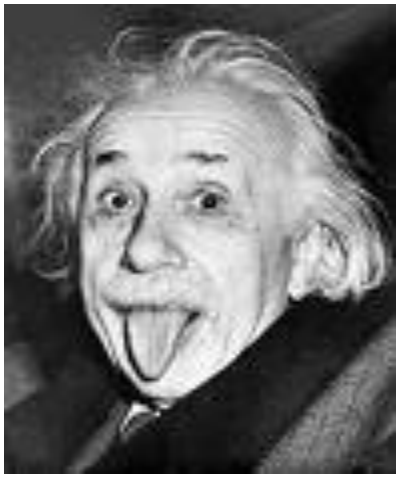
SMARTc

SIMULATION MODELING ADAPTIVE RESPONSE
FOR THERAPEUTICS IN CANCER



« The madness is to always behave the same way and expect a different result ...»
Albert Einstein

« It makes science with facts as is a house with stones: but the **accumulation of facts is not science** any more than a pile of stones is a house »

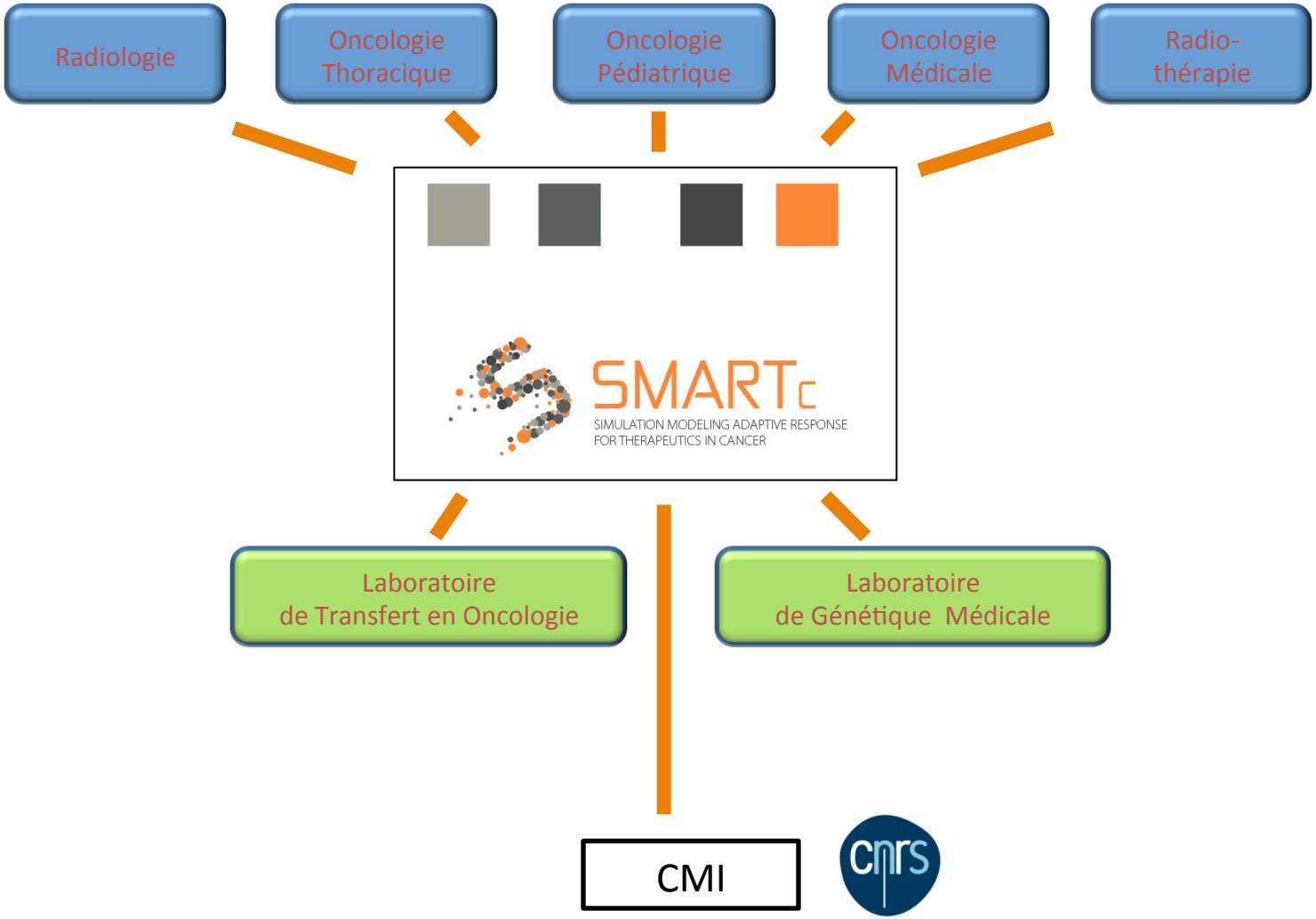
Henri Poincaré

Network:

Assistance Publique Hôpitaux de Marseille

Aix*Marseille université

Inserm



SMARTc
SIMULATION MODELING ADAPTIVE RESPONSE FOR THERAPEUTICS IN CANCER

Metronomic chemotherapy in human lung cancer: mathematical modeling for an optimal schedule

Presented by Raphaël Serre [2]

Xavier Elharrar [1,2], Dominique Barbolosi [2], Joseph Ciccolini [2], Christophe Meille [2,3], Christian Faivre [2], Bruno Lacarelle [2], Nicolas André [2,4,5], Fabrice Barlesi [1,2,4]

1 Aix Marseille University; Assistance Publique Hôpitaux de Marseille. Multidisciplinary Oncology and Therapeutic Innovations dept, Marseille, France;
2 Aix Marseille University, SMARTc Pharmacokinetics Unit, Inserm S_911 CRO2, Marseille, France;
3 Novartis; disclaimer: C. Meille was not affiliate to Novartis at the time of the analysis;
4 Aix Marseille University; Assistance Publique Hôpitaux de Marseille. Centre d'Essais Précoces en Cancérologie de Marseille APHM CLIP², Marseille, France;
5 Paediatry Oncology Unit, Assistance Publique Hôpitaux de Marseille, Marseille, France.

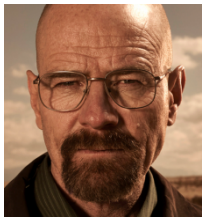
Outline

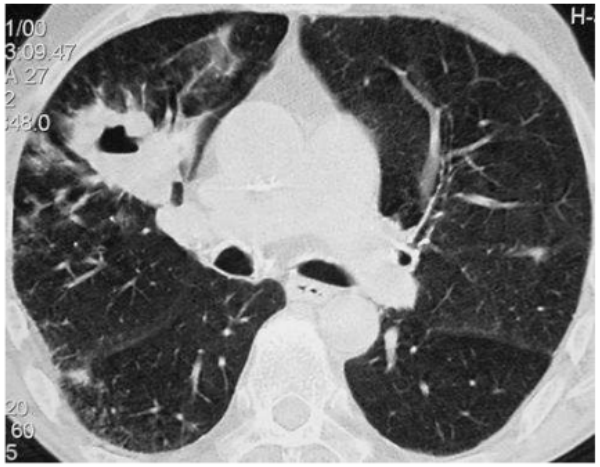
- Clinical challenges
  - Human lung cancer
  - Carcinogenesis
  - Treatments
  - Chemotherapy
    - Maximum Tolerated Dose (MTD)
    - Metronomic schedule
- Mathematical modeling of metronomic chemotherapy
  - PK model
  - Interface model
  - PD model
    - Toxicity model
    - Efficacy model
- Application
  - Theoretical results
  - Ongoing phase-1 clinical trial
- Conclusion, Q&A

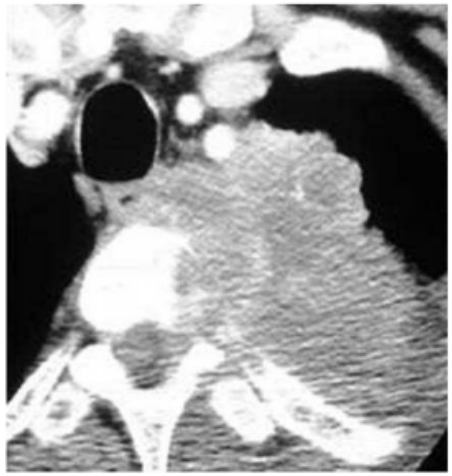
CLINICAL CHALLENGES

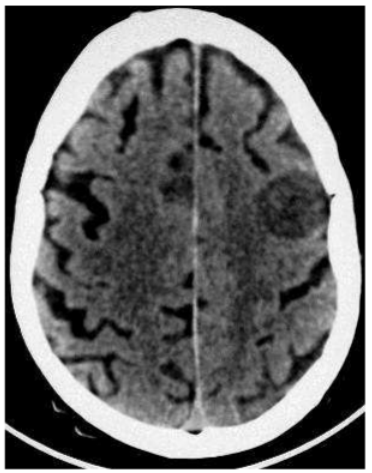
Human lung cancer: epidemiology

- (FR) 40 000 cases, 30 000 death per year
- 5Y survival rate = 14%: #1 killer cancer
- *10% of non-tobacco related cases*

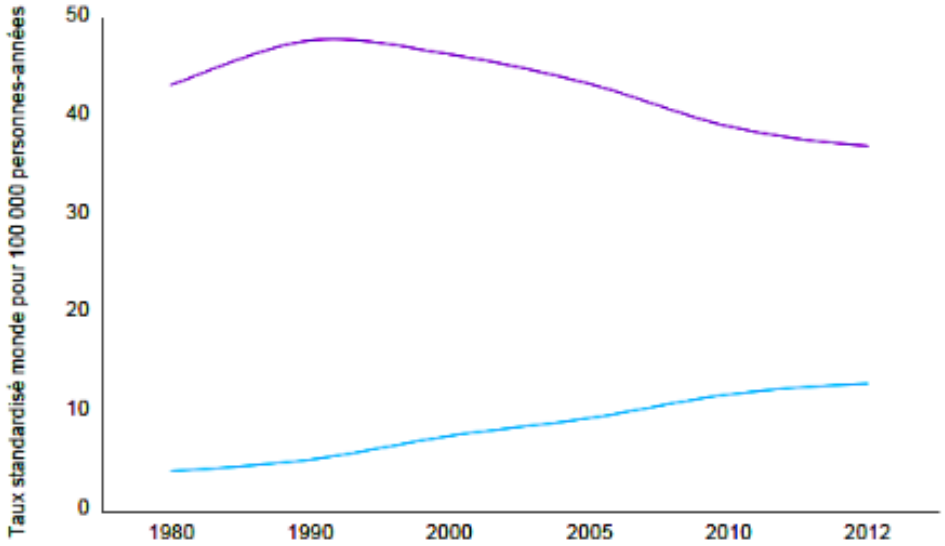


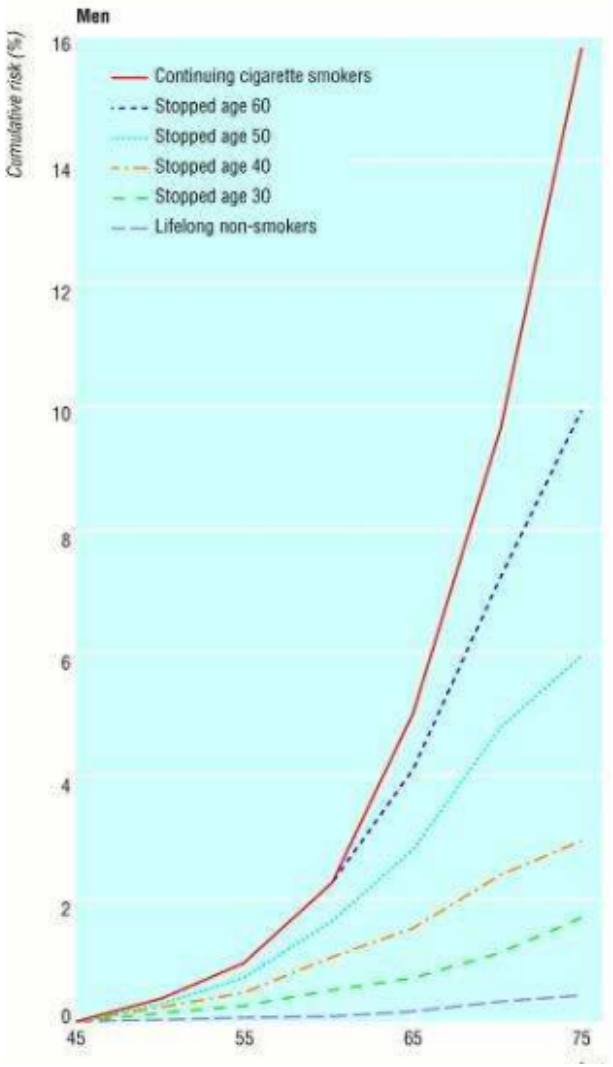






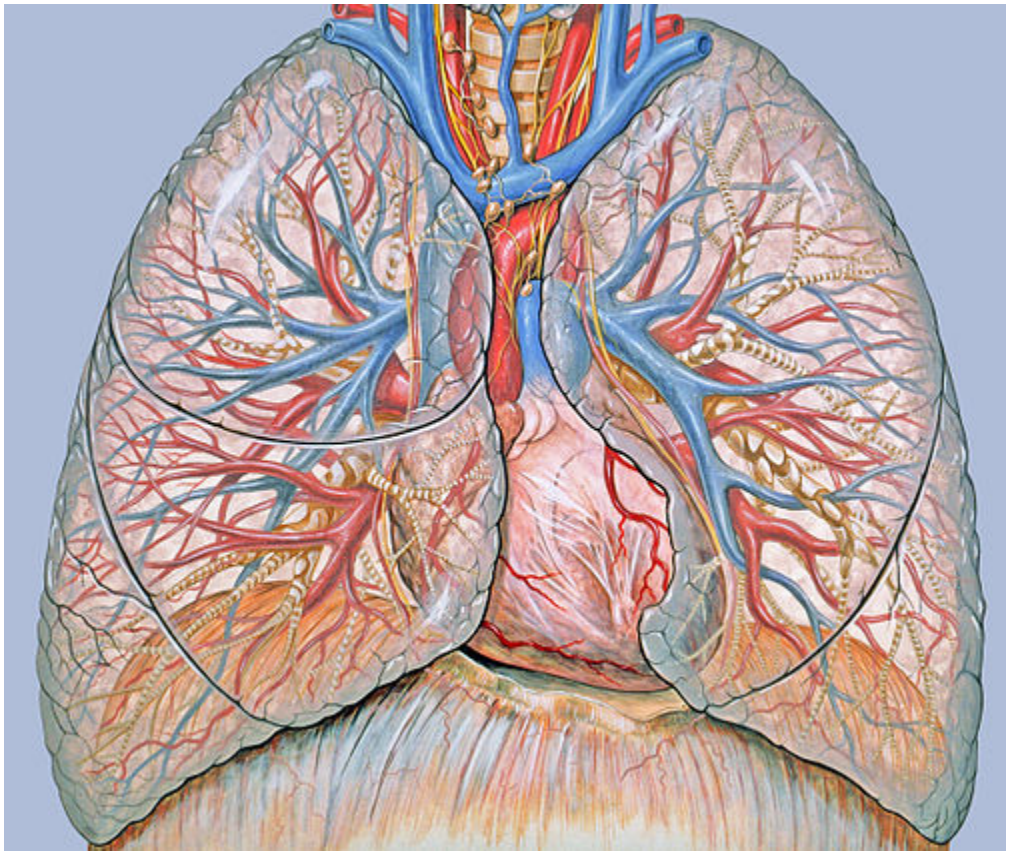
Tobacco++++ 90% of cases





Carcinogenesis

- Chronic **inflammation** (tobacco++, toxics…)
- progressive acquisition of gene **mutations**
- Emergence and multiplication of **« immortal » clones**
- Acceleration of tumor growth
  - Neutralization of the anti-tumor **immune response**
  - **Neo-vascularization**
- Tumor **dissemination** to distant sites (metastasis)
- Death



Treatments of human lung cancer

- Surgery++ but…
  - « **Lungs don't hurt** »→ >75% diagnosed when it is too late for surgical resection
  - 20% of LC = small cells lung cancer → no surgical resection
- Radiotherapy
- Targeted therapies
- Immunotherapies
- **Chemotherapy** *MTD or metronomics*

Chemotherapy

- **Maximum Tolerated Dose**
  - High dose
  - 4 to 6 cycles (*21 days*)
  - Combination of 2 drugs
    - Platinum-based antineoplastics: **cisplatine, carboplatine**
    - gemcitabine, pemetrexed, docetaxel, paclitaxel or **vinorelbine**
  - Typical rest period between doses: **7 to 14 days**
  - Can't shorten rest period because of toxicities
  - Rest period→ **resistant clones** , **tumor repopulation** ☹
  - PFS: 5 to 9 months depending on studies

- **Metronomics**
  - Dose < MTD
  - « continuous » schedule with no (*or much shorter*) rest period
  - single agent (ex: **vinorelbine)**
  - **anti-angiogenic effect** (?)
  - **Less resistance** (?)
  - Progression Free Survival: schedule dependent, stage dependent, TBD
  - most efficient schedule: TBD

Metronomic Vinorelbine

- benchmark protocol
  - 150 mg / week split into **3 oral doses**
  - 50 mg **D1** + 50 mg **D3** + 50 mg **D5**
  - Schedule empirically determined by several studies (from 20 to 70mg; Briassoulis & al 2009)
  - Response rates
    - 11% in heavily pre-treated patients, OS 9m (N=46)
    - 19% as a first line treatment of non-operable NSCLC stage IIIB or IV, OS 9m (N=43, age>70)
    - ☺ safer option for elder patients
    - 1st line: lower RR than typical MTD protocols? ☹

A phase II study of metronomic oral vinorelbine administered in the second line and beyond in non-small cell lung cancer (NSCLC): a phase II study of the Hellenic Oncology Research Group.
Kontopodis E[1], Hatzidaki D, Varthalitis I, Kentepozidis N, Giassas S, Pantazopoulos N, Vardakis N, Rovithi M, Georgoulias V, Agelaki S.

Metronomic oral vinorelbine as first-line treatment in elderly patients with advanced non-small cell lung cancer: results of a phase II trial (MOVE trial).
Camerini A[1], Puccetti C[2], Donati S[3], Valsuani C[4], Petrella MC[5], Tartarelli G[6], Puccinelli P[7], Amoroso D[8].

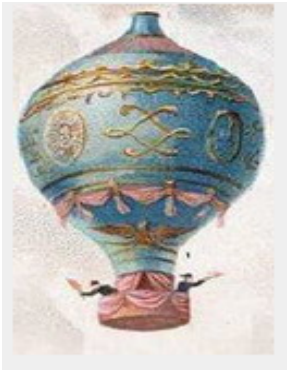
Computational Oncology & Stratégies Métronomiques

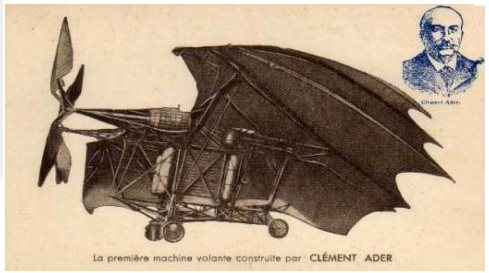
- Exemple de la vinorelbine métronomique (sein, NSCLC):

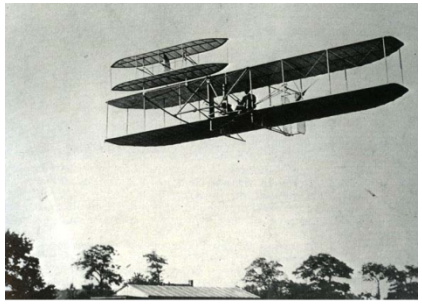
PI	Year	Setting	Dose	Schedule	Recommended dose
Briassoulis	2009	various	20-70 mg	TIW continous	50 mg
Pallis	2011	NSCLC	40-70 mg	TIW 1 week on / 3 weeks off	60 mg
Addeo	2010	Breast	70	TIW 3 on/1off	70 mg
Radjev	2011	various	20-50	Daily 1 on/1 off or 3 on/1 off	none
Addeo	2012	Breast	70	TIW 3 on/1 off	70 mg
Kontopodis	2013	NSCLC	50	TIW 3 on/1 off	50 mg
Briassoulis	2013	various	30-50	TIW continuous	50 mg
Cazzaniga	2014	Breast	40	TIW continuous	40 mg

Metronomics: next steps ?

Judah Folkman
1933-2008
Founder of **angiogenesis research**.
Discoverer of **angiostatin** and **endostatin**, of the anti-angiogenics effect of several compounds (such as **Thalidomide**) and proved their anti-cancer effect if given with a **metronomic** schedule.
His work led to the development of **Bevacizumab** (Avastin) in 2004.







MATHEMATICAL MODELING OF METRONOMIC CHEMOTHERAPY

Computational Oncology & Stratégies Métronomiques

Cancer Chemother Pharmacol (2014) 74:647–652
DOI 10.1007/s00280-014-2546-1

SHORT COMMUNICATION

Metronomics chemotherapy: time for computational decision support

Dominique Barbolosi · Joseph Ciccolini · Christophe Meille · Xavier Elharrar · Christian Faivre · Bruno Lacarelle · Nicolas André · Fabrice Barlesi

Cancer Chemother Pharmacol (2013) 71:1013–1019
DOI 10.1007/s00280-013-2095-z

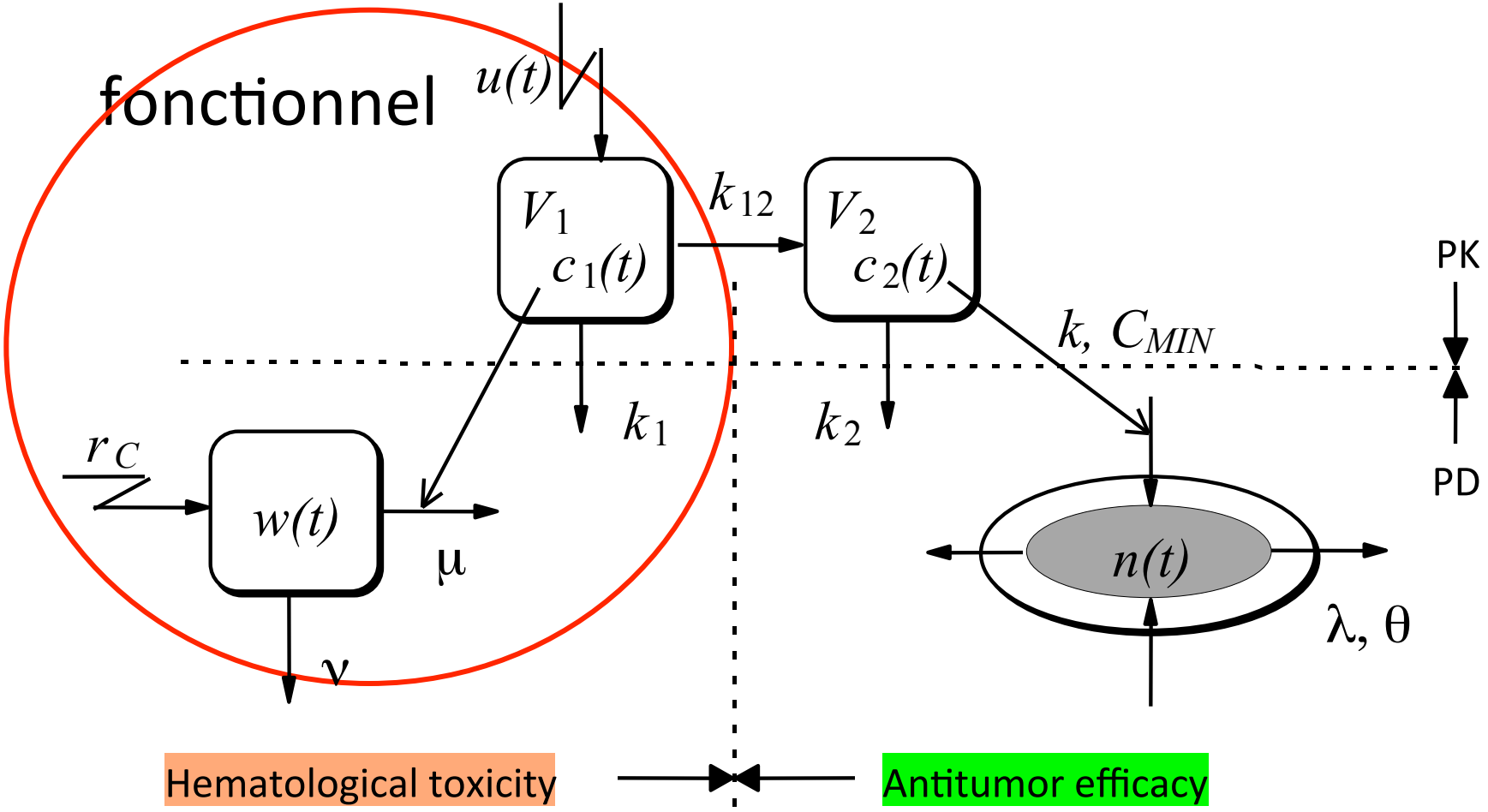
ORIGINAL ARTICLE

A mathematical model for the administration of temozolomide: comparative analysis of conventional and metronomic chemotherapy regimens

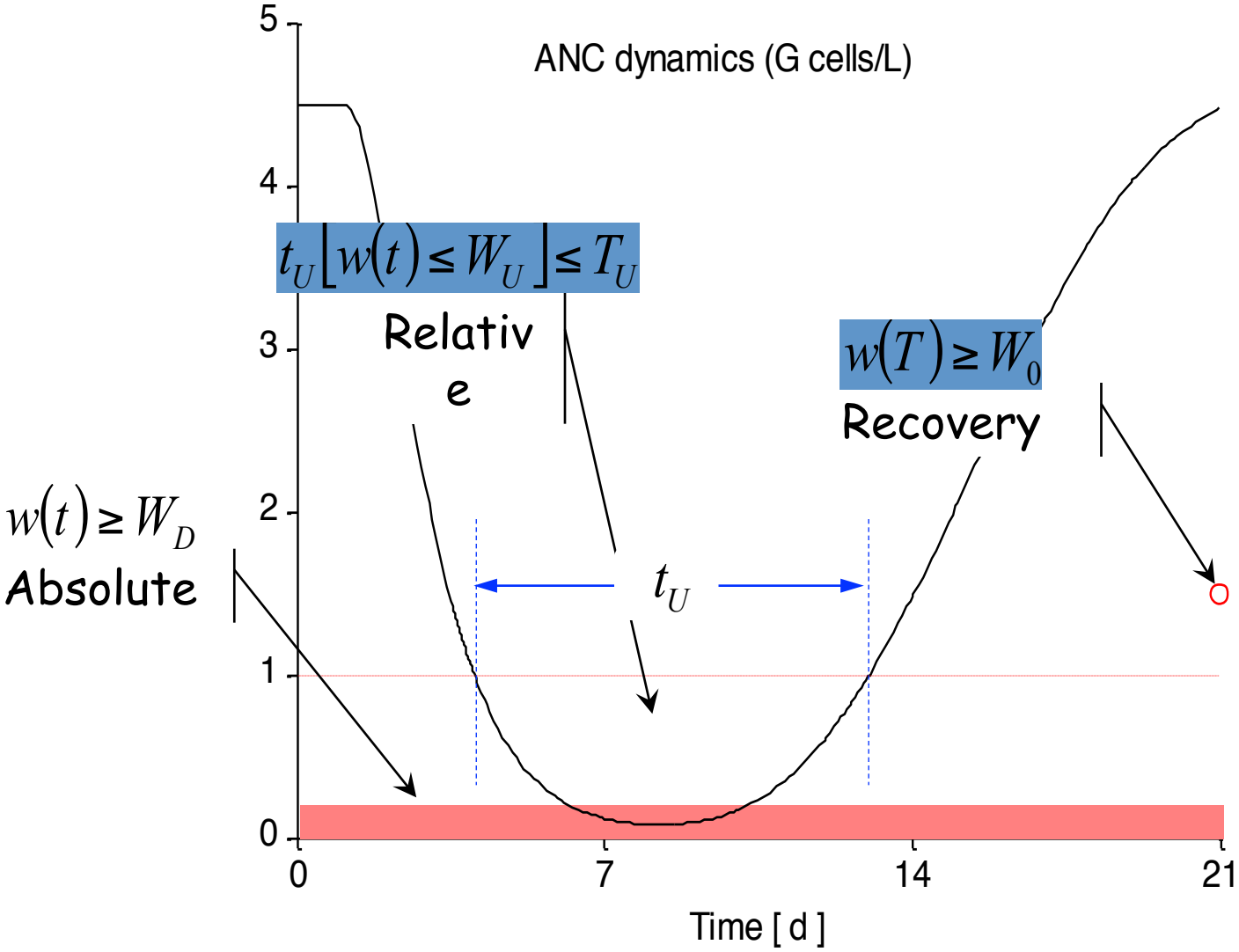
C. Faivre · D. Barbolosi · E. Pasquier · N. André

2013, 2014

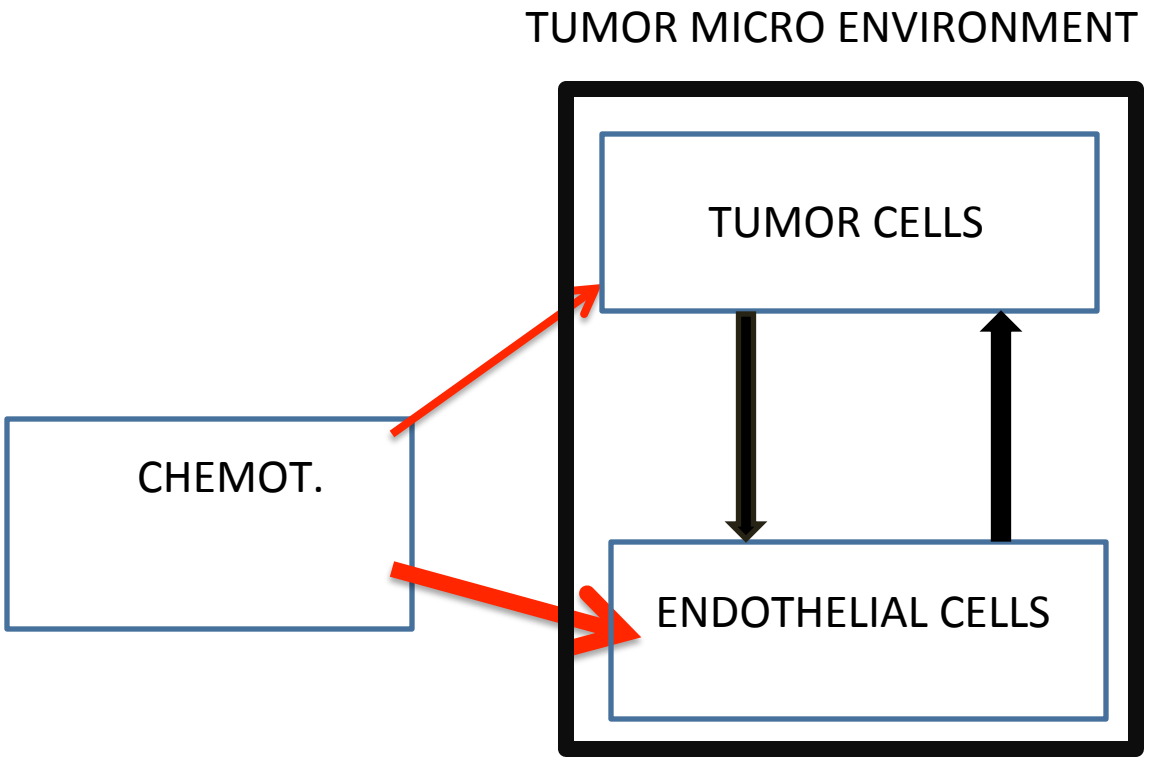
PK-PD: functionnal scheme



Hematotoxicity profile



Metronomic chemotherapy: principle



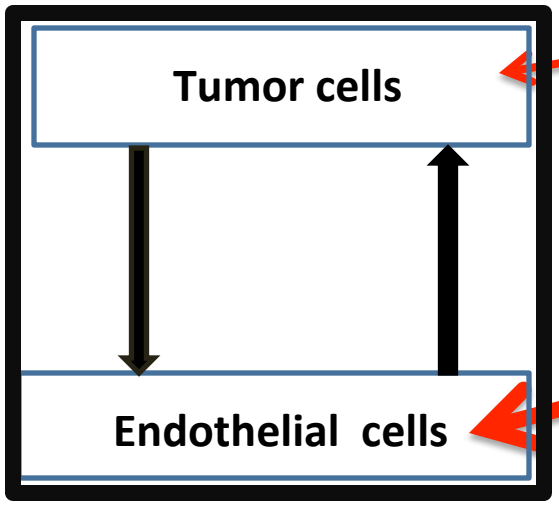
PK model

$$\frac{dy_1}{dt} = -k_a y_1 + u(t)$$

$$\frac{dy_2}{dt} = -k_e y_2 + \frac{k_a}{V} y_1$$

PD model

Tumoral system



$$\dot{y}_5(t) = \lambda_3 y_6 \ln(\frac{\theta}{y_5}) y_5 - N_1(t) y_5$$

$$\dot{y}_6(t) = R_{in}(1 + \frac{E_{\max} y_5}{E_{50} + y_5}) - (R_{out} + N_2(t)) y_6$$

$$\dot{y}_3(t) = -\lambda_1 \exp(-\gamma_1 y_3) y_3 + (y_2 - c_{\min,1}) H(y_2 - c_{\min,1})$$

$$\dot{y}_4(t) = -\lambda_2 \exp(-\gamma_2 y_4) y_4 + (y_2 - c_{\min,2}) H(y_2 - c_{\min,2})$$

Interface model

$$y_7(t) = (y_2 - c_{\min}) H(y_2 - c_{\min})$$

$$N_1(t) = \alpha_1 y_3 \exp(-R_{es} y_7)$$

$$N_2(t) = \alpha_2 y_4$$

PK model

$$\frac{dy_1}{dt} = -k_a y_1 + u(t)$$

$$\frac{dy_2}{dt} = -k_e y_2 + \frac{k_a}{V} y_1$$

PD model

$$\dot{y}_5(t) = \lambda_3 y_6 \ln\left(\frac{\theta}{y_5}\right) y_5 - N_1(t) y_5$$

$$\dot{y}_6(t) = R_{in}\left(1 + \frac{E_{\max} y_5}{E_{50} + y_5}\right) - (R_{out} + N_2(t))$$

Interface model

$$\dot{y}_3(t) = -\lambda_1 \exp(-\gamma_1 y_3) y_3 + (y_2 - c_{\min,1}) H(y_2 - c_{\min,}$$

$$\dot{y}_4(t) = -\lambda_2 \exp(-\gamma_2 y_4) y_4 + (y_2 - c_{\min,2}) H(y_2 - c_{\min}$$

$$y_7(t) = (y_2 - c_{\min}) H(y_2 - c_{\min}$$

$$N_1(t) = \alpha_1 y_3 \exp(-R_{es} y_7)$$

$$N_2(t) = \alpha_2 y_4$$

PK model

- Y1 : oral Vinorelbine
- Y2 : plasma Vinorelbine
- Ka, Ke, V : PK parameters
- $dy\downarrow 1 \, /dt = -k\downarrow a \, y\downarrow 1 + u(t)$
- $dy\downarrow 2 \, /dt = -k\downarrow e \, y\downarrow 2 + k\downarrow a \, /V \, y\downarrow 1$

Interface model ***Meille*** *& al, 2008*

- Y3 = «exposure» of tumor cells to vinorelbine
- Y4 = «exposure» of epithelial cells to vinorelbine
- B1, b2 → saturable clearance rates

$$dy\downarrow 3\ /dt = -a\downarrow 1 \exp(-b\downarrow 1\ y\downarrow 3\ )y\downarrow 3 + (y\downarrow 2 - c\downarrow 1\ )H(y\downarrow 2 - c\downarrow 1\ )$$

$$dy\downarrow 4\ /dt = -a\downarrow 2 \exp(-b\downarrow 2\ y\downarrow 4\ )y\downarrow 4 + (y\downarrow 2 - c\downarrow 2\ )H(y\downarrow 2 - c\downarrow 2\ )$$

An interface model for dosage adjustment connects hematotoxicity to pharmacokinetics
C. Meille A. Iliadis D. Barbolosi N. Frances G. Freyer 2008 J Pharmacokinet Pharmacodyn

PD model: efficacy ***Faivre*** *& al 2013*

- Y5 = tumor mass (*Gompertz growth model*)
- Y6 = tumor **vascularization**, values in [0; 1]
- N1 = AUC of tumor exposure to Vinorelbine

$$\dot{y}_5 = \lambda y_6 \log\left(\frac{K}{y_5}\right) y_5 - N_1 y_5$$

$$\dot{y}_6 = R - (R + N_2) y_6$$

$$N_1 = \exp(-res \cdot y_7) \cdot u_1 \cdot y_3, \quad N_2 = u_2 y_4,$$

$$\dot{y}_7 = (y_2 - c_1) H(y_2 - c_1)$$

A mathematical model for the administration of temozolomide: comparative analysis of conventional and metronomic chemotherapy regimens

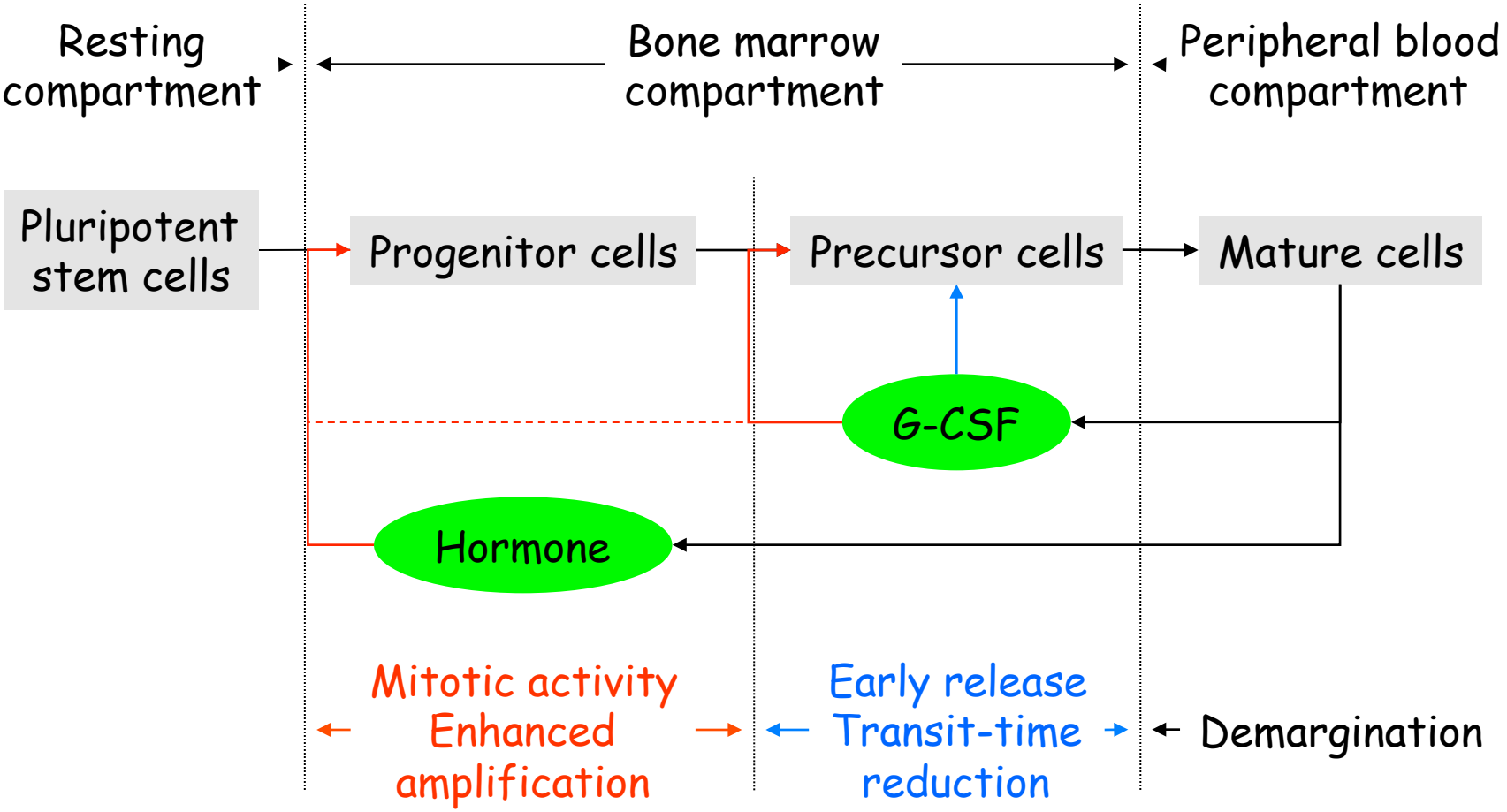
C. Faivre D. Barbolosi E. Pasquier N. Andre

PD model : toxicity. **Meille** & al 2008

- Disturbed hematopoiesis model described in Meille & al 2008
- **Stem** cells produce **progenitor** cells that mature into **neutrophils**, with a **delay**.
- Cytotoxic drugs have 2 effects
  - **Direct** toxicity on progenitor cells
  - **Indirect** toxicity by slowing production of progenitor cells
- Negative feedback loop to ensure reversion to equilibrium

An interface model for dosage adjustment connects hematotoxicity to pharmacokinetics
C. Meille A. Iliadis D. Barbolosi N. Frances G. Freyer 2008 J Pharmacokinet Pharmacodyn

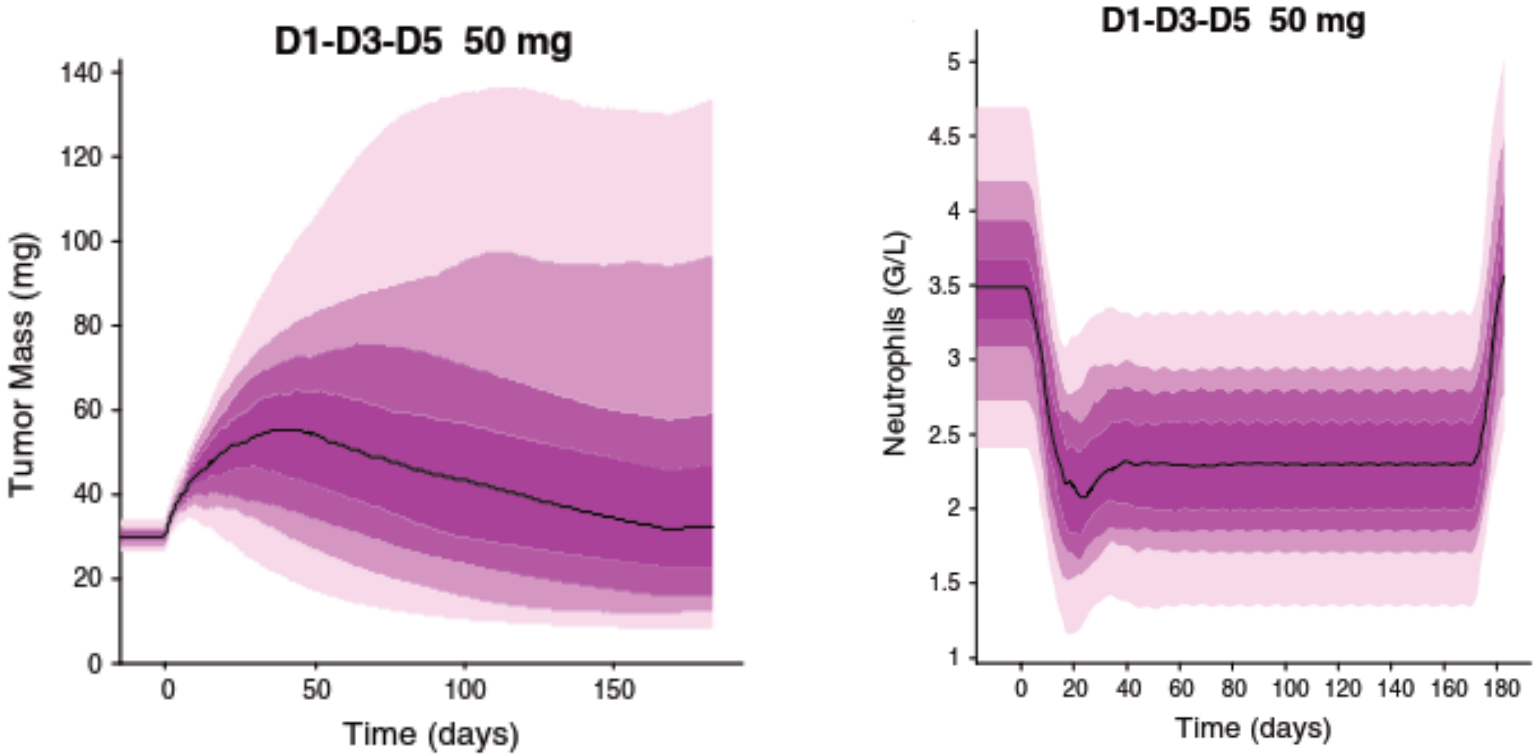
Haematopoiesis



APPLICATIONS

Explaining experimental results

- Calibration of the benchmark protocol on published experimental data



Enhancing the metronomic protocol

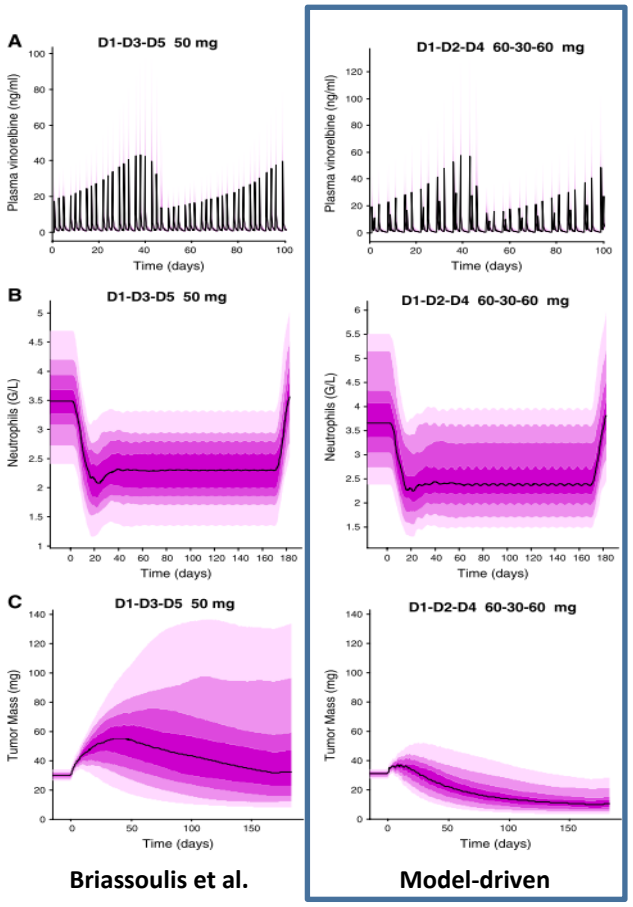
- Constraints
  - **neutrophil count**: *no less* than benchmark *(i.e. **50mg D1 50 D3 50 D5**)*
  - **Same total dose** = 150 mg/wk
  - « not too far » from benchmark
  - Same administration route = **oral** *(no IV)*
  - **Easy** dosing protocol (at home, no nurse)
- Objective: reduce expected tumor mass and variance
- Solution: **60mg D1 30mg D2 60mg D4**

Computational Oncology & Stratégies Métronomiques

PK

Tox

Eff.



Briassoulis et al.

Model-driven

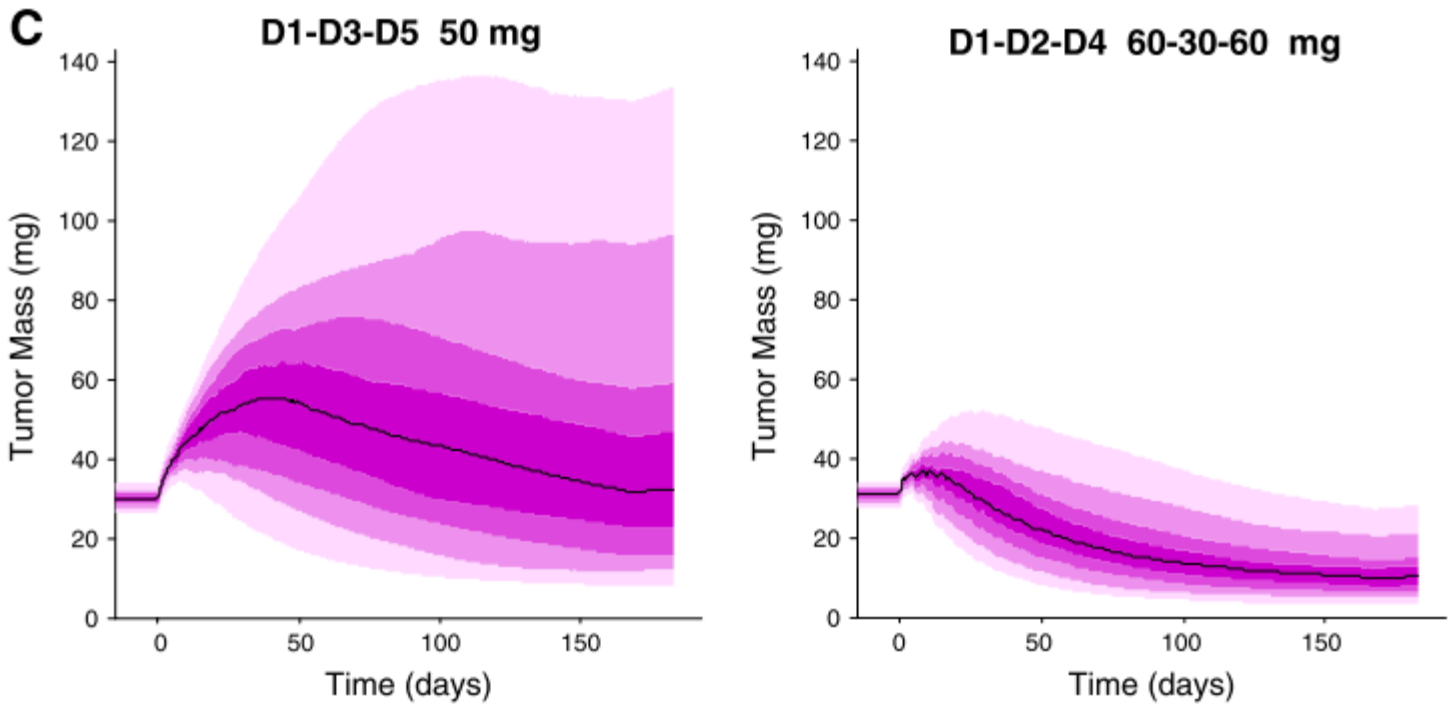
DIFFERENT PK

SAME TOXICITY

BETTER CLINICAL OUTCOME

A*Midex Initiative d'excellence Aix-Marseille

PIERRE FABRE ONCOLOGY


C
D1-D3-D5 50 mg
Tumor Mass (mg)
Time (days)
0
20
40
60
80
100
120
140
0
50
100
150
D1-D2-D4 60-30-60 mg
Tumor Mass (mg)
Time (days)

Ongoing phase-1 clinical trial

- stringent doses and toxicity constraints → **approval for phase-1 clinical trial**
- Clinical trial managed by **Fabrice Barlesi**, MD, PhD, *Assistance Publique – Hôpitaux de Marseille, Multidisciplinary Oncology and therapeutic Innovations Department*
- Mathematical analysis managed by **Dominique Barbolosi,** PhD *SMARTc pharmacokinetics unit, INSERM S_911 CRO2 Aix-Marseille University*
- Started in september 2015
- 12 patients enrolled (→+/- 25)

CONCLUSION

Take-home messages

- **QUIT SMOKING**
- Chemotherapies could stay with us longer than expected
- Metronomics chemotherapy produces its anti-tumor effect through its anti-angiogenic effect
- There is little or no resistance, even over long periods, contrary to MTD
- Risk of metronomics: inefficacy++
- Mathematical modeling can increase efficacy while keeping toxicities in check
- Only simple strategies that can be **trusted by clinicians** and take into account their **practical constraints** stand a chance to be tested

QUESTIONS & ANSWERS