The metronomic chemotherapy in patients with NSCLC

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PragueONCO 2019

Overview

Why metronomic > Biological background

How metronomic > Pharmacologic background

When metronomic > First-line setting as ideal

Who metronomic > Patient selection

What's new with metronomic > 2018(9) clinical data

Why metronomic

Biological background

Metronomic chemotherapy(mCT) : definition

"Indeed, metronomic chemotherapy may be better defined as a frequent, regular administration of drug doses designed to **maintain low, but active, range of concentrations** of chemotherapeutic drugs during prolonged periods of time without inducing excessive toxicities."

Bocci & Kerbel. Nat Rev Clin Oncol, 2016

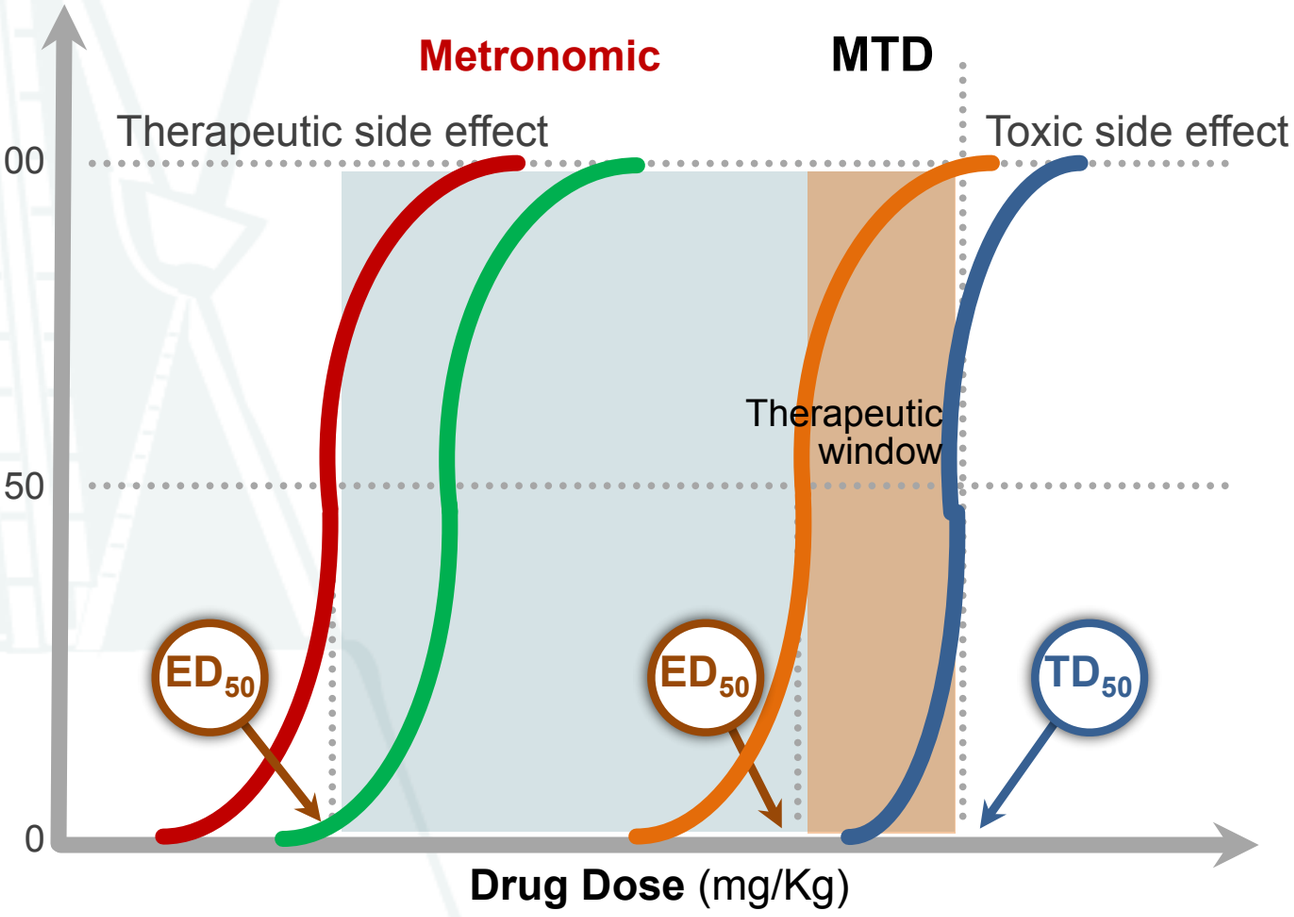
"Metronomic chemotherapy is defined as the **minimum biologically effective dose of a chemotherapic agent** given as a continuous dosing regimen with no prolonged drug-free breaks that leads to antitumour activity "

Klement G.L & Kamen BA J Paediatr. Haematol. Oncol 2011

"The cumulative doses administered over the course of long-term metronomic treatments can be similar or even higher than those administered in conventional MTD regimens, making the terminology 'low dose chemotherapy' somewhat misleading."

André N, et al. Nat Rev Clin Oncol 2014

The therapeutic index of chemotherapic agents



Tumor cells citotoxicity/ Myelosuppression

$TI = TD_{50} / ED_{50} \approx 1.5$

ImmuneStimulation/ Antiangiogenic activity

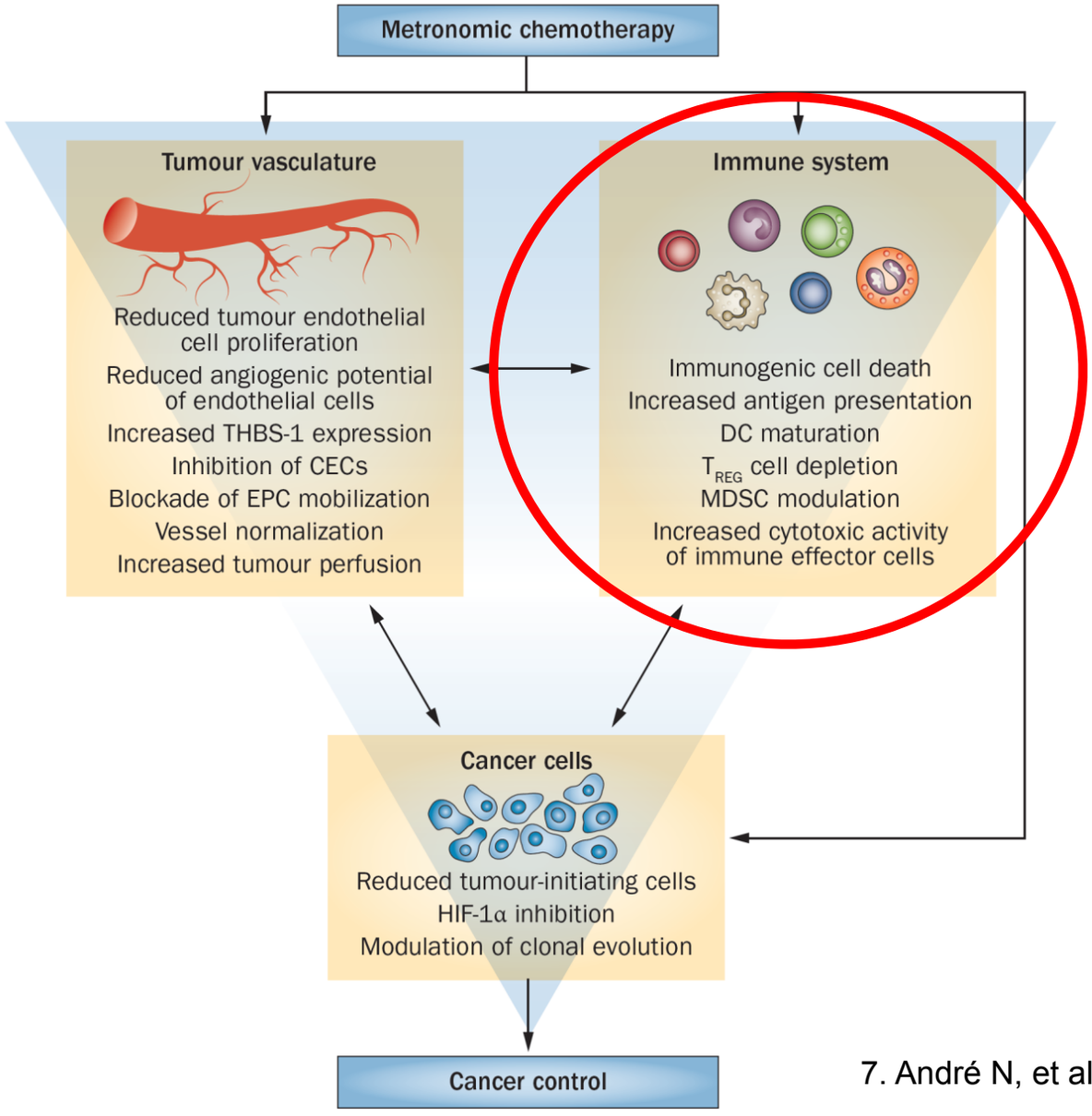
$TI = TD_{50} / ED50 \approx 5$

TD: toxic dose
ED: effective Dose

MTAs administered with a right dose, lower than MTD, are active on tumor vasculature and immune system

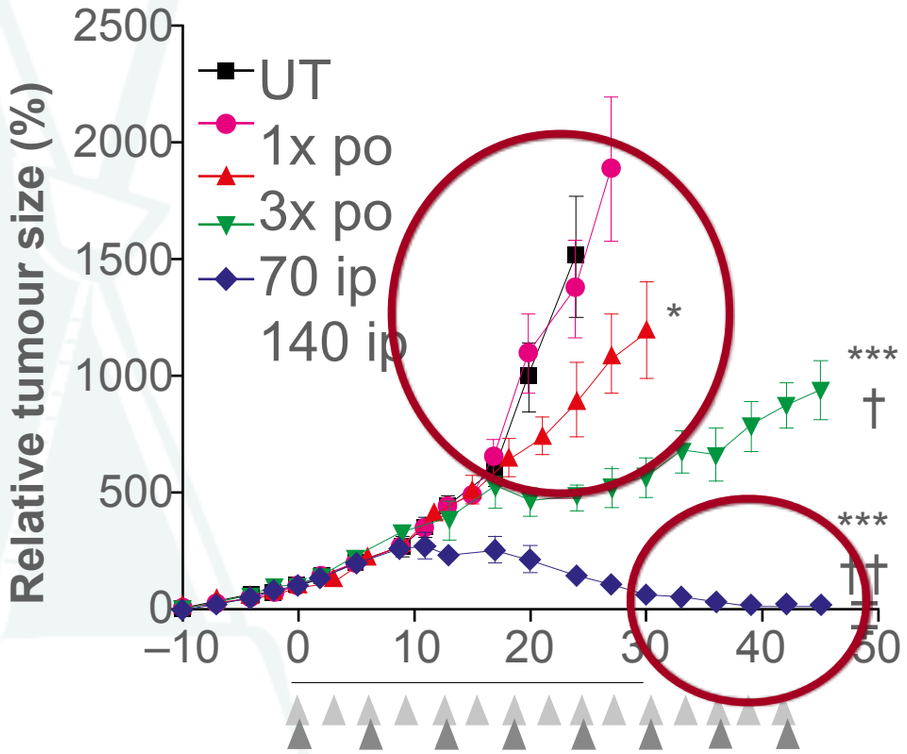
Patel JN et al. Cancer Chemother Pharmacol. 2015; Mross J Ca Ther Res 2012

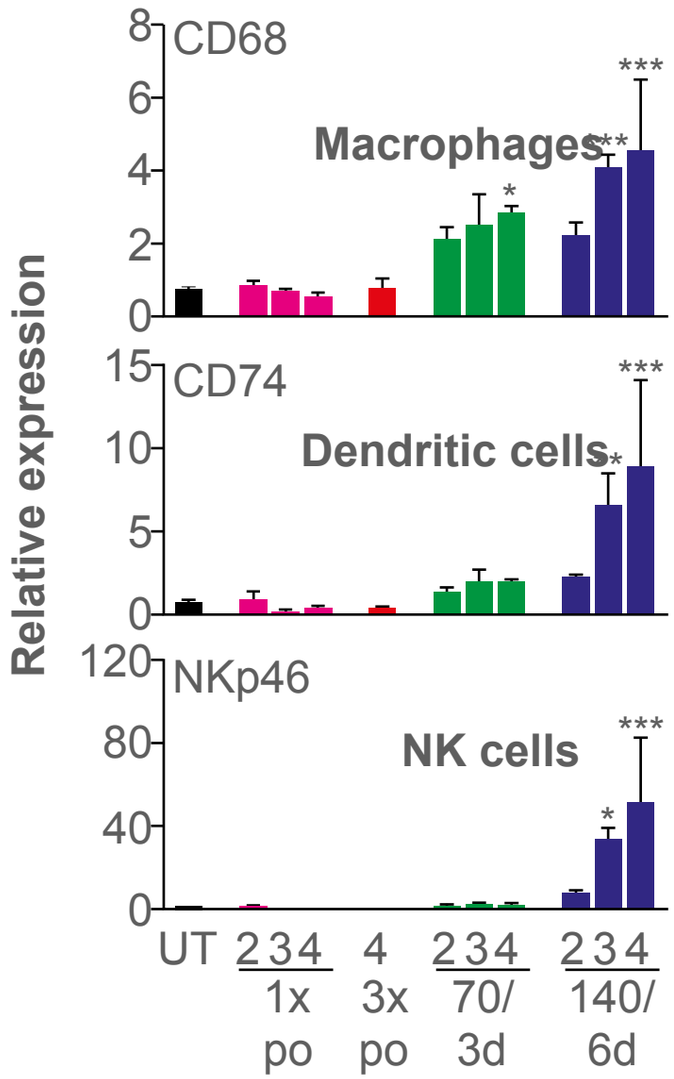
mCT: immuno-stimulation



7. André N, et al Nat Rev Clin Oncol,, 2014

Correlation between mCT& Immunity

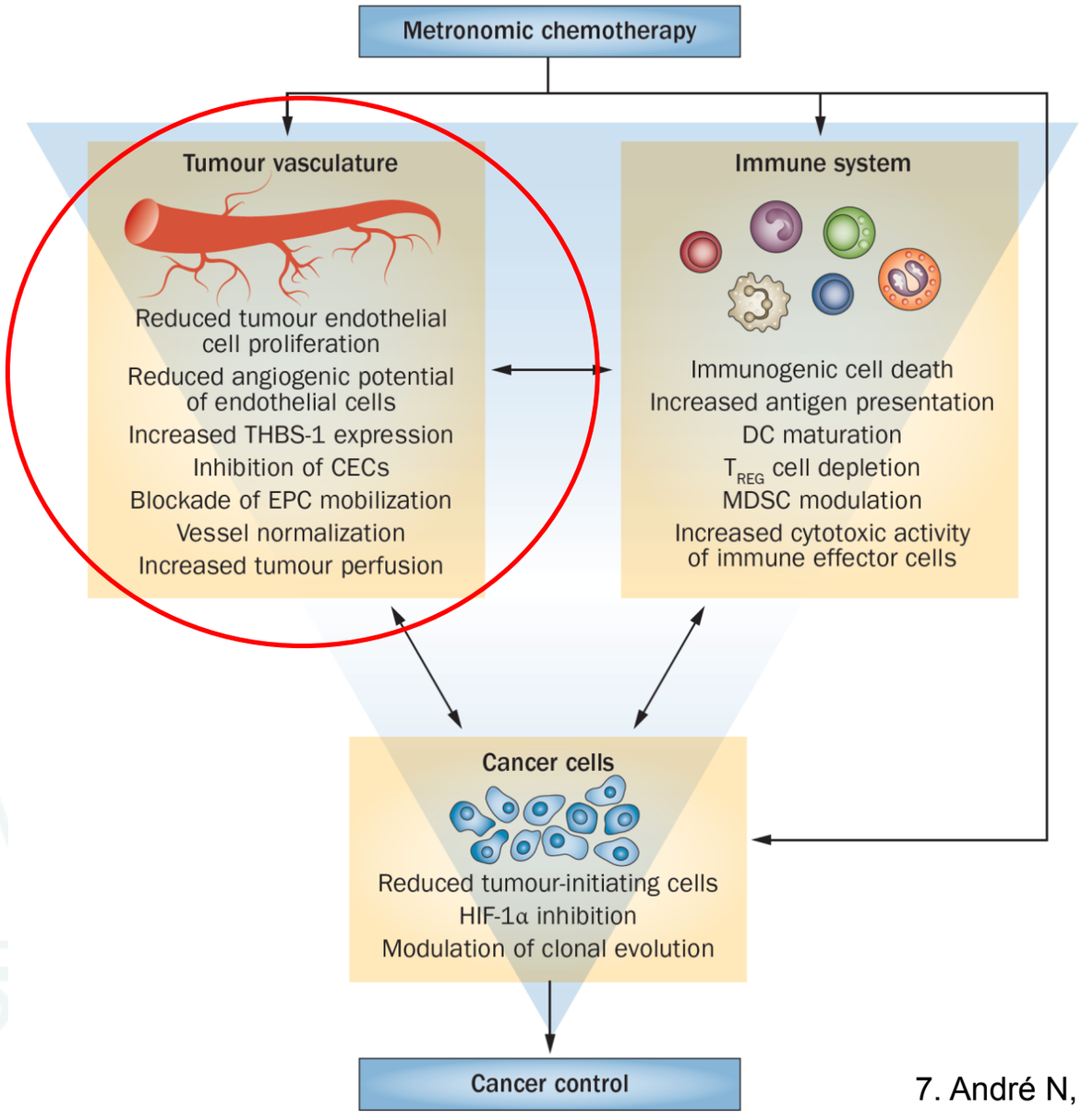




- *p<0.05; **p<0.01; ***p<0.001 vs. UT on Day 24
- †p<0 .01; ††p<0.001 vs 3× po schedule on Day 30
- ‡p<0.05 vs 70 ip schedule on Day 30
  ip = intraperitoneal injection; po = oral treatment; UT = untreated

Chen CS et al. Neoplasia

Metronomic chemotherapy: a multitarget therapy

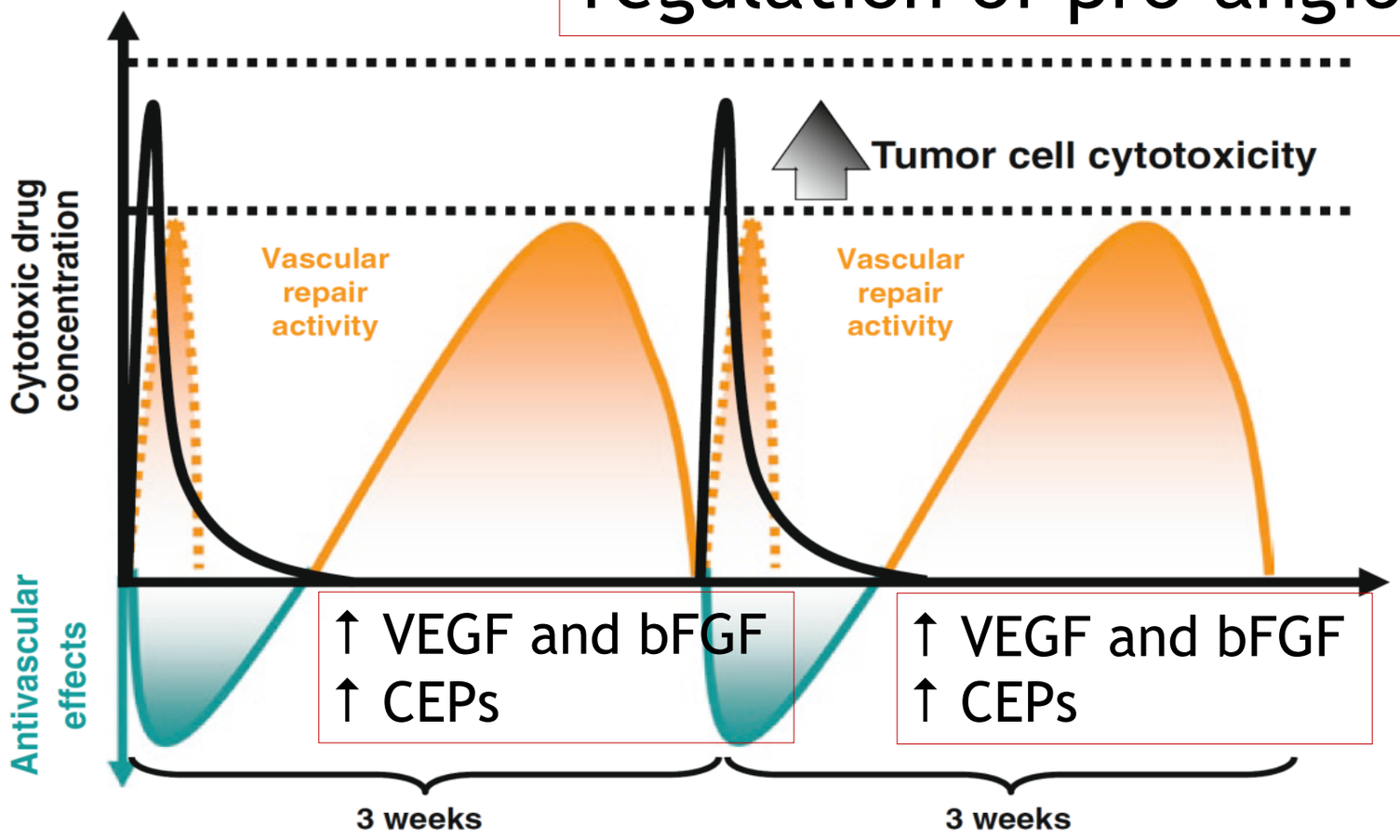


7. André N, et al Nat Rev Clin Oncol,, 2014

MTD Chemotherapy

MTD regimens

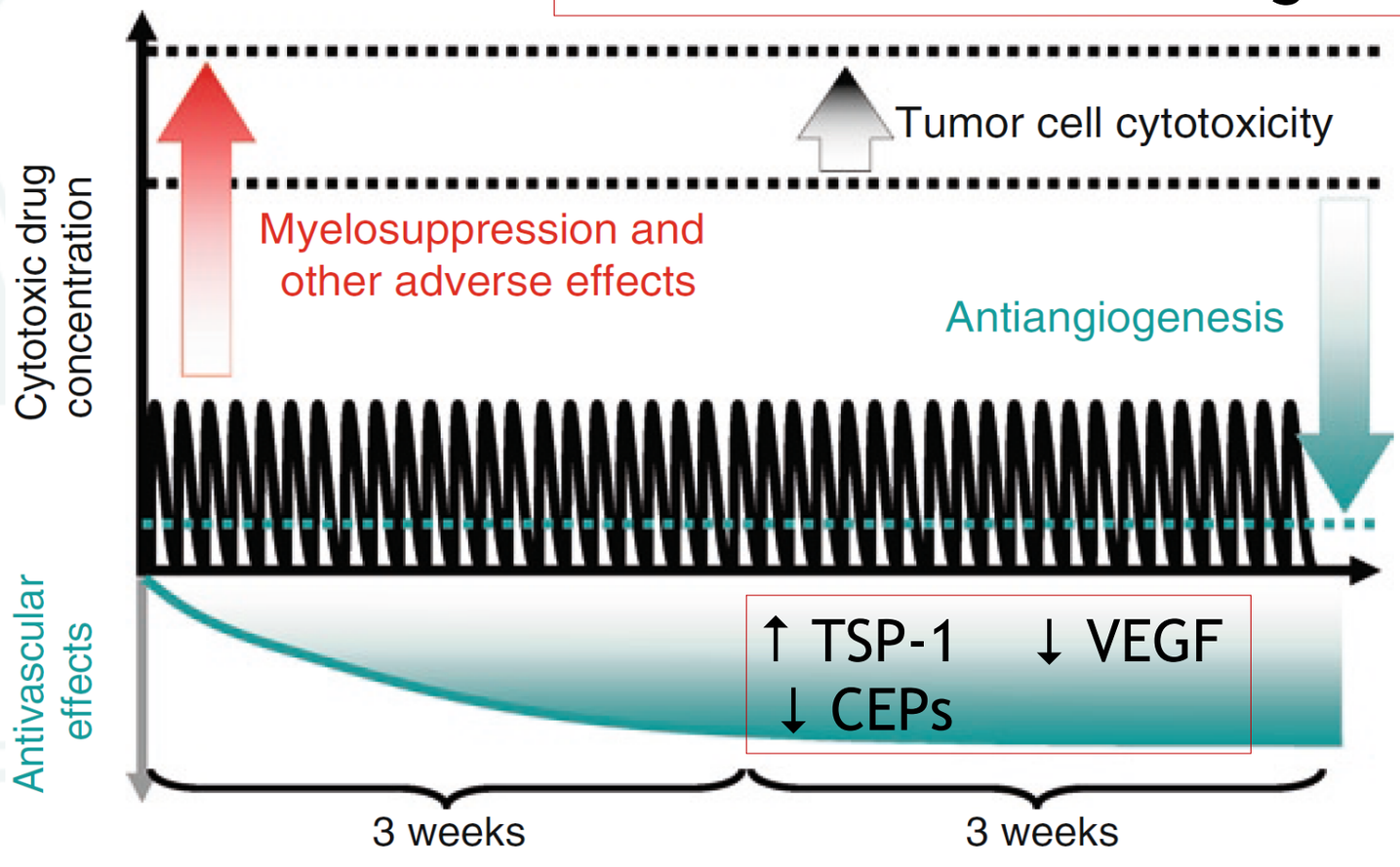
Vascular repair activity during the drug-free periods because of up-regulation of pro-angiogenic factors



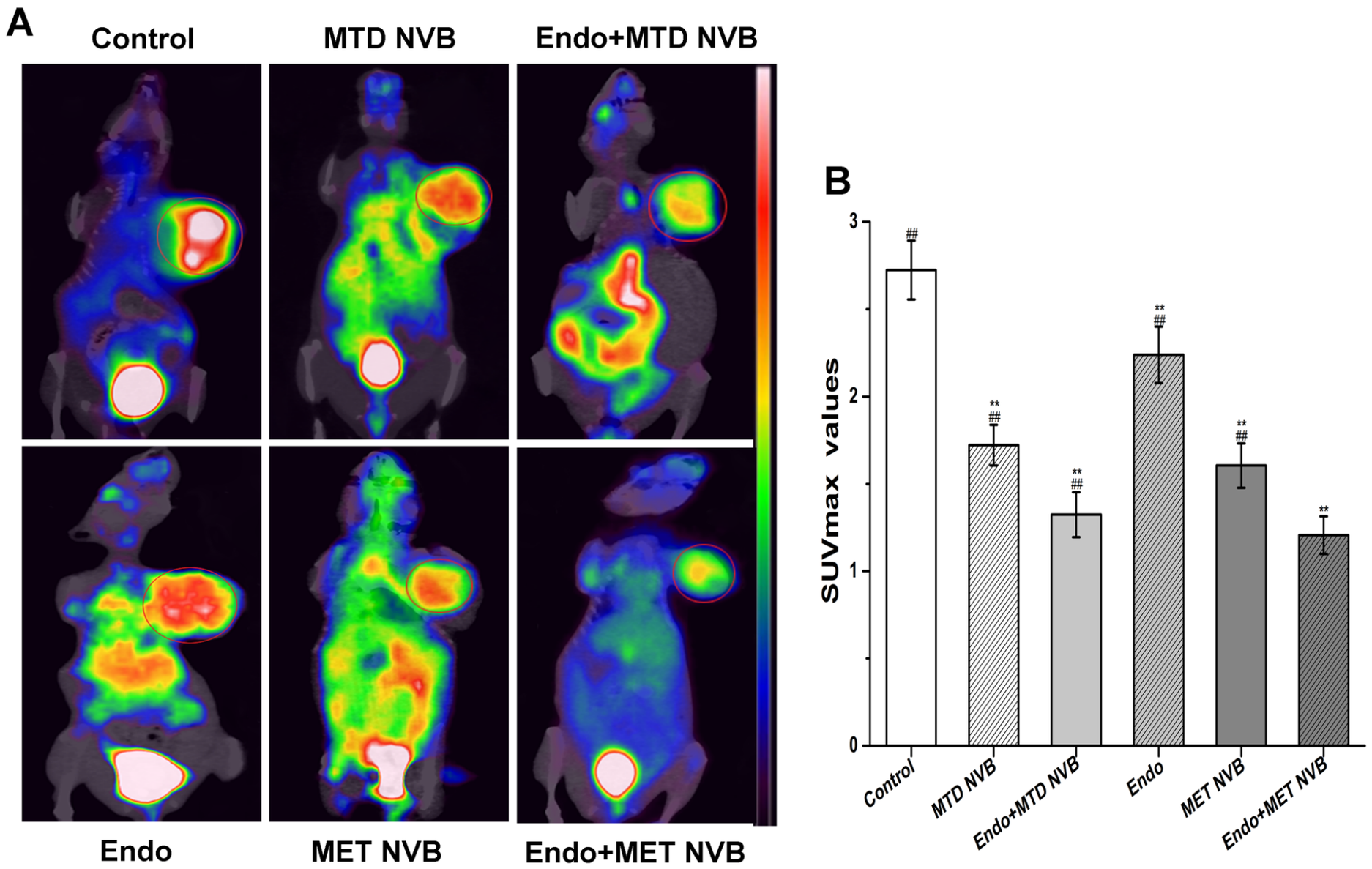
Emmenegger U, Chou A, Bocci G. 2010, Springer

Metronomic Chemotherapy

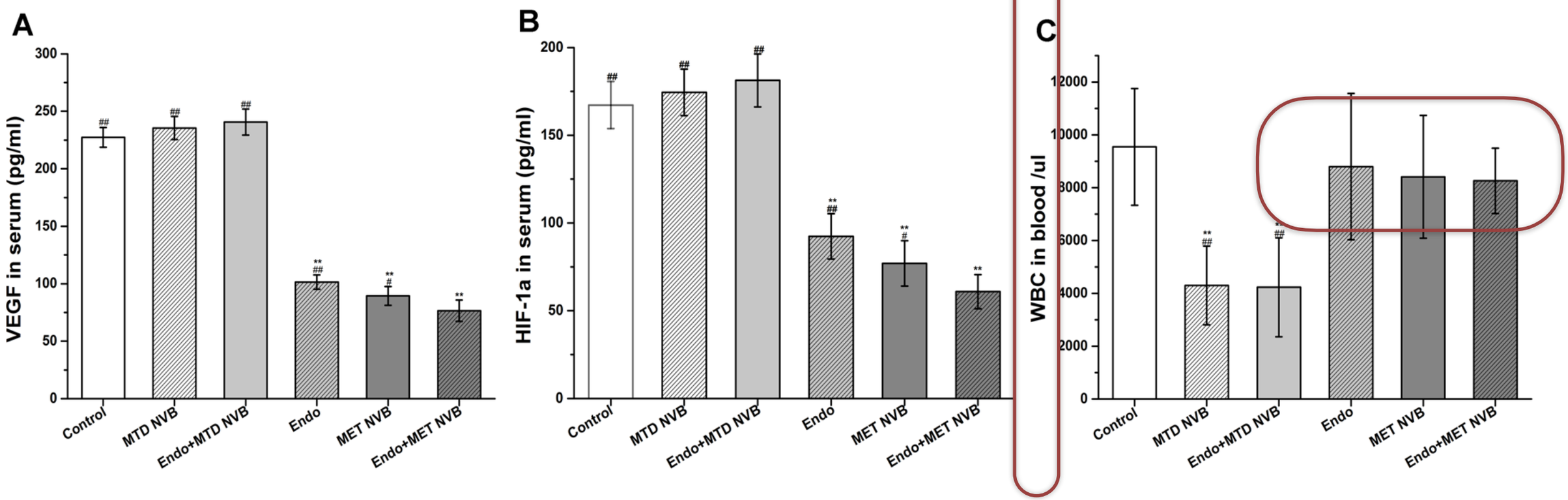
Metronomic administration → Increase of the antivascular effects by blocking the recovery of new vascularization without increasing adverse events



Emmenegger U, Chou A, Bocci G. 2010, Springer



Qin et al. BMC Cancer 2018



Qin et al. BMC Cancer 2018

Personal view #1

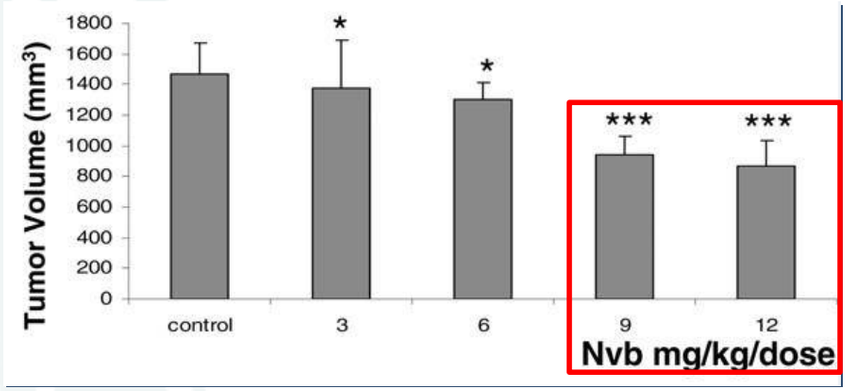
- Metronomic therapy is not chemotherapy!

- Metronomic therapy is an anti-angiogenic and immunological treatment!

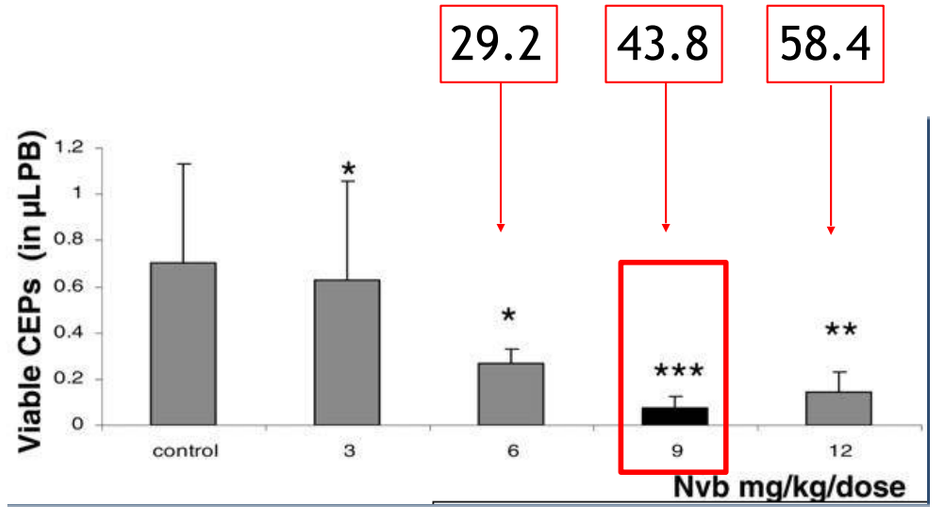
How metronomic

Pharmacological background

Optimal biological dose of metronomic VNR
CEPs as pharmacodynamic marker



MDA-MB-231/LM2-4 human breast cancer treated with **oral VNR administered by gavage 3 times a week, at the indicated doses** (1)

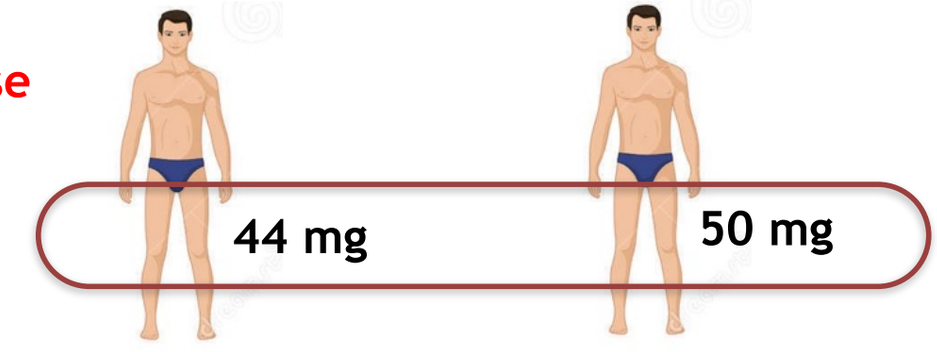


Black columns represent the optimal therapeutic doses in each case that **induce the most significant decline in viable CEP levels and a reduction in tumor volumes, with minimal or no toxicity** (1)

Shaked Y et al. Blood 2005

9 mg/kg

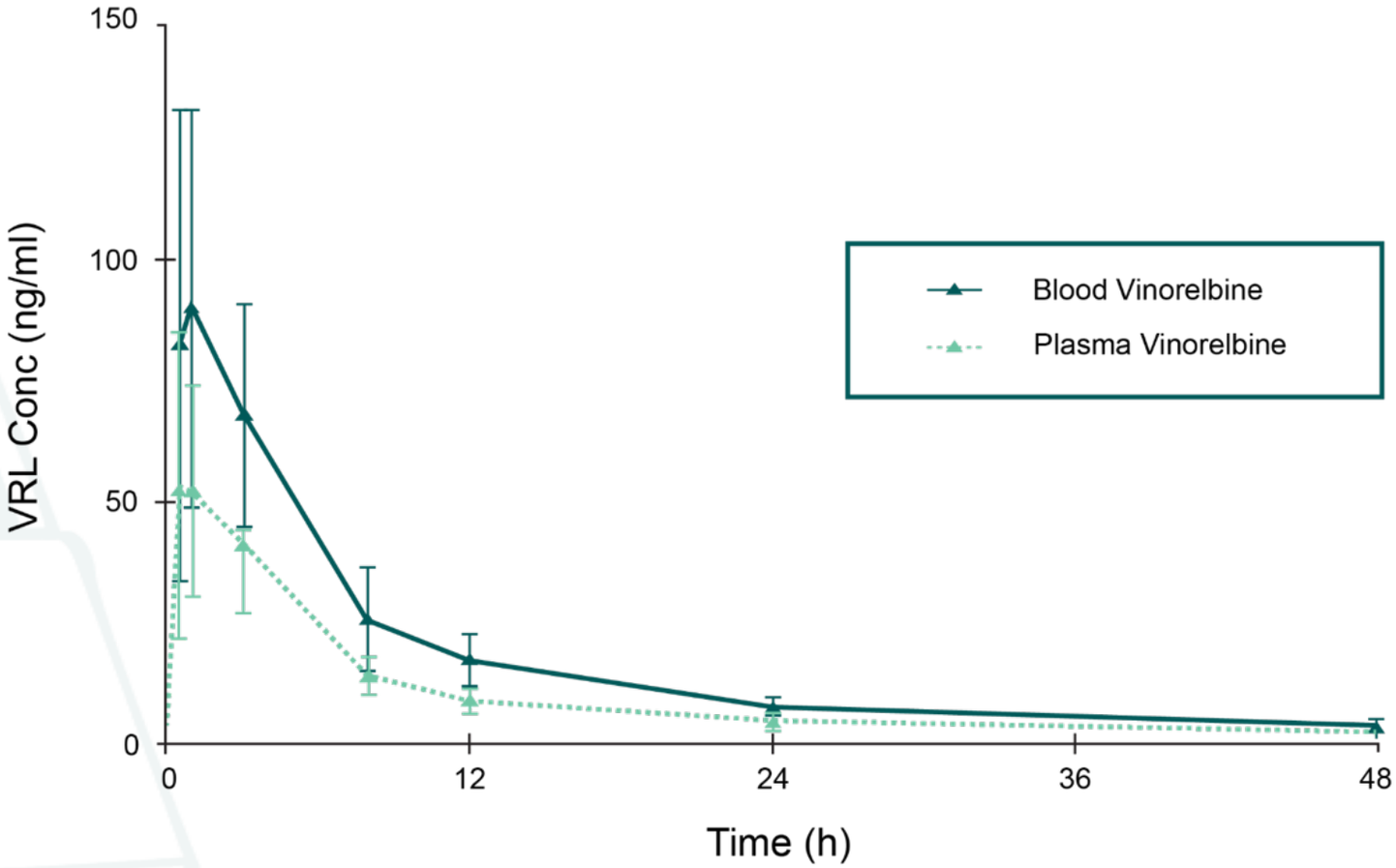
human equivalent dose (HED)



BSA 1.6 **BSA 1.8**

Reagan-Shaw, et al. FASEB 2007

mVNR AS SINGLE-AGENT CT: RATIONALE FOR TIW CONTINUOUSLY ORAL NAVELBINE ADMINISTRATION



Elimination half-life: about 40 hours

Bonneterre, Piccart. Annals of Oncology 2001

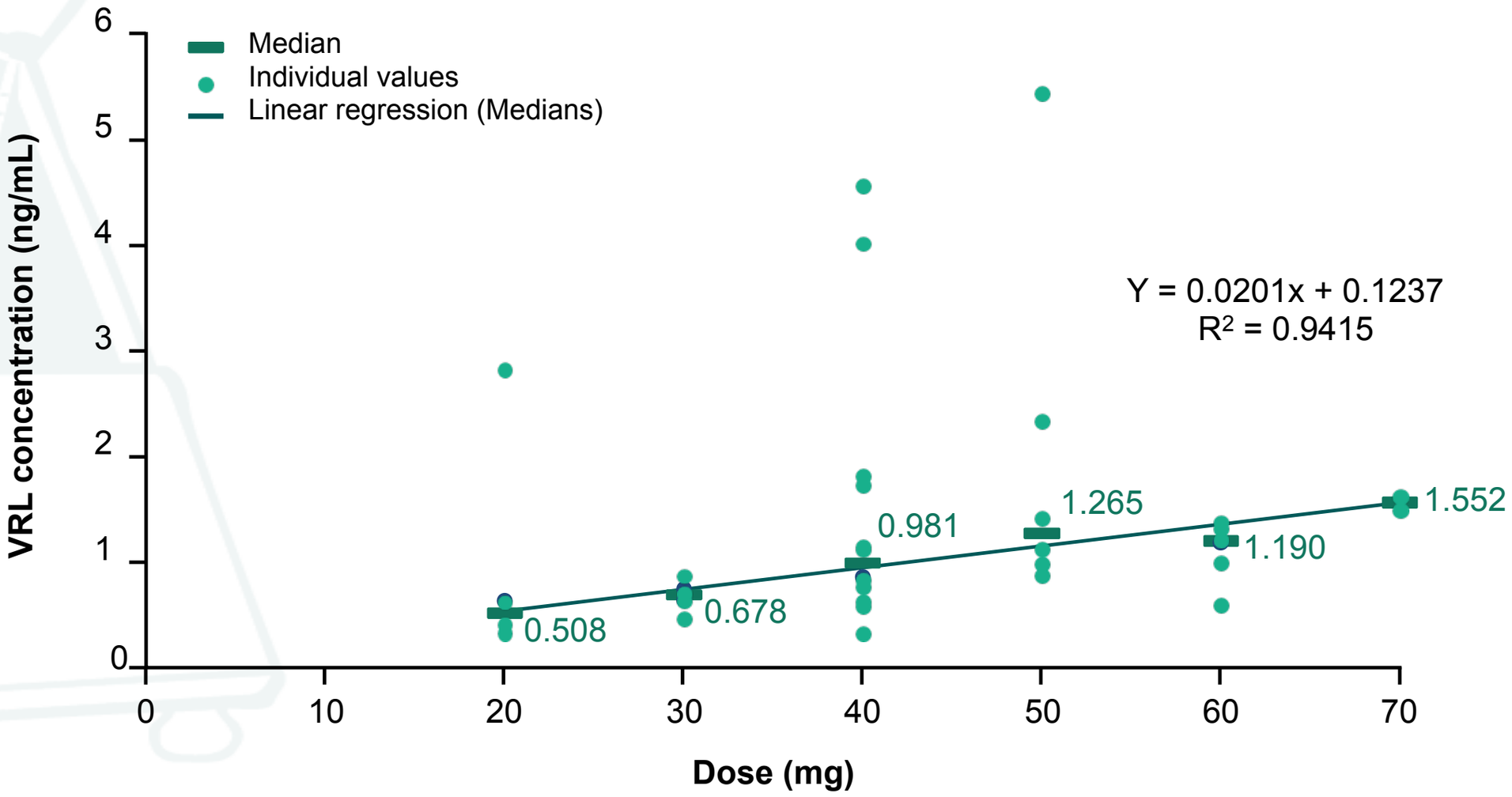
PHARMACOKINETICS OF mVNR

Standard dose 30 mg/m^2 i.v. → C_{max} 1130±636 ng/ml

Leveque et al. Clin Pharmacokinet 1996,31: 184

vinorelbine displayed
linear pharmacokinetics

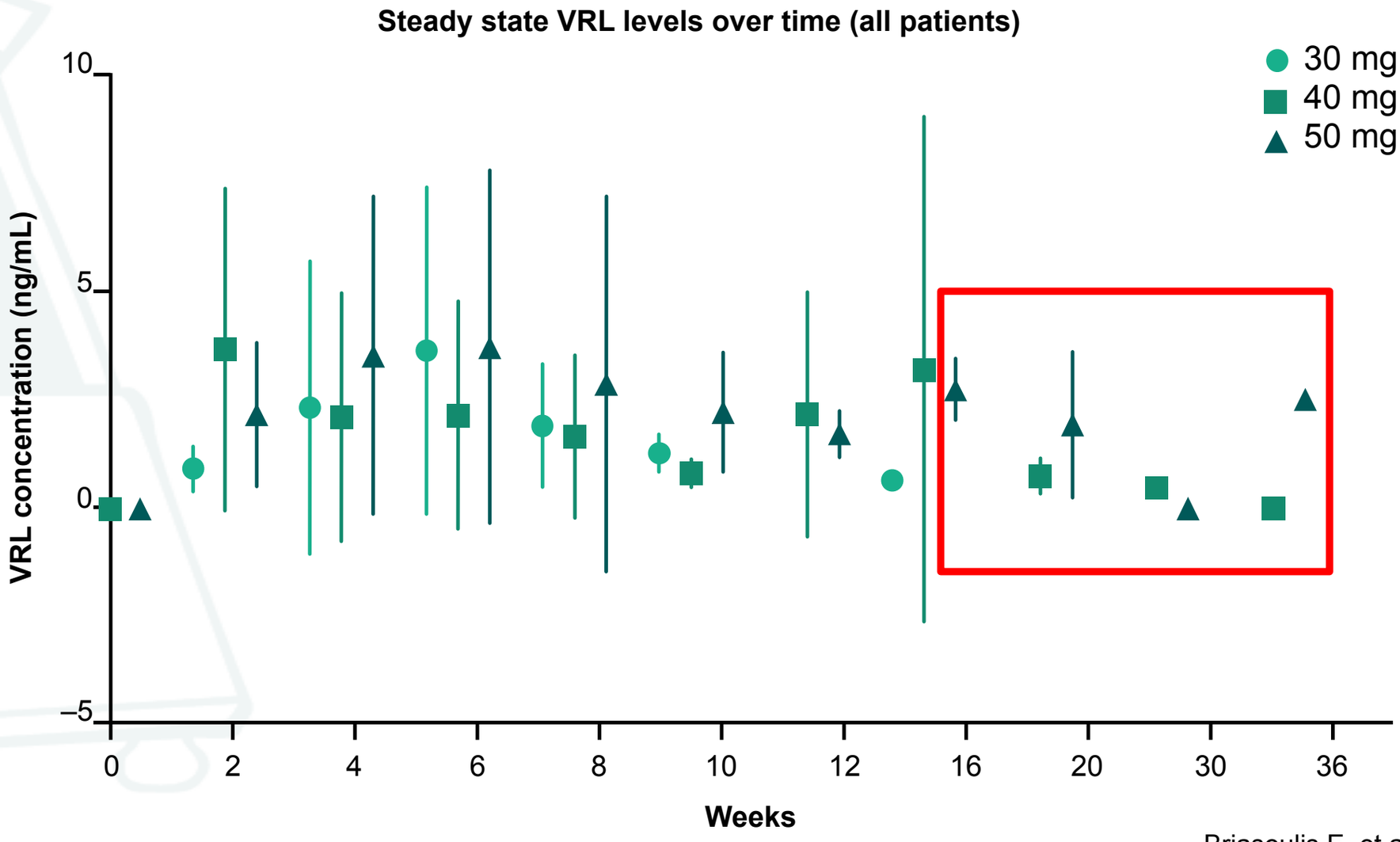
VNR $T_{1/2}$= 40h



Briasoulis E. et al, Clin Cancer Res 2009

STEADY-STATE VNR CONCENTRATIONS FOLLOWING METRONOMIC ORAL DOSING

the blood C_{ss} for vinorelbine was attained after 14 days of treatment, and this compound did not show **any evidence of accumulation** during months of successive treatment



Briasoulis E. et al, BMC Cancer 2013

Personal view #2

- Lots of data with mVNR showing a linear and foreseeable pharmacokinetics!

- Strong biological/pharmacological background for dosing in human!

When metronomic First-line setting as ideal

mVNR: Phase IA Study

- **62 Patients with advanced refractory cancer (14 NSCLC)**
- **Schedule: escalating doses 40-70 mg total dose 3 times a week continuously**

Briasoulis E. et al, Clin Cancer Res 2009

mVNR: Phase IA Study

- **19 Patients with advanced refractory cancer (14 NSCLC)**
- **Schedule: escalating doses 20-50 mg total dose 3 times a week continuously**

Rajdev L et al. Cancer Chemother Pharmacol 2011

mVNR: Phase IB Study

- **73 Patients with advanced refractory cancer (31 NSCLC)**
- **Schedule: 30 or 40 or 50 mg total dose 3 times a week continuously**

Briasoulis E. et al, BMC Cancer 2013

MOVE TRIAL

Camerini *et al. BMC Cancer* (2015) 15:359
DOI 10.1186/s12885-015-1354-2

BMC Cancer

RESEARCH ARTICLE Open Access

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)

Andrea Camerini*, Cheti Puccetti, Sara Donati, Chiara Valsuani, Maria Cristina Petrella, Gianna Tartarelli, Paolo Puccinelli and Domenico Amoroso

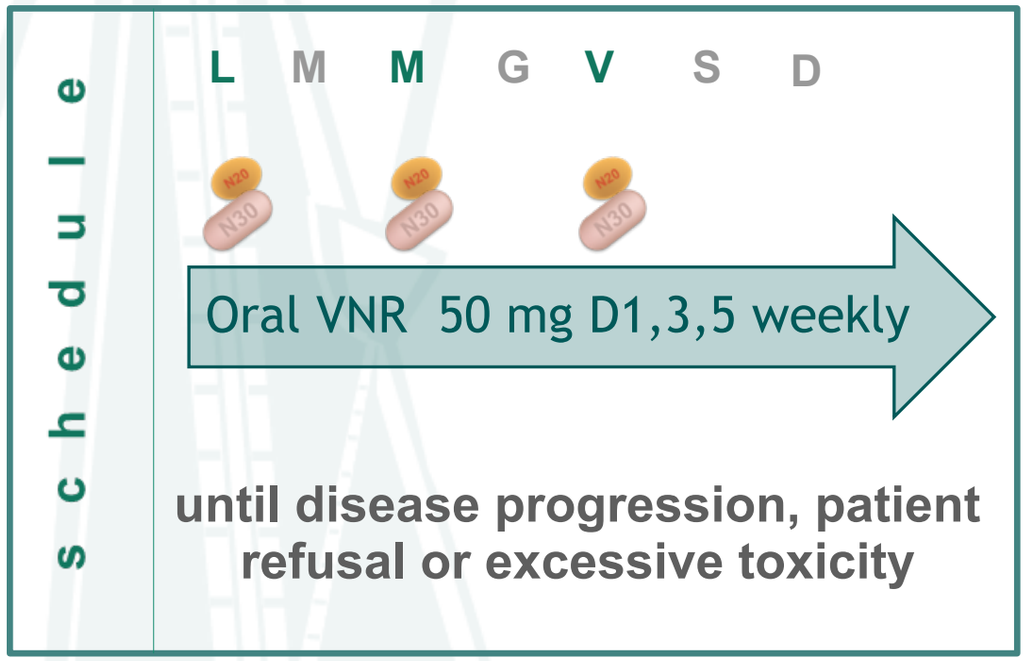


Table 1 Baseline study population characteristics (n = 43)	
Age (yrs)	
median (range)	80 (70 - 92)
Sex (M/F)	36/7
ECOG PS (0/1/2)	0/16/27
Stage (IIIB/IV)	16/27
Smoke (never/past/current)	1/23/19
Serious co-morbid illnesses	
median (range)	3 (0 - 6)
Histology (n/%) Squamous cell carcinoma Adenocarcinoma Large-cell carcinoma Undifferentiated	 24/43 (55.8%) 11/43 (25,6%) 4/43 (9,3%) 4/43 (9.3)

Primary end points:

- Clinical Benefit (CR+PR+SD>12wks)
- Safety

Secondary end points:

- TTP
- OS
- QoL

Camerini et al, BMC Cancer 2015

Efficacy

Table 2 Clinical efficacy data at final analysis on 43 patients	
median Number of cycles [range]	5 [1 – 21]
Treatment response (n - %) CR PR SD PD	 1/43 - 2.3% 7/43 - 16.3% 17/43 - 39.5% 18/43 - 41.9%
Clinical benefit (CR+PR+SD>12)	25/43 - 58.1%
ORR	8/43 - 18.6%
mTTP [range] months	5 [2 - 21]
mOS [range] months	9 [3 - 29]
Percentage of alive patients (n - %) year 1 year 2	 16/43 - 37.2% 4/43 - 9.3%

Safety

Treatment-related toxicities at final analysis (n = 43)		
Toxicity NCI-CTCv3	All grade	Grade 3-4
Non-hematological Fatigue Nausea Vomiting Diarrhea Mucositis Sensorial neuropathy	 32.4% 8.0% 5.0% 10.5% 4.5% 2.4%	 0.1%* 0% 0% 0.1%* 0.1%* 0%
Hematological Anemia Leukopenia Neutropenia	 44.0% 3.2% 4.0%	 0.1%* 0% 0.1%*

*Rounded to 0.1%

Prospective clinical trials with metronomic Vinorelbine

Author/ Year	Phase/ Line	Schedule	n	RR/DCR* (%)	mPFS (mo)	mOS (mo)
Briasoulis 2009	Phase IA Pretreated	**mVNR** 20-70 mg D1,3,5 /weekly	62 (**14 NSCLC**)	15 / 47	ND	ND
Briasoulis 2013	Phase IB I, II, III lines	**mVNR** 30 or 40 or 50 mg D1,3,5 /weekly	73 (**31 NSCLC**)	5.5 / ND	Median TTF 8 weeks	ND
Kontopodis 2013	Phase II Pretreated	**mVNR** 50 mg D1,3,5 /weekly	46	11 / 30.5	2.2	9.4
Camerini 2015	Phase II Ist line	**mVNR** 50 mg D 1,3,5 /weekly	43	CB** 18.6 / 58**	TTF: 5	9
Lumachi 2016	Phase II Ist line	**mVNR** 40 or 50 mg D 1,3,5 / weekly	20	20 / 45	TTP: 3	7.8
Tzimopoulos 2016	Phase II Ist line	**mVNR** 40 mg D 1,3,5 /weekly	34	20 / 60	PFS: 7	NR
De Juliis 2016	Phase II Ist line	**mVNR** 50 mg D 1,3,5 /weekly	16	81 / 100	PFS: 6	15
Mencoboni 2017	Phase II Ist line	**mVNR** 50 mg D 1,3,5 /weekly	76	14.5 / 50	3	8
Banna 2018	Phase II I-n line	**mVNR** 30 mg D 1,3,5 /weekly	50	8 / 32	2.7	7.3
Bilir 2018	Phase II Ist line	**mVNR** 30 mg D 1,3,5 /weekly	35	26 / 69	4	7

**CB (Clinical Benefit): CR +PR+SD > 12 weeks

*DCR (Disease Control Rate): CR+PR+SD

NR: not reported

Focus on safety of metronomic vinorelbine

Author/ Year	Phase/ Line	Schedule	n	RR/DCR* (%)	mPFS (mo)	mOS (mo)	G3/4 Tox
Camerini 2015	Phase II Ist line	**mVNR** 50 mg D 1,3,5 / weekly	43	CB** 18.6 / 58**	TTF: 5	9	0,5%
Lumachi 2016	Phase II Ist line	**mVNR** 40 or 50 mg D 1,3,5 /weekly	20	20 / 45	TTP: 3	7.8	0%
Tzimopoulos 2016	Phase II Ist line	**mVNR** 40 mg D 1,3,5 / weekly	34	20 / 60	PFS: 7	NR	0%
De Juliis 2016	Phase II Ist line	**mVNR** 50 mg D 1,3,5 / weekly	16	81 / 100	PFS: 6	15	0%
Mencoboni 2017	Phase II Ist line	**mVNR** 50 mg D 1,3,5 / weekly	76	14.5 / 50	3	8	7%
Banna 2018	Phase II I-n line	**mVNR** 30 mg D 1,3,5 / weekly	50	8 / 32	2.7	7.3	11%
Bilir 2018	Phase II Ist line	**mVNR** 30 mg D 1,3,5 / weekly	35	26 / 69	4	7	6%

Differences in toxicities among treatments*

Toxicity	MTD CT	Targeted	Immuno	Metronomic
Neutropenia / thrombocytopenia	+++	-	-	+
Anaemia	+++	-	-	-
Diarrhoea / constipation	+	++	+++	+
Hypothyroidism	-	+	++	-
Pneumonitis	-	+	++	-
Fatigue	++	++	++	+
Rash	+	+++	++	+
Nausea	+++	+	+	+
Vomiting	+++	+	+	+
Alopecia	+++	+	-	+

*Adapted from IASLC update: Immunotherapy for Lung Cancer 2016 (M. O'Brien) 2016, 01, 13

Personal view #3

- Metronomic vinorelbine is a real option in first-line setting!

- Safety is a cornerstone of mVNR!

Who metronomic

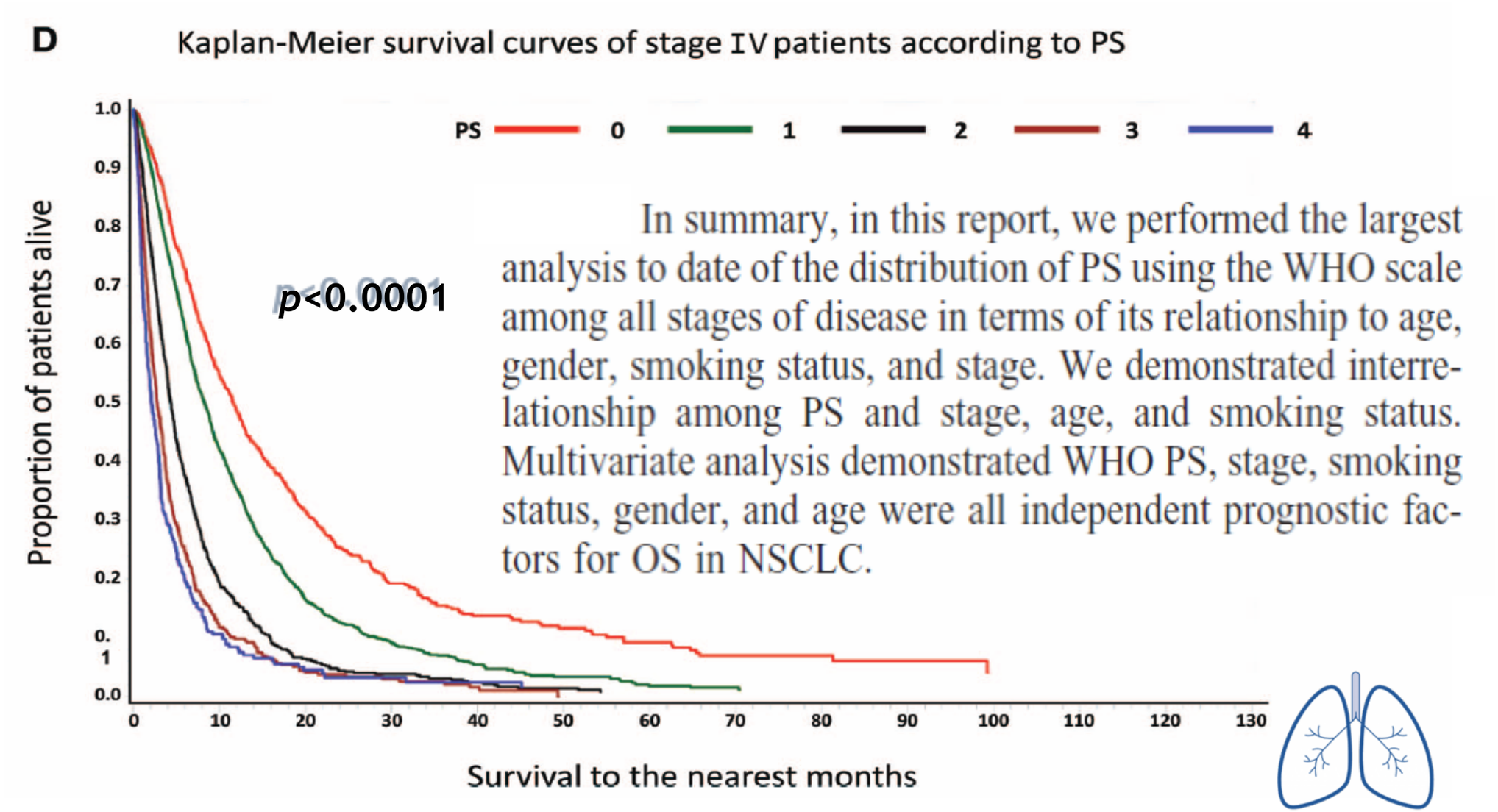
Patient selection

The (half) dark side

The dark side of the moon Pink Floyd *1973*

Performance Status and Smoking Status Are Independent Favorable Prognostic Factors for Survival in Non-small Cell Lung Cancer

A Comprehensive Analysis of 26,957 Patients with NSCLC



In summary, in this report, we performed the largest analysis to date of the distribution of PS using the WHO scale among all stages of disease in terms of its relationship to age, gender, smoking status, and stage. We demonstrated interrelationship among PS and stage, age, and smoking status. Multivariate analysis demonstrated WHO PS, stage, smoking status, gender, and age were all independent prognostic factors for OS in NSCLC.

T Kawaguchi et al, JTO 2010

VOLUME 26 · NUMBER 1 · JANUARY 1 2008

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Age and Comorbidity As Independent Prognostic Factors in the Treatment of Non–Small-Cell Lung Cancer: A Review of National Cancer Institute of Canada Clinical Trials Group Trials

Timothy R. Asmis, Keyue Ding, Lesley Seymour, Frances A. Shepherd, Natasha B. Leighl, Tim L. Winton, Mario Whitehead, Johanna N. Spaans, Barbara C. Graham, and Glenwood D. Goss

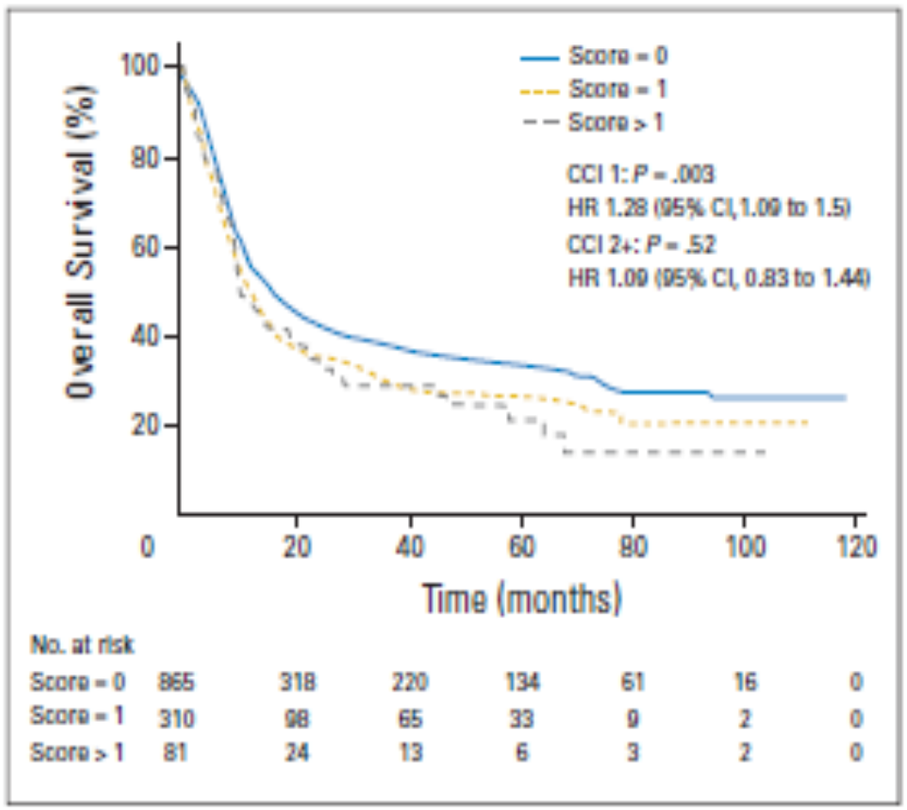


Fig 2. Overall survival by Charlson comorbidity index (CCI) score. HR, hazard ratio.

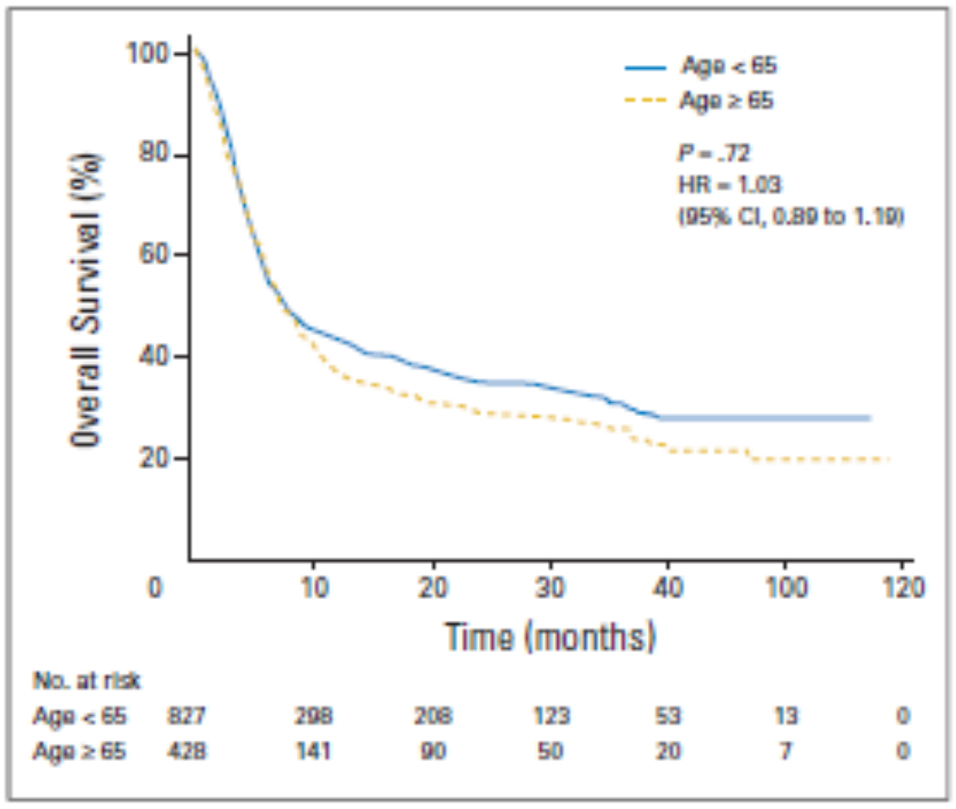
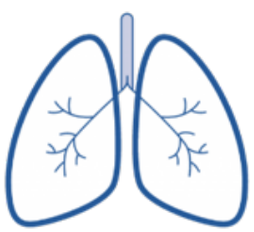


Fig 1. Overall survival by age. HR, hazard ratio.

Conclusion

In these large, randomized trials, the presence of comorbid conditions (CCIS ≥ 1), rather than age more than 65 years, was associated with poorer survival.

J Clin Oncol 26:54-59. © 2008 by American Society of Clinical Oncology



Review

Treatment of Unfit Patients With Advanced Non–Small-Cell Lung Cancer: Definition Criteria According an Expert Panel

Filippo De Marinis,[1] Emilio Bria,[2] Paul Baas,[3] Marcello Tiseo,[4] Andrea Camerini,[5] Adolfo Gino Favaretto,[6] Cesare Gridelli[7]

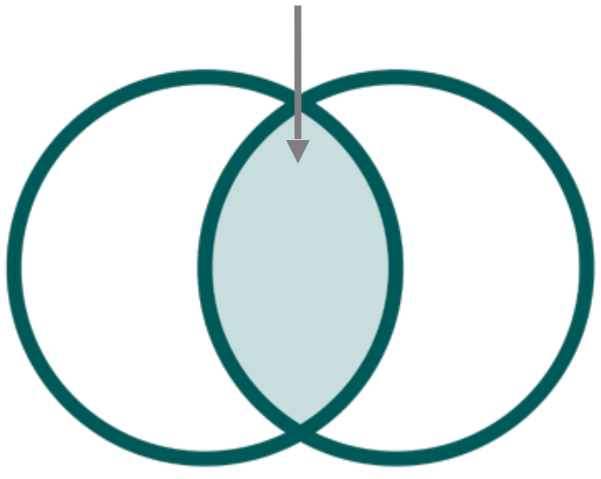
Table 2 Criteria to Define Patients With Non–Small-Cell Lung Cancer Unfit for Chemotherapy

Factor	Unfit for Cisplatin-Based Chemotherapy	Unfit for Carboplatin-Based Chemotherapy	Unfit for Single-Agent Chemotherapy
Age	Not any cutoff, but alert if >75 years, on the basis of unexpected toxicities, competitive risks, and relative benefit of chemotherapy	Not any cutoff, but alert if >80 years, on the basis of: unexpected toxicities, competitive risks, and relative benefit of chemotherapy	Not any cutoff
PS	PS >1 according to ECOG	PS >2 according to ECOG	PS >2 according to ECOG
Renal function	Creatinine clearance (measured or calculated) <60 mL/min	No absolute restriction; alert if creatinine clearance (measured or calculated) <45 mL/min	No absolute restriction, unless specific drug restriction
Heart failure	NYHA >I	NYHA >II	NYHA >II
Previous cerebrovascular event	Exclusion criteria	No absolute restriction	No absolute restriction
Uncontrolled HTN	Exclusion criteria for severe uncontrolled HTN	No absolute restriction	No absolute restriction
Neuropathy	CTCAE v4 >1: exclusion criteria	No absolute restriction	No absolute restriction, unless specific drug restriction
Hearing loss	CTCAE v4 >1: exclusion criteria	No absolute restriction	No absolute restriction
Symptomatic brain metastases	Exclusion criteria due to forced hydration	No absolute restriction	No absolute restriction
Severe psychiatric disorders	Exclusion criteria due to low compliance to toxicity	No absolute restriction	No absolute restriction
Absence of caregiver support	Exclusion criteria due to the high chance to need of home supportive care	No absolute restriction	No absolute restriction

Abbreviations: CTCAE = Common Toxicity Criteria for Adverse Events; ECOG = Eastern Cooperative Oncology Group; HTN = hypertension; NYHA = New York Heart Association; PS = performance status.

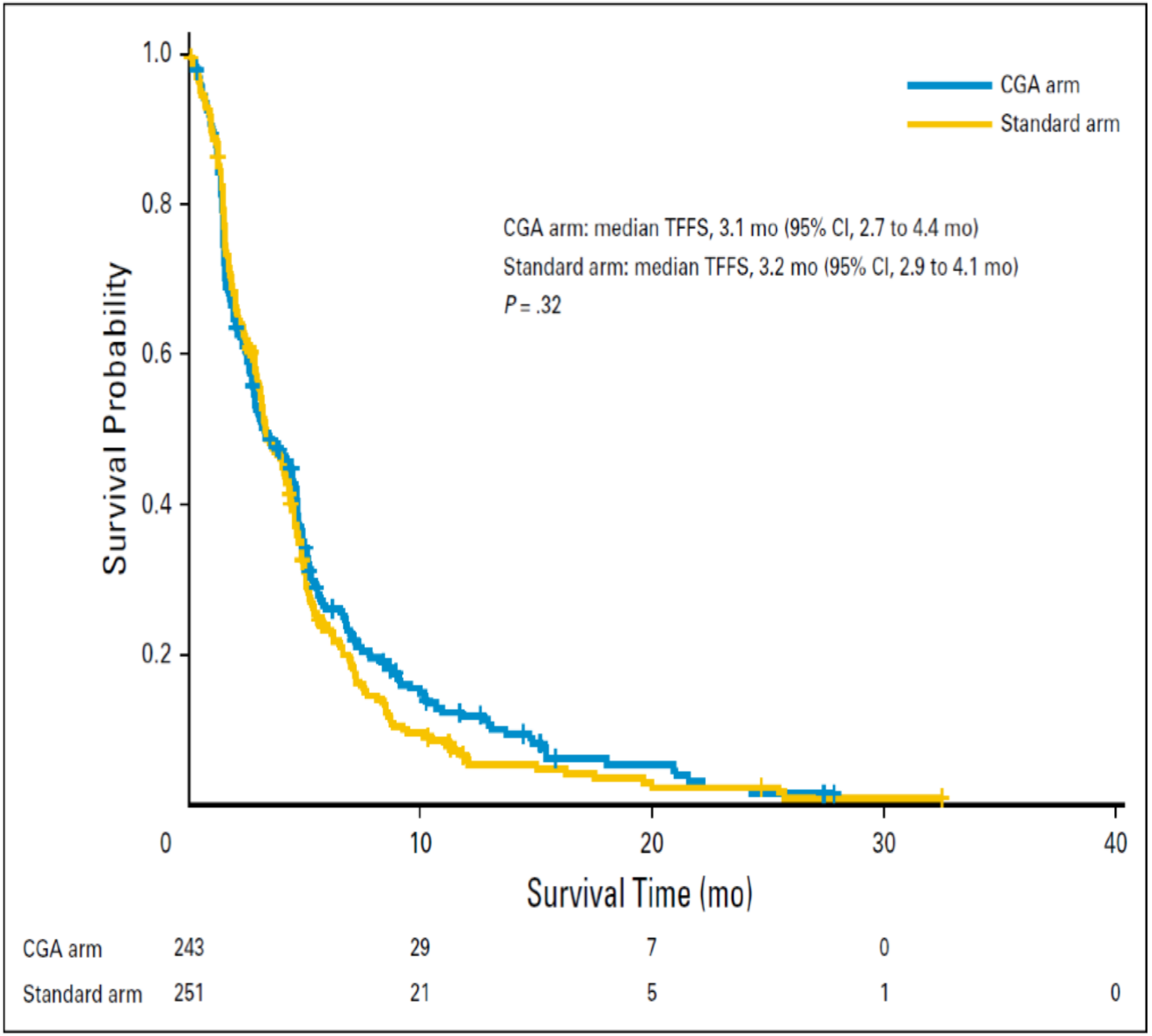
SUMMARY OF “FIT MonoCT” CHARACTERISTICS

- Elderly (age > 75-80y)
- ECOG PS > 1
- Heart Failure (NYHA > 1)
- Renal Failure (CrCl < 60-45 mL/min)
- Neuropathy/Earing loss (CTCAE v4 > 1)
- Bone Marrow “fragility”



Co-morbidity

De Marinis et al, Clin Lung Cancer 2015



Corre et al. JCO 2016

Elderly (Low PS)
all wt PDL1<50%

Screening

G8[1]

VES-13[2]

Flemish[3]

CGA[4]

Age/PS[5]

BSC — 20%

Single — 40%

Direct[6-8] treatment

Single — 40%

Doublet

(1) Bellera et al. *Ann Oncol* 2012
(2) Saliba et al. *J Am Geriatr Soc* 2001
(3) Braes et al. *Age Ageing* 2009
(4) Wildiers et al. *JCO* 2014
(5) Corre et al. *JCO* 2016
(6) Extermann et al. *Cancer* 2012
(7) De Marinis et al. *Clin Lung Cancer* 2015
(8) Hurria et al. *JCO* 2011

Personal view #4

- We can offer different treatment options in elderly and low-Ps patients!

- Treatment should be tailored based on (molecular) clinical items helped by scores!

What's new with metronomic 2018/19 clinical data

Metronomic vinorelbine “Pipeline”

Chemo-switch maintenance

MANILA (mVNR maintenance)

complete

MTD vs mVNR

TEMPO-LUNG Study mVNR vs VNR

complete

Real-life experience

Metanalysis

complete

UNFIT-Oss

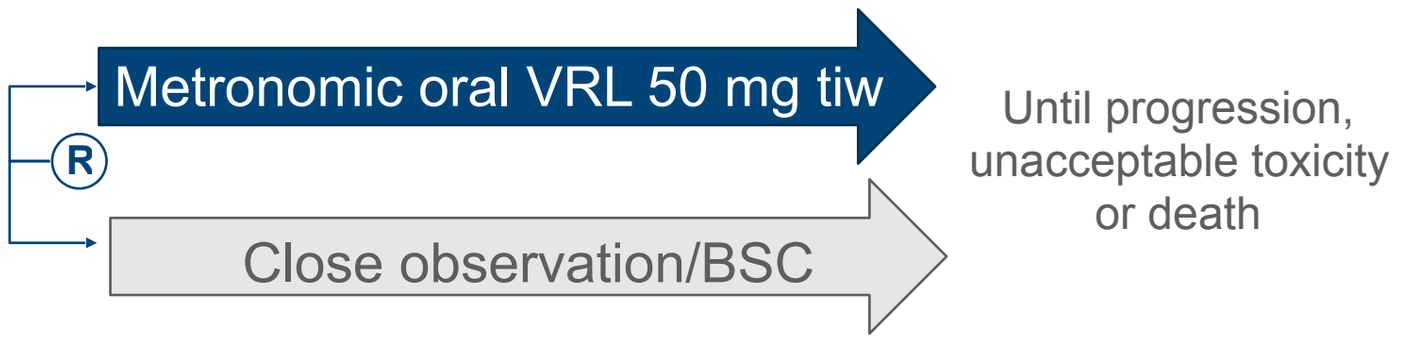
ongoing

MOON Oss

complete

Metronomic oral VRL as chemo-swicth maintenance (ONC-MANILA study)

Estimated enrolment: 120 patients with stage IIIB/IV NSCLC and stable disease after prior 1st-line platinum-based chemotherapy



- Primary endpoint: PFS
- Key secondary endpoints
  - OS
  - ORR
  - Duration of response
  - Duration of post-progression survival
  - Quality of life
  - Safety

http://clinicaltrials.gov/show/NCT02176369

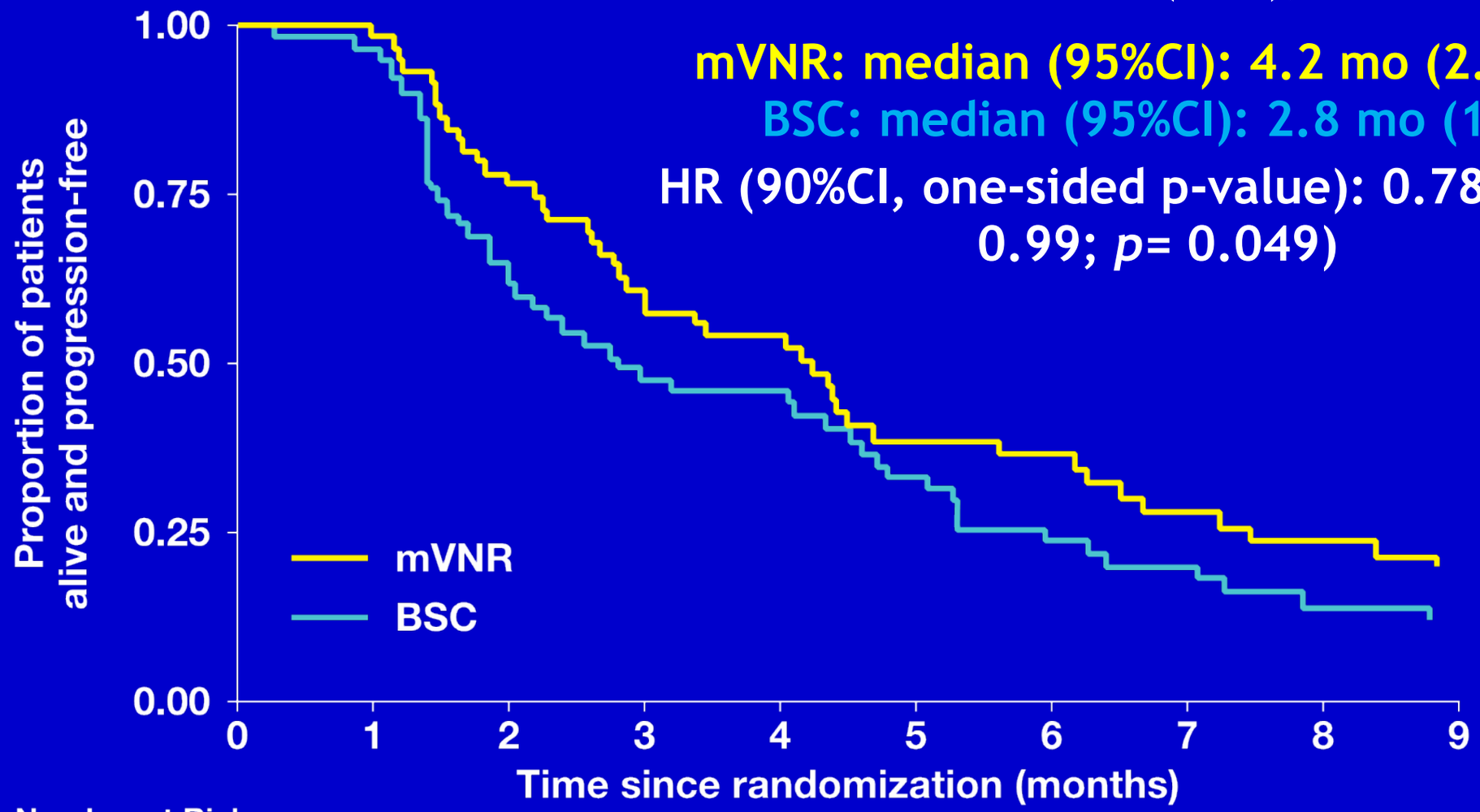
MA.NI.LA. : Progression Free Survival ITT

PFS events: VNR 51/61 (84%); BSC 54/59 (92%)

mVNR: median (95%CI): 4.2 mo (2.8-5.6)

BSC: median (95%CI): 2.8 mo (1.9-4.6)

HR (90%CI, one-sided p-value): 0.78 (0.58 - 0.99; *p*= 0.049)



Number at Risk

mVNR	61	34	17	9
BSC	59	27	13	6

mVNR in unfit* NSCLC TEMPO LUNG Trial

Accrual complete

•RANDOMISATION

- •ARM A:
- •NAVELBINE 60 mg/m2 weekly, for cycle 1, then 80 mg/ m2 weekly for subsequent cycles according to haematological tolerance and investigator's decision.
- •Until disease progression

- •ARM B:
- •NAVELBINE Oral 50 mg total dose 3 days/week
- •Until disease progression

Expected feb 19 good feelings!!

*Appropriate previous adjuvant platinum-based chemotherapy for resected NSCLC within 6-12 months; Creatinine Clearance < 60 ml/min; Heart Failure NYHA class II-III; Hearing Loss > Grade 2; Medical condition impairing platinum-based chemotherapy according to physician's opinion

Pierre Fabre Study Code: PM 0259 CA 232 J1

EudraCT Number: 2014-003859-61

Clinical and Translational Oncology
https://doi.org/10.1007/s12094-018-1989-y

RESEARCH ARTICLE

Metronomic oral vinorelbine for the treatment of advanced non-small cell lung cancer: a multicenter international retrospective analysis

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Table 2: Clinical efficacy data.

Number of cycles (median - range)	**6 [1 – 25]**
Treatment response (n - %)	
CR **2/270 (0.7%)**	
PR	**46/270 (17.1%)**
SD	**119/270 (44.1%)**
PD	**103/270 (38.1%)**
ORR	**48/270 (17.8%)**
DCR	**167/270 (61.9%)**
Overall TTP (median - range)	**5 [1 - 21] months**
TTP first-line	**7 [1 - 21] months**
TTP second-line	**5.5 [1 - 19] months**
TTP subsequent-line	**4 [1 - 19] months**
Overall OS (median - range)	**9 [1 - 36] months**
OS first-line	**10 [1 - 31] months**
OS second-line	**8 [1 - 36] months**
OS subsequent-line	**6.5 [2 - 29] months**
OS sequence (median - range)	
metronomic - immunotherapy	**14 [7 - 36] months**

Table 3: All grade (left column) and grade 3/4 (right column) treatment-related toxicities (n = 270, total delivered cycles 1253).

Toxicity (n/%)	**All grade**	**Grade 3-4**
Overall	**790/1253 (49%)**	**25/1253 (2%)**
Non-haematological		
Fatigue	**25%**	**0.5%**
Nausea	**15%**	**0.2%**
Vomiting	**6%**	**0.2%**
Diarrhea	**6%**	**0.2%**
Mucositis	**7%**	**0.2%**
Sensorial neuropathy	**6%**	**0%**
Constipation	**12%**	**0%**
Haematological		
Anemia	**19%**	**0.4%**
Leuko/neutropenia	**8%**	**0.3%**
Thrombocytopenia	**4%**	**0%**
Dose reduction (n/%)		**20/270 (7.4%)**
Dose delay (n/%)		**29/270 (10.1%)**

matched the selected MeSH terms : 14 studies

Phase 1 evaluating mathematical model in various maligant diseases

–**Elharrar X et al. 2016** : *A phase Ia/Ib clinical trial of metronomic chemotherapy based on a mathematical model of oral vinorelbine in metastatic non-small cell lung cancer and malignant pleural mesothelioma: rationale and study protocol. DOI: ttps://doi.org/10.1186/s12885-016-2308-z*

Schedule of vinorelbine administation week on / week off

–**Rajdev L. et al. 2011**: *DOI; http://doi.org/10.1007/s00280-011-1580-5*

–**Guetz et al. 2017**:*Metronomic treatment of advanced non-<small-cell lung cancer with daily oral vinorelbine - a Phase I trial. DOI: https://doi.org/10.2147/OTT.S122106*

Publication in Mandarin ; no answer from author

–**Yao S. et al. 2017**: *Efficacy and Toxicity of Metronomic Oral Vinorelbinen in Advanced Non-small Cell Lung Cancer after Failure to Multiple-lines Treatments. Doi https://doi.org/10.3779/j.issn.1009-3419.2017.11.03*

Redundant publication

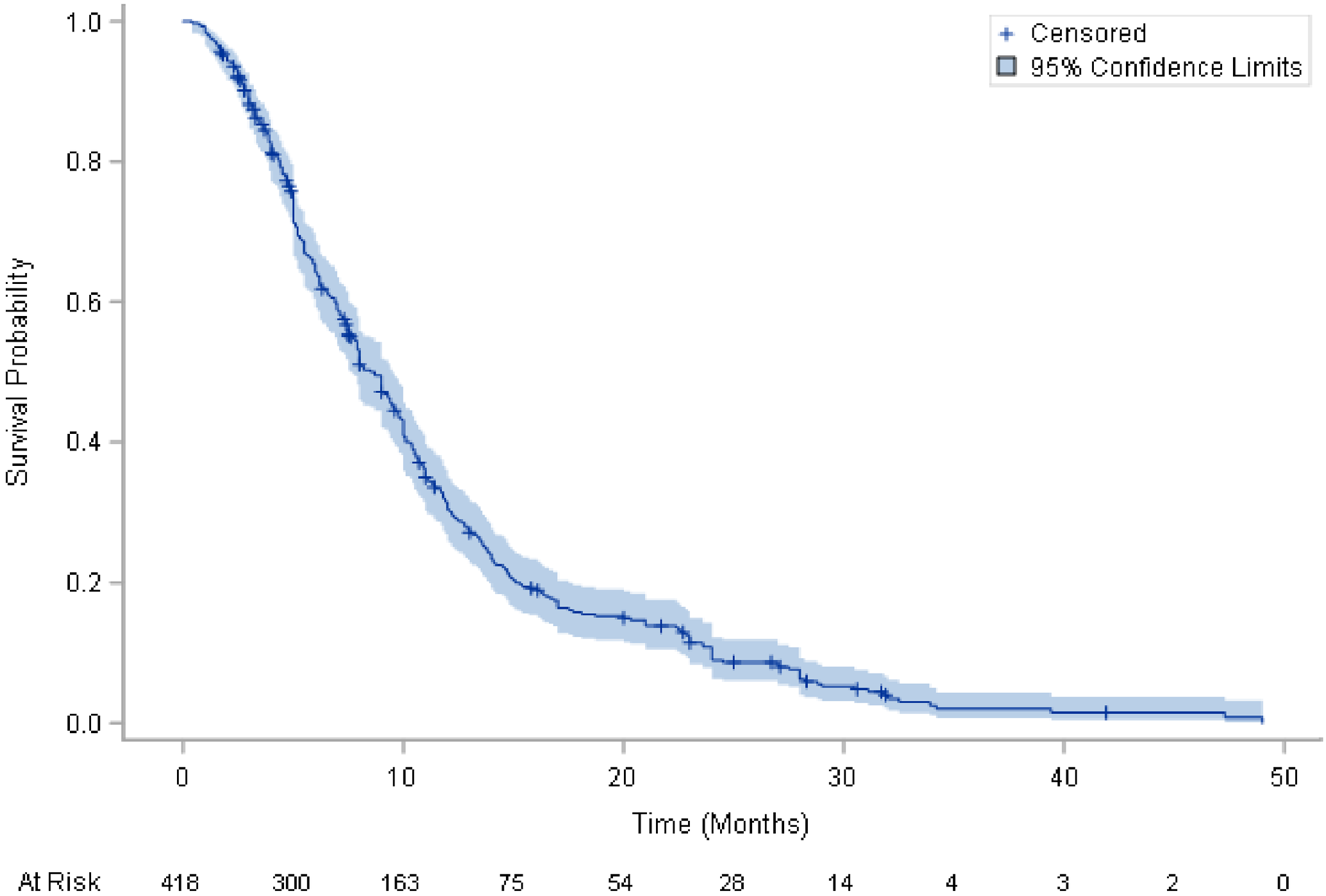
–**Briasoulis E. et al. 2009**: *Dose-ranging study of metronomic oral vinorelbine in patients with advanced refractory cancer. DOI https://doi.org/10.1158/1078-0432.CCR-09-0970*

Nine eligible studies with first author's willingness to participate
N=421 patients

Ineligible patients:
PS > 2: n = 2
No survival information n = 1

Intention-to-treat population
N=418 patients

Pujol et al submitted



Pujol et al submitted

MOVIDA trial: Metronomic oral vinorelbine + durvalumab in first-line platinum unfit NSCLC (Phase II Italy/Swiss)

IFCT trial: Metronomic oral vinorelbine + atezolizumab in second-line post platinum NSCLC (Phase II France)

Metronomic oral vinorelbine + Nivolumab in post platinum NSCLC (Phase II Singapore)

Table 3
Studies of metronomic therapy.

Setting	Population	Study (ref)	Regimen	Outcome
Advanced breast cancer	No minimum age	Dellapasqua et al. [67]	Cyclophosphamide 50 mg/d Capecitabine 500 mg tid Bevacizumab 10 mg/kg q 14d	RR 48% Median TTP 42 weeks Minimal toxicity
	T2 + ER + ve pts aged >70 yrs unsuited to conventional chemotherapy	Bottini et al. [68]	Letrozole with or without cyclophosphamide 50 mg/d	RR higher (88% versus 72%) in pts receiving additional cyclophosphamide; and VEGF expression significantly less than with letrozole monotherapy
	Women with at least one prior endocrine therapy for M+ disease; mean age 65 yrs	Schwartzberg et al. [69]	Capecitabine 1500 or 2000 mg given in divided doses, added to intravenous (i.v.) fulvestrant	Activity described as substantial and toxicity as low; HFS most frequent AE, but Gr3 or greater in fewer than 10%
	ER + ve, postmenopausal women; no lower age limit	Aurilio et al. [70]	Cyclophos 50 mg/d and methotrexate 2.5 mg bd on d 1 and 4 added to im fulvestrant	Long term disease control achieved with minimal toxicity
Advanced cancer phase I	No lower limit on age	Rajdev et al. [71]	Metronomic oral vinorelbine	Activity reported; drug well tolerated
NSCLC stage IIIb/IV	First line; aged over 70 years (median 79 years); median 3.5 serious comorbidities	Camerini et al. [63]	Oral vinorelbine 50 mg three times per week until progression	ORR only 13% but 50% had SD for >12 weeks; median OS 9.5 months. Only 4 episodes of Gr 3 (and no Gr 4) toxicity in 32 pts
Ovarian cancer	Recurrent, platinum resistant Recurrent	Barber et al. [72] Garcia[73]	Cyclophosphamide 50 mg/d plus bevacizumab	RR 42%: OS 20 months in responders, but only 9mo in non-responders Median OS 17 months

Clinical and Translational Oncology
https://doi.org/10.1007/s12094-018-1856-x

CLINICAL GUIDES IN ONCOLOGY

General recommendations paper on the management of older patients with cancer: the SEOM geriatric oncology task force's position statement

R. Gironés Sarrió[1] · M. Antonio Rebollo[2] · M. J. Molina Garrido[3] · C. Guillén-Ponce[4] · R. Blanco[5] · E. Gonzalez Flores[6] · J. Saldaña[2] · On behalf of the Spanish Working Group on Geriatric Oncology of the Spanish Society of Medical Oncology (SEOM)

Finally, oral chemotherapy is an appealing option in seniors, due to better compliance in administering it and greater convenience compared to intravenous chemotherapy. Metronomic chemotherapy can represent a means of decreasing toxicity [48–50], thereby enhancing quality of life; moreover, several studies have pointed out the antiangiogenic and immunomodulating effects of this mode of administration [51].

Take-home messages

Metronomic approach is not chemotherapy!

Sound data on oral mVNR in first (an later) line!

Clinical patient selection is a cornerstone

Metronomic treatment is safer than MTD and (at least) as effective

From a great 2018 to combos with immunotherapy, guidelines and random