From Metronomic to…. Chaotic Therapy?

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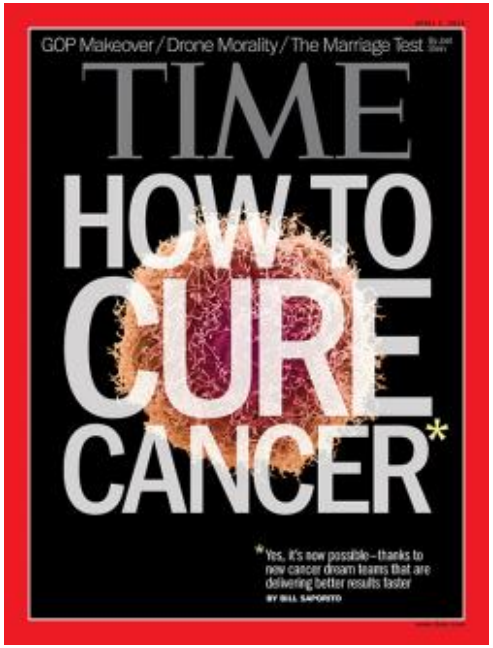
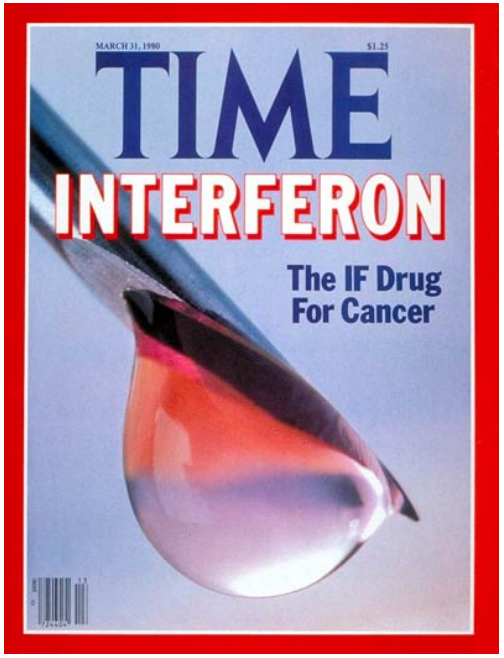
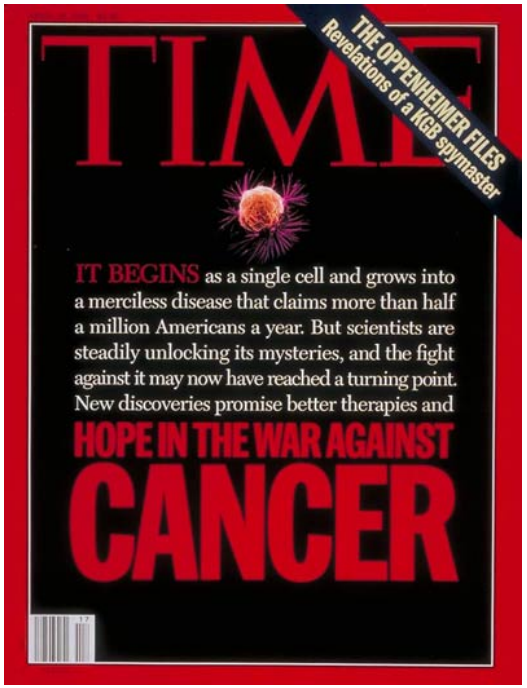
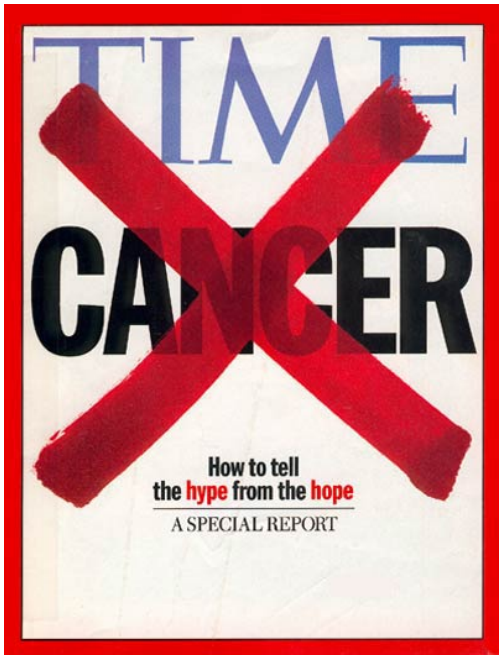
DECLARATION

- I have no conflict of interest to declare

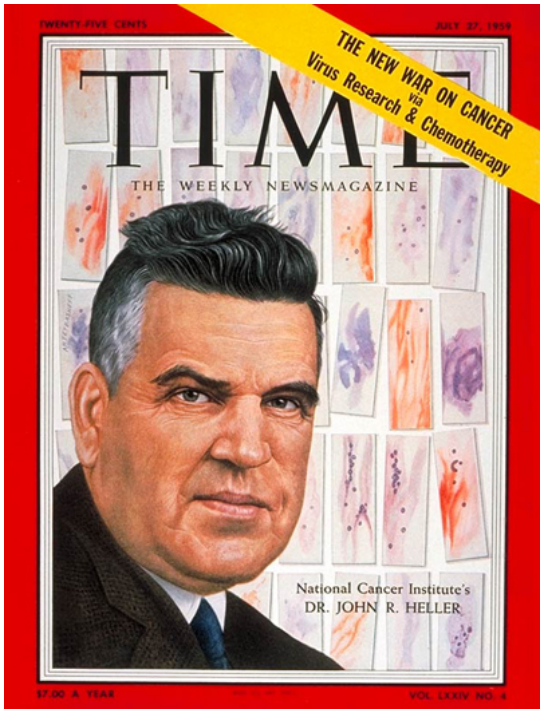

GOP Makeover / Drone Morality / The Marriage Test
TIME
HOW TO CURE CANCER*
*Yes, it's now possible – thanks to new cancer dream teams that are delivering better results faster
BY BILL SAPORITO


MARCH 31, 1980
$1.25
TIME
INTERFERON
The IF Drug For Cancer


THE OPPENHEIMER FILES
Revelations of a KGB spymaster
TIME
IT BEGINS as a single cell and grows into a merciless disease that claims more than half a million Americans a year. But scientists are steadily unlocking its mysteries, and the fight against it may now have reached a turning point. New discoveries promise better therapies and
HOPE IN THE WAR AGAINST CANCER


TIME
CANCER
How to tell the hype from the hope
A SPECIAL REPORT


FIFTY CENTS
MARCH 19, 1973
TIME
Toward Control of CANCER
Immunologist Robert Good

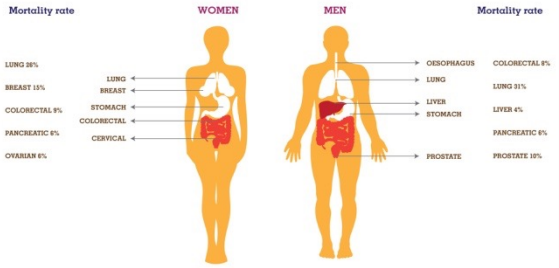

TWENTY-FIVE CENTS
JULY 27, 1959
THE NEW WAR ON CANCER via Virus Research & Chemotherapy
TIME
THE WEEKLY NEWSMAGAZINE
National Cancer Institute's DR. JOHN R. HELLER
$7.00 A YEAR
VOL. LXXIV NO. 4

CANCER Global Killer

The disease accounts for 7.4 million deaths worldwide.
It's the leading cause of death worldwide, causing around 13% of all deaths worldwide.

Leading types and their mortality rate each year

The most frequent types of cancer worldwide



There are more than 100 types of cancers; any part of the body can be affected.

In the developed world

1 in 3 people will develop cancer during their lifetimes

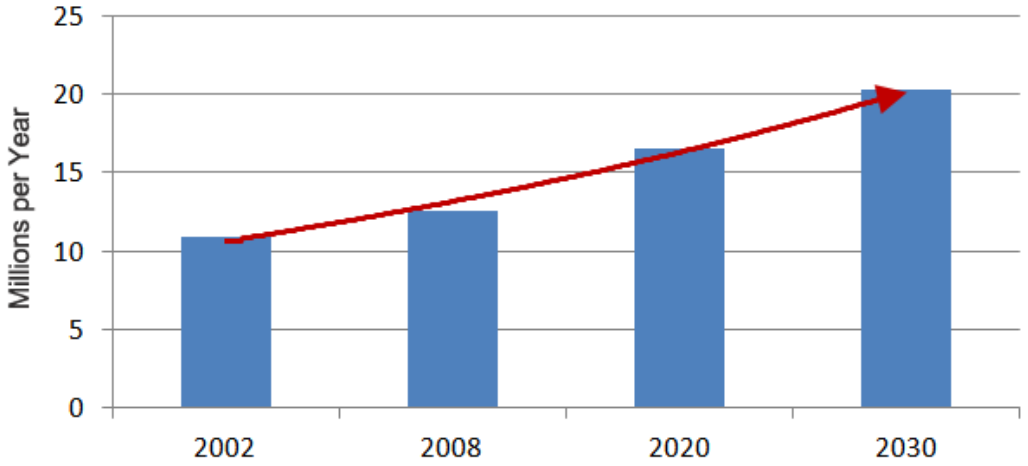
1 in 9 people have a risk of developing cancer again if they survived the first

2 in 9 people have an increased risk of developing a second primary cancer

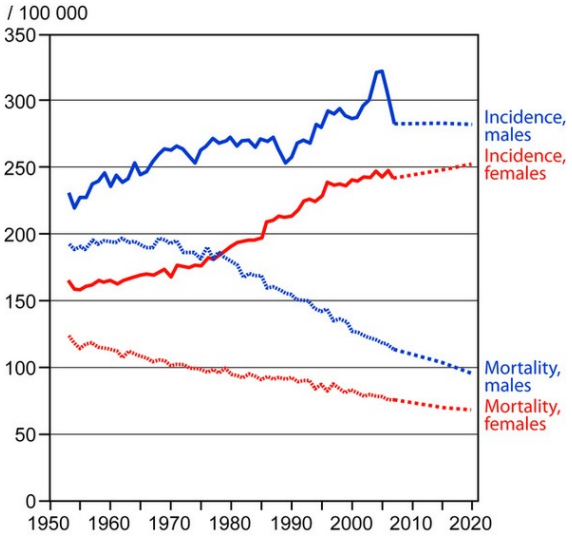
70% of all cancer deaths occur in low and middle income countries.

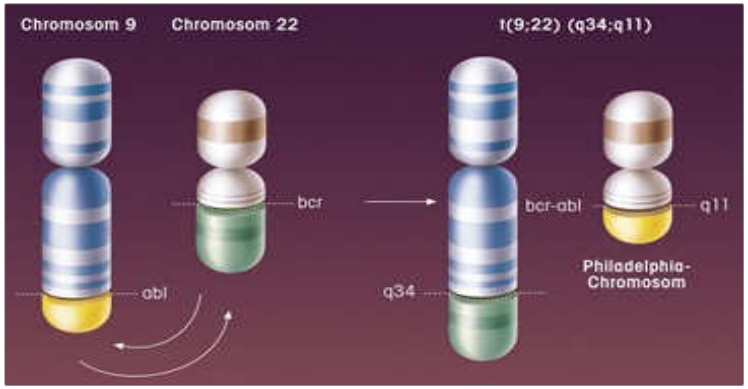
More than 30% of cancer could be prevented, mainly by not smoking tobacco, having a healthy diet, being physically active and preventing infections that may cause cancer. Third of cancers could be cured if detected early and treated adequately.

Incidence of New Cancers Worldwide Will DOUBLE Between 2002 and 2030

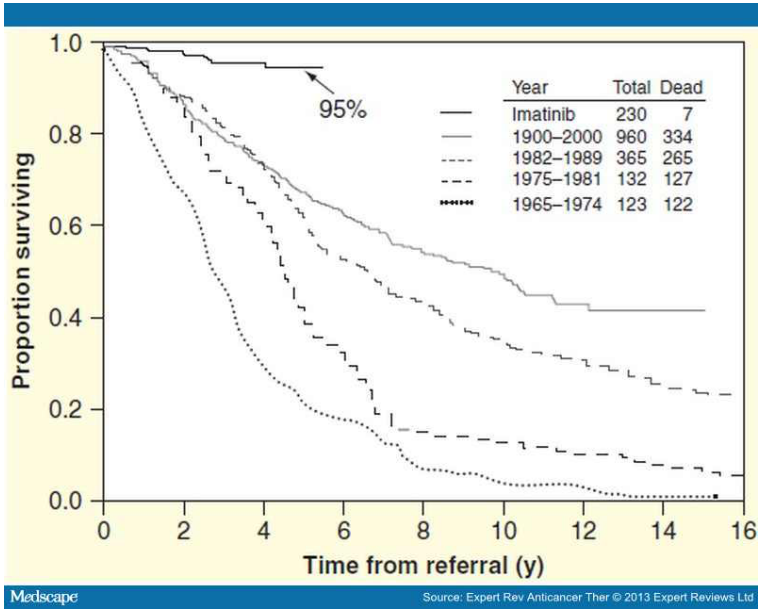


Source: US Center for Disease Control





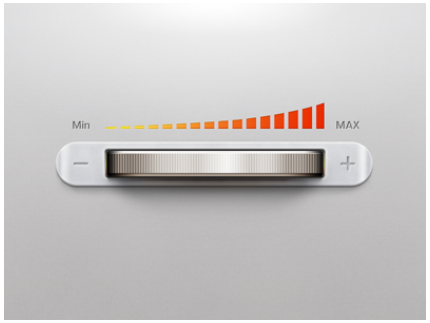
Chronic Myeloid Leukemia



Simple predictable disease
= Simple treatment

GLEEVEC

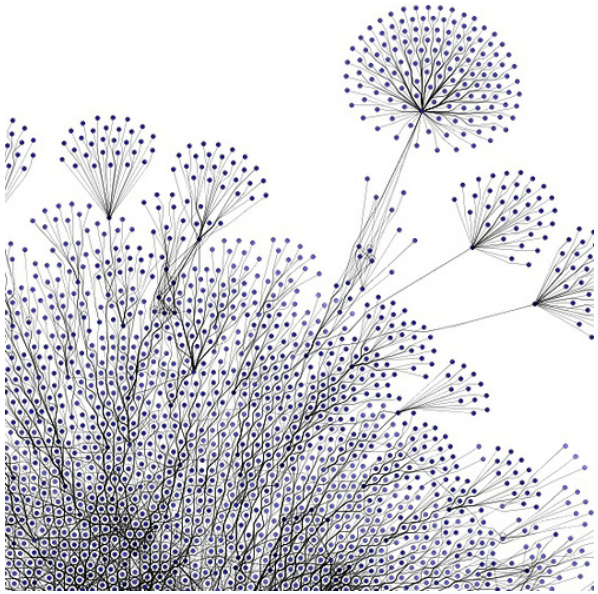
- Same dose
- Every day



Adjust
- PK
- Toxicity/Resistance

Simple predictable disease
= Simple treatment

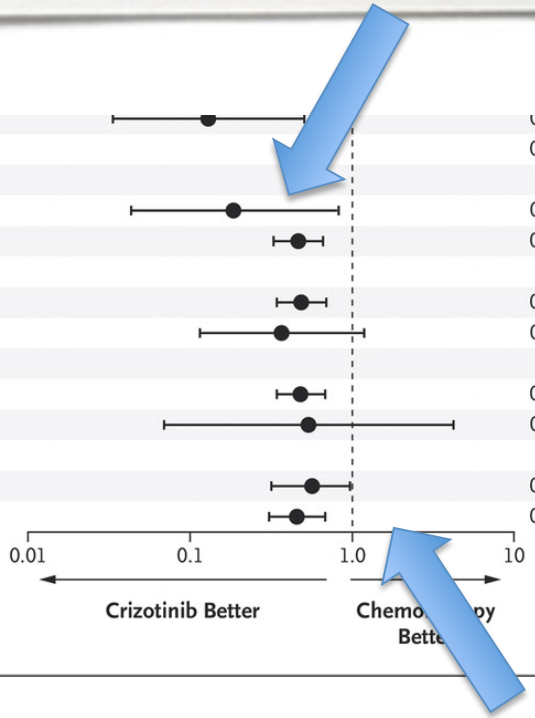
GLEEVEC



Complex unpredictable disease ???

Gleevec: The Exception that Proves the Rule…?

>1 yr	35	0.14 (0.04–0.51)
≤1 yr	308	0.52 (0.40–0.68)
ECOG performance status		
2	18	0.19 (0.05–0.76)
0 or 1	324	0.47 (0.36–0.62)
Adenocarcinoma		
Yes	322	0.49 (0.37–0.64)
No	21	0.37 (0.12–1.10)
Type of disease		
Metastatic	336	0.48 (0.37–0.63)
Locally advanced	7	0.54 (0.07–3.91)
Brain metastases		
Yes	92	0.57 (0.35–0.93)
No	251	0.46 (0.34–0.63)

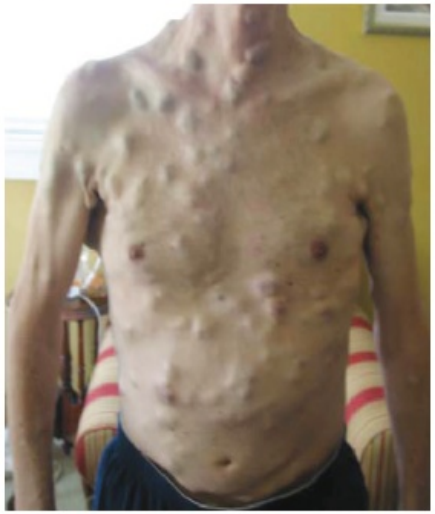


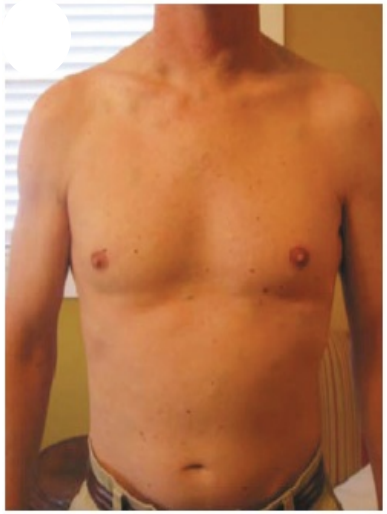
170 pt/arm

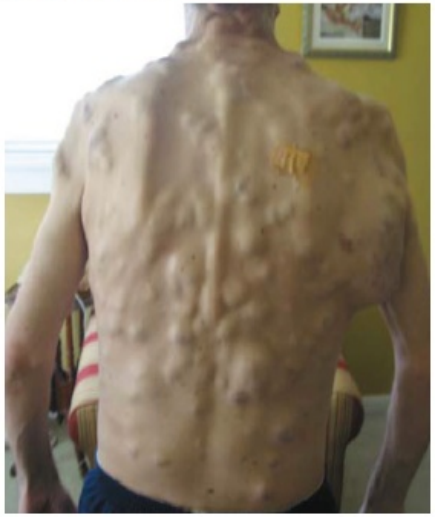
First-line crizotinib versus chemotherapy in ALK-positive lung cancer.
Solomon B al.
N Engl J Med. 2014;371(23):2167-77.

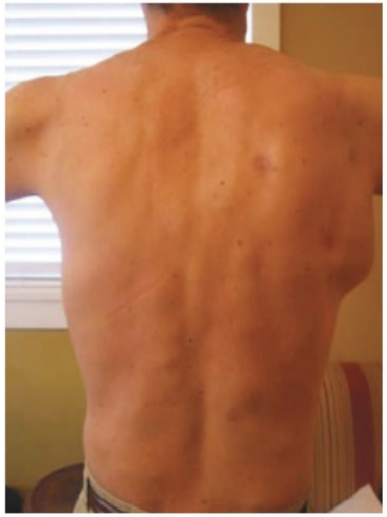
The NEW ENGLAND JOURNAL of MEDICINE

B-RAF inhibitor: PLX4032

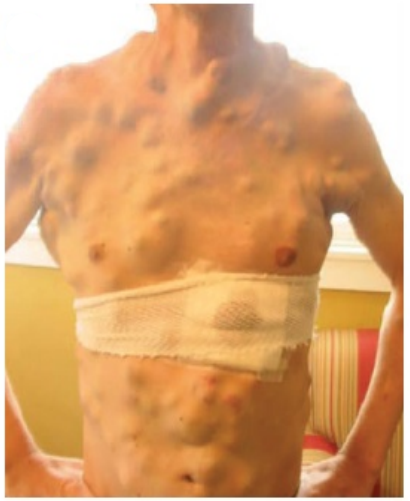






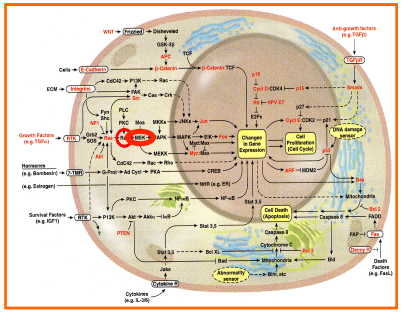


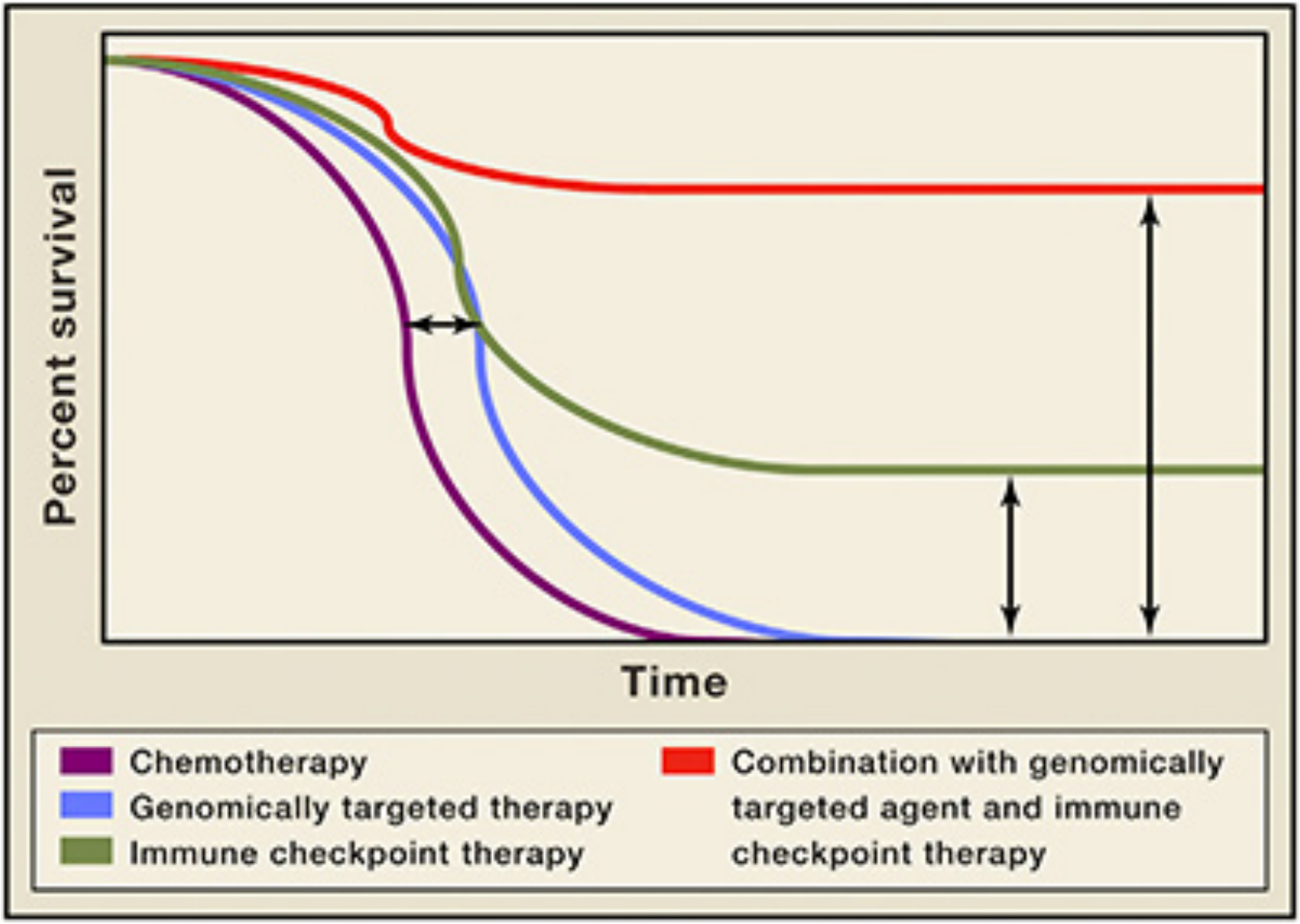
(Wagle **et al.**, **J. Clin. Oncol**. 2011)



23 weeks of treatment: widespread disease relapse (visceral, subcutaneous)

MEK1 mutation associated to resistance to B-RAF inhibitor





J. Caputo Elsevier Connect

Evolution of Chemotherapy

will lead us to present innovative
alternative ways of administering
metronomic chemotherapy [2–4]
tion of chemotherapeutic drugs at
without prolonged drug-free brea
i.e. modulating the dose and frequ
trations in order to maintain a cons
chemotherapy is expected to bring

Please cite this article in press as
precision medicine. Semin Cance

treatments for cancer patients, thanks to the advances made in biology, chemistry, physics, mathematics and engineering (Fig. 1).

Here we will try to address th
the early theoretical concepts tha
widespread use of what is now ca
apy" – i.e. the administration of c
maximum tolerated dose (MTD), w
cures to allow for the patient to
related toxicities. We will explain

* Corresponding author at: SMARTc, Pharmacokinetics Unit, Faculté de Pharmacie de Marseille, 27 Bd Jean Moulin, 13385 Marseille 05, France.
E-mail address: joseph.ciccolini@univ-amu.fr (J. Ciccolini).

http://dx.doi.org/10.1016/j.semcancer.2015.09.002
1044-579X/

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precision medicine. Semin Cancer Biol (2015), http://dx.doi.org/10.1016/j.semcancer.2015.09.002

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without prolonged drug-free b
i.e. modulating the dose and fr
trations in order to maintain a c
chemotherapy is expected to br

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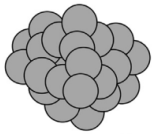
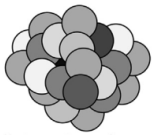
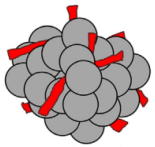
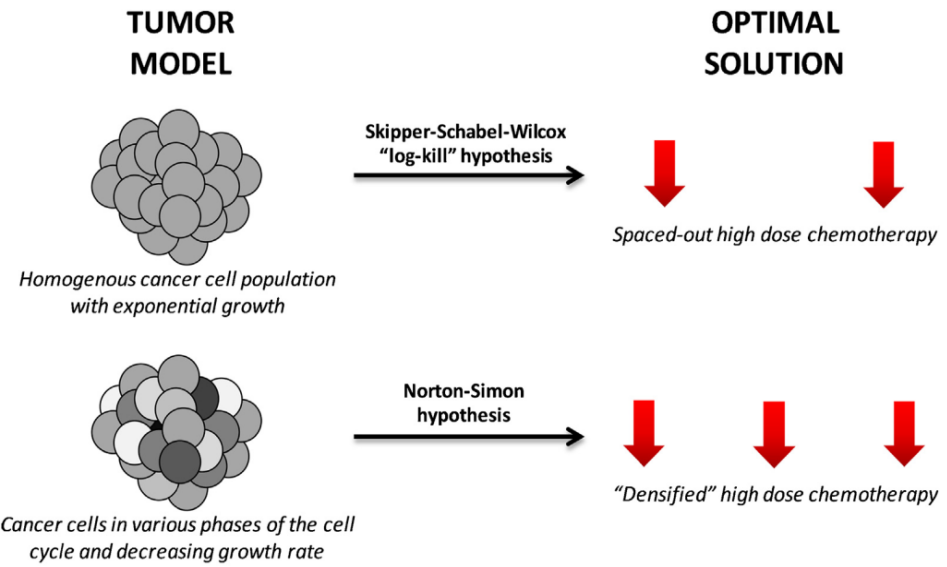
Evolution of Chemotherapy

TUMOR MODEL		OPTIMAL SOLUTION
 *Homogenous cancer cell population with exponential growth*	**Skipper-Schabel-Wilcox "log-kill" hypothesis** →	*Spaced-out high dose chemotherapy*
 *Cancer cells in various phases of the cell cycle and decreasing growth rate*	**Norton-Simon hypothesis** →	*"Densified" high dose chemotherapy*
 *Angiogenesis-dependent tumor growth*	**Metronomic chemotherapy concept** →	*Frequent low-dose chemotherapy*
 *Ecosystem ruled by evolutionary laws*	**Adaptive therapy concept** →	*Varying doses and schedules of chemotherapy*
 *"Real" tumor in "Real" individuals*	**Personalized therapy concept** →	**Computer-driven, covariate-based chemotherapy regimens**



curve if the dose is increased (amplitude modul
Increased doses will typically result in fewer cycles p
time. Using growth factors, some recent protocols
attempted to maintain the same dose but with an inc
frequency, this is referred to as dose density.[16] C, Repre
tive curve if the frequency is increased, likely resultin
necessity to decrease the unit dose. The major issue dis
here and reviewed by others in Ref. 8, is how to insure t
effective dose (OBD or MEC) is used so that under c
which would result in treatment failure but not toxicity
be detected and hence avoided. D, Which is best? A sur
of the prior 3 pictures is combined here. As suggested in
and in the concept of dose density reviewed in Ref. 16
may be some need to merge our standard, time p
empiric successes with the new theme developed arou
notion that a tumor is complex, having multiple cells
providing a number of different targets. These decisio
be made through a better understanding of tumor bi
cell-cell interactions and more facile ways of assayi
MECs and OBDs, which by definition will increase the e
of chemotherapy.

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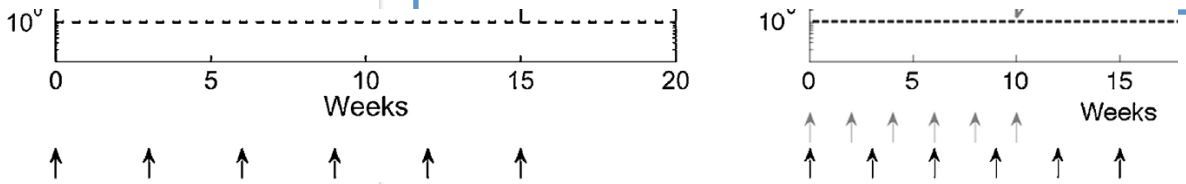


Fig. 3. Left: Skipper–Schabel–Wilcox log-kill model. Tumor growth is exponential (linear in log-scale) and each cycle of chemother
of the tumor volume (as opposed to a constant amount of cells). This is reflected by a constant log-kill. The simulation assumes a lo
tumor mass) over six three-weeks cycles, for an initial total tumor load of 10^9 cells, the first cycle starting at Day-0. The dashed line
MTD chemotherapy approaches consider as the goal to achieve for eradication of the disease. Right: Norton–Simon model. Un
exhibits a decreasing specific growth rate. The Norton–Simon hypothesis implies a larger log-kill for smaller tumors and suggests t
protocol. This is illustrated by comparison of a three-weeks regimen (black curve) and a densified two-weeks regimen (gray cu
tumor burden and thus larger probability of "cure". However, note that when tumor regrows, both schedules have the same time

Please cite this article in press as: Benzekry S, et al. Metronomic reloaded: Theoretical models bringi
precision medicine. Semin Cancer Biol (2015), http://dx.doi.org/10.1016/j.semcancer.2015.09.002

"You've got six months,
aggressive treatment we ca
that seem much lor

PENN RADIATION ONCOLOGY

With permission: Carto

Evolution of Chemotherapy

computer-based personalized chemotherapy protocols.

theoretical and mathematical models and discuss ways they can be improved to better take into account the complexity and rapid evolution of tumors and ultimately optimize treatment efficacy. This will lead us to present innovative theoretical models that support alternative ways of administering chemotherapy. These include metronomic chemotherapy [2–4] – i.e. the frequent administration of chemotherapeutic drugs at relatively low, non-toxic doses, without prolonged drug-free break – and adaptive therapy [5,6] – i.e. modulating the dose and frequency of chemotherapy administrations in order to maintain a constant tumor volume. Metronomic chemotherapy is expected to bring substantial benefit over existing

MTD regimen by interfering
or the tumor micro-environ
developing metronomic che
implementing computationa
mizing metronomic regimen
modeling support.

2. Historical concepts

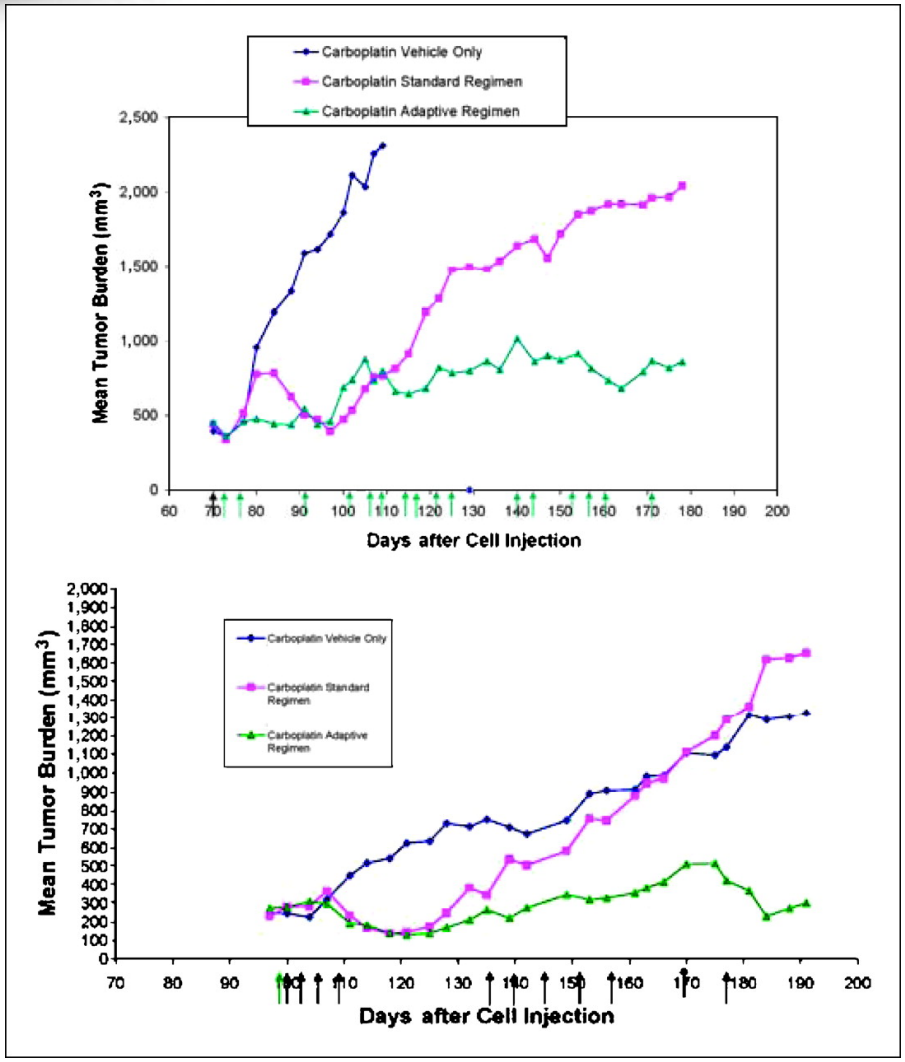
Fifty years ago, Skipper,
to introduce theoretical co

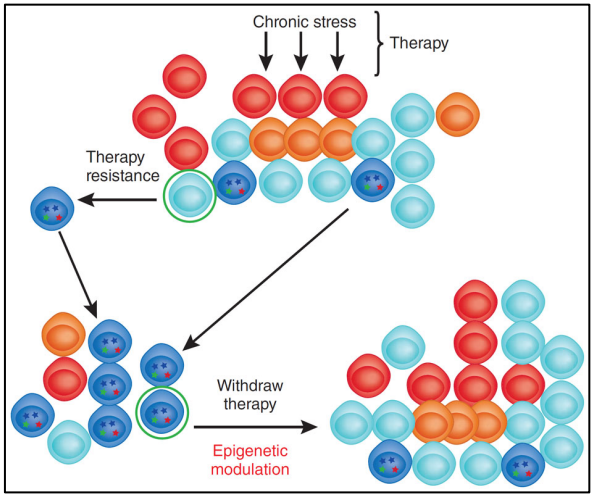
Please cite this article in press as: Benzekry S, et al. Metronomic reloaded: Theoretical models bri
precision medicine. Semin Cancer Biol (2015), http://dx.doi.org/10.1016/j.semcancer.2015.09.002

Robert A. Gatenby et al.
Cancer Res 2009;69:4894-4903

AACR American Association for Cancer Research

Cancer Research





NATURE MEDICINE • VOLUME 6 • NUMBER 5 • MAY 2000

Chemotherapeutic drugs—more really is not better

Recent insights into the molecular mechanisms that regulate the process of metastasis and the complex interactions between metastatic cells and host factors have provided a biological foundation for the design of more effective therapies.

Isaiah J. Fidler & Lee M. Ellis

«… Cancer is a chronic disease and should be treated as such… »

NATURE|Vol 459|28 May 2009

A change of strategy in the war on cancer

Patients and politicians anxiously await and increasingly demand a 'cure' for cancer. But trying to control the disease may prove a better plan than striving to cure it, says **Robert A. Gatenby**.

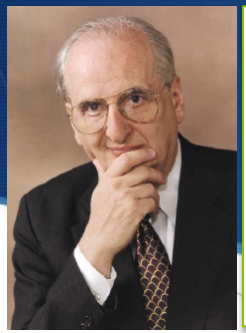
For cancer, seek and destroy or live and let live?

André Nature 2009

Evolution of Chemotherapy

GLEEVEC

CHEMOTHERAPY



[CANCER RESEARCH 60, 1878–1886, April 1, 2000]

Antiangiogenic Scheduling of Chemotherapy Improves Efficacy against Experimental Drug-resistant Cancer[1]

Timothy Browder, Catherine E. Butterfield, Birgit M. Kräling, Bin Shi, Blair Marshall, Michael S. O'Reilly, and Judah Folkman[2]

Laboratory of Surgical Research [T. B., C. E. B., B. M. K., B. S., B. M., M. S. O., J. F.] and Division of Hematology/Oncology [T. B.], Children's Hospital; Departments of Surgery and Cell Biology, Harvard Medical School [J. F.]; Department of Pediatric Oncology, Dana-Farber Cancer Institute [T. B.]; and the Joint Center for Radiation Therapy [M. S. O.], Boston, Massachusetts 02115

Continuous low-dose therapy with vinblastine and VEGF receptor-2 antibody induces sustained tumor regression without overt toxicity

Giannoula Klement,[1] Sylvain Baruchel,[2] Janusz Rak,[1] Shan Man,[1] Katherine Clark,[1] Daniel J. Hicklin,[3] Peter Bohlen,[3] and Robert S. Kerbel[1]

[1]Sunnybrook and Women's College Health Sciences Centre, Biological Sciences Program, Division of Cancer Biology Research, and Toronto-Sunnybrook Regional Cancer Centre, Toronto, Ontario M4N 3M5, Canada; Department of Medical Biophysics, University of Toronto, Ontario, Canada
[2]Hospital for Sick Children, Department of Pediatrics, Division of Hematology/Oncology, New Agent and Innovative Therapy Program, Toronto, Ontario M5G 1X8, Canada
[3]ImClone Systems Inc., New York, New York 10014, USA

The Journal of Clinical Investigation | April 2000 | Volume 105 | Number 8

Less is more, regularly: metronomic dosing of cytotoxic drugs can target tumor angiogenesis in mice

Commentary

See related article, pages R15–R24.

Douglas Hanahan,[1,2] Gabriele Bergers,[1,2] and Emily Bergsland[2,3]

[CANCER RESEARCH 60, 1878–1886, April 1, 2000]

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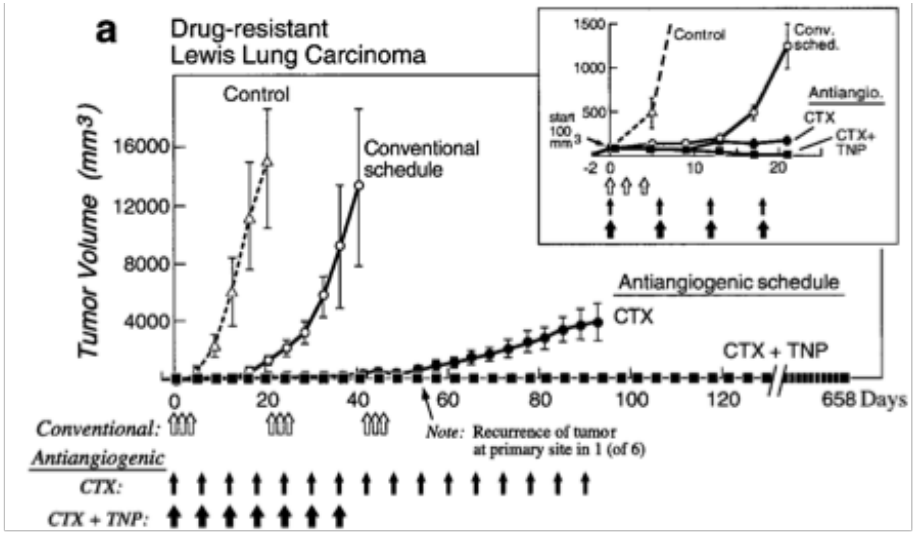
« Low dose : anti-angiogenic scheduling »



- activity in S&R cell lines
- Cyclophosphamide, 5FU, purinethol

- Good tolerance

- Lung cancer
- Breast cancer
- Leukemias

--- Target the endothelium AND NOT CANCER CELLS

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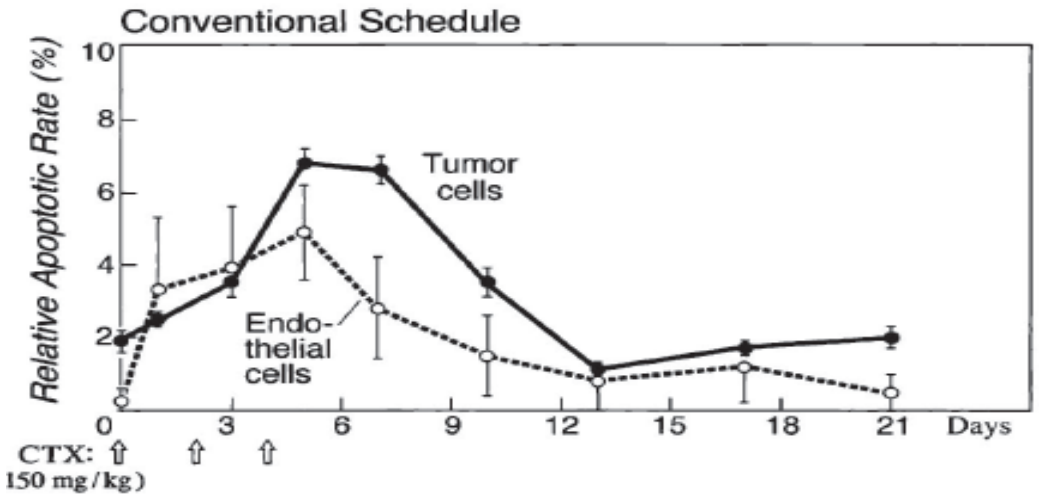
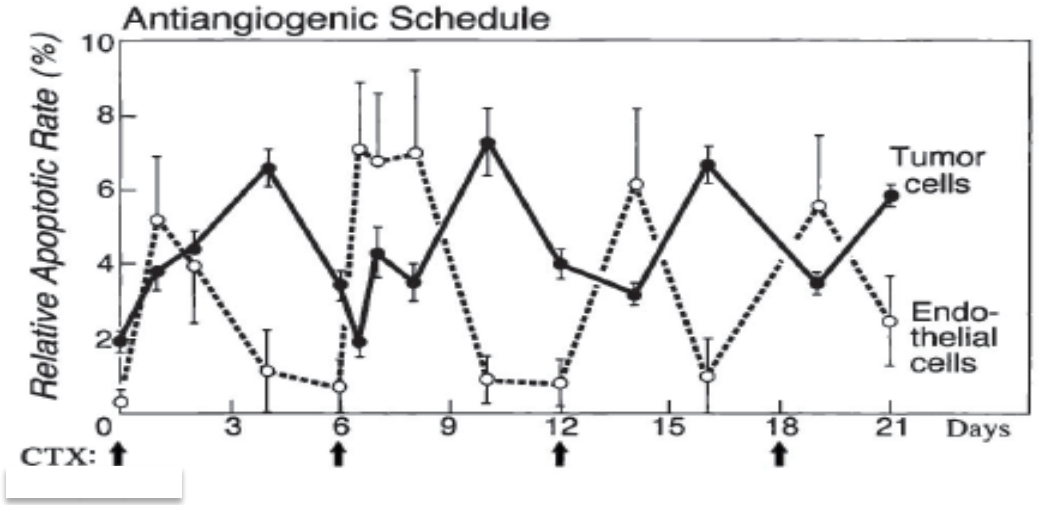
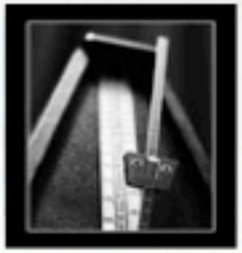
[1] Supported by NIH Grant P01 CA45548 (to J. F.) and by a grant to Children's Hospital from EntreMed, Inc. T. B. was a recipient of an American Cancer Society Clinical Oncology Career Development award for the first part of these studies.

[2] To whom requests for reprints should be addressed, at Children's Hospital, Hunnewell 103, 300 Longwood Avenue, Boston, MA 02115.

omitted in the CByD2F1/J mice harboring EMT-6/CTX beca
idiosyncratic toxicity and in therapy of L1210 leukemia becau
direct antileukemic effect. Preparation of cyclophosphamide an
of tumors were performed as described previously (6). For combi
periments with TNP-470, all drugs were administered s.c. Mice
experiments were fed a "Western-type" diet with 42% of calories fro







The Effect of 6-Mercaptopurine on the Duration of Steroid-induced Remissions in Acute Leukemia: A Model for Evaluation of Other Potentially Useful Therapy

From the Acute Leukemia Group B

Emil J Freireich, Edmund Gehan, Emil Frei III, Leslie R. Schroeder, Irving J. Wolman, Rachad Anbari, E. Omar Burgert, Stephen D. Mills, Donald Pinkel, Oleg S. Selawry, John H. Moon, B. R. Gendel, Charles L. Spurr, Robert Storrs, Farid Haurani, Barth Hoogstraten and Stanley Lee

blood

1963 21: 699-716

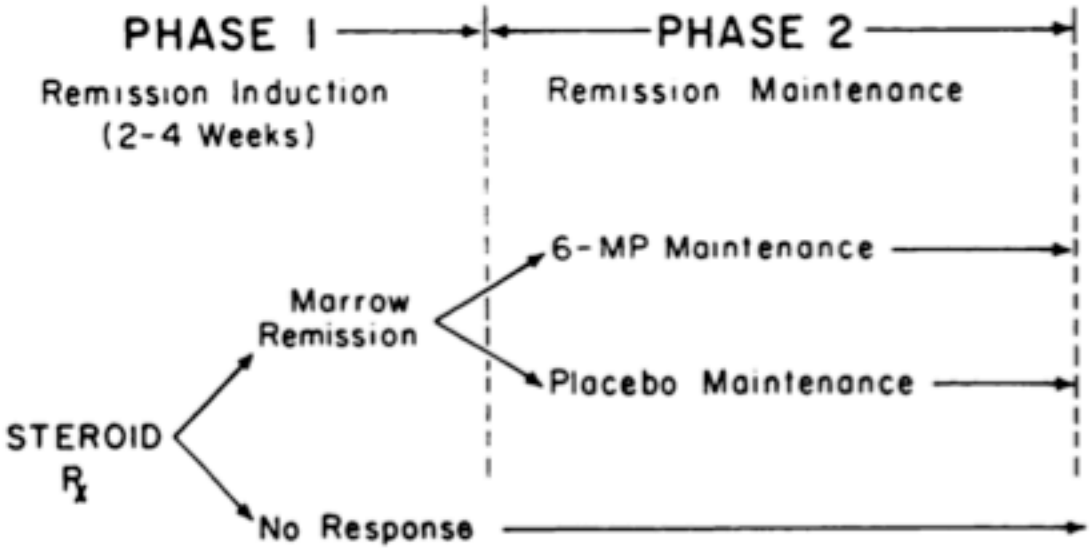
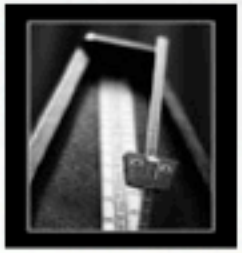


Fig. 1.—Design of the study.



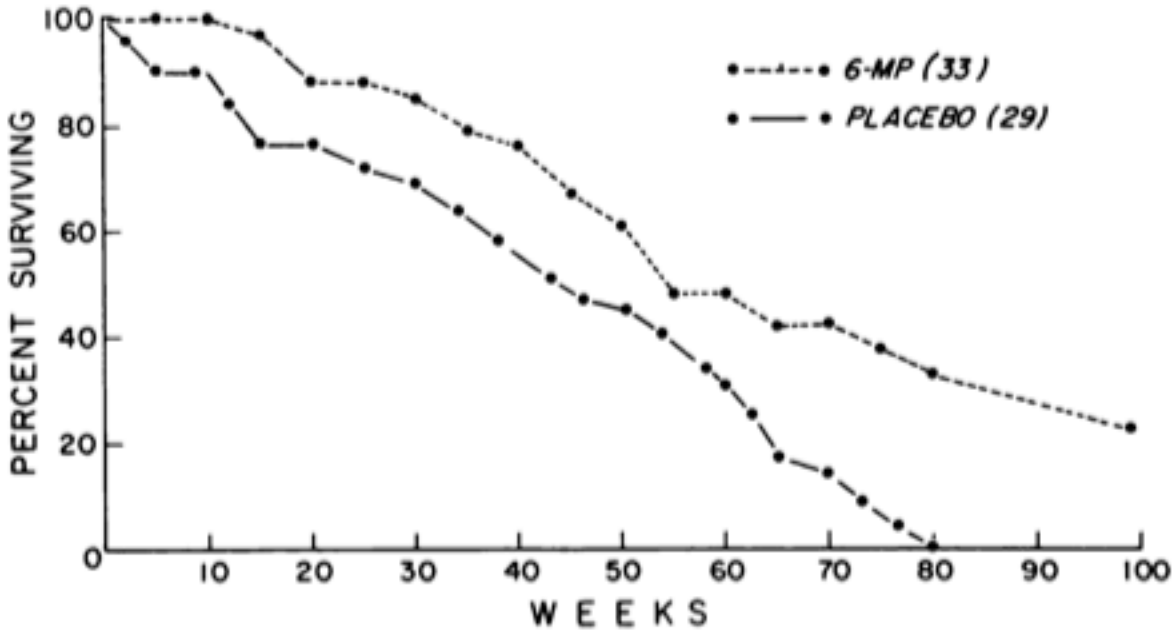


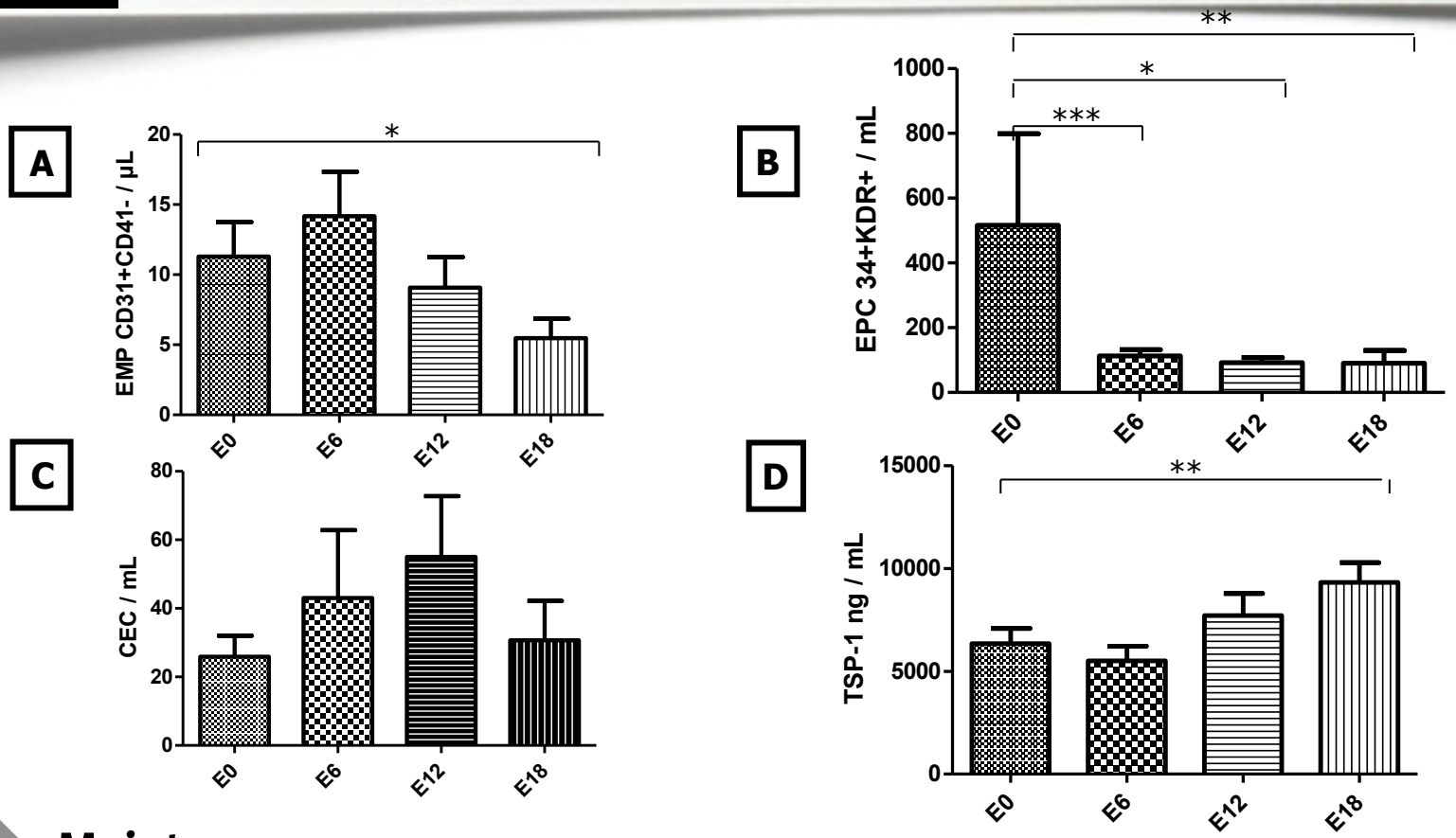
Fig. 4.—Survival from start of Phase II treatment to death.

« Low dose purinethol » increases survival in children with ALL

period of time ranging from 2 to 3 years [1]. Interestingly, metronomic chemotherapy (MC), which relies on the frequent administration of chemotherapy at low doses,

retrospect, as the early prototype of successful M

Angiogenesis plays a role in the pathoge progression of hematological malignancies [6]



Maintenance

- puts the endothelium to rest:
- decreases its activation and mobilization of EPC
- associated with an increase in TSP-1

André Oncotarget 2015

METRONOMICS 1.0

- **Metronomic Chemotherapy**
  - Frequent administration & low dose chemotherapy without long breaks (**Kerbel *Nat Rev Cancer* 2004**)
  - « Less is more, regularly »
  - Overcomes resistance, CHANGE THE TARGET !!!

METRONOMICS 1.0

- **Metronomic Chemotherapy**
  - Frequent administration & low dose chemotherapy without long breaks (Kerbel *Nat Rev Cancer* 2004)
  - « Less is more, regularly »
  - Overcomes resistance, CHANGE THE TARGET !!!

- **What is a small dose?**

- **What is a repeated administration?**

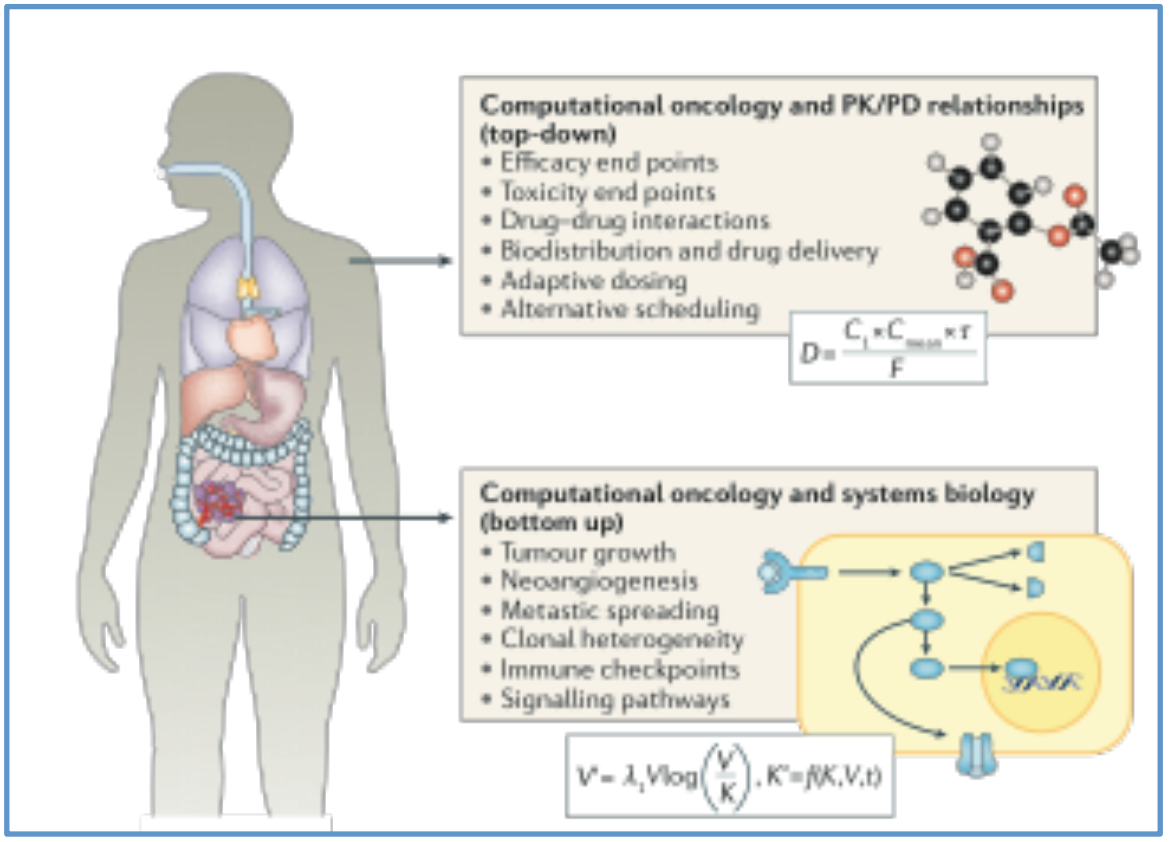
- **What is a long period of time?**

Marseille (CEPCM), Hospital of La Timone, AP-HM, Marseille 13005, France. Correspondence to N.A. (nicolas.andre@ap-hm.fr)

doi:10.1038/nrclinonc.2015.204
Published online 24 Nov 2015

application of this concept to cancer systems biology (that is, computational and mathematical modelling of the biological networks underlying tumorigenesis), that exploits the constant improvements in computing resources, has contributed greatly to the analysis of large datasets relating to complex signalling networks[2]. Indeed, huge databases of diverse information

NATURE REVIEWS | CLINICAL ONC

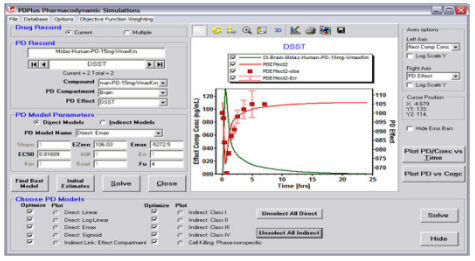


Modelling & Simulation

- **Mathematical modeling** can help to **identify an optimal solution** among **numerous combinations**.

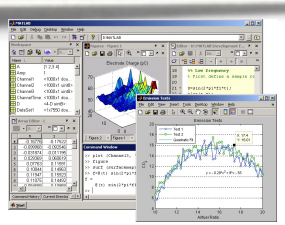
- This strategy is based upon the use of any data made available likely to help **building a mathematical model** and identifying its parameters.

+ PubMed



- Once built and validated, **the model** can generate *in silico* an infinity of **simulations** untill **a solution to a given problem is found**.

MetroGem Study



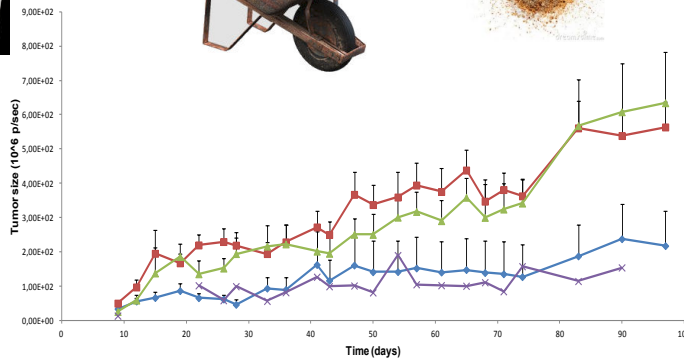
Control

100 mg/kg

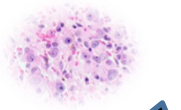
Metro
1 mg/kg

Metro
0.5 mg/kg

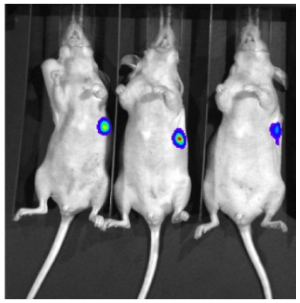
80 time less drug !!!!!



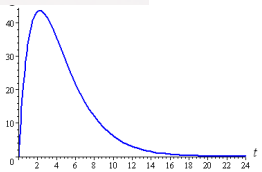
Neuroblastoma
Xenograft



Angiogenesis
Inflamation

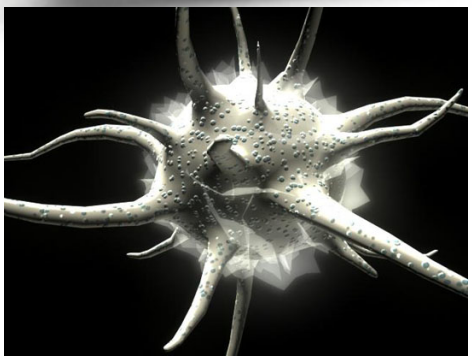


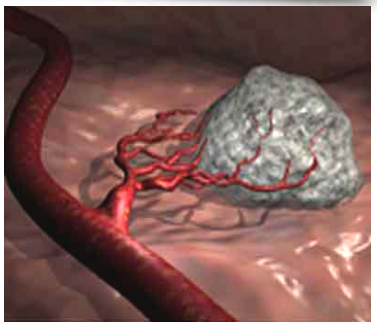
Efficacy/Toxicity



Pharmacokinetics

METRONOMICS 2.0





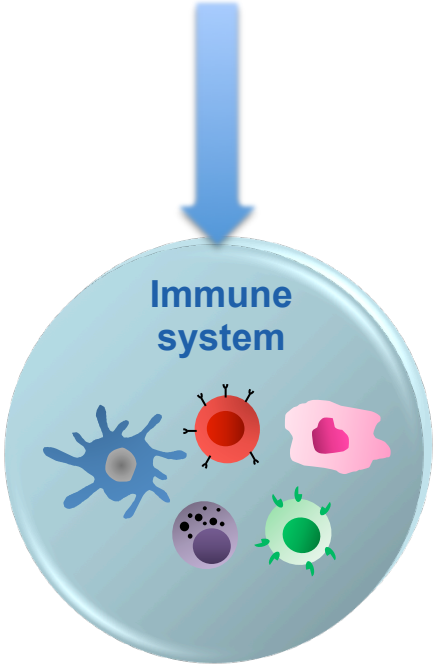
The Multi-targeted nature of Metronomic Chemotherapy

Metronomic chemotherapy: new rationale for new directions

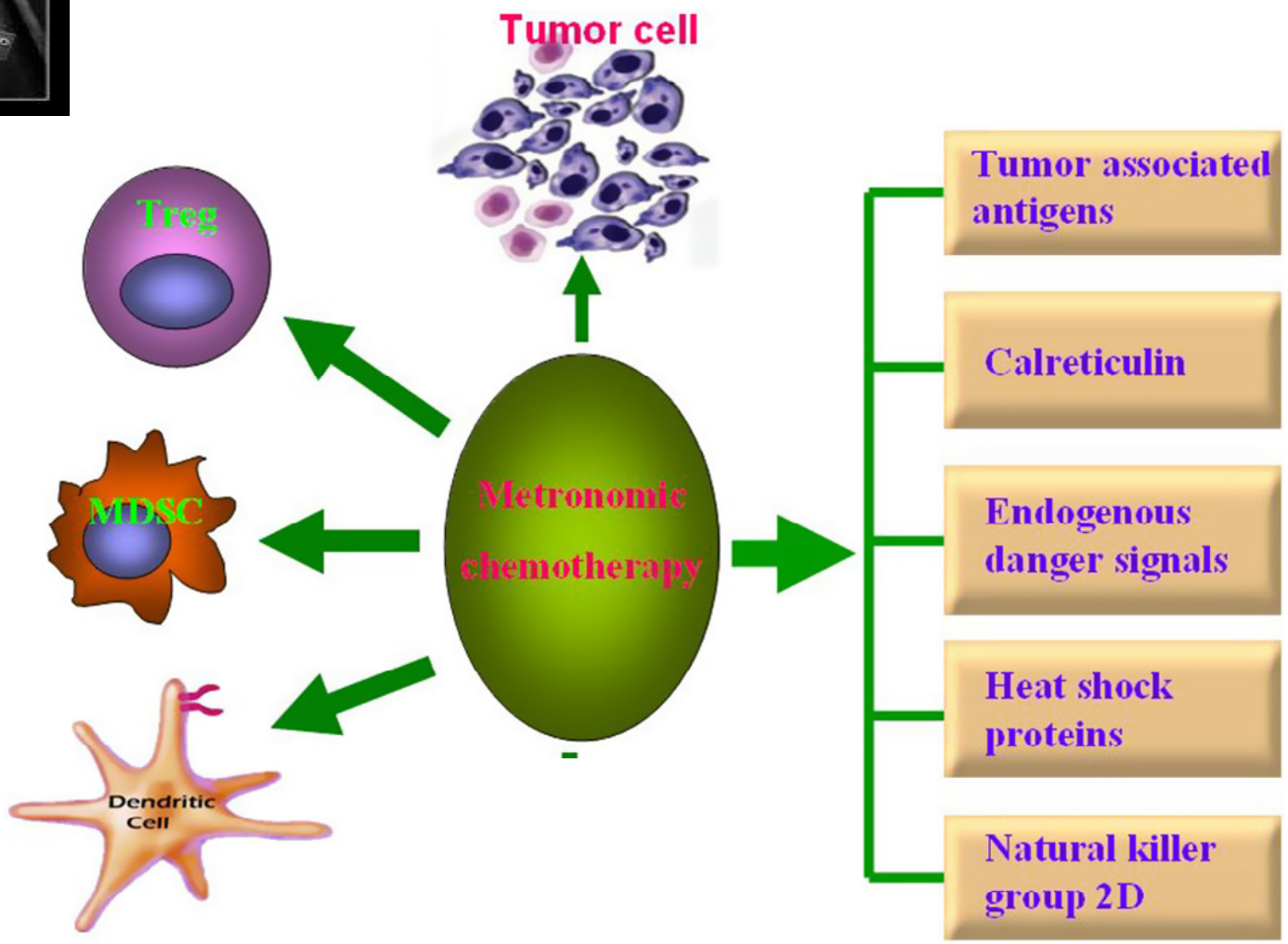
Eddy Pasquier, Maria Kavallaris and Nicolas André

NATURE REVIEWS | CLINICAL ONCOLOGY

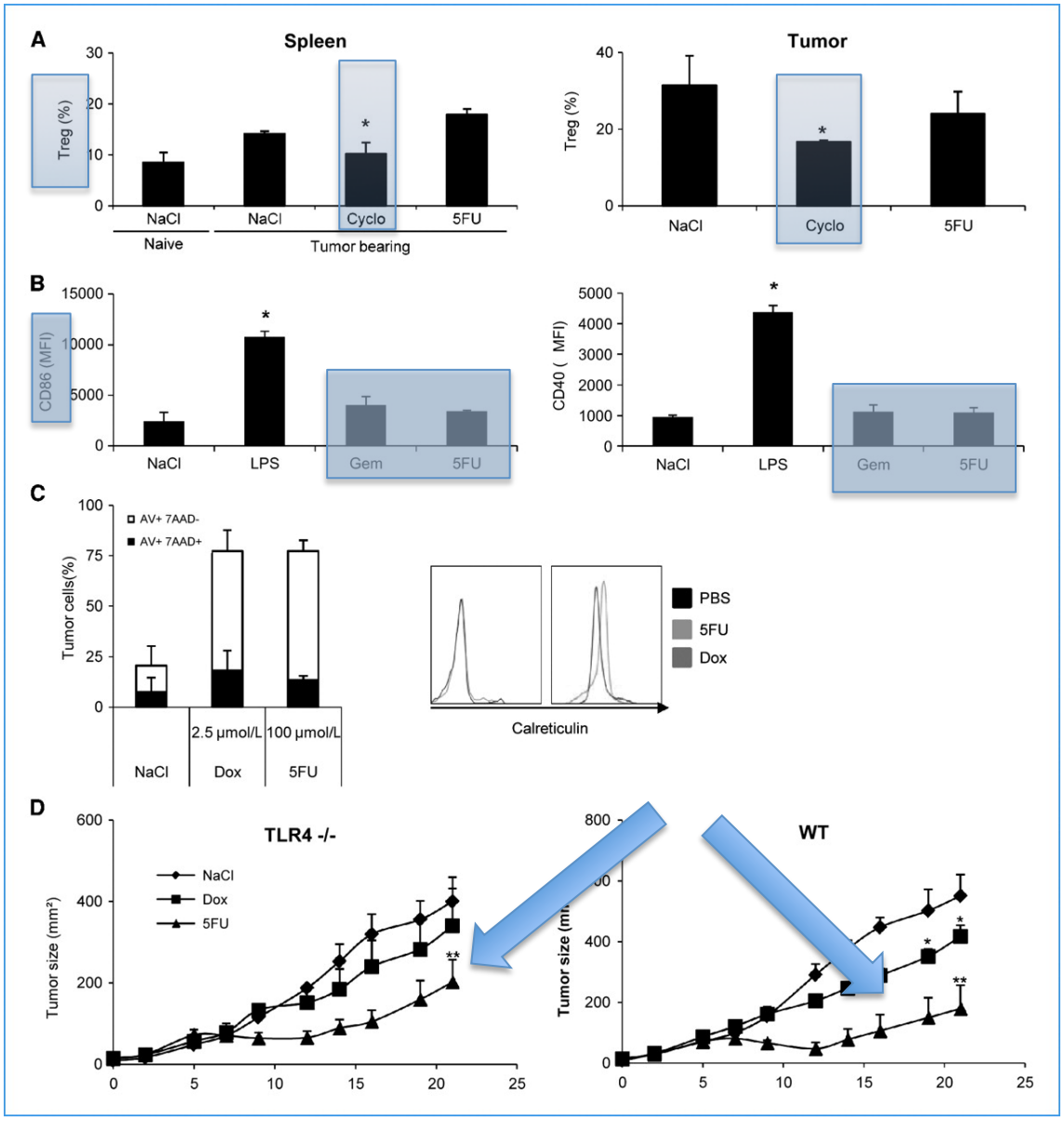
Metronomic Chemotherapy



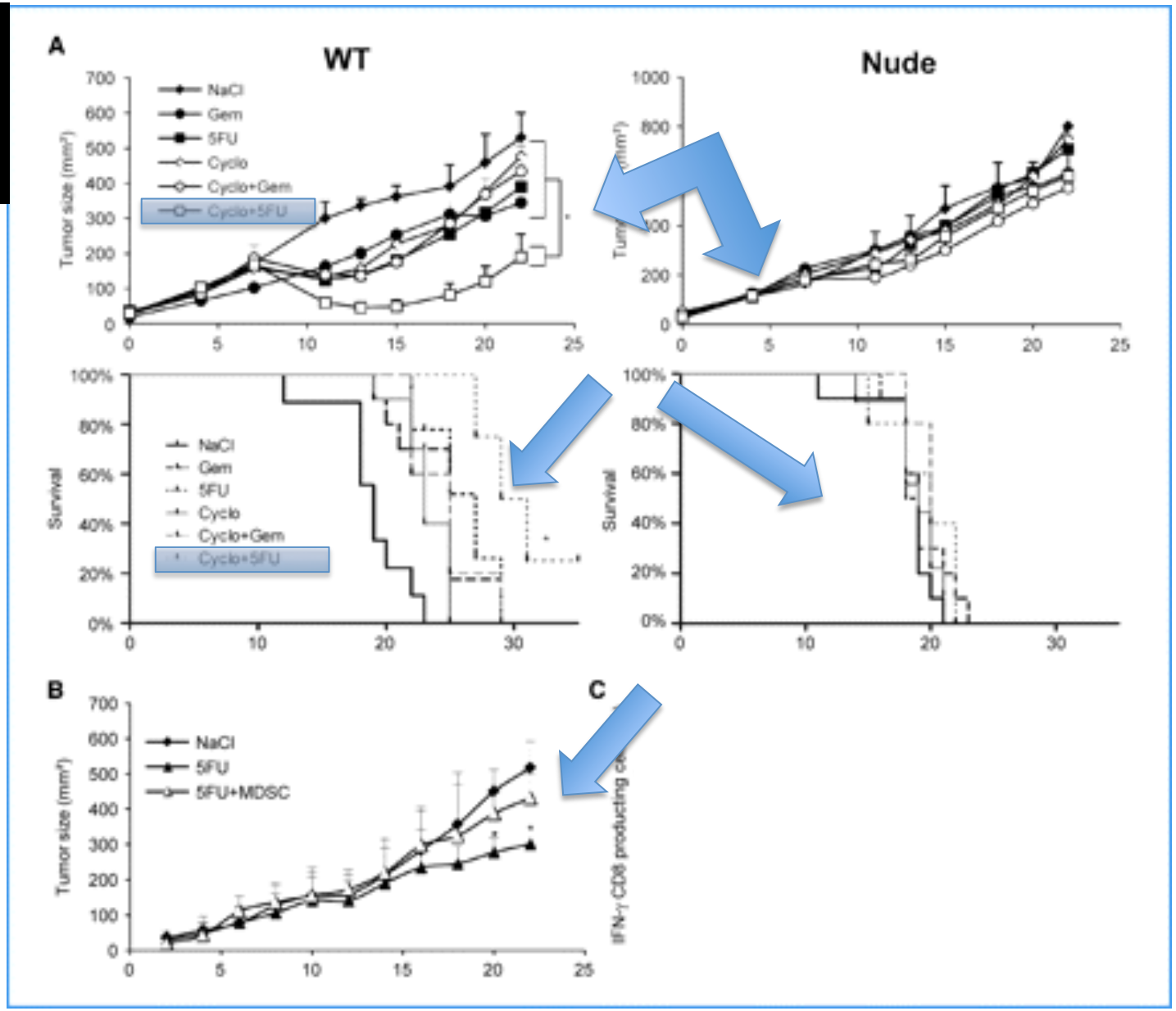
Metronomic & Immunity



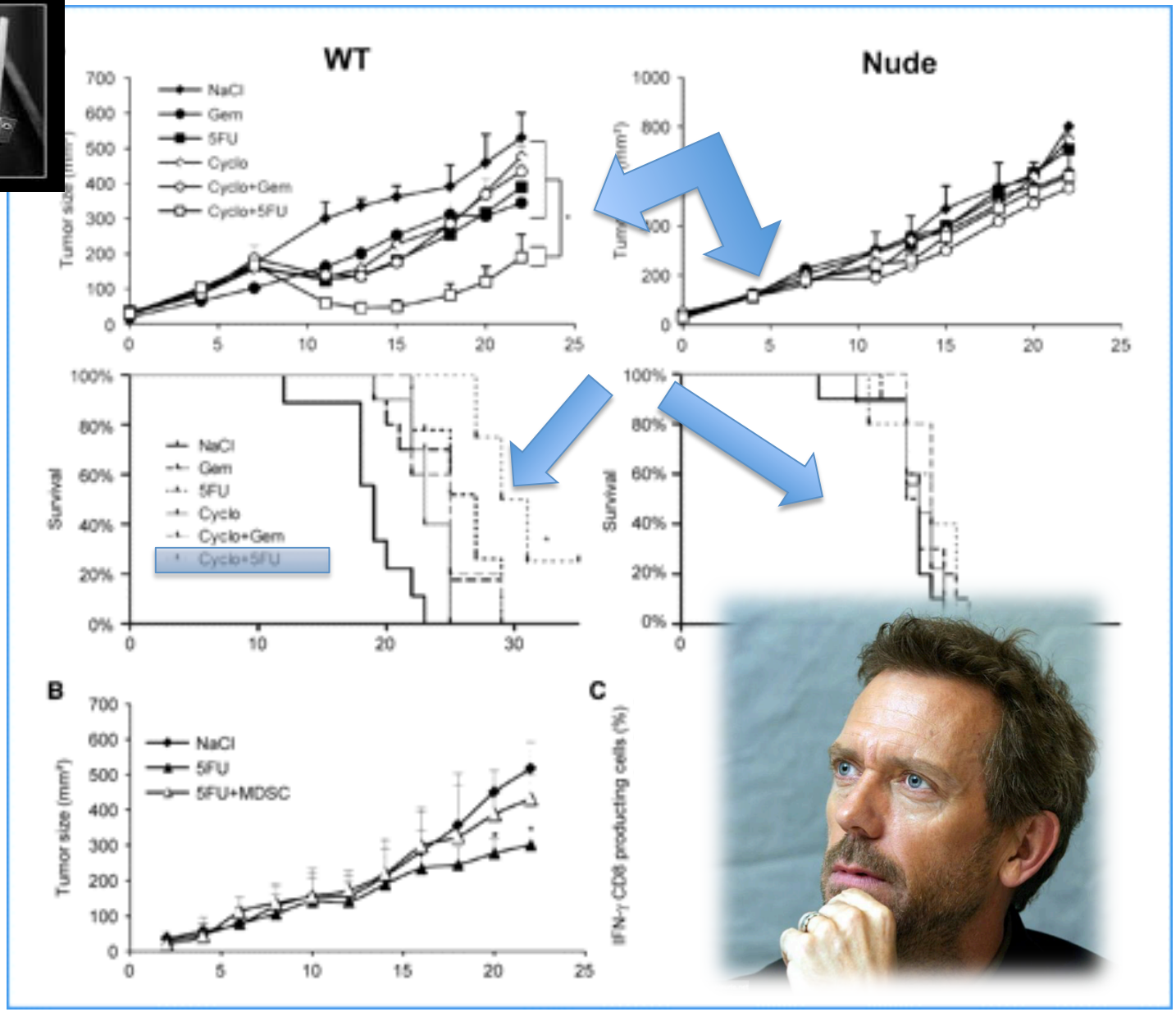
Yi-Bin Hao Cancer Letters 2014



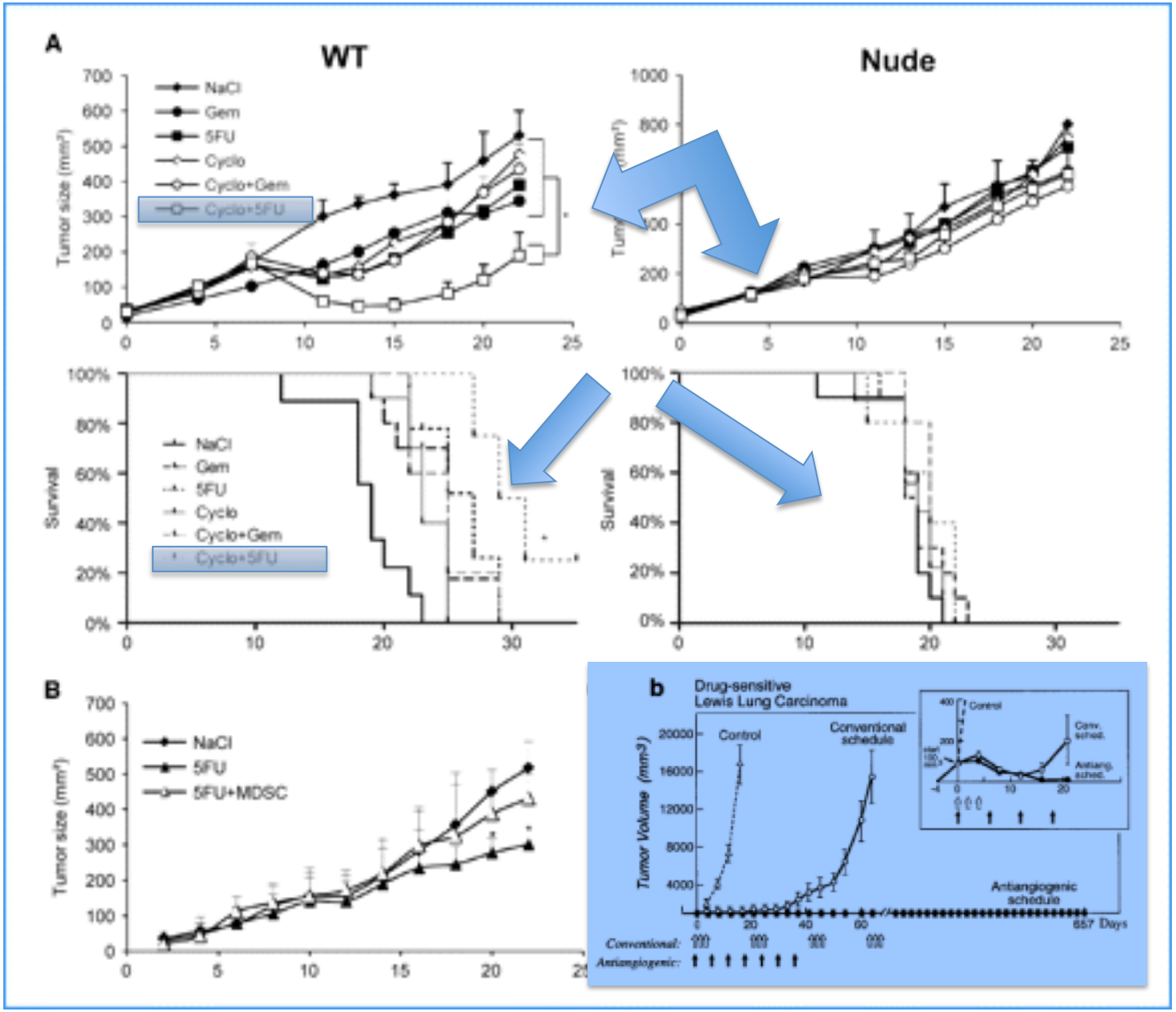
Vincent and al. *5FU selectively kills tumor-associated myeloid-derived suppressor cells resulting in enhanced T cell-dependent antitumor immunity* Cancer Research 2010



Vincent and al. *5FU selectively kills tumor-associated myeloid-derived suppressor cells resulting in enhanced T cell-dependent antitumor immunity* CR 2010

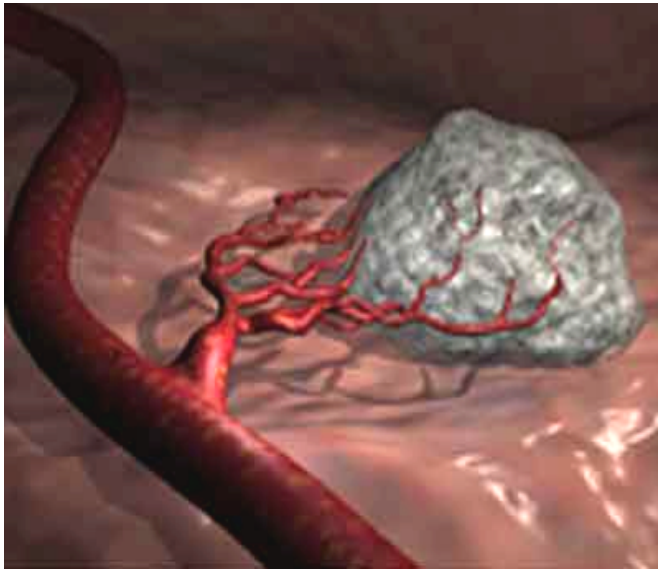


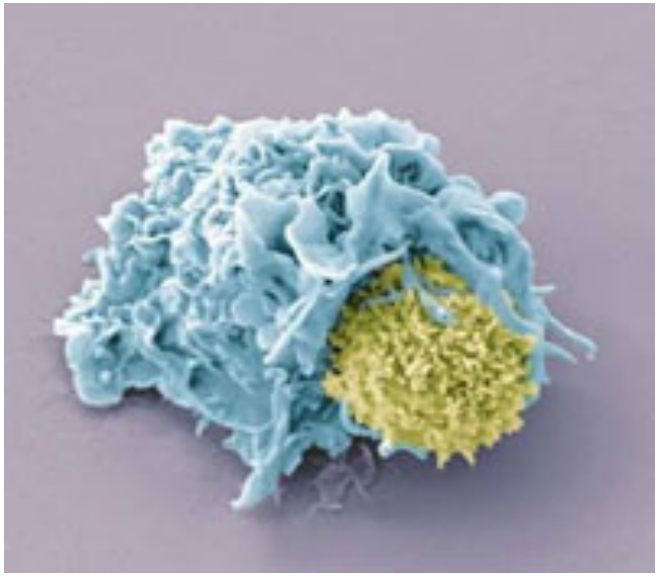
Vincent and al. 5FU selectively kills tumor-associated myeloid-derived suppressor cells resulting in enhanced T cell-dependent antitumor immunity CR 2010



Vincent and al. 5FU selectively kills tumor-associated myeloid-derived suppressor cells resulting in enhanced T cell-dependent antitumor immunity CR 2010

?





example, metron

intermittent drug dosing, e.g., the 6-day repeating metronomic schedule empirically found to be most efficacious by Browder et al. [1], as well as daily oral low-dose treatment regimens, which are proposed to be even more effective in killing tumor endothelial cells [5,6]. Metronomic drug schedules have been evaluated in clinical trials, primarily using daily dosing regimens, with promising results [7–9]. Recent studies have shown that other mechanisms, notably antitumor immunity, may also be activated by metronomic chemotherapy. For example, metronomic administration of gemcitabine and docetaxel

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University, 5 Cummington Mall, Boston, MA 0221
[1]This work was supported in part by grant CA0492
Health (to D.J.W.). The authors have no conflictin
[2]This article refers to supplementary materials, whic
Figures W1 to W5 and are available online at www
[3]These authors contributed equally to this work.
Received 20 November 2013; Revised 24 Decembe

DOI 10.1593/neo.131910

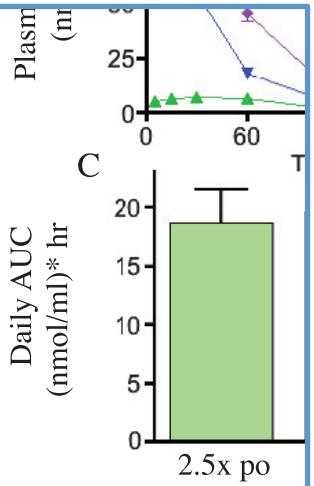


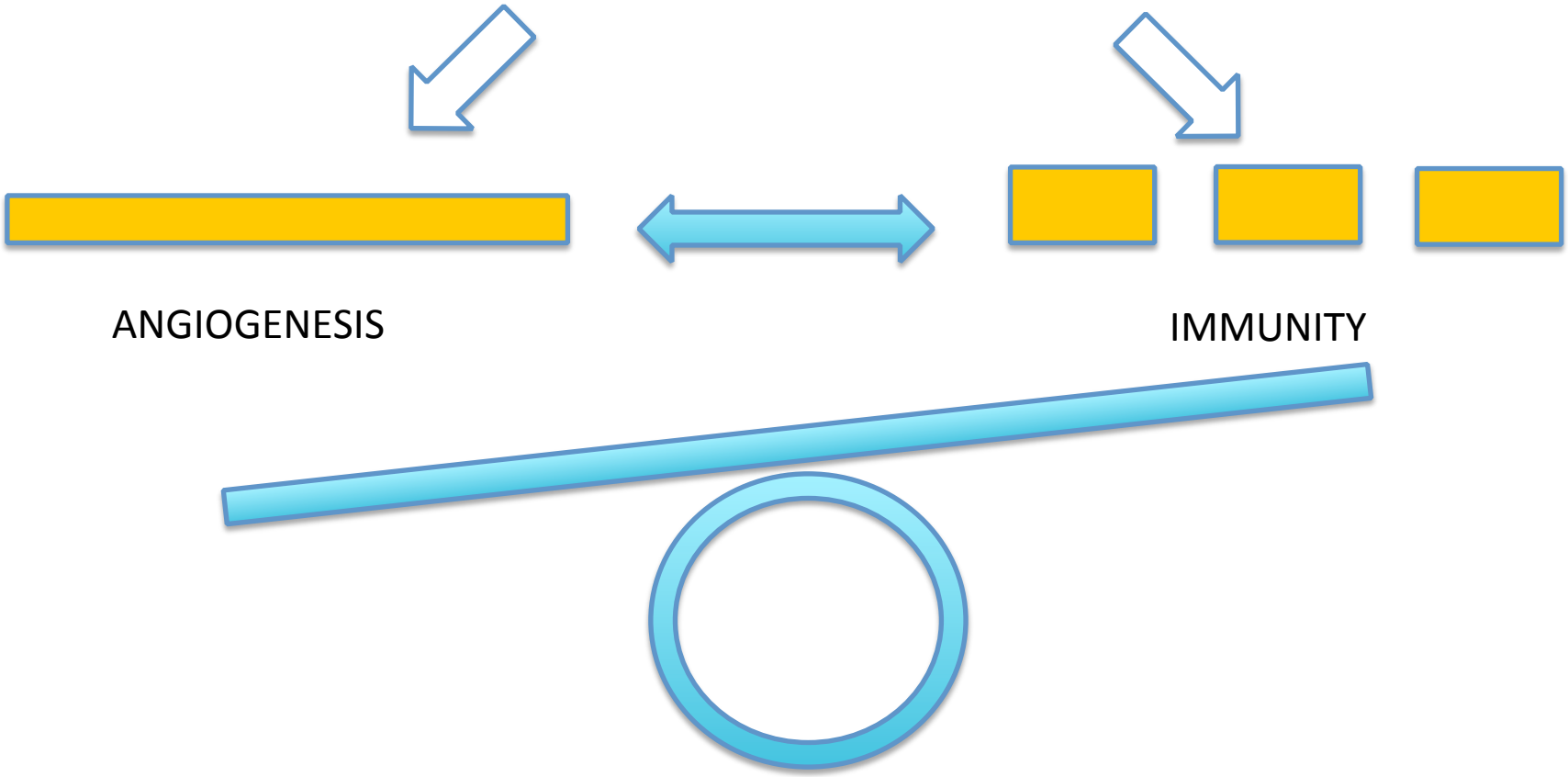
Figure 1. Impact of metronomic schedule on
in SCID mice, either untreated (UT) or given
70 mg/kg BW (3× po) or by i.p. injection ever
the mean ± SE tumor volumes for $n = 5$ to 6 mi
.01 and $^{\&\&\&}P < .001$ compared to 3× p.o. sche
with Bonferroni multiple comparison correctio
bearing SCID mice following metronomic CPA
SCID mice treated with the indicated metrono
data in B and normalized to adjust for the fre
(D) qPCR analysis of host (mouse) macrophage
untreated or treated with the indicated metro
24 (based on A), corresponding to 6 days after
mean ± SE for each treatment group and tim
point (n = 2-5 mice per group) *versus* UT con
parison correction for one tumor randomly sel

METRONOMIC CHEMOTHERAPY

ANGIOGENESIS

IMMUNITY

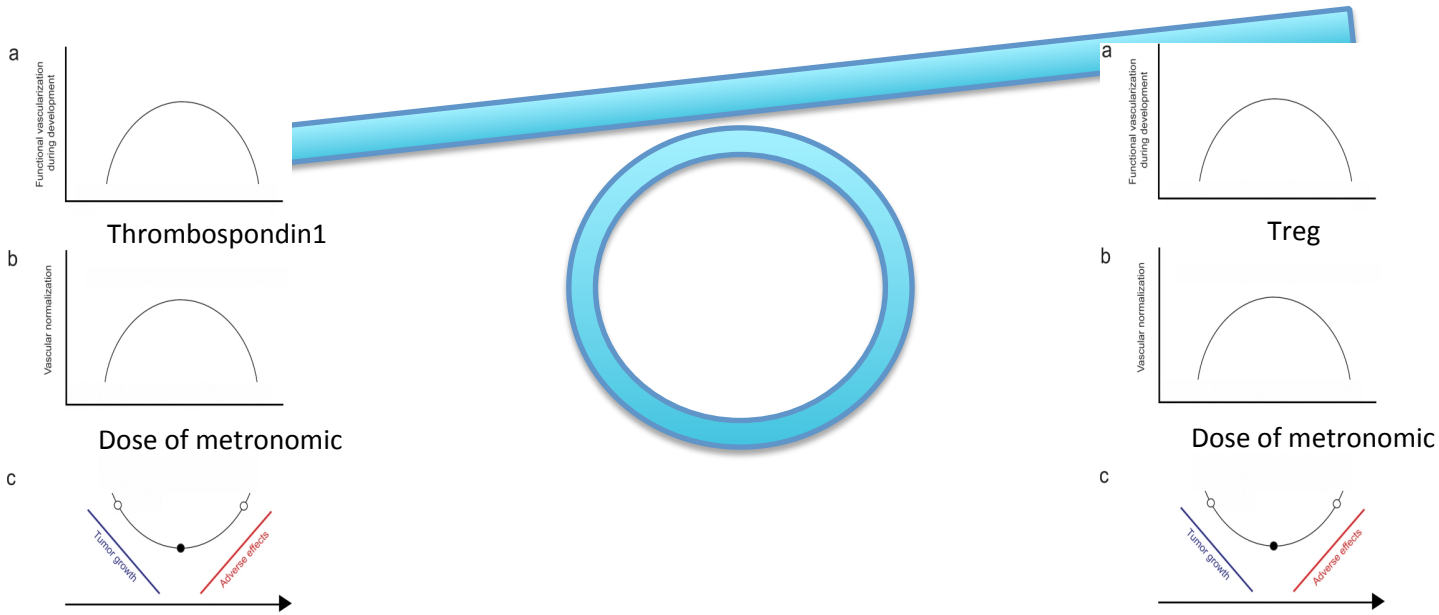
METRONOMIC CHEMOTHERAPY



METRONOMIC CHEMOTHERAPY

ANGIOGENESIS

IMMUNITY



FALSE

TRUE

FALSE

TRUE

Chemotherapy

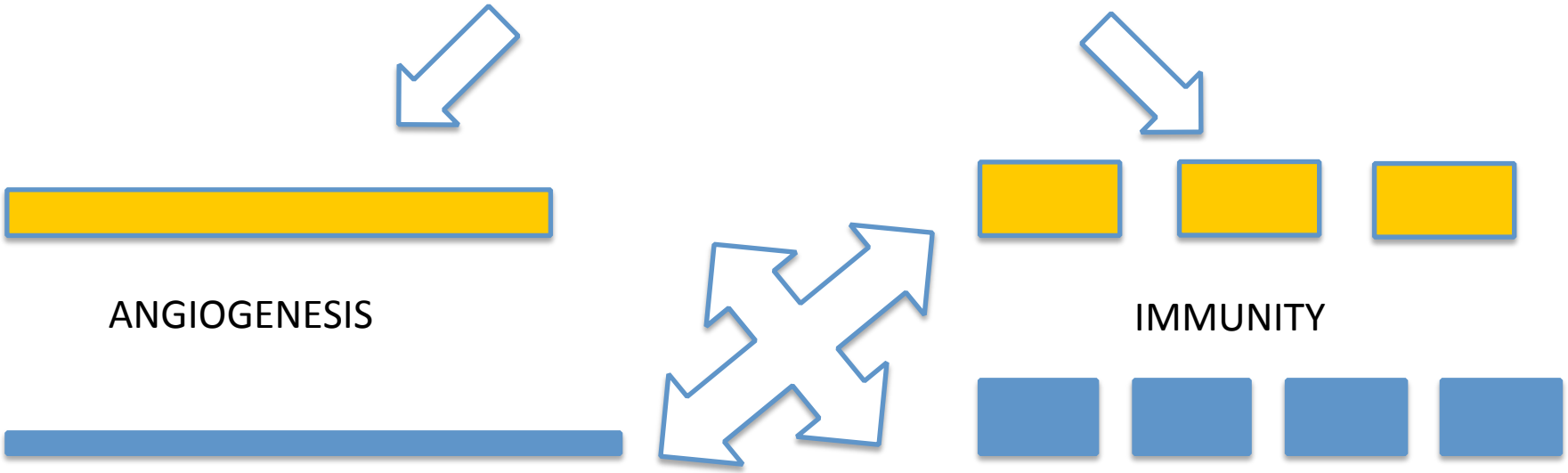
Metronomic temozolomide (cyclophosphamide)

TMZ TMZ TMZ TMZ TMZ TMZ TMZ TMZ
TMZ TMZ TMZ TMZ TMZ TMZ TMZ TMZ

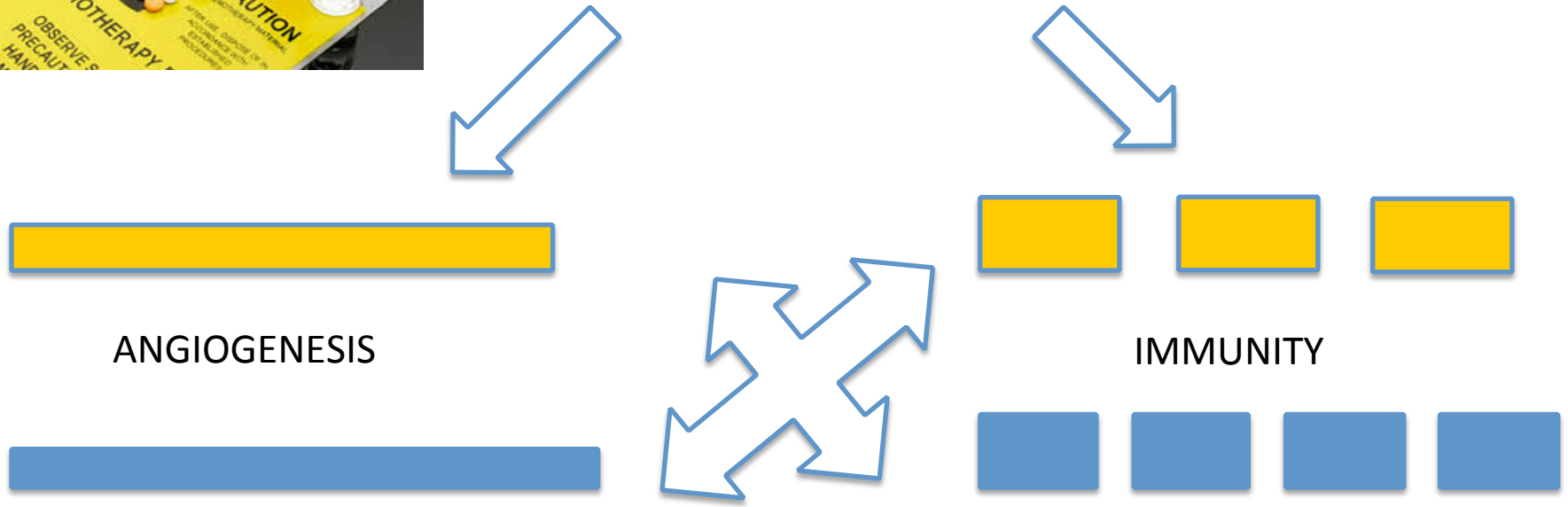
Metronomic Antiangiogenic treatment ????

[Shevchenko IJC 2013], [Rozados Oncol Res 2010] [Ghirighelli CCI 2007] [Vincent CR 2010].

METRONOMIC CHEMOTHERAPY

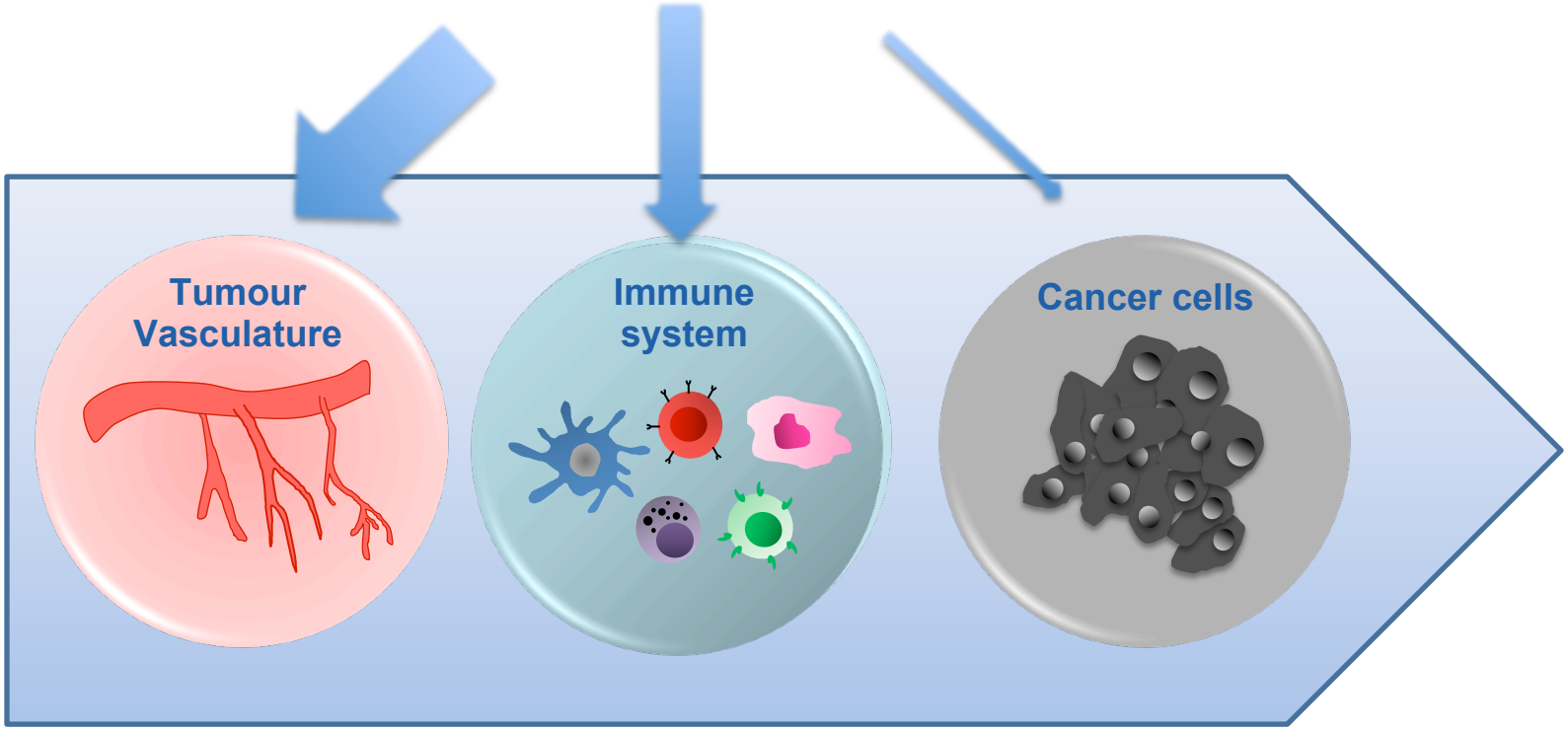


METRONOMIC CHEMOTHERAPY



2, 3, 4 drugs
Together, sequentially
More than 2 effects & different targets
Toxicity (which impacts on anticancer effects)

Metronomic Chemotherapy 2.0



Eddy Pasquier, Maria Kavallaris and Nicolas André

NATURE REVIEWS | CLINICAL ONCOLOGY

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Capecitabine Versus Classical Cyclophosphamide, Methotrexate, and Fluorouracil As First-Line Chemotherapy for Advanced Breast Cancer

Martin R. Stockler, Vernon J. Harvey, Prudence A. Francis, Michael J. Byrne, Stephen P. Ackland, Bernie Fitzharris, Guy Van Hazel, Nicholas R.C. Wilcken, Peter S. Grimison, Anna K. Nowak, M. Corona Gainford, Akiko Fong, Lisa Paksec, Tatiana Sourjina, Diana Zannino, Val Gebski, R. John Simes, John F. Forbes, and Alan S. Coates

reduced by one level (to 75% of starting dose) in 82 (3
women and by two levels (to 50% of starting dose) in
women (15%). Dose escalation of intermittent capecita
1,000 mg/m^2 twice daily to 1,250 mg/m^2 twice daily) was a
11 (10%) of 107 women, six of whom experienced an ac
requiring a dose reduction within two cycles.

The average duration of chemotherapy was longer
signed capecitabine than in those assigned CMF (9 months,
6 months, 5.5 cycles; Appendix Table A1, online only).

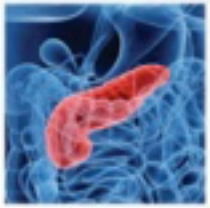
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma

Roger Stupp, M.D., Warren P. Mason, M.D., Martin J. van den Bent, M.D., Michael Weller, M.D., Barbara Fisher, M.D., Martin J.B. Taphoorn, M.D., Karl Belanger, M.D., Alba A. Brandes, M.D., Christine Marosi, M.D., Ulrich Bogdahn, M.D., Jürgen Curschmann, M.D., Robert C. Janzer, M.D., Samuel K. Ludwin, M.D., Thierry Gorlia, M.Sc., Anouk Allgeier, Ph.D., Denis Lacombe, M.D., J. Gregory Cairncross, M.D., Elizabeth Eisenhauer, M.D., and René O. Mirimanoff, M.D., for the European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups and the National Cancer Institute of Canada Clinical Trials Group*

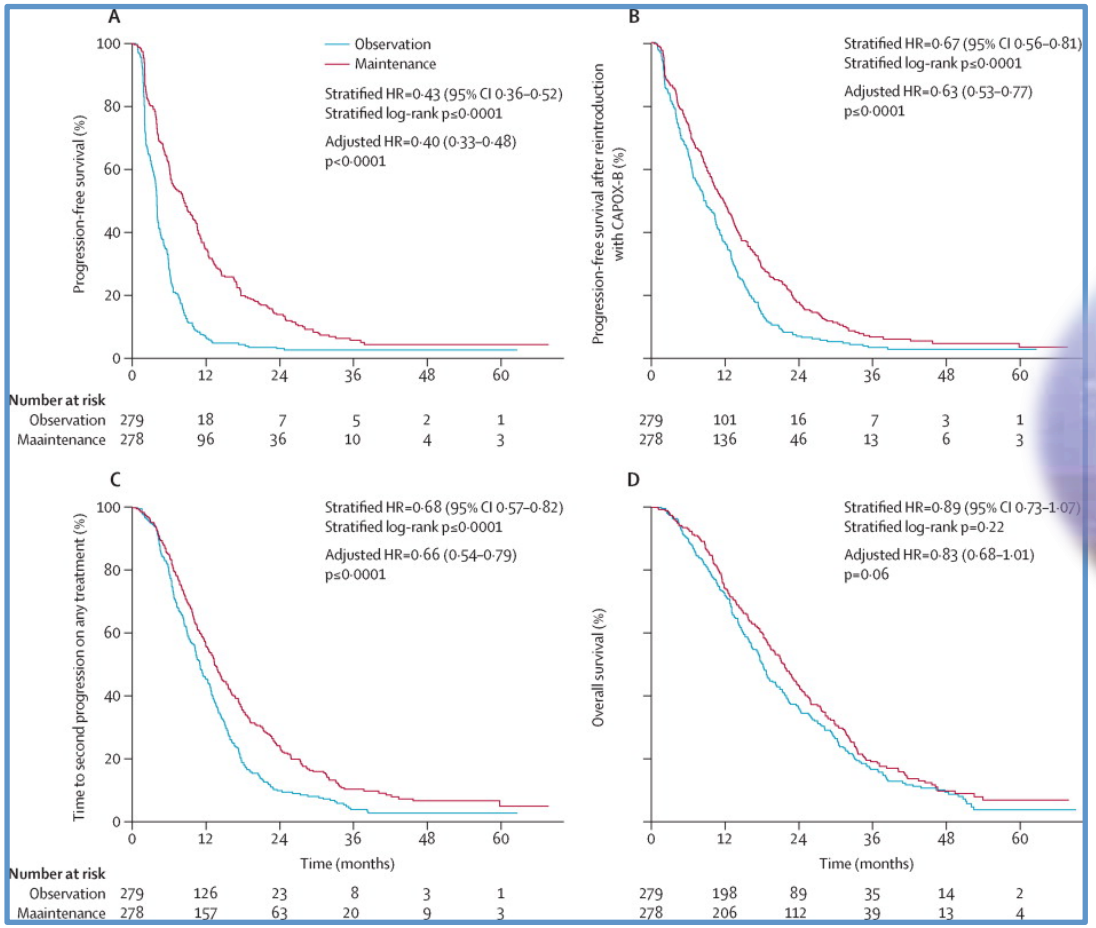
teria may have served to exclude pa
worst prognosis, who may not be
therapy. Moreover, most patients l
debulking surgery. The relatively lor
disease progression (approximately
in both groups) is also noteworthy.
survival may reflect either patient s
early detection of tumor progressio
regular radiographic assessment. F



Maintenance treatment with capecitabine and bevacizumab in metastatic colorectal cancer (CAIRO3): a phase 3 randomised controlled trial of the Dutch Colorectal Cancer Group

THE LANCET

385, 9980, 1843–1852, 2015



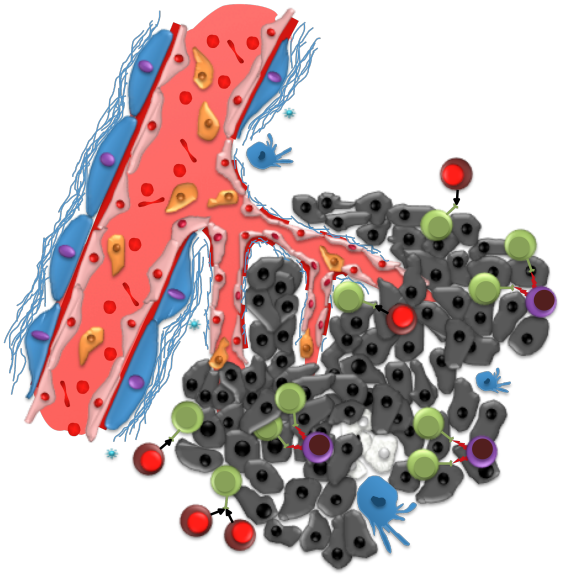
METRO-SFCE01

1. Metronomic regimen for children with refractory disease
2. Multi-drug
3. Low toxicities

   (no temo- no eto)
4. Mainly Oral
5. Pro-immune and antiangiogenic

   Treg

   Activate Dendritic cells

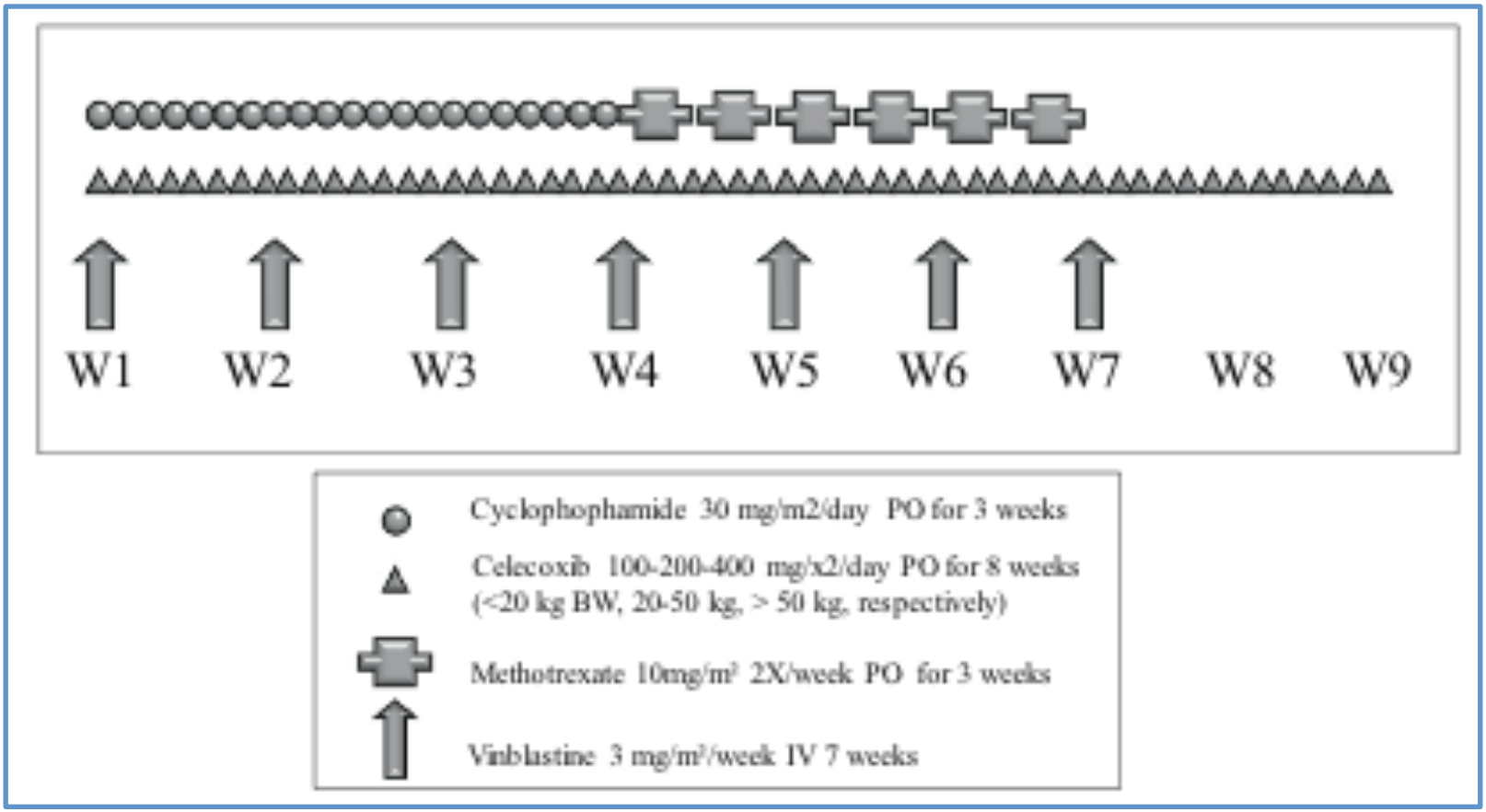


Pasquier, André NRCO 2010

Pilot study of a pediatric metronomic 4-drug regimen

Nicolas André[1,2], Sylvie Abed[1], Daniel Orbach[3], Corinne Armari Alla[4], Laetitia Padovani[5], Eddy Pasquier[2,6], Jean Claude Gentet[1], Arnauld Verschuur[1,2]

Oncotarget, December, Vol.2, No 12



Pt nb	Sex	Tumour Type	Indication	Age (year)	Weight (kg)	Previous Lines of Treatment	HD-CT	RX	Previous Treatments Metronomic	Last TTP	Time on treatment	Best Response	Follow-up Weeks	Status
1	M	Medulloblastoma	PD	5.5	16	3	yes	yes	etoposide	8	8	PD	17	DOD
2	M	Rhabdoid Renal Tumor	PD	12	23	3	no	yes	etoposide	6	13	PD	33	DOD
3	M	Medulloblastoma	PD	9	22	3	no	yes	etoposide	8	14	PD	52	AWD
4	F	Osteosarcoma	M*	11.5	43	3	no	no	no	6	52	CR	68	AWD
5	M	Neuroblastoma	M	6	20	4	no	yes	COMBAT	6	8	PD	12	DOD
6	M	Nephroblastoma	M	12	46	4	yes	yes	no	5	14	PD	22	DOD
7	F	Osteosarcoma	M	16	40	3	no	no	no	25	6	PD	14	DOD
8	M	RMS	M**	20	54	2	no	yes	mb-cyclo/tmz	16	52	CR	56	CR
9	F	Osteosarcoma	M***	16	52	2	no	no	no	6	24	CR	72	AWD
10	M	Hodgkin Lymphoma	PD	18	45	4	yes****	yes	no	?	20	PR	24	AWD
11	M	Glioblastoma	PD	9.5	44	3	no	yes	tmz	4	6	PD	6	DOD
12	F	Medulloblastoma	PD	12	34	3	no	yes	etoposide	6	6	PD	16	DOD
13	F	Supratentorial PNET	PD	11	30	2	yes	yes	no	34	14	PD	27	AWD
14	M	Medulloblastoma	PD	14	24	4	no	yes	no	32	6	PD	22	DOD
15	M	Osteosarcoma	PD	10	56	3	no	no	no	12	14	PD	30	DOD
16	M	Osteosarcoma	PD	8.5	27	1	no	no	no	84	24	PD	25	AWD

Pt nb	Sex	Tumour Type	Indication	Age (year)	Weight (kg)	Previous Lines of Treatment	HD-CT	RX	Previous Treatments Metronomic	Last TTP	Time on treatment	Best Response	Follow-up Weeks	Status
1	M	Medulloblastoma	PD	5.5	16	3	yes	yes	etoposide	8	8	PD	17	DOD
2	M	Rhabdoid Renal Tumor	PD	12	23	3	no	yes	etoposide	6	13	PD	33	DOD
3	M	Medulloblastoma	PD	9	22	3	no	yes	etoposide	8	14	PD	52	AWD
4	F	Osteosarcoma	M*	11.5	43	3	no	no	no	6	52	CR	68	AWD
5	M	Neuroblastoma	M	6	20	4	no	yes	COMBAT	6	8	PD	12	DOD
6	M	Nephroblastoma	M	12	46	4	yes	yes	no	5	14	PD	22	DOD
7	F	Osteosarcoma	M	16	40	3	no	no	no	25	6	PD	14	DOD
8	M	RMS	M**	20	54	2	no	yes	mb-cyclo/tmz	16	52	CR	56	CR
9	F	Osteosarcoma	M***	16	52	2	no	no	no	6	24	CR	72	AWD
10	M	Hodgkin Lymphoma	PD	18	45	4	yes****	yes	no	?	20	PR	24	AWD
11	M	Glioblastoma	PD	9.5	44	3	no	yes	tmz	4	6	PD	6	DOD
12	F	Medulloblastoma	PD	12	34	3	no	yes	etoposide	6	6	PD	16	DOD
13	F	Supratentorial PNET	PD	11	30	2	yes	yes	no	34	14	PD	27	AWD
14	M	Medulloblastoma	PD	14	24	4	no	yes	no	32	6	PD	22	DOD
15	M	Osteosarcoma	PD	10	56	3	no	no	no	12	14	PD	30	DOD
16	M	Osteosarcoma	PD	8.5	27	1	no	no	no	84	24	PD	25	AWD

Pt nb	Sex	Tumour Type	Indication	Age (year)	Weight (kg)	Previous Lines of Treatment	HD-CT	RX	Previous Treatments Metronomic	Last TTP	Time on treatment	Best Response	Follow-up Weeks	Status
1	M	Medulloblastoma	PD	5.5	16	3	yes	yes	etoposide	8	8	PD	17	DOD
2	M	Rhabdoid Renal Tumor	PD	12	23	3	no	yes	etoposide	6	13	PD	33	DOD
3	M	Medulloblastoma	PD	9	22	3	no	yes	etoposide	8	14	PD	52	AWD
4	F	Osteosarcoma	M*	11.5	43	3	no	no	no	6	52	CR	68	AWD
5	M	Neuroblastoma	M	6	20	4	no	yes	COMBAT	6	8	PD	12	DOD
6	M	Nephroblastoma	M	12	46	4	yes	yes	no	5	14	PD	22	DOD
7	F	Osteosarcoma	M	16	40	3	no	no	no	25	6	PD	14	DOD
8	M	RMS	M**	20	54	2	no	yes	mb-cyclo/tmz	16	52	CR	56	CR
9	F	Osteosarcoma	M***	16	52	2	no	no	no	6	24	CR	72	AWD
10	M	Hodgkin Lymphoma	PD	18	45	4	yes****	yes	no	?	20	PR	24	AWD
11	M	Glioblastoma	PD	9.5	44	3	no	yes	tmz	4	6	PD	6	DOD
12	F	Medulloblastoma	PD	12	34	3	no	yes	etoposide	6	6	PD	16	DOD
13	F	Supratentorial PNET	PD	11	30	2	yes	yes	no	34	14	PD	27	AWD
14	M	Medulloblastoma	PD	14	24	4	no	yes	no	32	6	PD	22	DOD
15	M	Osteosarcoma	PD	10	56	3	no	no	no	12	14	PD	30	DOD
16	M	Osteosarcoma	PD	8.5	27	1	no	no	no	84	24	PD	25	AWD

Pt nb	Sex	Tumour Type	Indication	Age (year)	Weight (kg)	Previous Lines of Treatment	HD-CT	RX	Previous Treatments Metronomic	Last TTP	Time on treatment	Best Response	Follow-up Weeks	Status
1	M	Medulloblastoma	PD	5.5	16	3	yes	yes	etoposide	8	8	PD	17	DOD
2	M	Rhabdoid Renal Tumor	PD	12	23	3	no	yes	etoposide	6	13	PD	33	DOD
3	M	Medulloblastoma	PD	9	22	3	no	yes	etoposide	8	14	PD	52	AWD
4	F	Osteosarcoma	M*	11.5	43	3	no	no	no	6	52	CR	68	AWD
5	M	Neuroblastoma	M	6	20	4	no	yes	COMBAT	6	8	PD	12	DOD
6	M	Nephroblastoma	M	12	46	4	yes	yes	no	5	14	PD	22	DOD
7	F	Osteosarcoma	M	16	40	3	no	no	no	25	6	PD	14	DOD
8	M	RMS	M**	20	54	2	no	yes	mb-cyclo/tmz	16	52	CR	56	CR
9	F	Osteosarcoma	M***	16	52	2	no	no	no	6	24	CR	72	AWD
10	M	Hodgkin Lymphoma	PD	18	45	4	yes****	yes	no	?	20	PR	24	AWD
11	M	Glioblastoma	PD	9.5	44	3	no	yes	tmz	4	6	PD	6	DOD
12	F	Medulloblastoma	PD	12	34	3	no	yes	etoposide	6	6	PD	16	DOD
13	F	Supratentorial PNET	PD	11	30	2	yes	yes	no	34	14	PD	27	AWD
14	M	Medulloblastoma	PD	14	24	4	no	yes	no	32	6	PD	22	DOD
15	M	Osteosarcoma	PD	10	56	3	no	no	no	12	14	PD	30	DOD
16	M	Osteosarcoma	PD	8.5	27	1	no	no	no	84	24	PD	25	AWD

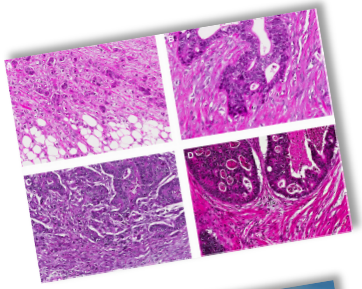
"Always give a grave prognosis, my boy! If they die, you're accura
live, you're skilled!"

Metronomics in patients

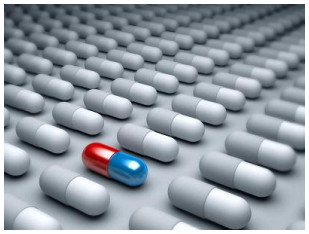
450 publications about metronomics in humans

Key Points :

1) Which agents?
2) Which tumours?
3) Which doses?
4) Which setting?
5) Which schedule?
6) Breaks or no breaks?
7) Which Outcome?



METRONOMICS 3.0

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2 Biological Sciences Platform, Sunnybrook Research Institute, Toronto, ON, Canada
3 Department of Biostatistics and Bioinformatics, Roswell Park Cancer Institute, Buffalo, NY, USA
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*Corresponding author. Tel: +1 716 8454464; E-mail: John.Ebos@roswellpark.org

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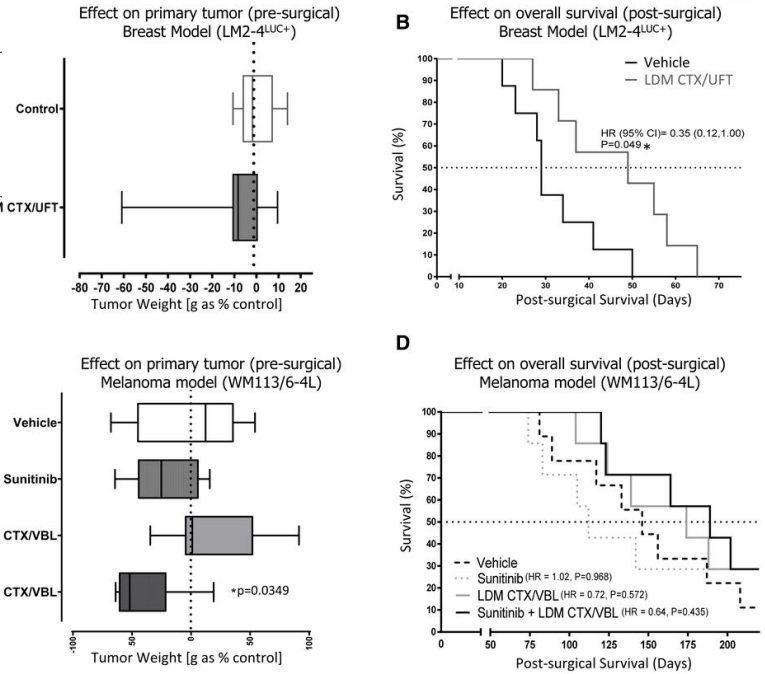
EMBO Molecular Medicine



D

Drug – Dose – Durat
Sunitinib – 60mg/kg – 1
Axitinib – 100mg/kg – 1
B20 – 5mg/kg – 14 days

Figure 3.

Marseille (CEPCM), Hospital of La Timone, AP-HM, Marseille 13005, France. Correspondence to N.A. (nicolas.andre@ap-hm.fr)

doi:10.1038/nrclinonc.2015.204
Published online 24 Nov 2015

application of this concept to cancer systems biology (that is, computational and mathematical modelling of the biological networks underlying tumorigenesis), that exploits the constant improvements in computing resources, has contributed greatly to the analysis of large datasets relating to complex signalling networks[2]. Indeed, huge databases of diverse information

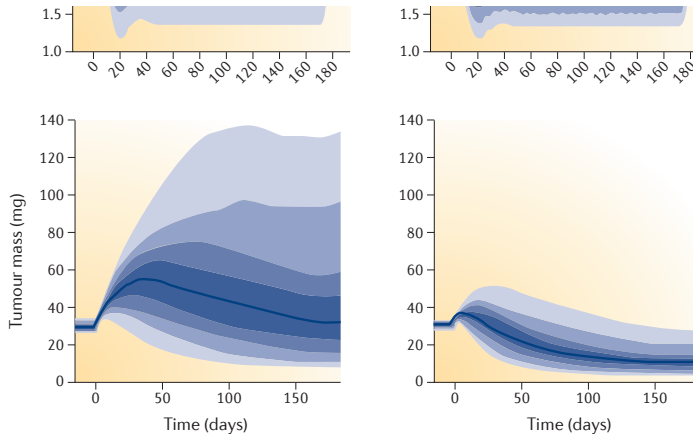


Figure 4 | **Example of PK/PD simulation to optimize a vinorelbine treatment regi**
regimen, incorporating a 50 mg fixed dose of vinorelbine on days 1, 3 and 5 (D1-D3-D5
can provide substantial clinical benefit to many patients; however, mathematical model
alternative dynamic dosing schedule (right panels) of 30 mg, 60 mg and 30 mg on days 1
respectively, which was predicted to achieved a higher antiproliferative efficacy (lower
safety profile based on absolute neutrophil count (middle panels)[112]. Shading represents
obtained from Springer International Publishing © Barbolosi, D. *et al. Cancer Chemothe*

safety–efficacy multiscale model describing the PK/PD relationships between docetaxel and epirubicin, allowing the best *in silico* drug-dosing regimen (that is, docetaxel first and epirubicin 1 day later, a sequence opposite to that usually performed with these drugs) for each patient to be tested in a phase Ib trial[101]. To date, 17 patients have been recruited and the proposed regimen was both well tolerated, and achieved a response rate of 45%, a median progression-free survival of 10.4 months and a median survival of 54.6 months, which compares favourably to the results reported in initial publications of the docetaxel and epirubicin combination[102–108].

Planning metronomic
nomic chemotherapy i
to be fully determined[1
paradigm that illustrate
ule can alter the mech
example, canonical cyt
genic or immune-stimu
understanding of metr
mathematical modelli
approaches can facilit
of conventional versus
the innumerable perm

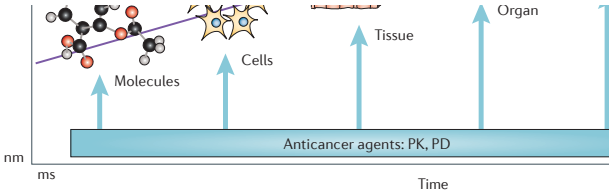


Figure 2 | **Multiscale modelling in oncology.** Multiscale modelling can be used to simulat
processes related to cancer development. Simulations can be performed at the level of mol
at the cellular level, the tissue level, the organ level, and/or the ultimately at the whole-body
frames. Then, the effects of several inputs, such as molecular or genetic profiling, or grading
can be modelled. Characteristics of the anticancer agents alone or combination can also be
The model can eventually predict different kinds of outcome at each level (survival, clinical a
decreases in tumour volume, target inhibition, and molecular pathway inhibition) and at dif

thalidomide + celecoxib + fenofibrate (oral
bevacizumab (IV, 2×/month), intraventricu

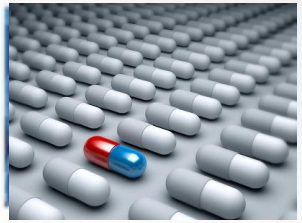
*Details regarding the other cohorts of patients are not given. Abbreviations: CB, clinical benefit; CR, complete respo
MTD, maximum tolerated dose; NA, not available; PR, partial response; PSA, prostate-specific antigen; RR, response

Clinical experience in children

Over the past 4 years, more clinical experience of metronomic chemotherapy in children has been gained (Table 5).[172–182] The addition of a metronomic combination of vinblastine, celecoxib and cyclophophamide to standard MTD chemotherapy was investigated in children with newly diagnosed metastatic Ewing sarcoma.[178] Although, there was an increased toxicity in irradiated sites, there was also increased EFS for patients with isolated pulmonary metastasis compared with historical controls. Similarly, the addition of metronomic maintenance was a favourable prognostic factor in children with embryonal rhabdomyosarcoma who had metastatic spread to the lungs.[183]

A multimodal metronomic protocol for children with relapsing embryonal brain tumours was assessed using the four-drug metronomic protocol of either continuous oral thalidomide and celecoxib with alternating oral etoposide and cyclophosphamide based on an earlier study,[184] combined with intrathecal etoposide and cytarabine, bevacizumab and fenofibrate. An EFS of 85% and 69% at 12 and 24 months, respectively, was observed in seven patients with medulloblastoma. Based on these promising results, the
gated in an internatio
exciting recent develo
paediatric oncology r
approach that comb
and irinotecan with
dren with refractory
an overall survival r
of 80 weeks, a rando
ated.[187] Metronomic t
in LMICs.[25] For exa
nomic combination
and methotrexate re
dormancy in three
blastoma.[173] Buildin
added valproic acid t
backbone and observ
in a child with metast
randomized phase I
nomic regimen[184] has
this regimen with be
no curative option.[188]
way in the paediatric

André *Nature Reviews Clinical Oncology* 2014



METRONOMICS

- **ORAL, NON TOXIC, low cost**
- **CLINICAL ACTIVITY**
- **MULTI-TARGETTED**
  - **Angiogenesis**
  - **Immune system**
  - **Stroma**
  - **Cancer cells & stems cells**
- **COMBINATION (sequential / associated)**
  - Drug repositioning
  - Chemotherapy
  - Immunotherapy +++
  - Target therapy
- **COMPUTATIONAL METRONOMIC**

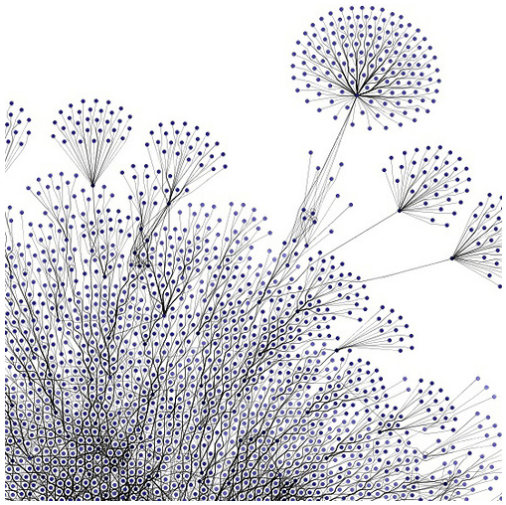
  PK, biomarkers, molecular biology

CHAOTIC THERAPY

Simple predictable disease
= Simple treatment

GLEEVEC

CHAOTIC THERAPY



Complex unpredictable disease ???

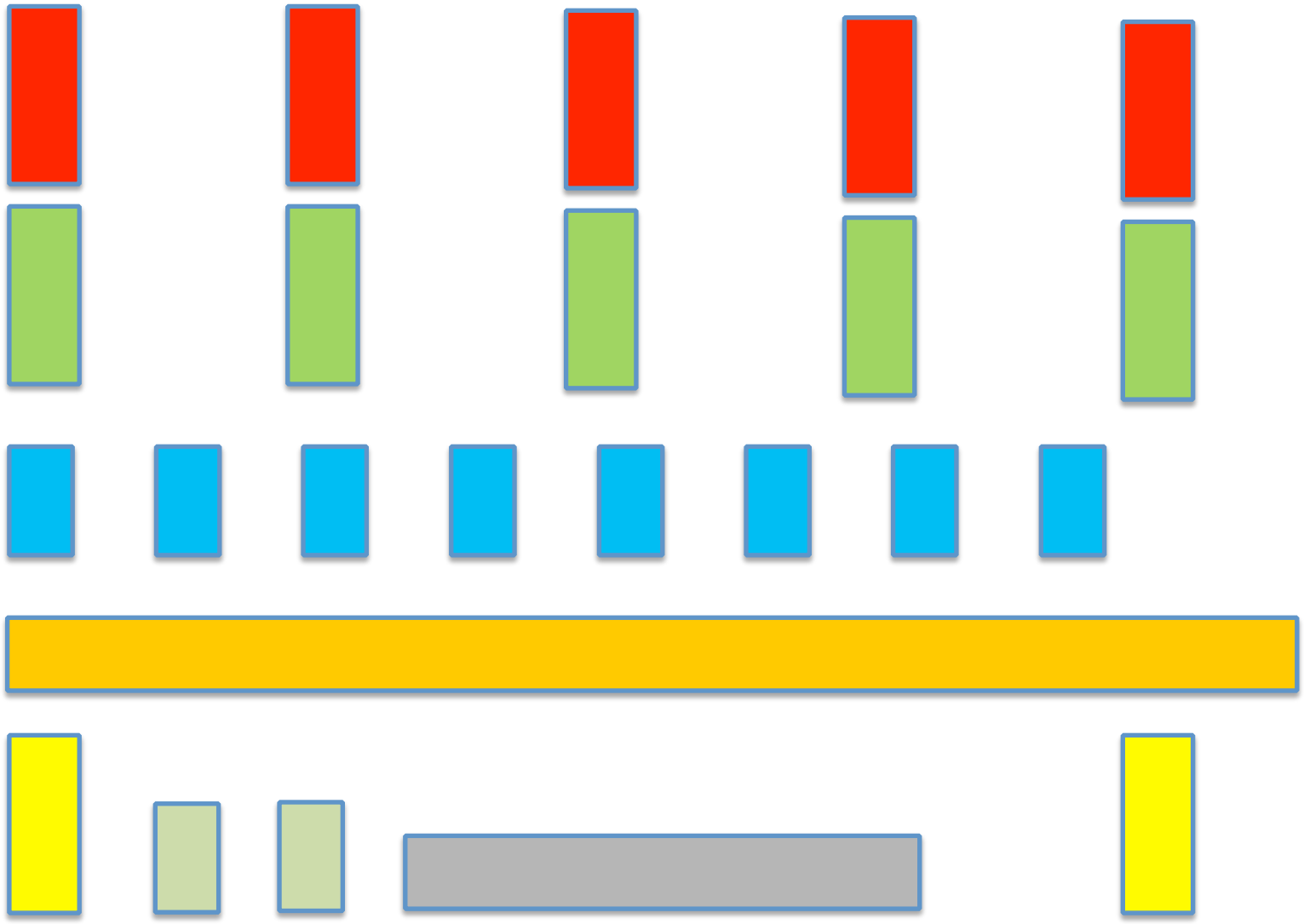
Can we overcome the adapting capacity of cancer ?…

Cancer is a chaotic system (MacKey Sciences 1977, Andrey Med Hypo 1989, Baum Eur J Cancer 1999, Cross Hum Path 1994)
High potential of evolution/adaptation

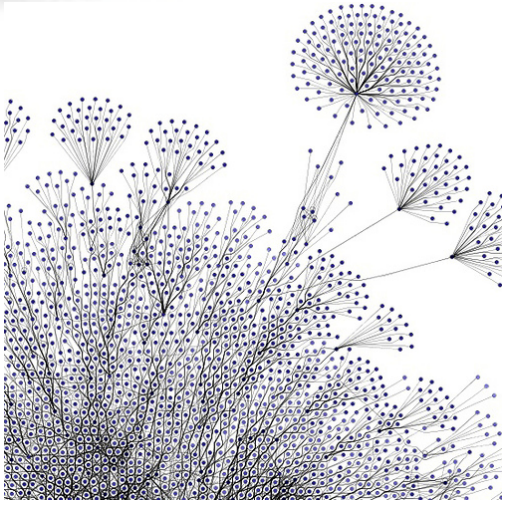
→ Generate ever changing unpredictable treatment
→ Fight chaos with chaos ?

Evolution of Chemotherapy

CHEMOTHERAPY

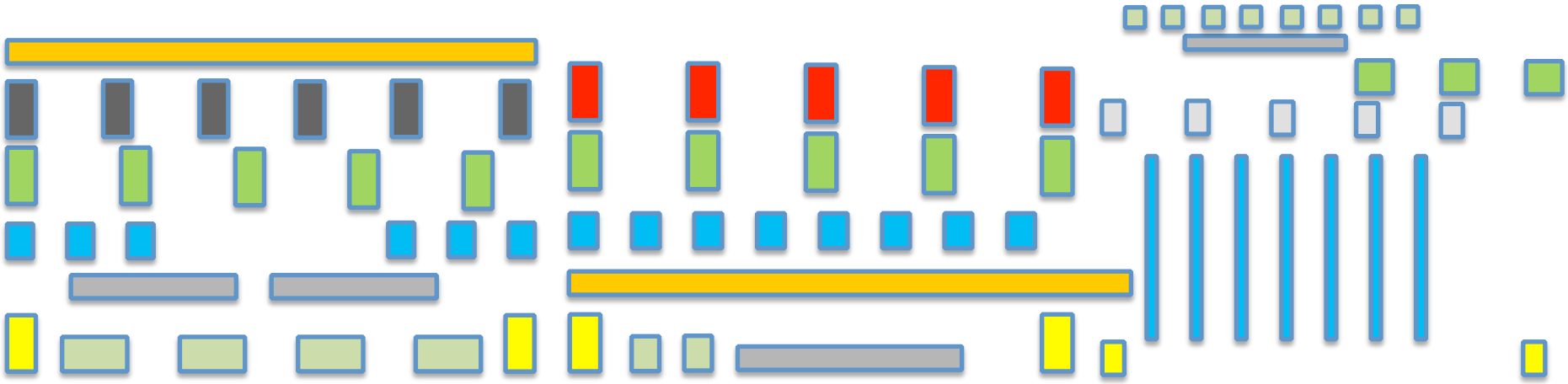


CHAOTIC THERAPY



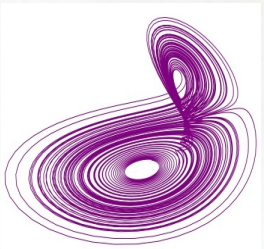
Complex unpredictable disease ???

CHAOTIC THERAPY



CHAOTIC THERAPY

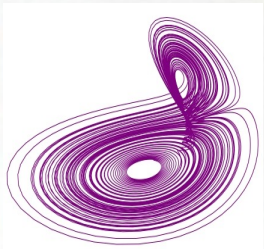
Out of control
Mess
Anarchy
Disorganized



Chaos ?

- Χάος / *Khaos :* yawning" or "gap",
- Greek mythology
- the primeval void
- before Gaia (earth), Tartarus, Eros (love)

- Fall in all direction
- Endless chasm, abyss

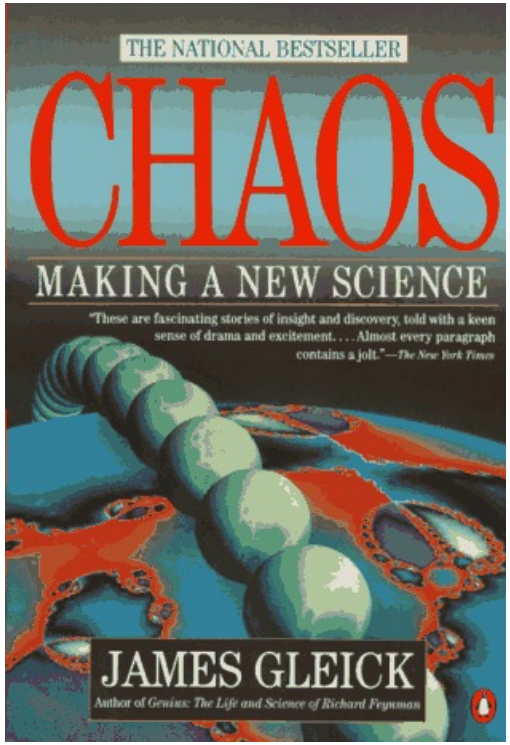


Chaos ?

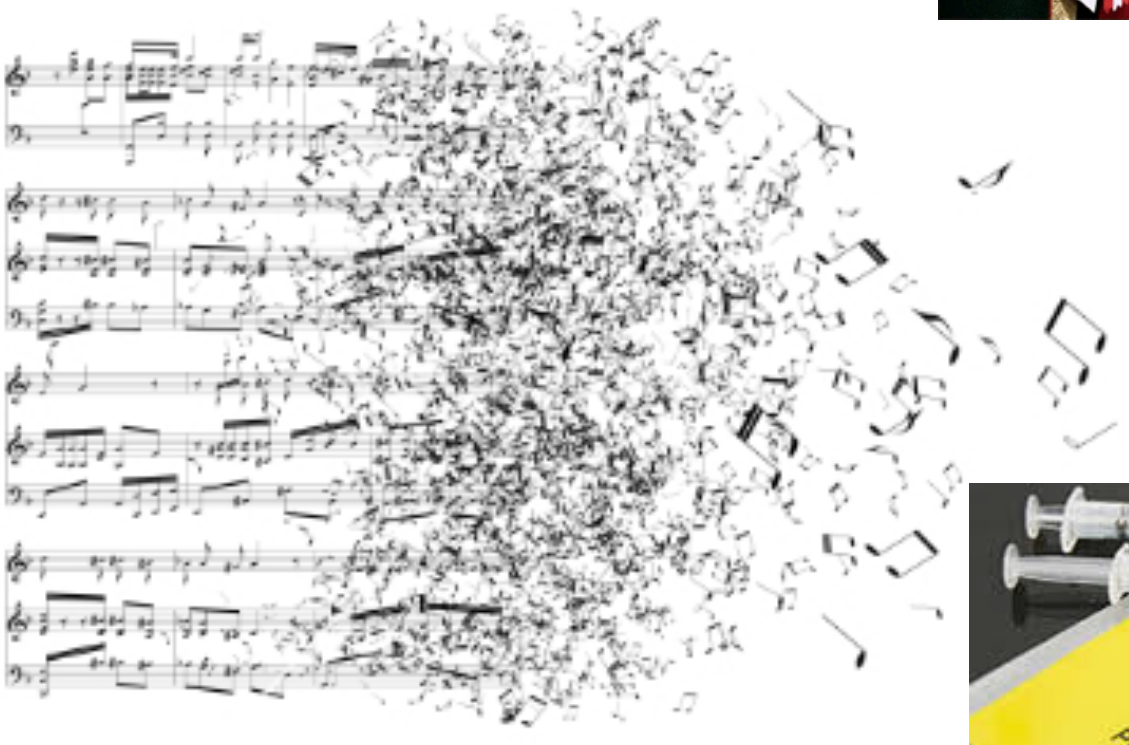
- Tien-Yien Li et James A. Yorke[(terminology)
- Way to solve problem otherwise unsolvable
- **Non linearity**
- **Dynamic (not always complex) system**
- **Strong dependence on initial conditions**
- **Sensitivity to initial conditions**

  (butterfly effect # domino cascade effect)
- **Unpredictable outcome**

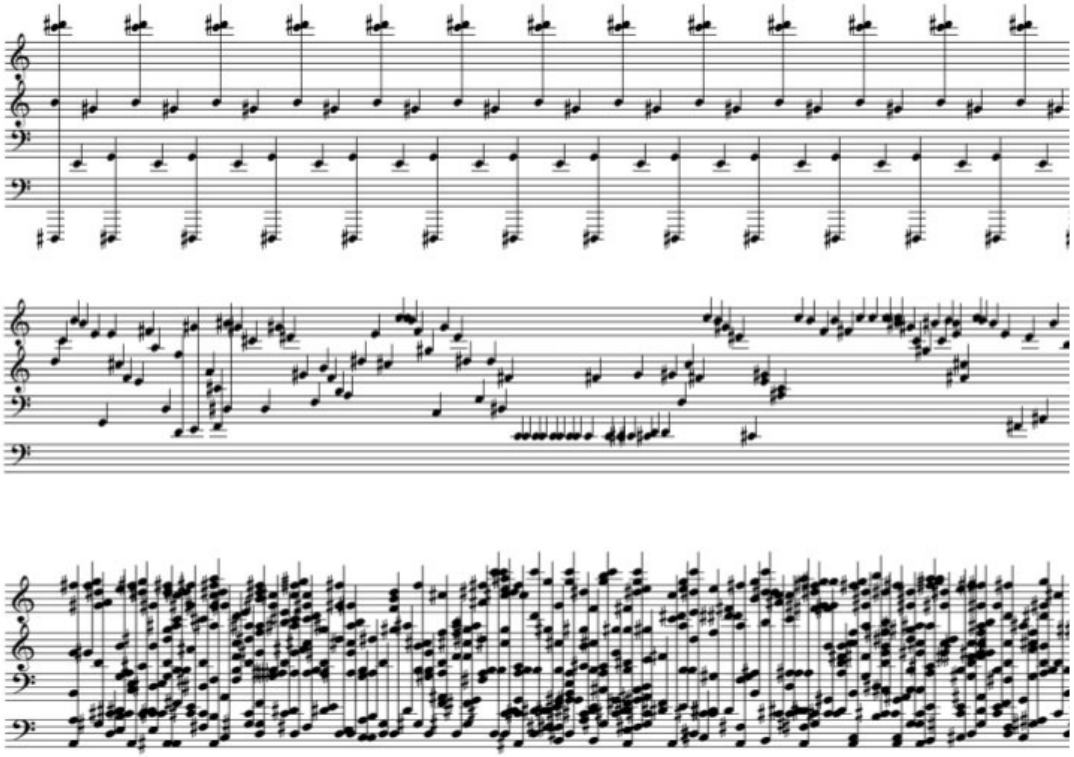
- Attractors, Sustained irregularity, Feedback….



…..If music was chaos……

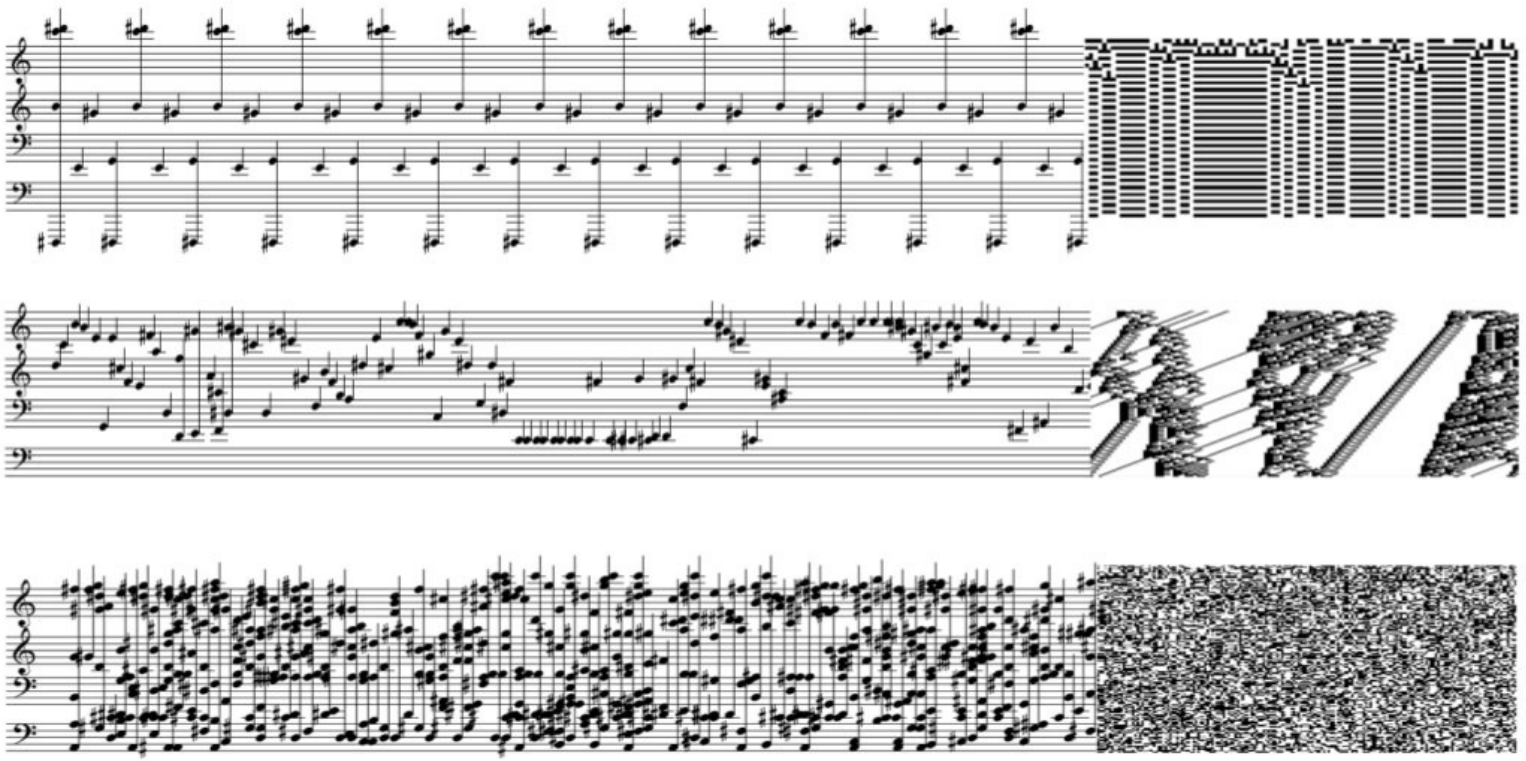


……Would not use that for my patients



SIMPLE

COMPLEX

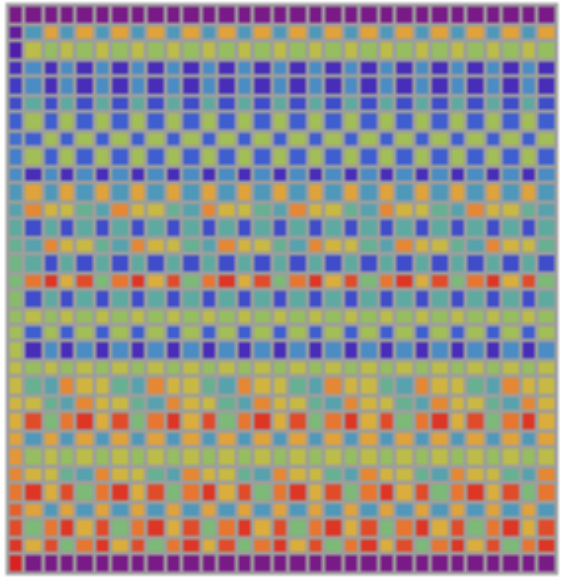


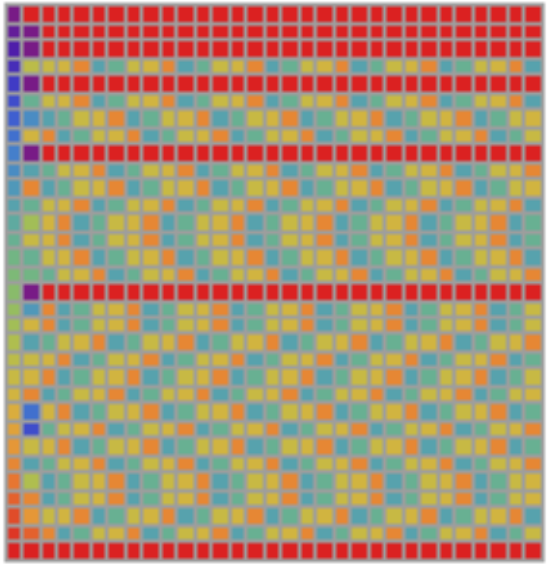
- 1 unit of 1 drug : Black
- Nothing :White

- Limits of quantity of drugs

- **Single drug Chaotic Regimen** : Doabble ?

http://www.noyzelab.com/research/ulamizer2.html





- 1 square: 1 unit of drug
- Each drug: different color
- Nothing: 1 color

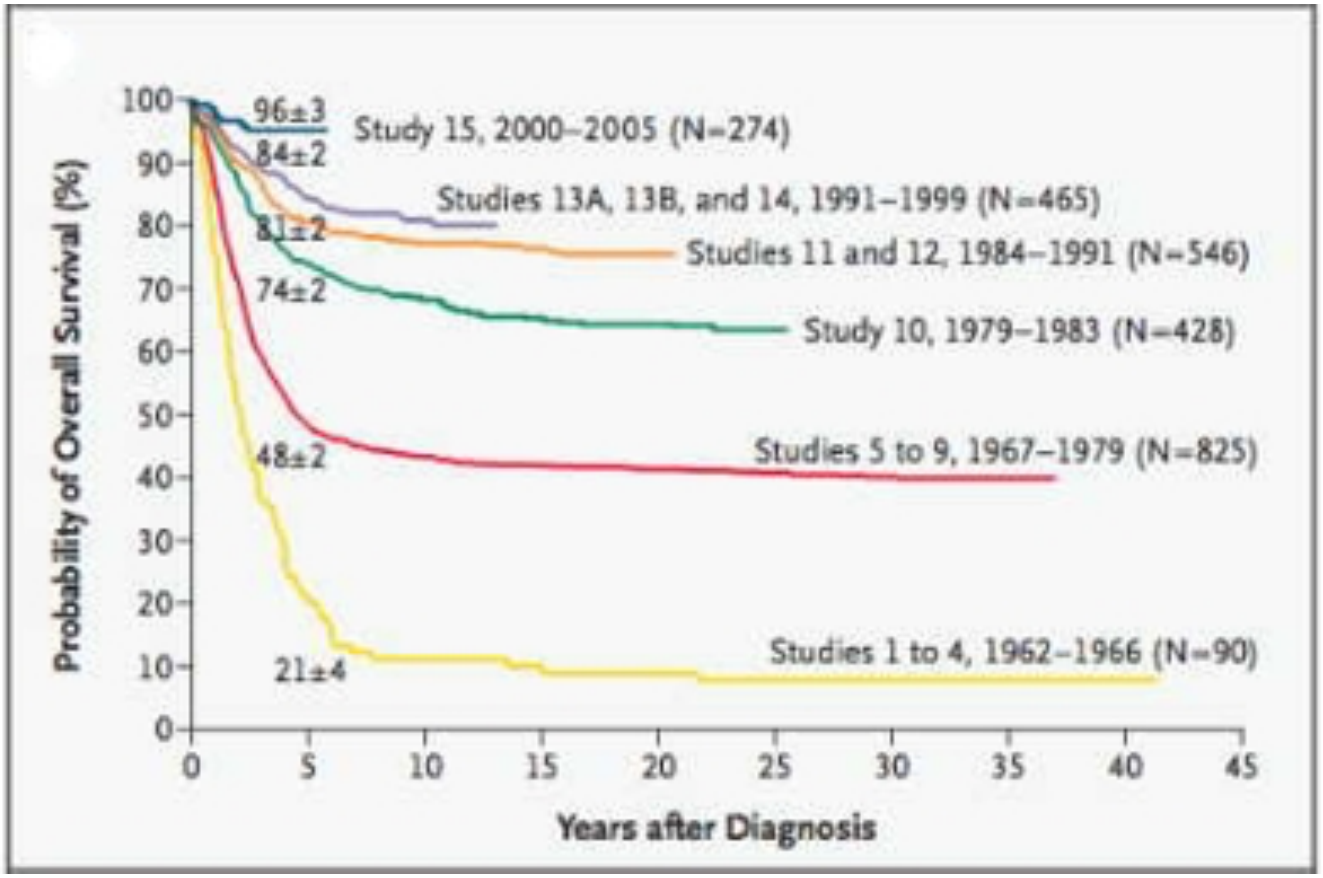
- Limits of quantity of drugs

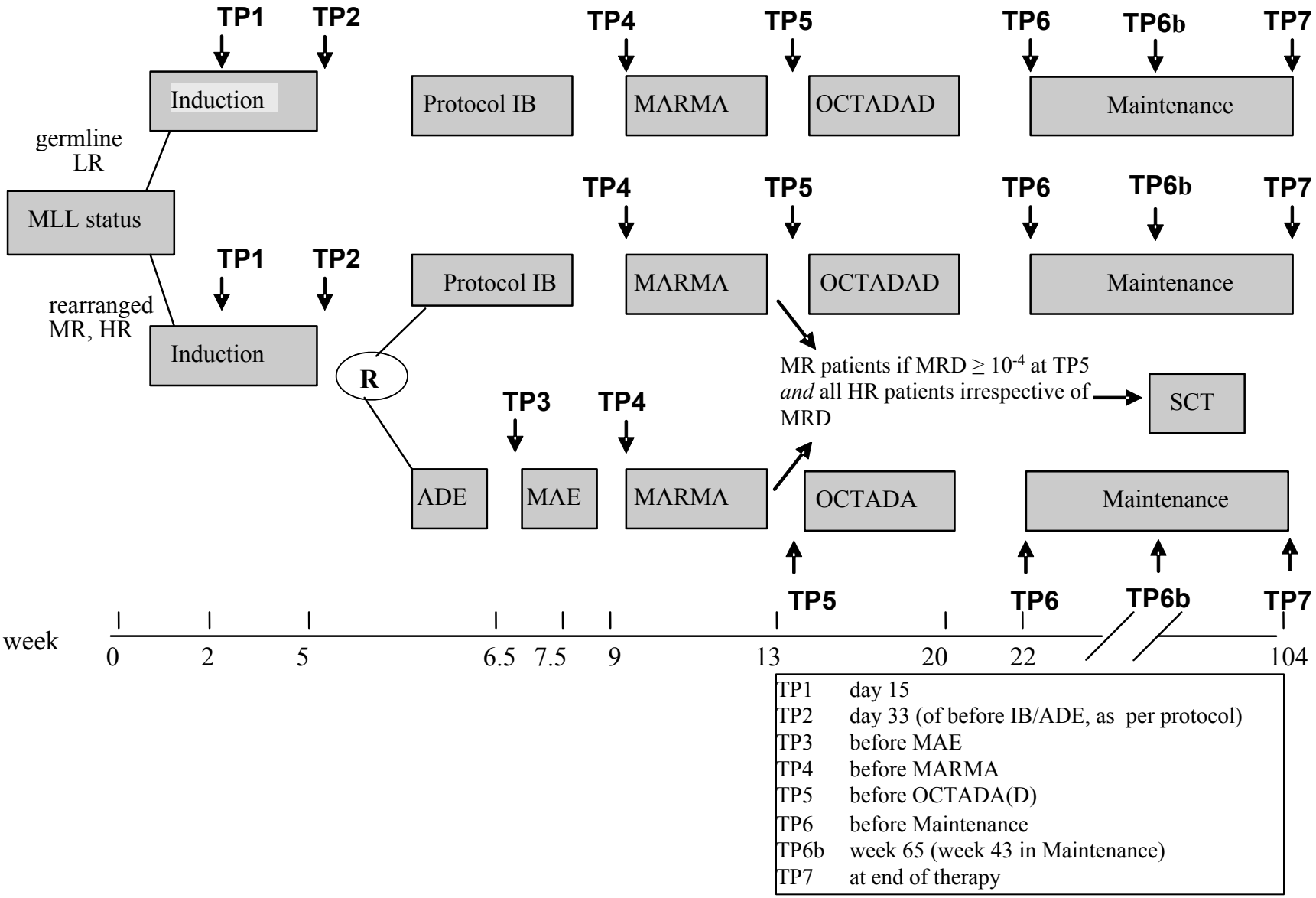
- Mulitple Drug Chaotic regimen : Doabble !

The NEW ENGLAND JOURNAL of MEDICINE

Acute Lymphoblastic Leukemia

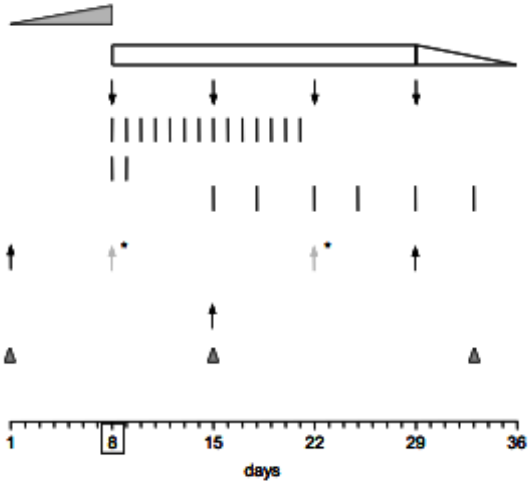
Ching-Hon Pui, Mary V. Relling, and James R. Downing,
N Engl J Med 2004; 350:1535-1548




TP1
TP2
Induction
germline
LR
MLL status
rearranged
MR, HR
Induction
R
Protocol IB
TP4
TP5
MARMA
OCTADAD
TP6
TP6b
TP7
Maintenance
Protocol IB
MARMA
OCTADAD
Maintenance
MR patients if MRD ≥ 10-4 at TP5
and all HR patients irrespective of
MRD
SCT
TP3
TP4
ADE
MAE
MARMA
OCTADA
Maintenance
TP5
TP6
TP6b
TP7
week
0
2
5
6.5
7.5
9
13
20
22
104
TP1 day 15
TP2 day 33 (of before IB/ADE, as per protocol)
TP3 before MAE
TP4 before MARMA
TP5 before OCTADA(D)
TP6 before Maintenance
TP6b week 65 (week 43 in Maintenance)
TP7 at end of therapy

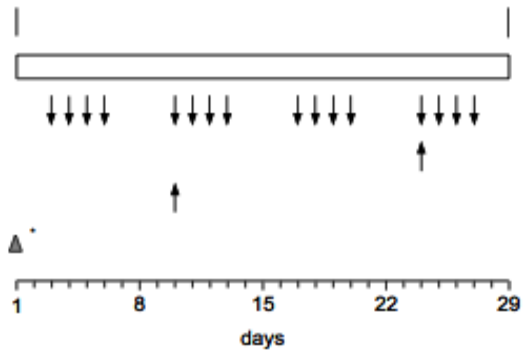
INDUCTION

PRED	PO/IV 60 mg/m²/day
DEXA	PO/IV 6 mg/m²/day
VCR	IV push 1.5 mg/m²/dose
ARA-C	IV 30min 75 mg/m²/dose
DNR	IV 1hr 30 mg/m²/dose
L-ASP (E.coli Asparaginase [illegible])	IV 1hr 10000 U/m²/dose
MTX/PRED	ITH acc. to age
*Only in case of initial CNS involvement.	
ARA-C/PRED	ITH acc. to age
BMP	



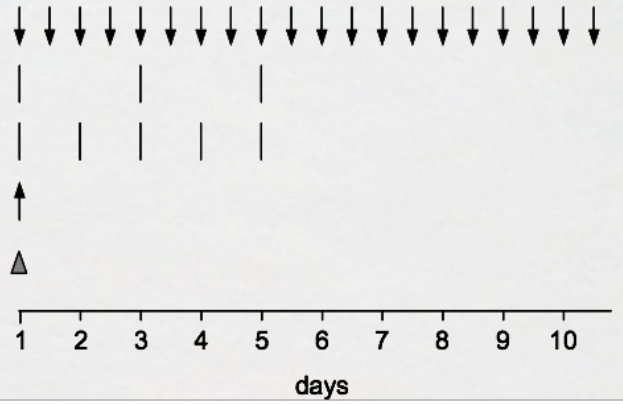
PROTOCOL IB

CPM	IV 1hr 1000 mg/m²/dose
6-MP	PO 60 mg/m²/day
ARA-C	IV push 75 mg/m²/dose
MTX/PRED	ITH acc. to age
ARA-C/PRED	ITH acc. to age
BMP (only if BMP at day 33 is inconclusive)	



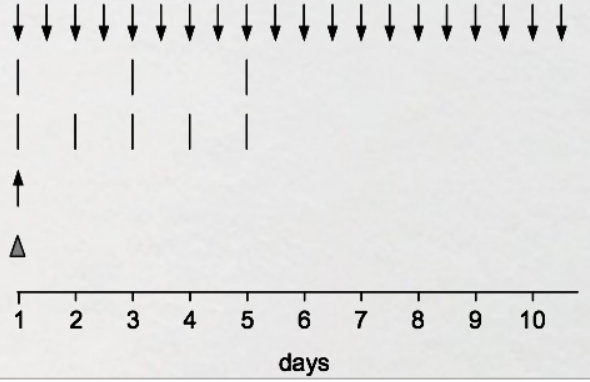
ADE

ARA-C	IV push 100 mg/m^2/dose
DNR	IV 1hr 50 mg/m^2/dose
Etoposide	IV 4hrs 100 mg/m^2/dose
ARA-C/PRED	ITH acc. to age
BMP	



MAE

ARA-C	IV push 100 mg/m^2/dose
Mitoxantrone	IV 1hr 12 mg/m^2/dose
Etoposide	IV 4hrs 100 mg/m^2/dose
MTX/PRED	ITH acc. to age
BMP	

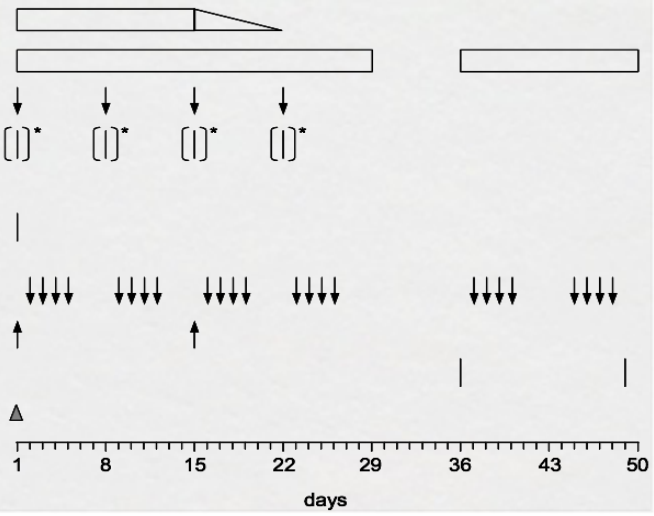


OCTADA(D)

DEXA	PO/IV 6 mg/m²/day
6-TG	PO 60 mg/m²/day
VCR	IV push 1.5 mg/m²/dose
(DNR	IV 1hr 30 mg/m²/dose)

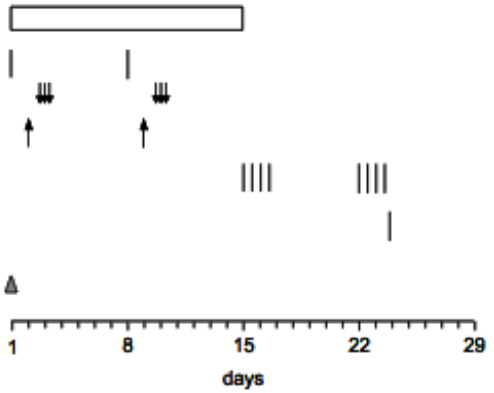
* DNR not for MR/HR patients randomised to the experimental arm.

PEG-ASP (ONCASPAR)	IV 1hr 2500 U/m²/dose
ARA-C	IV push 75 mg/m²/dose
ARA-C/PRED	ITH acc. to age
CPM	IV 1hr 500 mg/ m²/dose
BMP	

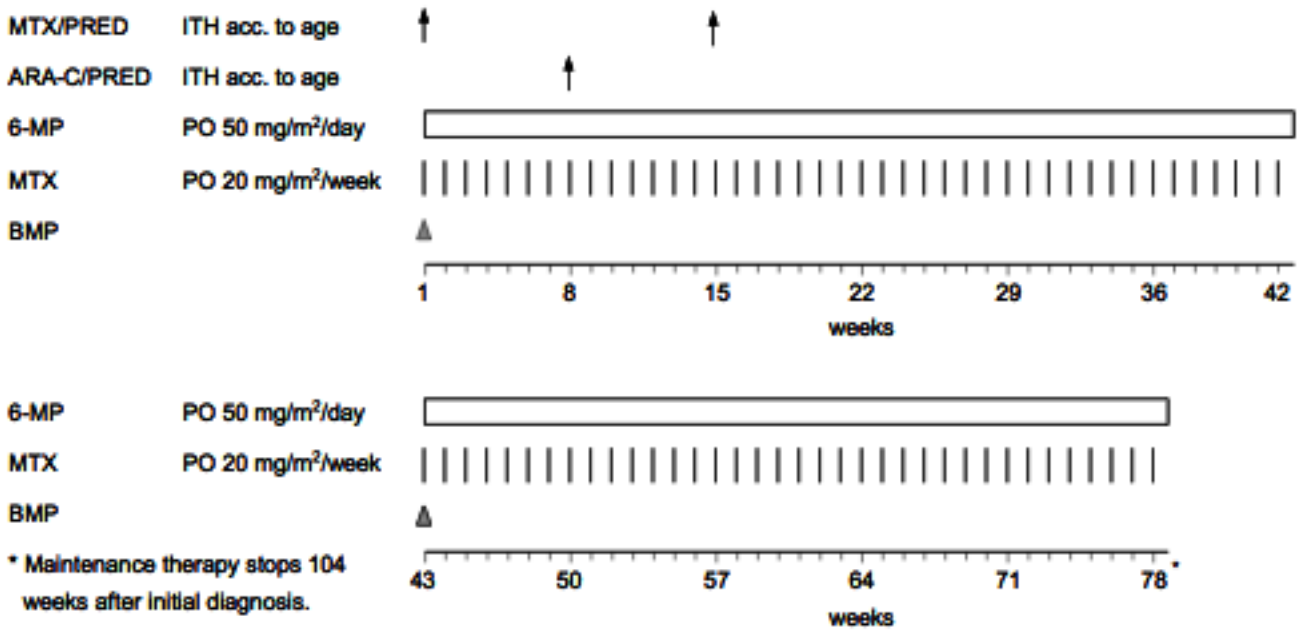


MARMA

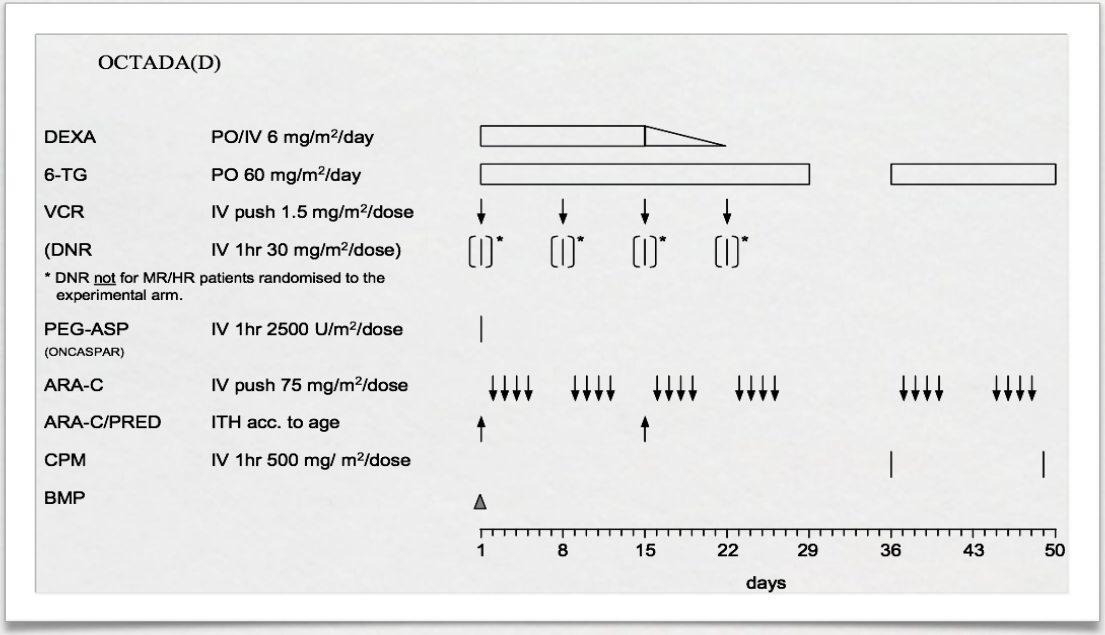
6-MP	PO 25 mg/m²/day
HD-MTX	IV 24hrs 5000 mg/m²/dose
Leucovorin-Rescue	PO/IV 15 mg/m²/dose
MTX/PRED	ITH acc. to age
ARA-C	IV 3hrs 3000 mg/m²/dose
PEG-ASP (ONCASPAR)	IV 1hr 2500 U/m²/dose
BMP	

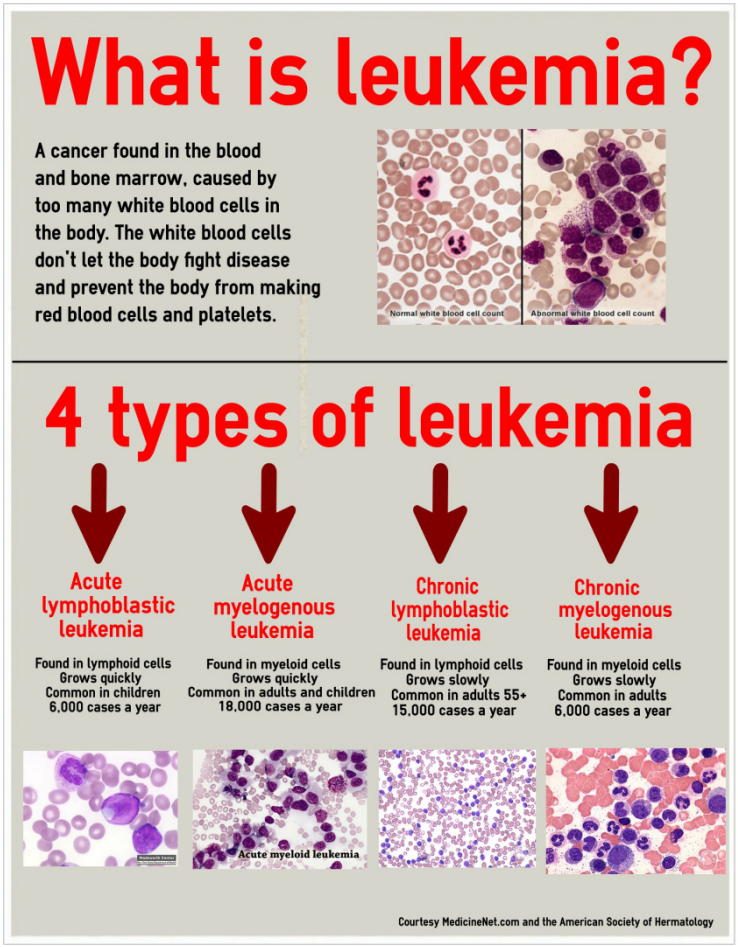


MAINTENANCE



* Maintenance therapy stops 104 weeks after initial diagnosis.


OCTADA(D)
DEXA
PO/IV 6 mg/m²/day
6-TG
PO 60 mg/m²/day
VCR
IV push 1.5 mg/m²/dose
(DNR
IV 1hr 30 mg/m²/dose)
* DNR not for MR/HR patients randomised to the experimental arm.
PEG-ASP
(ONCASPAR)
IV 1hr 2500 U/m²/dose
ARA-C
IV push 75 mg/m²/dose
ARA-C/PRED
ITH acc. to age
CPM
IV 1hr 500 mg/ m²/dose
BMP
1
8
15
22
29
36
43
50
days



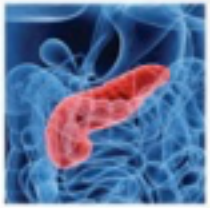
- 5 phases of treatments
  - different combinations
  - different intensities
  - different doses/agent

- 10 anti-cancer agents
- Asparaginase, AraC, Mito, Daunorubicin
- Vincristine, prednisone, dexamethasone,
- Cyclophosphamide, 6MP, 6TG, MTX…

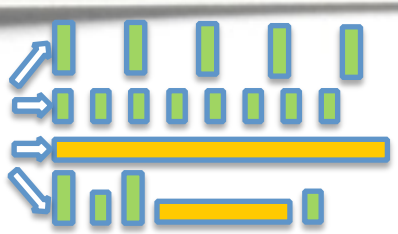
- IV, IT, Bolus/infusion

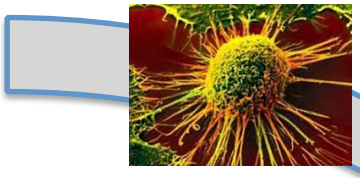
- **EVER CHANGING TREATMENT**
- Dose intensity
- Dose effect
- Metronomic
- Targets:
  cancer cells, cancer stem cells, micro-environement

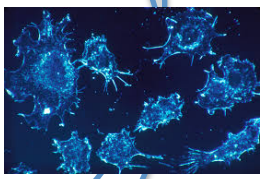
→ Same treatment
→ Unpredictable activity (reponse/progression cure/relapse toxicity)
→ AND unpredictable precise mechanisms of action

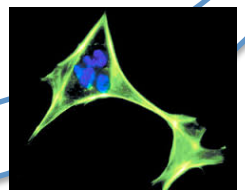


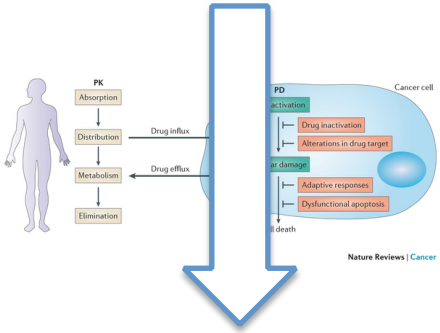
Cancer treatment : a chaotic system ?

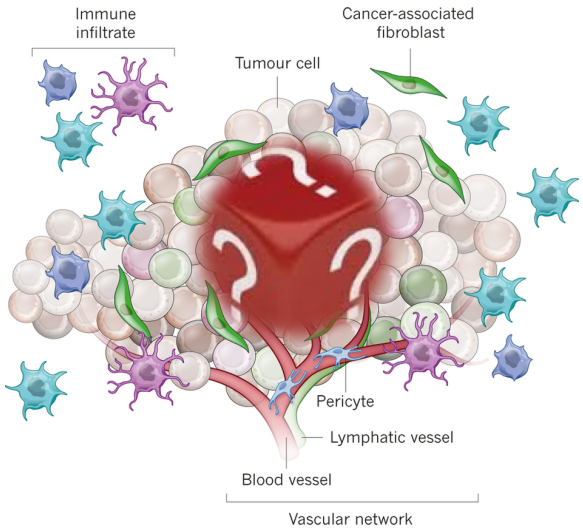












CHAOTIC THERAPY ?

Design a treatment

- **Clinically doabble (toxicity)**
- **Changing (Dynamic)**
- **Strong dependence on initial condition (disease, patients, ttt)**

- **Combinations of agents**
- **Doses & schedules**
- **Target cancer cells,**
- **Target microenvironement**

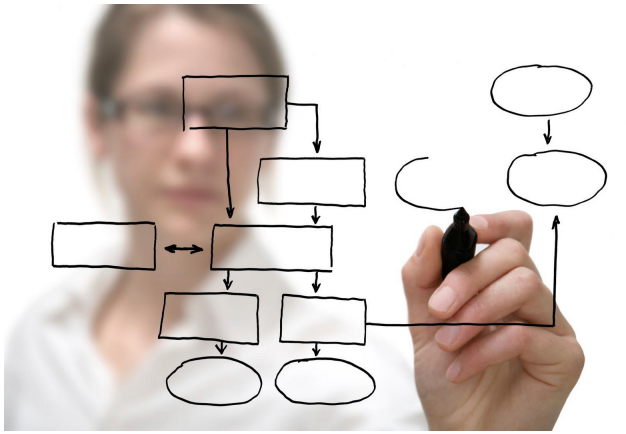
Good Idea ? CHAOTIC THERAPY

Input from mathematicians

→ **check for real chaotic characteristics**

Input from "modelisators"

→ **design chaotic treatment (1 to X drugs)**



Input from biologists

→ **test and validate the model**

→ **study resistance, mechanism of actions**

….test in patients

IF NOT CHAOTIC ….
« COMPLEX DYNAMIC THERAPY »

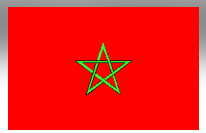

Scientific & Medical Innovation
Must be shared
Low and Middle Income Ccountries
Social innovation Mandatory

METRONOMICS GLOBAL HEALTH INITIATIVE

Network
Website
Meetings
Preclinical work
Clinical studies
Publications

Metronomics.newethicalbusiness.org

Metro-SMHOF



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