvre

Immunologistes

- Nathalie Chaput
- Clélia Coutzac