ESMO Preceptorship Programme – Colorectal Cancer

Multidisciplinary management, standards of care and future perspectives

Prague, 23th May 2014

Management of treatment-related side effects

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Azienda Ospedaliero-Universitaria Pisana

Università di Pisa

My disclosures

- ✓ I am a medical oncologist mainly committed to clinical and translational research in CRC
- ✓ I am not an expert in supportive care
- ✓ I am a superfan of the triplet FOLFOXIRI…

has this anything to do with being invited to deliver a talk on toxicities?

Agenda

1) "Traditional toxicities"

- ✓ Diarrhea
- ✓ Neurotoxicity
- ✓ Hypertension

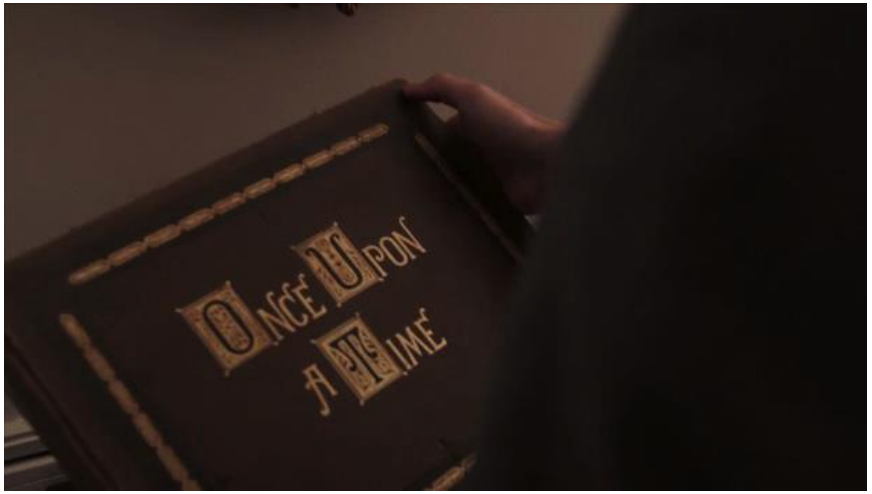
2) "Intensive combinations-related toxicities"

- ✓ FOLFOXIRI plus bev
- ✓ FOLFOXIRI plus anti-EGFRs

2) "New toxicities"

- ✓ Regorafenib related side-effects

“Traditional” toxicities



- ✓ Diarrhea
- ✓ Hand Foot Syndrome
- ✓ Neurotoxicity (oxaliplatin)
- ✓ Skin reaction (anti-EGFRs)
- ✓ Hypertension (anti-angio)

Diarrhea and modern treatments: how big is the problem?

Study	N	Regimen	Diarrhea G≥3 (%)
Diaz-Rubio E et al,	239	XELOX+bev	11
Oncologist 2012	241	XELOX+bev>bev	13
Tebbutt N. et al,	156	CAPE	11
	157	CAPE+bev	17
***J Clin Oncol* 2010**	158	CAPE+MITO+bev	16
Douillard J. et al,	322	FOLFOX	9
***J Clin Oncol* 2010**	327	FOLFOX+pani	18
Van Cutsem E et al,	599	FOLFIRI	16
NEJM 2009	599	FOLFIRI+cetux	11

Recommendations

- ✓ **Accurate assessment of symptoms**
- ✓ **Selection of appropriate management:**

Uncomplicated (G1 or 2)

- ✓ Dietary modifications and adequate oral hydration
- ✓ Start Treatment with loperamide
- ✓ (if G2) Hold cytotoxic chemotherapy until symptoms resolution

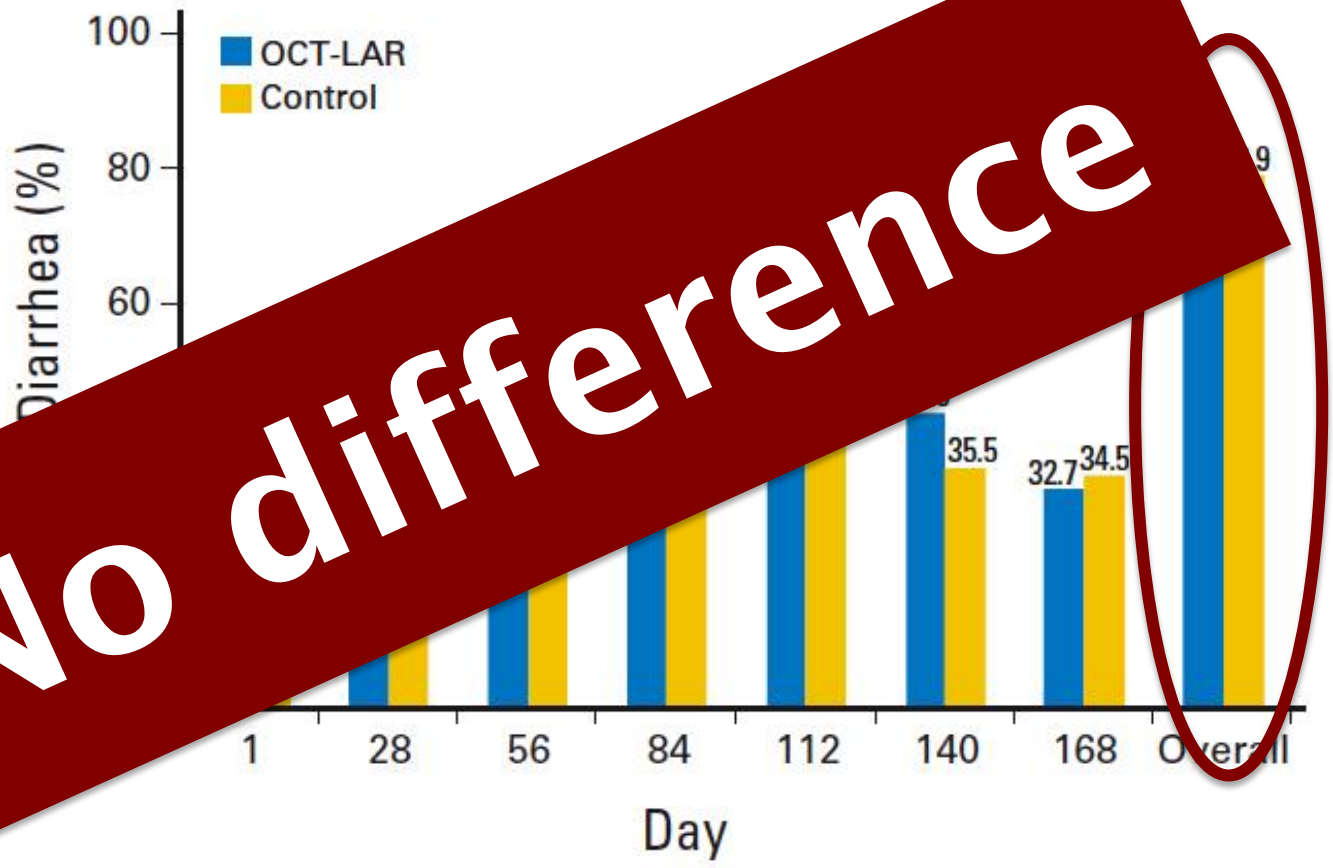
Complicated (>G3)

- ✓ Administer octreotide
- ✓ Start IV fluids and antibiotics if needed
- ✓ Stool work-up, CBC, electrolyte profile
- ✓ Discontinue cytotoxic chemotherapy until symptoms resolution and consider dose reduction

Benson III Al B et al. J Clin Oncol '04

Latest news: Octreotide to prevent CID

Randomized Phase III Trial Exploring the Use of Long-Acting Release Octreotide in the Prevention of Chemotherapy-Induced Diarrhea in Patients With Colorectal Cancer: The LARCID Trial



No difference

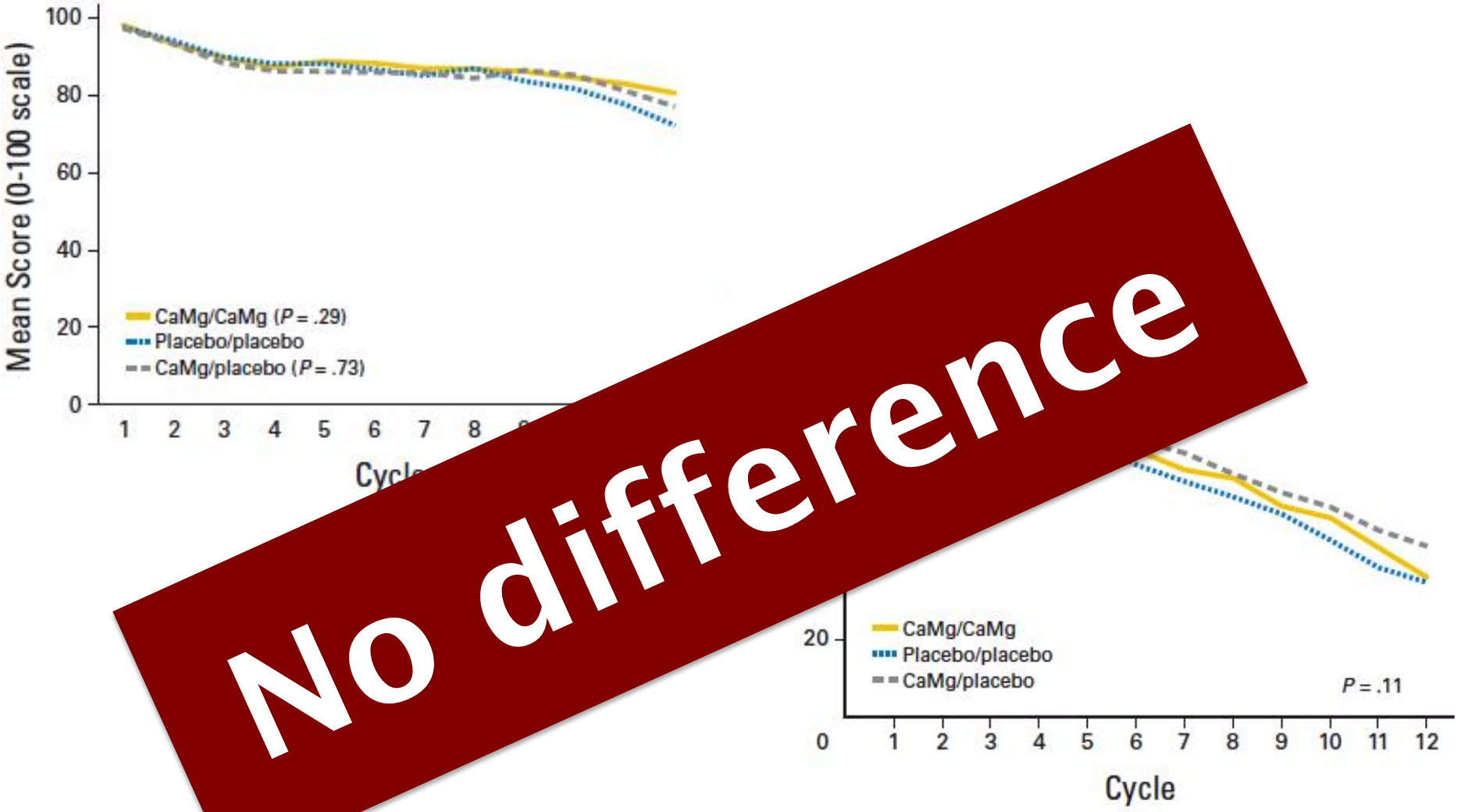
Hoff PM et al. J Clin Oncol '14

Oxa-induced neurotoxicity: what's that?

	Grade			
	1	2	3	4
Peripheral sensory neuropathy	Asymptomatic; loss of deep tendon reflexes or paresthesia	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated

CTCAE v4

Latest news: CaMg to prevent Oxa-induced neurotoxicity



No difference

Loprinzi et al, J Clin Oncol '14

Recommendations

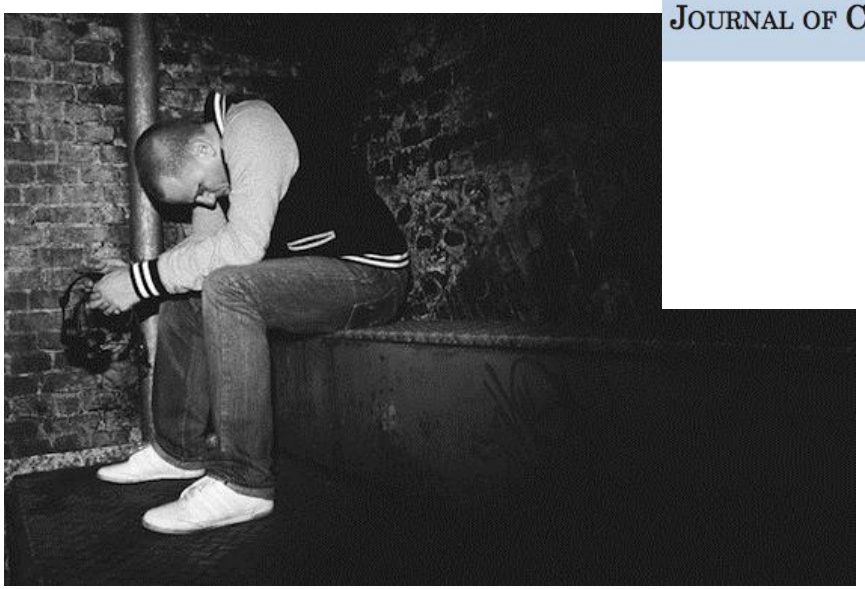
JOURNAL OF CLINICAL ONCOLOGY | ASCO SPECIAL ARTICLE

Prevention and Management of Chemotherapy-Induced Peripheral Neuropathy in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline

Hershman DL et al, JCO '14

- ✓ **Accurate assessment of symptoms**
- ✓ **Hold or interrupt treatments when G3 neurotox occurs**
- ✓ **On the basis of the paucity of high-quality, consistent evidence, there are no agents recommended for the prevention of CIPN.**

It seems to get very..depressing!



JOURNAL OF CLINICAL ONCOLOGY ASCO SPECIAL ARTICLE

Prevention and Management of Chemotherapy-Induced Peripheral Neuropathy in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline

Hershman DL et al, JCO '14

- ✓ **With regard to the treatment of existing CIPN, the best available data support a moderate recommendation for treatment with DULOXETINE**

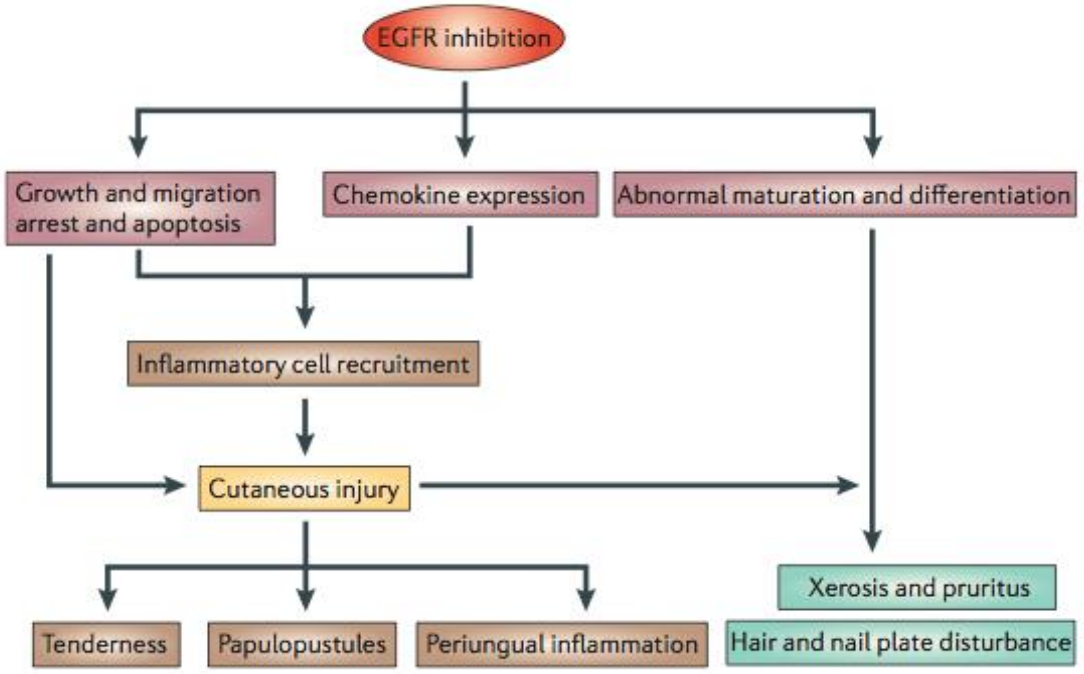
Lavoie Smith EM et al, JAMA '13

Skin Toxicity

REVIEWS

Mechanisms of cutaneous toxicities to EGFR inhibitors

Mario E. Lacouture



Lacouture ME, Nat Rev Cancer '06

Skin Toxicity

Contents lists available at SciVerse ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevierhealth.com/journals/ctrv

Complications of Treatment

Recommendations on management of EGFR inhibitor-induced skin toxicity: A systematic review

J.M. Baas [a,1], L.L. Krens [b,2], H.-J. Guchelaar [b,2], J. Ouwerkerk [a,1], F.A de Jong [c,3], A.P.M. Lavrijsen [d,4], H. Gelderblom [a,*]

Due to the small number of randomized controlled trials conducted in the field of EGFR inhibitor-induced skin toxicity so far,
it is not possible yet to generate evidence based guidelines on its management

Baas et al, Cancer Treat Rev '12

Skin Toxicity

Randomized clinical trials testing management EGFR inhibitor-induced of skin toxicity.

Study	EGFR agent	Tumor type	*n*	Treatment arms	Main aim of the study	Results
Jatoi et al.[68]	Various	Various	110	Sunscreen (SPF 60)	To decrease the incidence of skin toxicity	No difference between both groups (78% versus 80%; *p*-value 0.36)
Lacouture et al.[55]	Panitumumab	Colorectal	95	Placebo Prophylactic treatment[1]	To decrease the incidence of ⩾grade 2 skin toxicity	Significant decrease of ⩾grade 2 toxicity when treated with prophylaxis (29% versus 62%, OR 0.3, 95%CL 0.1 to 0.6)
Scope et al.[69]	Cetuximab	Colorectal	16	Reactive topical pimecrolimus	To decrease lesion count	Significant greater decrease of lesion count when treated with pimecrolimus (*p*-value <0.05)
Jatoi et al.[67]	Various	Various	61	No pimecrolimus Prophylactic oral tetracycline	To decrease the incidence of skin toxicity	No difference between both groups (70% versus 76%; *p*-value 0.61)
Scope et al.[57]	Cetuximab	Colorectal	48	Placebo I Prophylactic oral minocycline	To decrease lesion count	Lower lesion count when treated with minocycline (*p*-value 0.005)
				Placebo II Prophylactic tazarotene on right facial side Prophylactic tazarotene on left facial side	To decrease lesion count	No difference between both groups

SPF, sun protection factor.

[1] Including skin moisturizer, sunscreen, topical steroid and oral doxycycline.

[2] Any treatment deemed necessary by the physician.

Baas et al, Cancer Treat Rev '12

Hypertension

ELSEVIER

Canadian Journal of Cardiology 30 (2014) 534–543

Review

Hypertension Due to Antiangiogenic Cancer Therapy With Vascular Endothelial Growth Factor Inhibitors: Understanding and Managing a New Syndrome

Heather Yvonne Small, BSc(Hons),[a] Augusto C. Montezano, PhD,[a] Francisco J. Rios, PhD,[a] Carmine Savoia, MD,[b] and Rhian M. Touyz, MD, PhD[a]

[a] *Institute of Cardiovascular and Medical Sciences, British Heart Foundation Glasgow Cardiovascular Research Centre, University of Glasgow, UK*

[b] *Sapienza University of Rome, Rome, Italy*

Although SPECIFIC GUIDELINES ARE NOT YET AVAILABLE for the management of VEGFI-induced hypertension, ACE inhibitors and dihydropyridine calcium channel blockers are commonly used

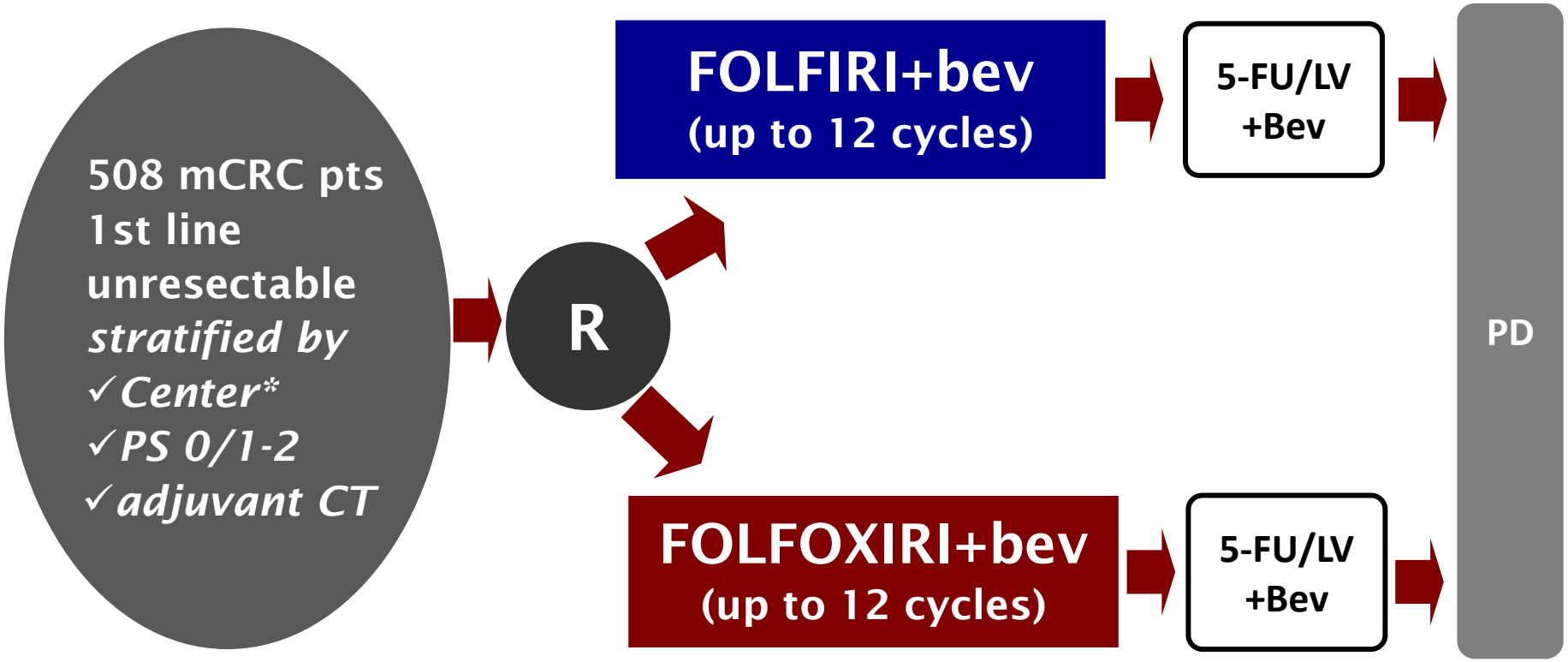
Small HY et al, Canadian J Cardiology '14

Intensive combinations…

What am I talking about?

- ✓ **FOLFOXIRI + bevacizumab**
- ✓ **FOLFOXIRI + anti-EGFRs**

TRIBE Study Design



*** 33 centers around Italy**

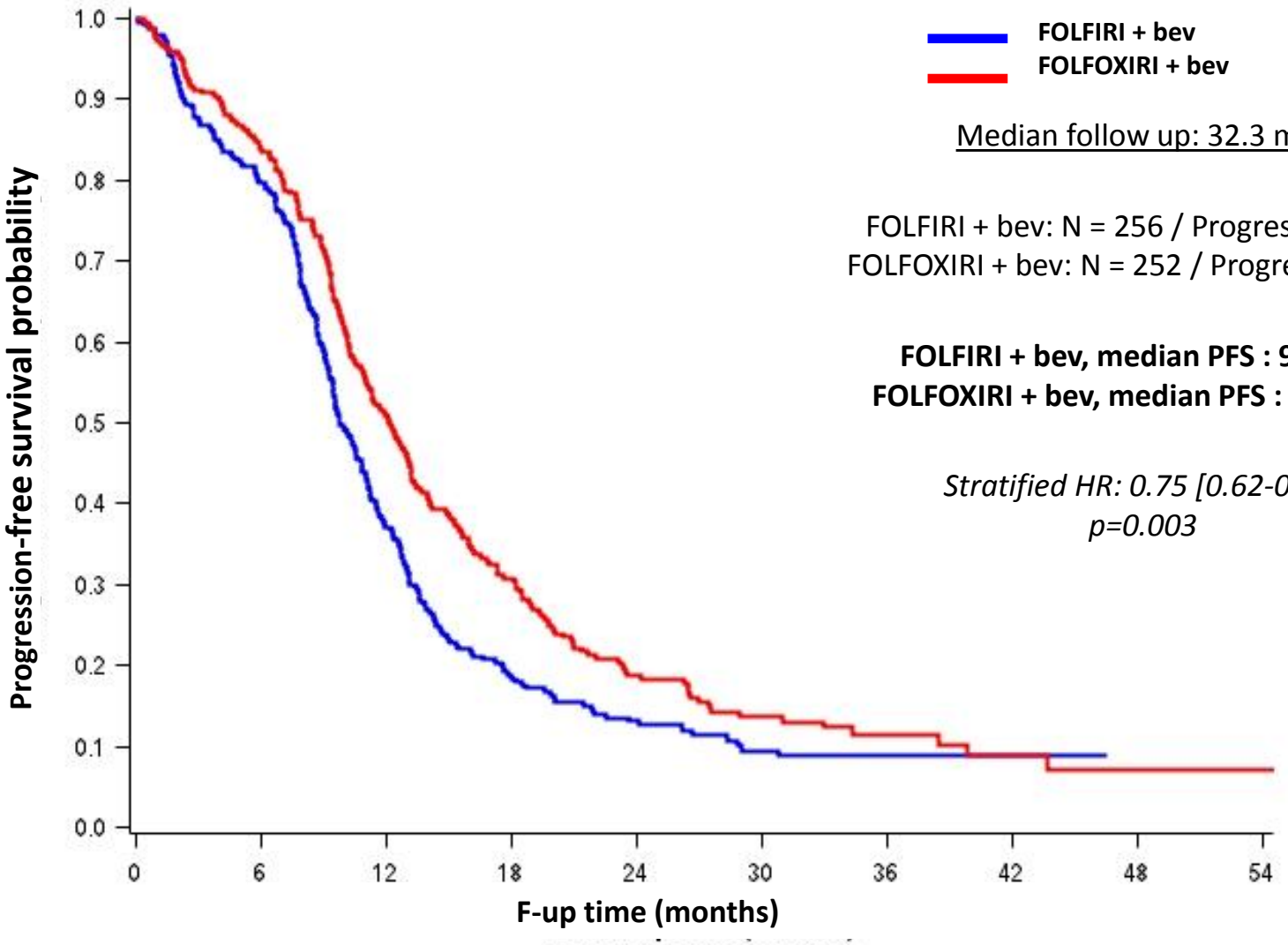
INDUCTION

MAINTENANCE

G.O.N.O
Gruppo Oncologico del Nord Ovest

Falcone et al, ASCO '13

Primary endpoint: PFS



FOLFIRI + bev
FOLFOXIRI + bev

Median follow up: 32.3 mos

FOLFIRI + bev: N = 256 / Progressed = 226
FOLFOXIRI + bev: N = 252 / Progressed = 213

FOLFIRI + bev, median PFS : 9.7 mos
FOLFOXIRI + bev, median PFS : 12.1 mos

Stratified HR: 0.75 [0.62-0.90]
p=0.003

Falcone et al, ASCO '13

Toxicity Profile – Safety population

G3/4 adverse events, % patients	FOLFIRI + bev Arm A N=254	FOLFOXIRI + bev Arm B N=250	p
Nausea	3	3	**1.000**
Vomiting	3	4	**0.492**
Diarrhea	11	19	**0.012**
Stomatitis	4	9	**0.048**
Neutropenia	20	50	**<0.001**
Febrile neutropenia	6	9	**0.315**
Neurotoxicity	0	5	**<0.001**
Hypertension	2	5	**0.157**
Venous Thrombosis	6	7	**0.593**
Arterial Thrombosis	2	1	**1.000**
Bleeding	1	1	**1.000**

Overall Safety

Patients, %	FOLFIRI + bev N = 254	FOLFOXIRI + bev N = 250
Serious AEs	19.7%	20.4%
Fatal AEs	3.5%	2.8%
Treatment-related deaths	1.6%	2.4%
Early deaths *(within 60 days from random)*	2.3%	3.2%

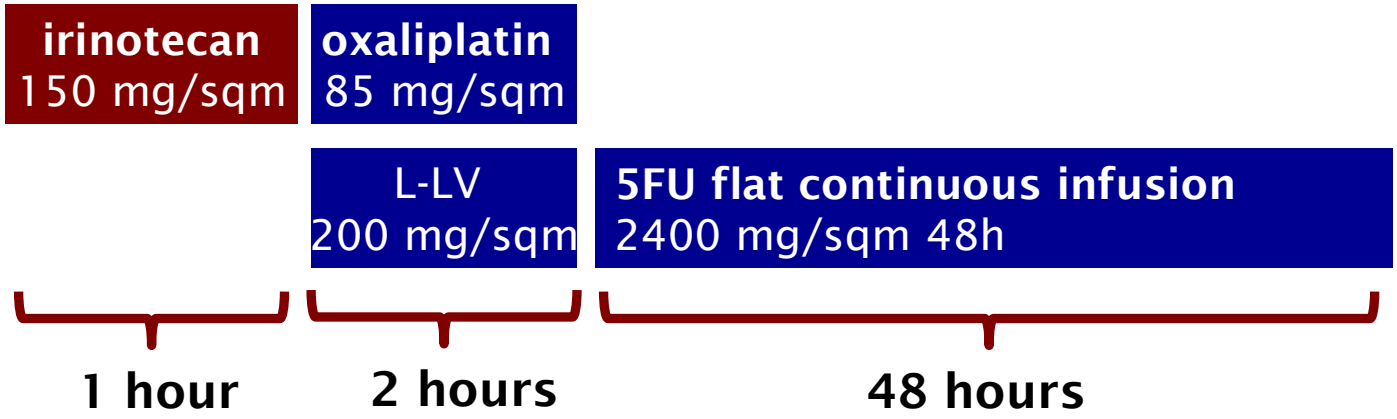
Falcone et al, ASCO Ann Meet '13

Triplets + anti-EGFRs: preliminary data

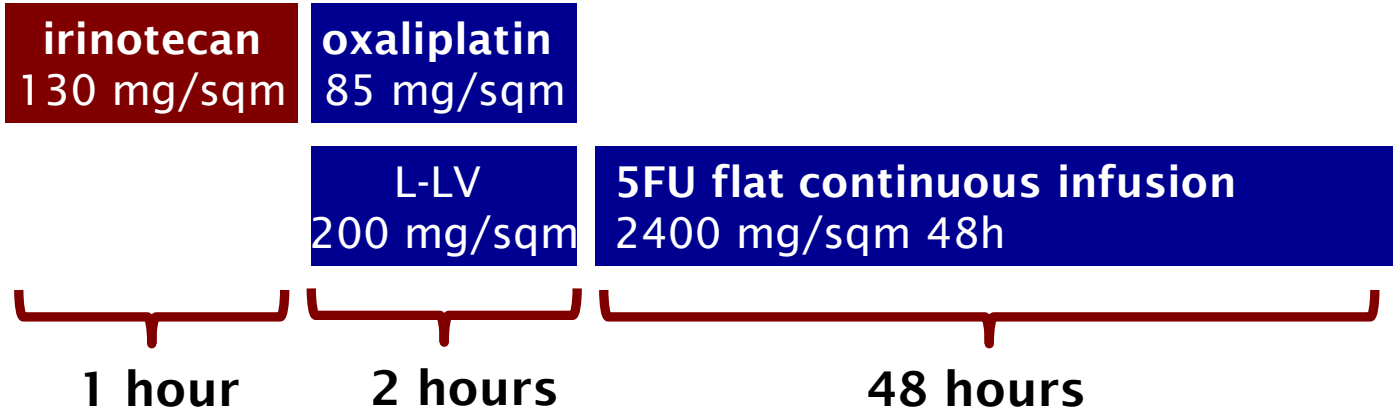
Author	N	Regimen	G3/4 Diarrhea (%)
Garufi *Br J Canc 2010*	43	Chrono-IFLO + Cetuximab	93% (36% after dose reduction)
Assenat, *Oncologist 2011*	42	FOLFIRINOX + Cetuximab	52%
Folprecht, *ASCO GI 2010*	20	mFOLFOXIRI + Cetuximab	25%
Saridaki, *Br J Cancer 2012*	30	FOLFOXIRI + Cetuximab	53%
Fornaro *Ann Oncol, 2013*	37	mFOLFOXIRI + Panitumumab	33%
Cremolini *ASCO, 2014*	72	mFOLFOXIRI + Cetuximab	21%

Triplet + anti-EGFR: not “the usual FOLFOXIRI”!

Fornaro
Ann Oncol, 2013



Cremolini
ASCO, 2014



Recommendations

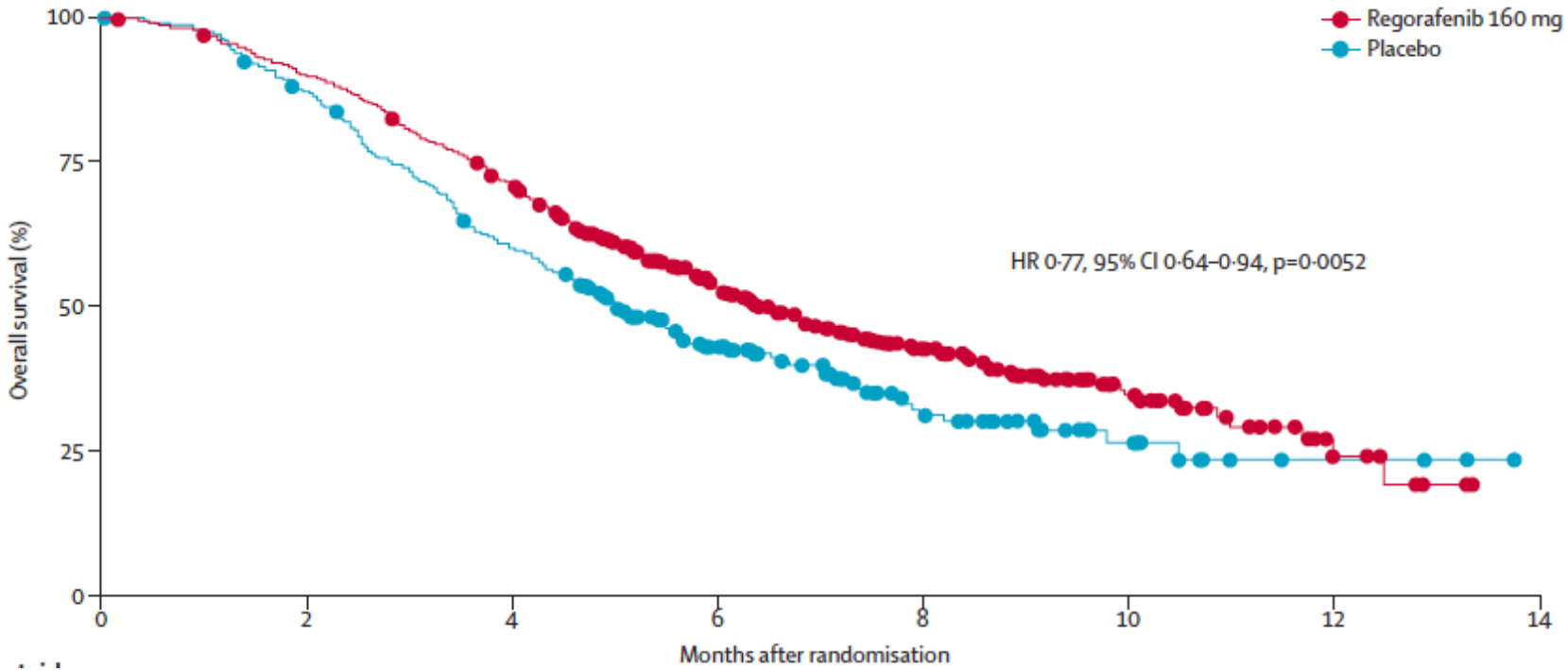
- ✓ Follow diarrhea management guidelines
- ✓ Hold treatment until toxicity resolution (<G2)
- ✓ Reduce doses according to protocol instructions
- ✓ Wait for more data on FOLFOXIRI + anti-EGFRs

“New” toxicities

Hand Foot Syndrome (HFS) and skin reactions caused by regorafenib

The CORRECT trial: results

Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial



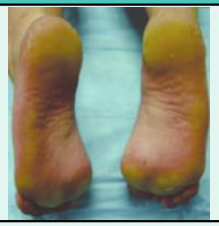
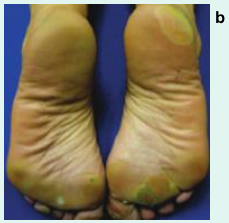
Grothey A et al. Lancet '13

Regorafenib-related AEs

Adverse event, %	Regorafenib		Placebo	
	Grade 3	Grade 4	Grade 3	Grade 4
Hand–foot skin reaction	17	0	5	<1
Fatigue	9	<1	28.1	4.7
Hypertension	7	0	1	0
Diarrhoea	7	<1	1	0
Rash/desquamation	6	0	0	0
Anorexia	3	0	3	0
Mucositis, oral	3	0	0	0
Thrombocytopenia	3	<1	1	0
Fever	1	0	0	0
Nausea	<1	0	0	0
Bleeding	0	0	0	0
Voice changes	<1	0	0	0
Weight loss	0	0	0	0

Grothey A et al. Lancet '13

Hand&Foot Skin Reaction

HFSR Grade[a]	Symptoms	Impact	Image
Grade 1	Numbness, dysesthesia, paraesthesia, tingling, painful swelling, erythema, or discomfort of the hands and feet	Does not disrupt the subject's normal activities	 b
Grade 2	Painful erythema and swelling of the hands or feet and/or discomfort	Affects the subject's normal activities	 b
Grade 3	Moist desquamation, ulceration, blistering or severe pain of the hands or feet, or severe discomfort	Causes the subject to be unable to work or perform activities of daily living	 c

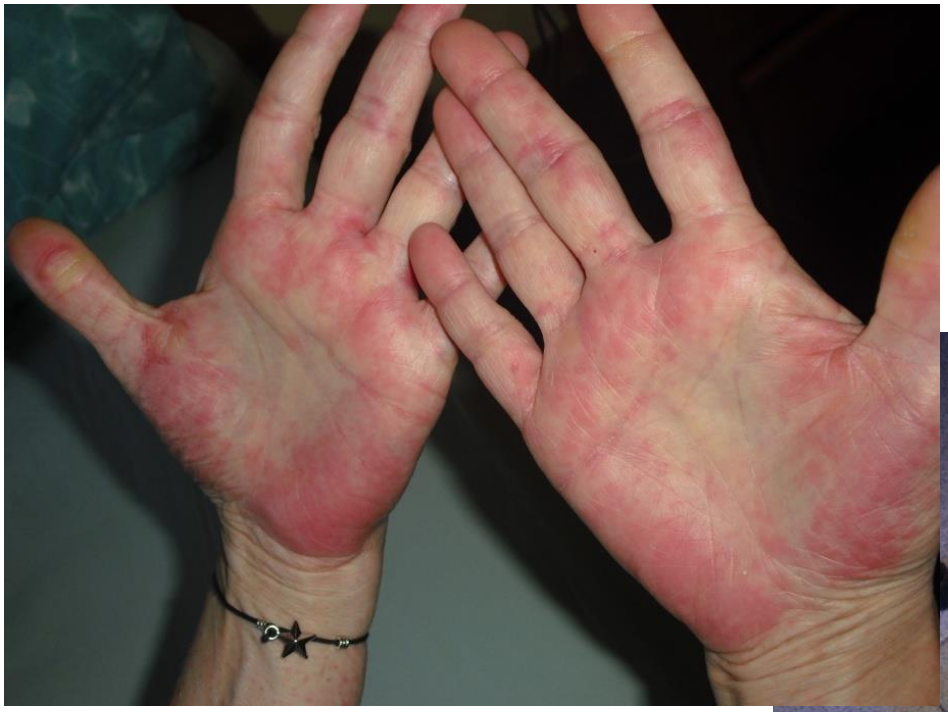
[a] NCI CTCAE v3.0 grading of HFSR.

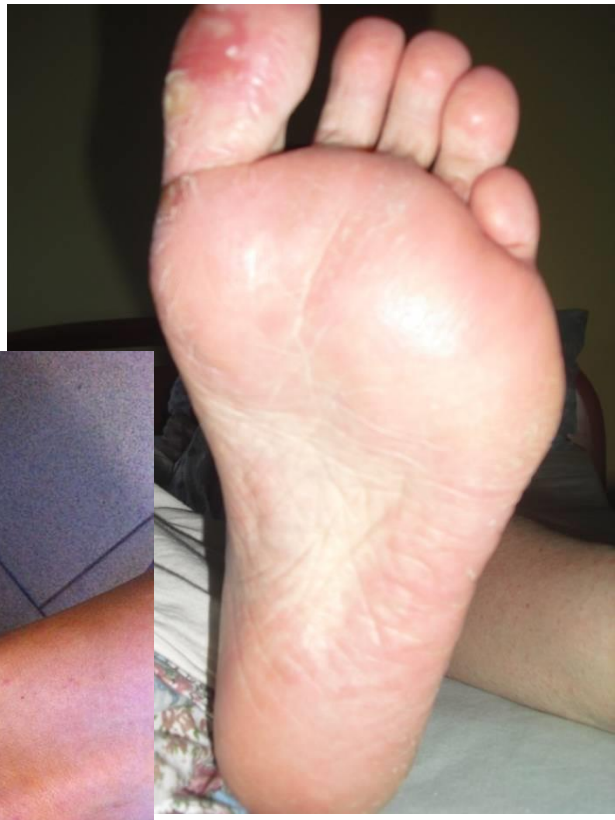
[b] Reprinted with permission from Lacouture ME, et al. *Oncologist*. 2008;13(9):1001-1011.

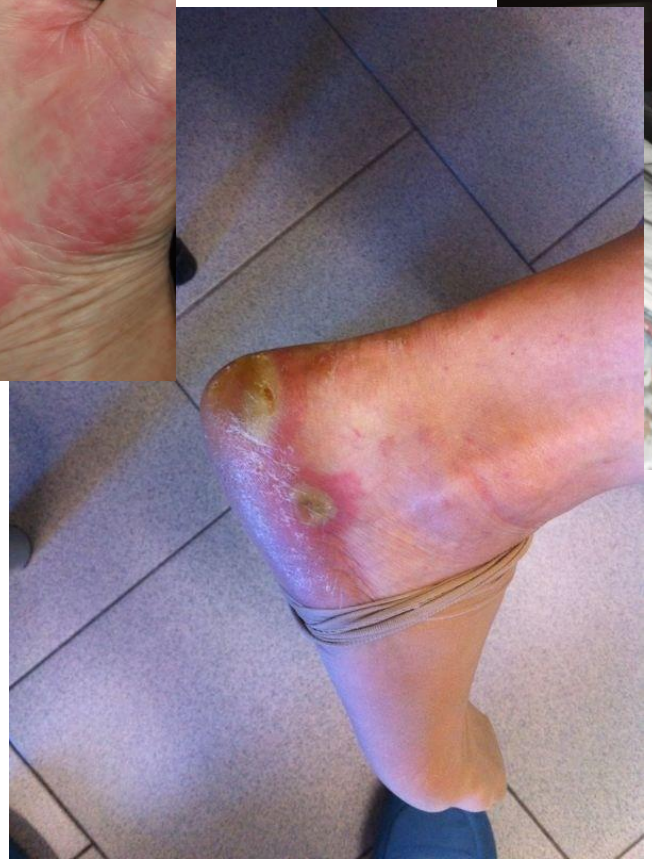
[c] Image used with permission from Taline Khoukas, MSN, ACNP-C.

Khoukaz et al, ONS '13

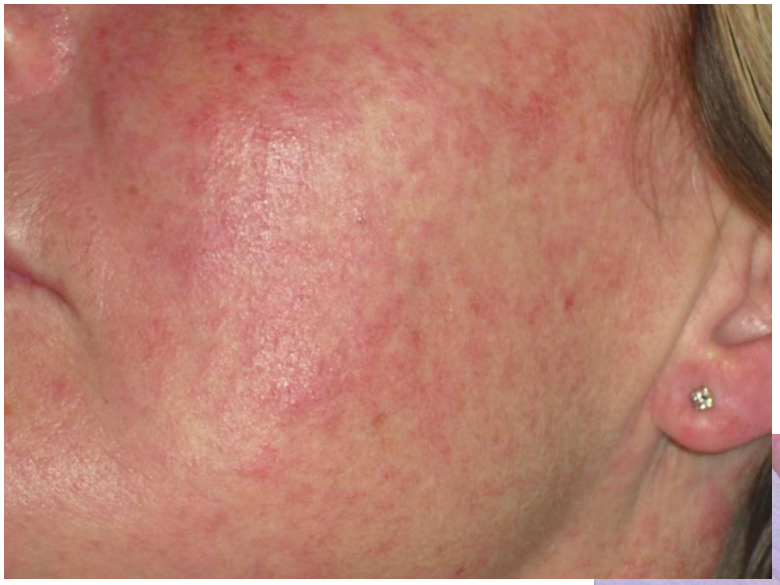
Hand&Foot Skin Reaction

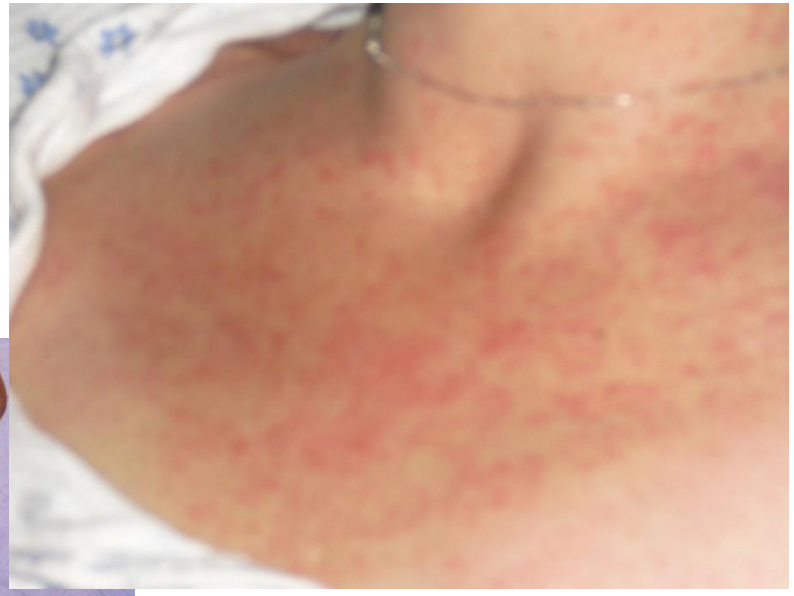


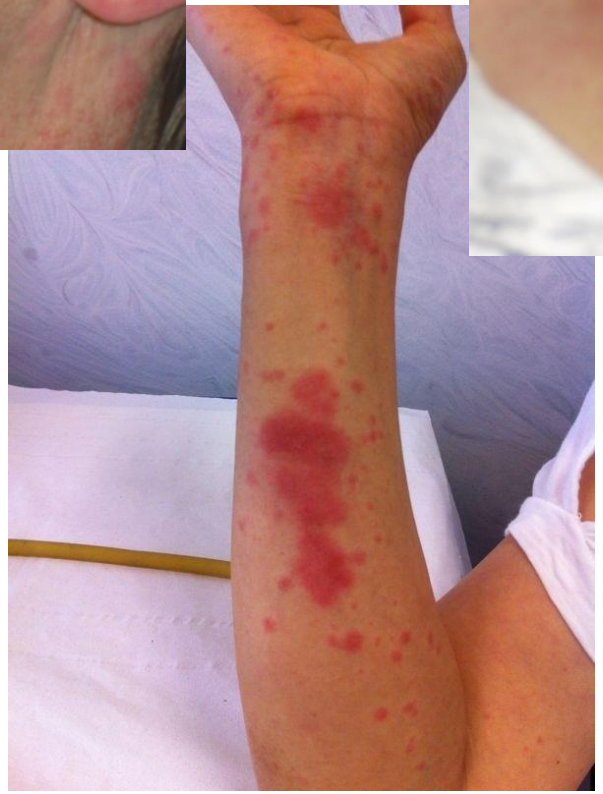




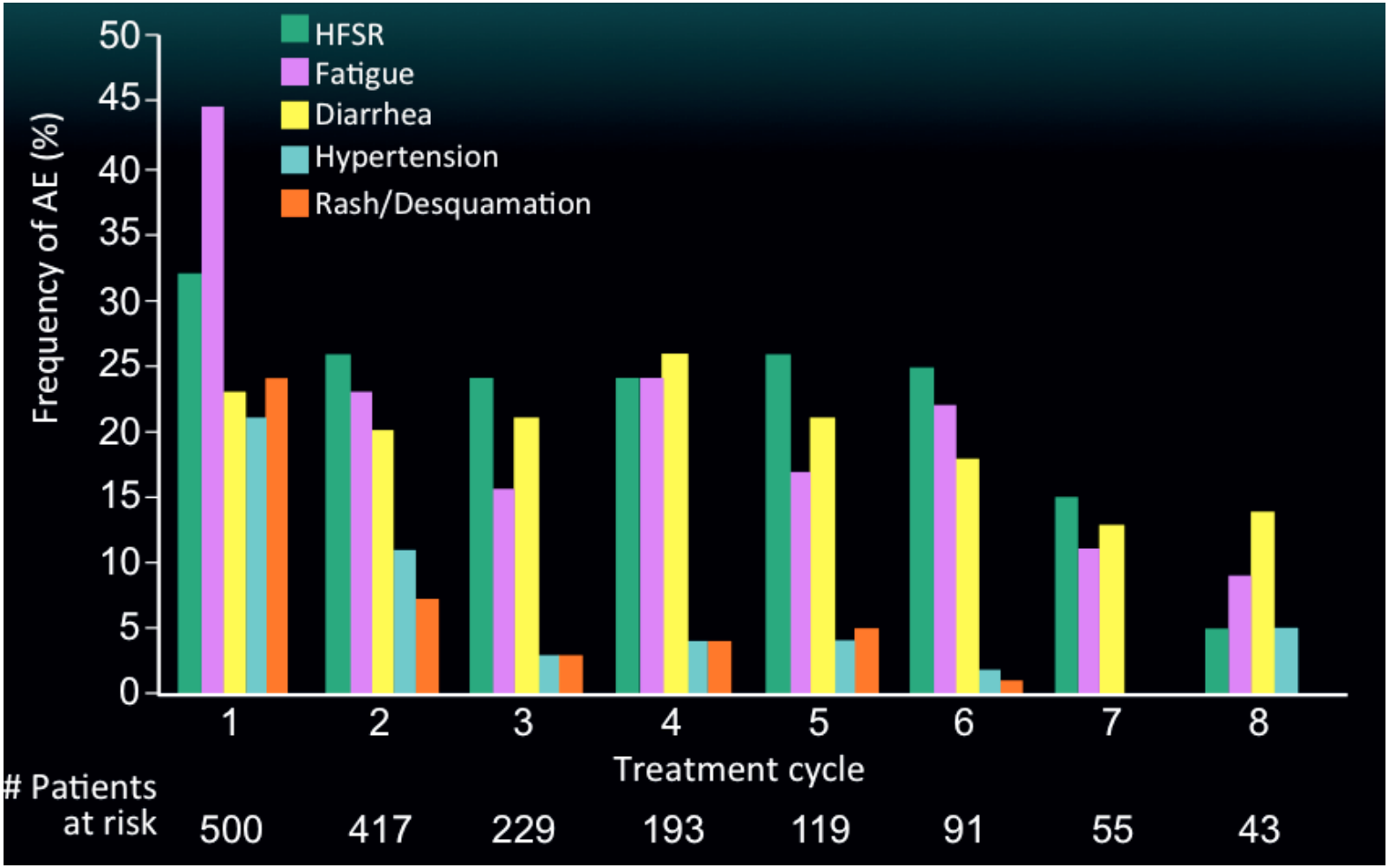
Skin rash







Adverse Events over time



Common AEs occur early and stabilize over time

Grothey et al, ASCO GI '13

Recommendation: Prevention

Preventative and supportive measures

- Regular use of emollients from initiation of regorafenib treatment and avoidance of those which are scented or contain alcohol
- During showering: contact with hot water should be minimized and mild soaps should be used. An antidandruff shampoo may also help to reduce scalp irritation
- Avoidance of extreme temperatures (severe cold or substantial heat) and direct sun exposure (sun protection cream) should be encouraged

Lacouture et al, Supp Care Cancer '11

Recommendation: Early Management

Patients should be advised to notify the onset of AEs to health-care providers as soon as they occur.

Clinical evaluations must be scheduled every 2 weeks in the first 2 months of treatment


SO WHAT?

In 2014 toxicities' management is still based on…

How can we move on?

- ✓ More drugs → more options
- ✓ More drugs → more toxicities

- ✓ More “good and reliable” studies on tox management
- ✓ Biomarkers of risk for developing specific toxicities
- ✓ Good translational research

Just to avoid “sad” and “confusing” stories…

DPYD

The Pharmacogenomics Journal (2013) 13, 389–395

www.nature.com/tpj

REVIEW

Evaluation of predictive tests for screening for dihydropyrimidine dehydrogenase deficiency

MC van Staveren[1], H Jan Guchelaar[2], ABP van Kuilenburg[3], H Gelderblom[4] and JG Maring[5]

UGT1*…

JOURNAL OF CLINICAL ONCOLOGY

EDITORIAL

Irinogenetics: How Many Stars Are There in the Sky?

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