



Management of toxicities of antiangiogenic/anti-EGFR agents

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MD Anderson
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Making Cancer History®

Angiogenesis inhibition: the hope

New England Journal of Medicine,
285:1182-1186, 1971

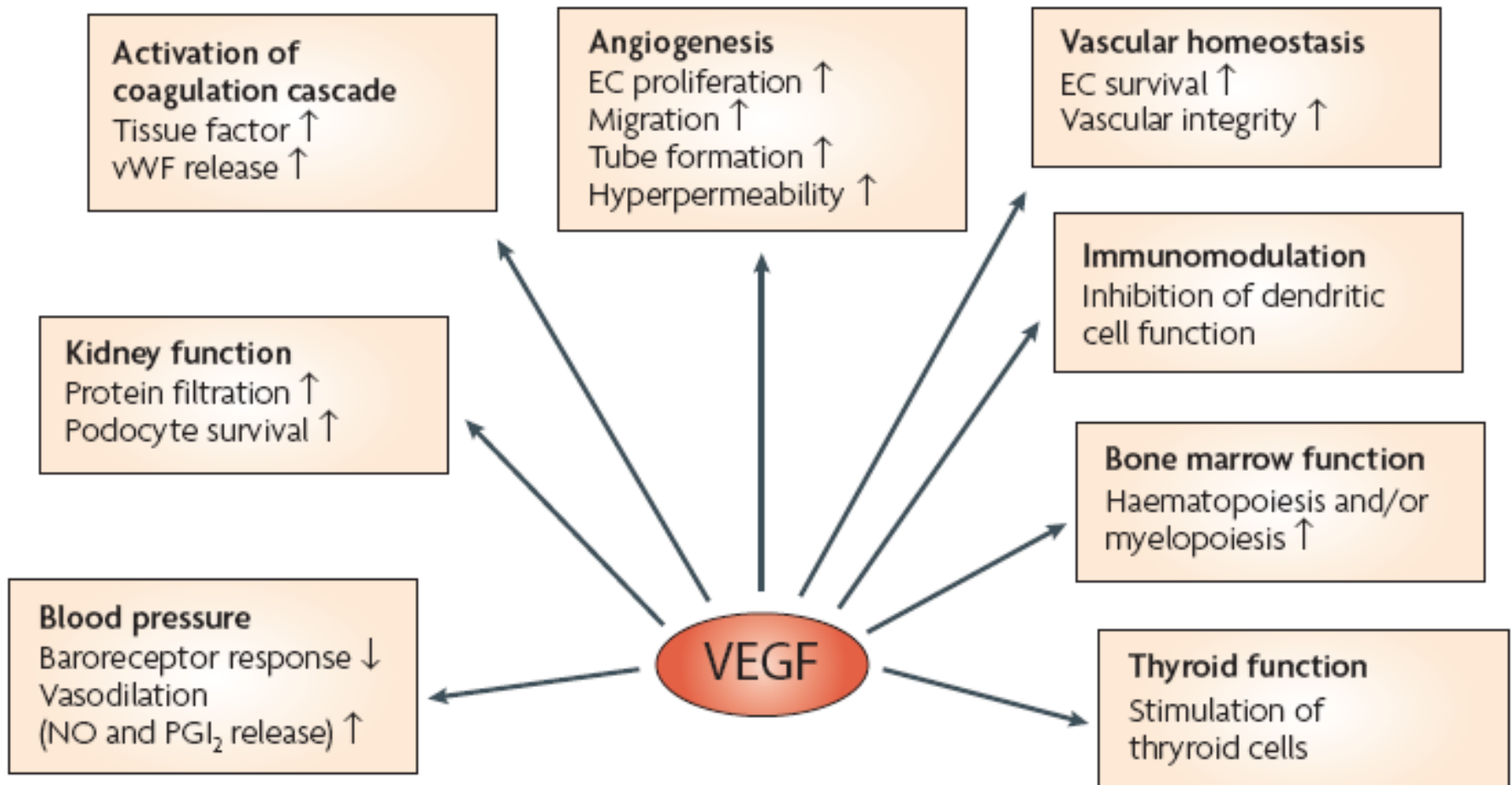
TUMOR ANGIOGENESIS: THERAPEUTIC IMPLICATIONS

JUDAH FOLKMAN, M.D.



- the term **anti-angiogenesis** is proposed to mean the prevention of new vessel sprouts from penetrating into an early tumor implant.
- an antibody to a tumor angiogenic factor (TAF) could be therapeutic, expected to have little or no toxicity

Physiological functions of VEGF



Toxicities attributed to VEGF pathway inhibitors

Type	Examples	Drug	Disease
Class effect	Hypertension Proteinuria Reversible posterior leukoencephalopathy	Most or all	Most or all
Drug-specific	Hair pigment changes Hypothyroidism QT prolongation	Sunitinib, cediranib, vandetanib etc.	

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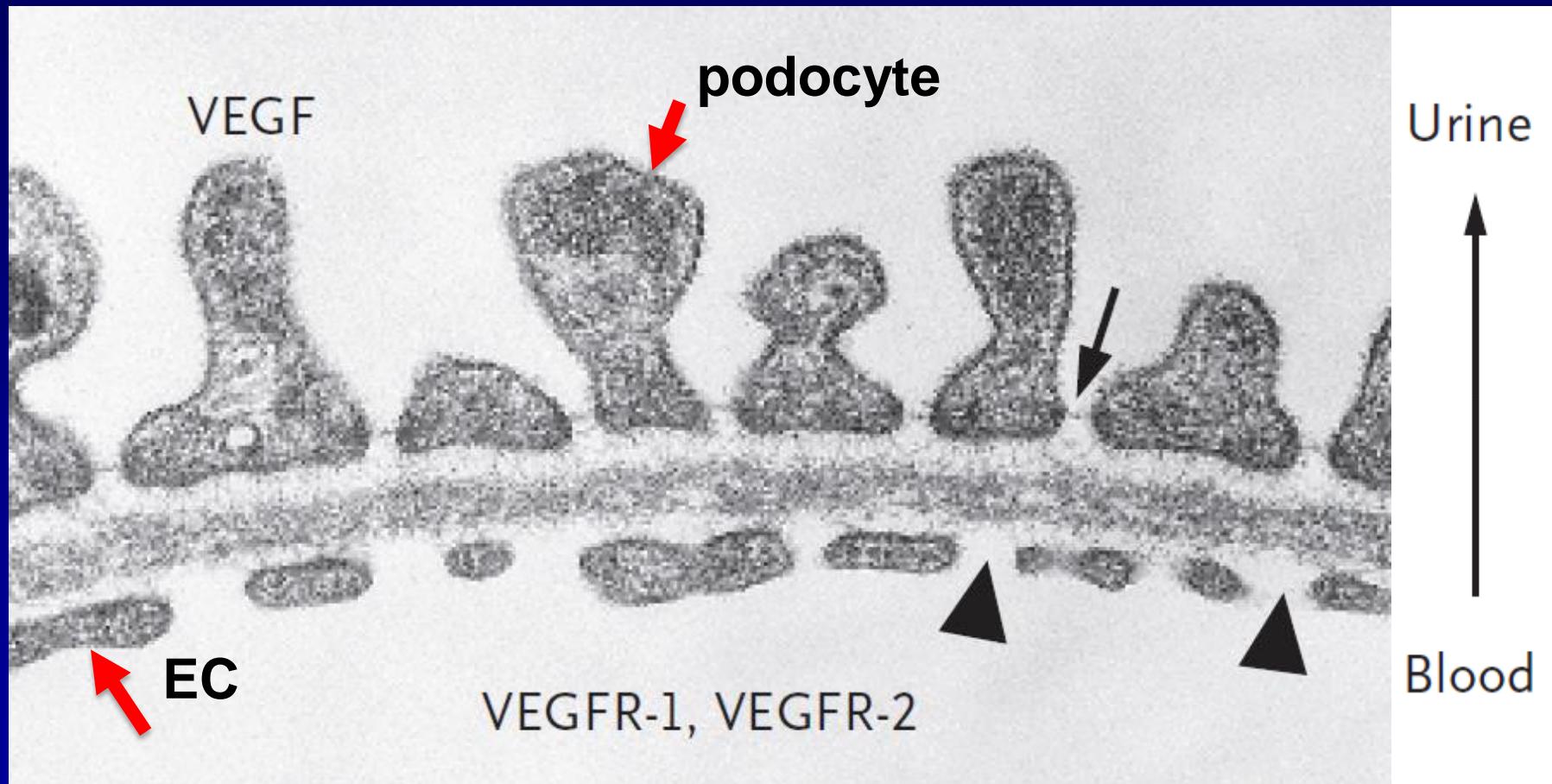
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Disease-specific	Hemoptysis, TE fistula GI perforation	BV, others	Lung Ovarian, GI
Chemo enhancing	Increased myelosuppression, neuropathy	Most or all	Most or all

Class effects

VEGF regulates glomerular barrier selectivity



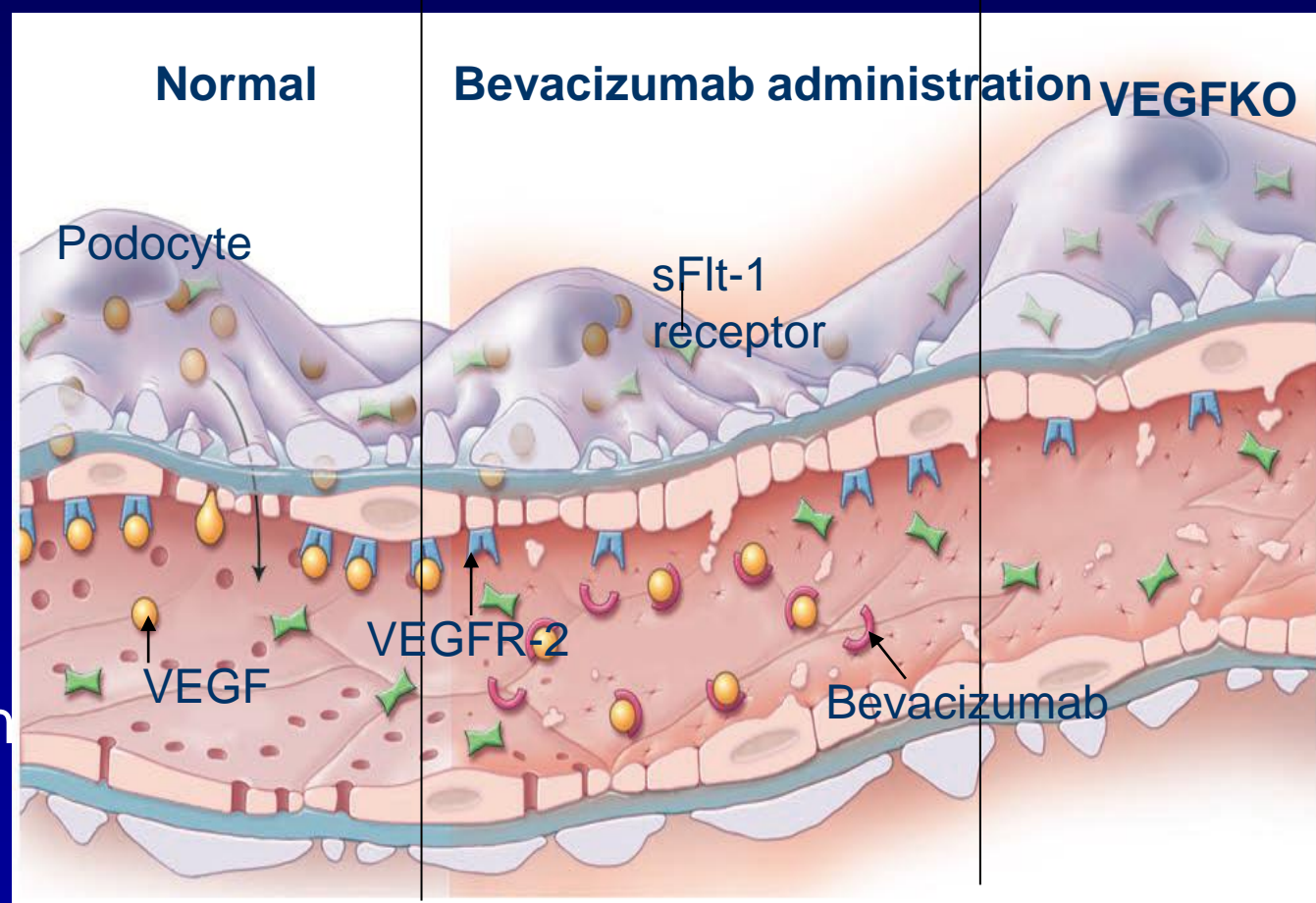
Absence of VEGF Signaling and the development of Renal TMA

- **Preeclampsia:**

- ↑ circulating sVEGFR-1
- Low VEGF
- HTN
- Proteinuria
- TMA

- **Anti-VEGF therapy** results in similar syndrome

- **Mouse model** recapitulates TMA



Frequency of proteinuria in BV trials

Table 5. Incidence of Proteinuria in Phase 2 and 3 Bevacizumab Trials

Reference	Cancer	Treatment	N	Overall Incidence	Grade 3/4
Kabbinavar (2003)	colon	FU/LV + bevacizumab 5 mg/kg or 10 mg/kg vs FU/LV	104	5 mg/kg, 23%; 10 mg/kg, 28%	0%
Hurwitz (2004)	colon	IFL + bevacizumab 5 mg/kg vs IFL	813	26.5%	0.8%
Kabbinavar (2005)	colon	FU/LV + bevacizumab 5 mg/kg vs FU/LV	209	38%	1%
Giantonio (2007)	colon	FOLFOX4 + bevacizumab 10 mg/kg vs FOLFOX4	829	NR	0.7%
Johnson (2004)	lung	PC + bevacizumab 7.5 mg/kg or 15 mg/kg vs PC	99	7.5 mg/kg, 21%; 15 mg/kg, 42%	1%
Sandler (2006)	lung	PC + bevacizumab 15 mg/kg vs PC	878	NR	3%
Yang (2003)	renal	bevacizumab 3 mg/kg or 10 mg/kg vs placebo	76	3 mg/kg, 41%; 10 mg/kg, 63%	6.5%
Escudier (2007)	renal	IFN + bevacizumab 10 mg/kg vs IFN alone	649	18%	7%

FOLFOX = fluorouracil, leucovorin, oxaliplatin; FU/LV = fluorouracil/leucovorin; IFL= irinotecan, fluorouracil, leucovorin; IFN = interferon alpha-2a; NR = not reported; PC = paclitaxel, carboplatin.

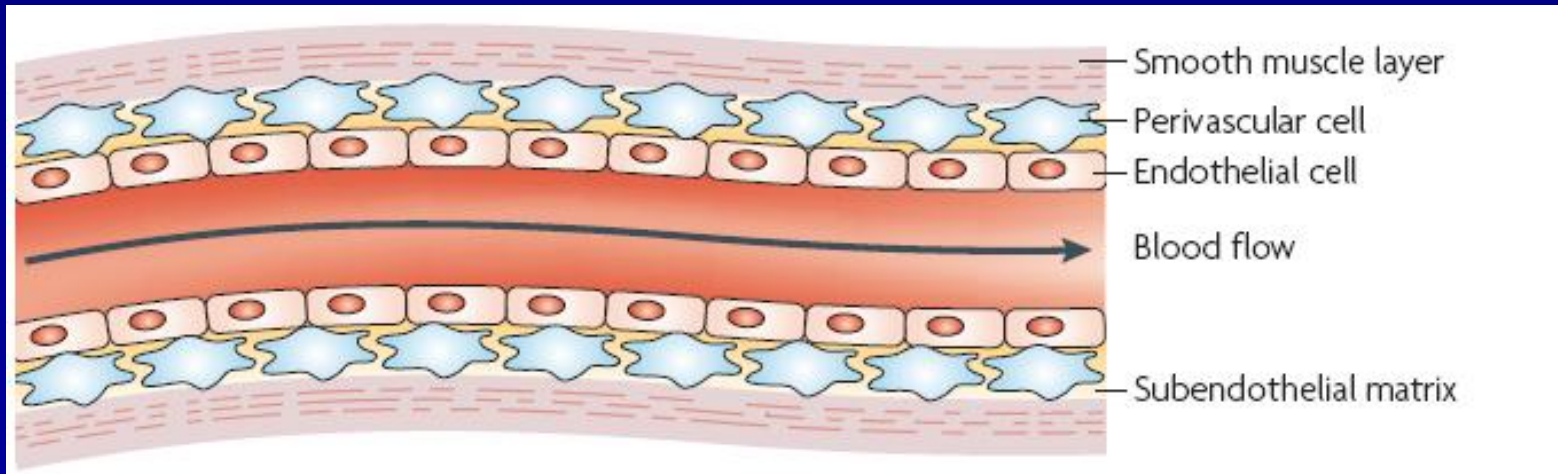
Proteinuria from VEGF inhibitors

- Suggested management:
 - Monitor at BL and thereafter
 - If Gr2 or 3, obtain 24 h protein
 - If <2 g/24 h, continue
 - If >2 g, hold until improvement
 - Discontinue for Gr4 proteinuria

Hypertension

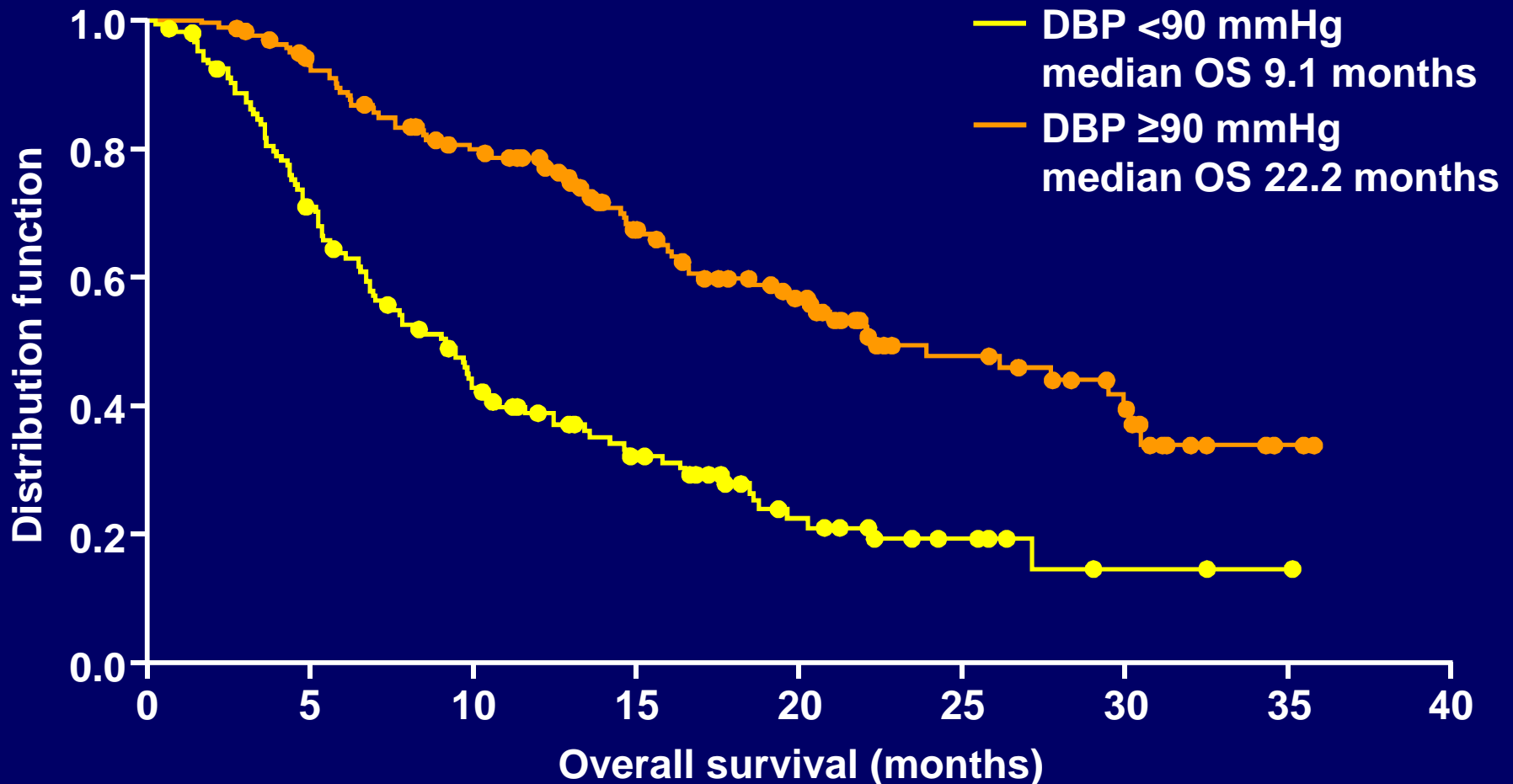
Hypertension: proposed mechanism

- Endothelial cells promote vasodilation via release of NO and PGI₂
- Mediated by VEGFR2
- Endothelial baroreceptors also affected
- VEGF blockade results in increased vascular resistance and systolic hypertension



Association of diastolic blood pressure (dBp) ≥ 90 mmHg with overall survival (OS) in patients treated with axitinib

B. Rini, J. H. Schiller, J. P. Fruehauf, E. E. Cohen, J. C. Tarazi, B. Rosbrook, A. D. Ricart, A. J. Olszanski, S. Kim, J. Spano. *J Clin Oncol* 26: 2008 (May 20 suppl; abstr 3543)



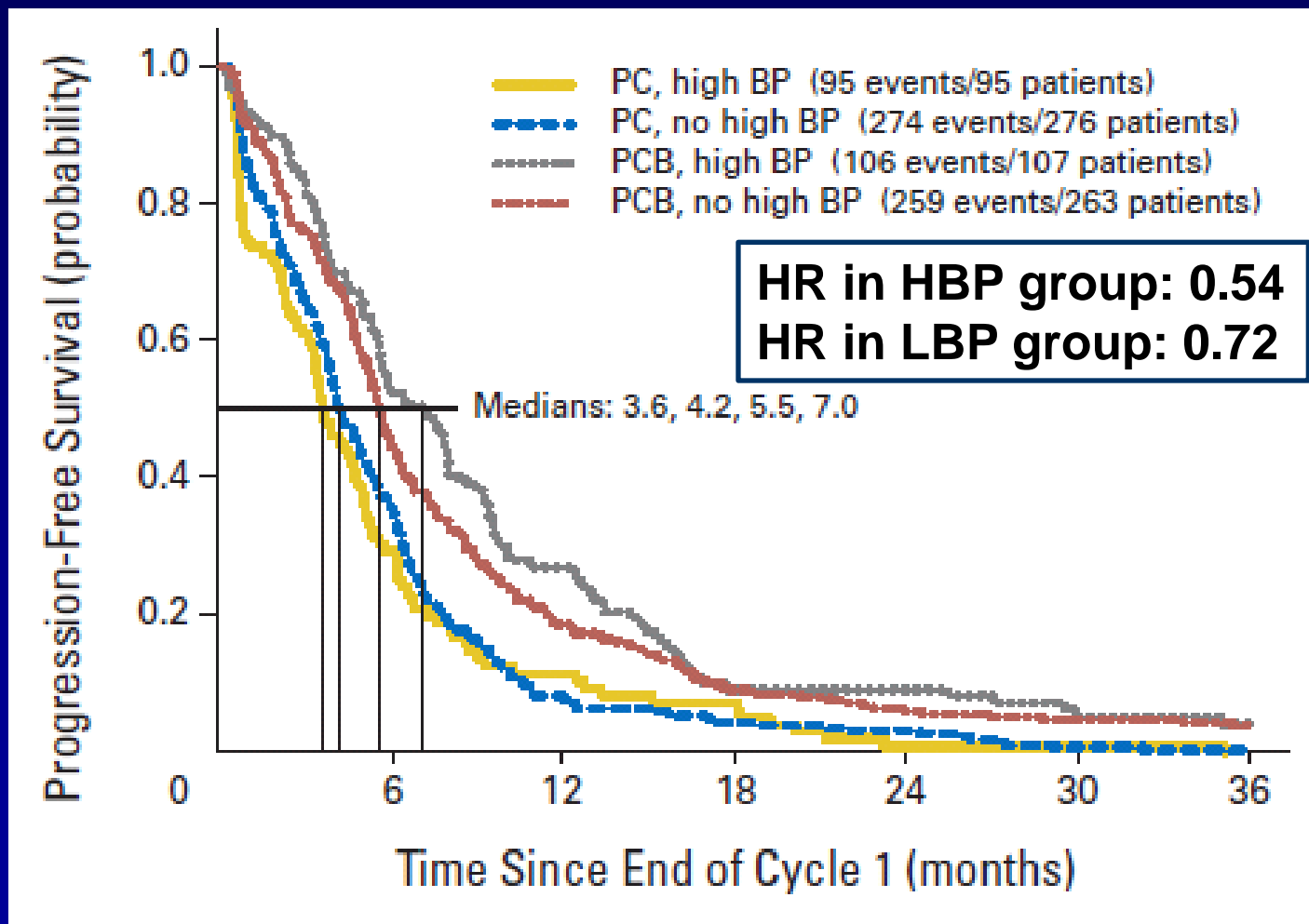
Non-Hematologic Toxicity from ECOG4599

	PC (% n) ≥Grade 3	PCB (% n) ≥Grade 3	p-value
Hemorrhage	3 (0.7)	19 (4.5)	<.001
Hemoptysis	1 (0.2)	8 (1.9)	0.04
CNS	0	4 (1.0)	0.03
GI	2 (0.5)	5 (1.2)	NS
Other	1 (0.2)	4 (1.0)	NS
Hypertension	3 (0.7)	25 (6.0)	<.001
Venous Thrombosis	13 (3.0)	16 (3.8)	NS
Arterial Thrombosis	4 (1.0)	8 (1.9)	NS

Hemoptysis: 7 deaths in PCB arm vs 1 in PC arm.

Other SAE: GI perforation, RPLS, CHF, wound healing complications.

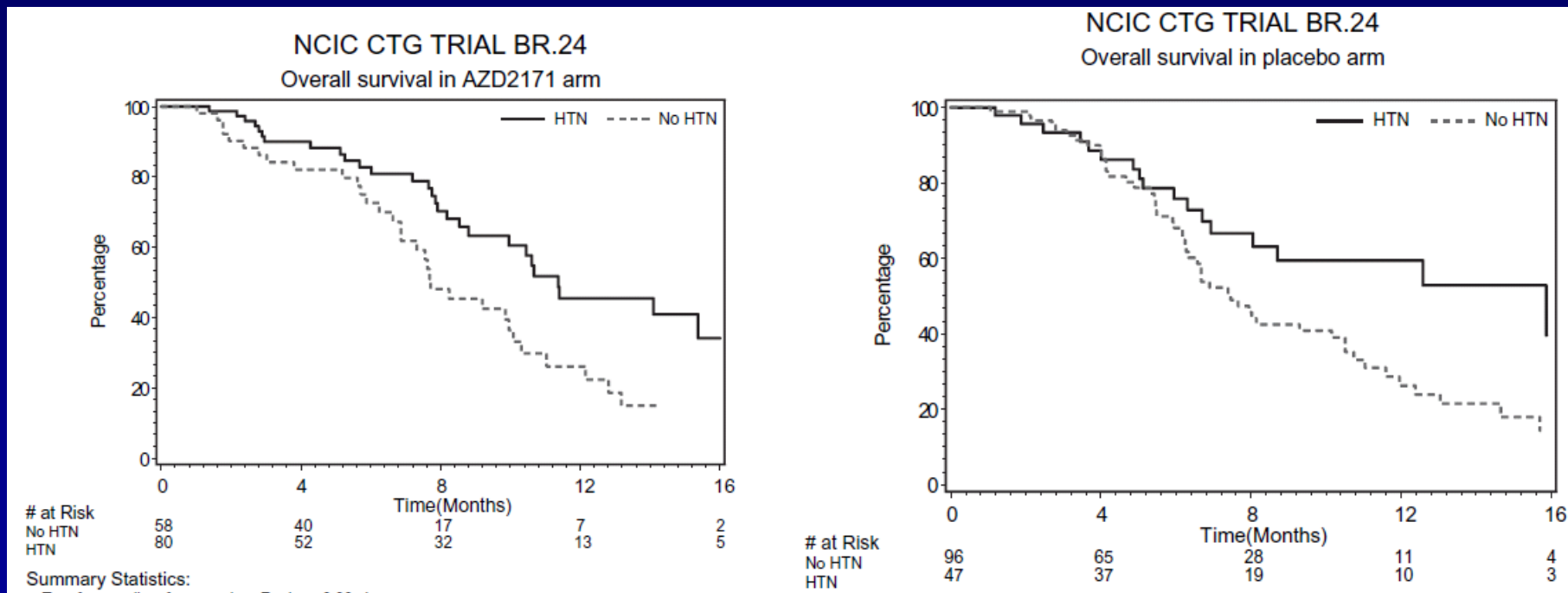
HTN as marker of PFS benefit for BV in ECO4599



HTN as marker of benefit for cediranib in BR24

Cediranib arm

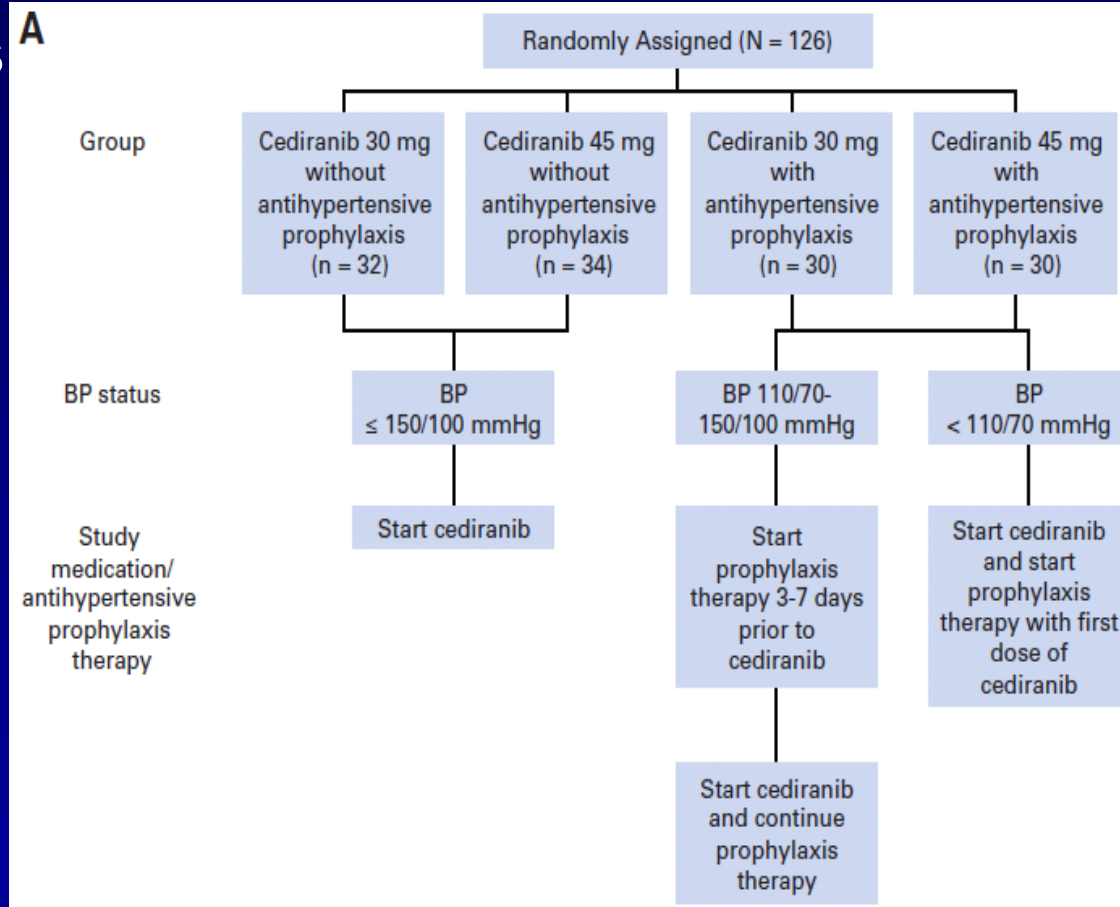
Placebo arm



HTN was associated with improved outcome in both study arms.

Prophylactic use of antihypertensives for VEGF inhibitors

- AZD2171+/- prophylaxis
- Severe HTN in 18 in control group vs 1 in prophylaxis group
- Prophylaxis did not result in fewer drug dose reductions
- Defined HTN regimen was effective when HTN recognized early



Antihypertensive algorithm for VEGF inhibitors

B

Mild to moderate hypertension

BP > 140/90 mmHg on two consecutive occasions > 24 hours apart, or increase in diastolic pressure by ≥ 20 mmHg or to ≥ 100 mmHg or increase in systolic pressure to ≥ 150 mmHg

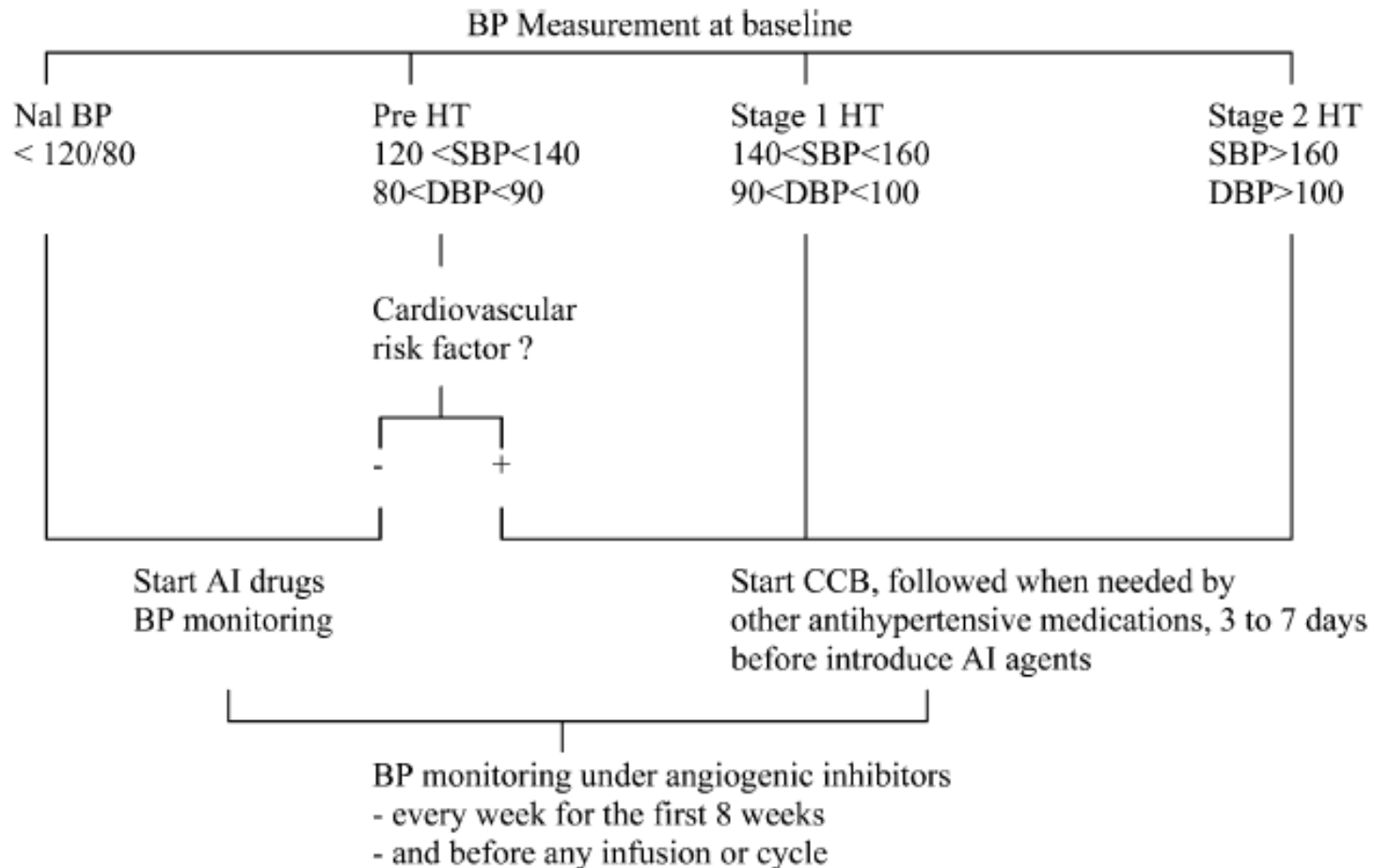
1. Continue cediranib at the same dose and introduce treatment with a CCB*
2. If BP still > 140/90 mmHg after 24 hours increase CCB dose
3. If BP still > 140/90 mmHg after a further 24 hours, add in an additional antihypertensive agent
4. If 24 hours later BP still remains uncontrolled or continues to increase, temporarily stop cediranib until BP $\leq 140/90$ mmHg
5. Restart cediranib (at the same dose or with dose reduction), when BP $\leq 140/90$ mmHg. Continue antihypertensive therapy
6. If BP remains uncontrolled or continues to increase despite dose reduction and maximal antihypertensive treatment, permanently stop cediranib

Severe hypertension

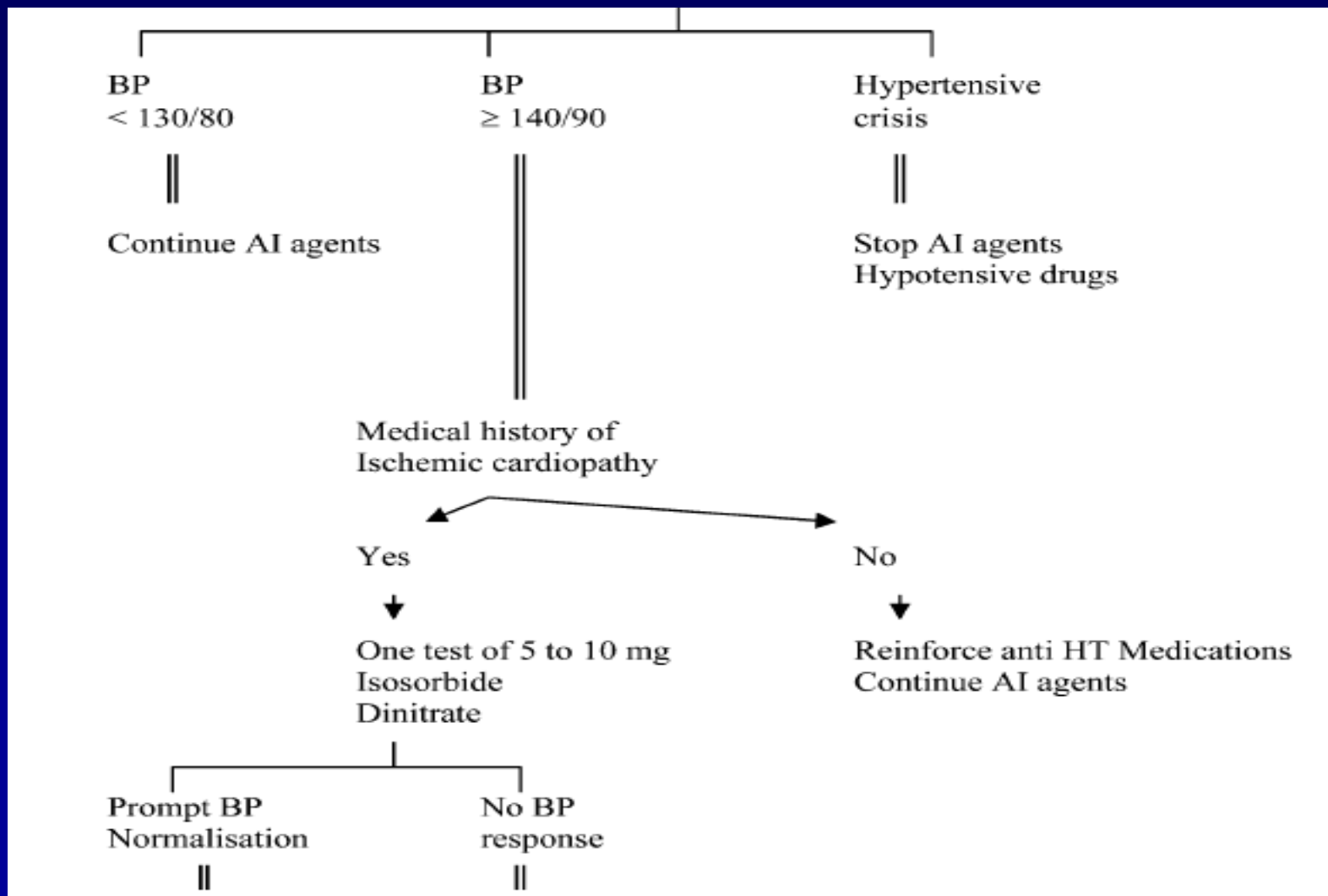
Increase in diastolic pressure to ≥ 110 mmHg or increase in systolic pressure to ≥ 180 mmHg on two readings > 1 hour apart

1. Temporarily stop cediranib and manage patient clinically (consider hospitalization and intravenous therapy as necessary)
2. If BP controlled to $\leq 140/90$ mmHg and where appropriate restart cediranib at a reduced dose level. Continue antihypertensive therapy and monitor BP closely (for at least 7 days to ensure steady state for cediranib)
3. If BP increases after reintroducing cediranib despite antihypertensive therapy, permanently stop cediranib

Proposed algorithm for initial management of HTN from AI



Proposed algorithm for management of persistent HTN from AI



Disease specific side effects:
Pulmonary hemorrhage

Randomized phase II trial of CP +/- BV for NSCLC: identification of novel toxicity (pulmonary hemorrhage) and associated risk factors

- Life threatening hemoptysis in 6/66 patients with carboplatin and paclitaxel (CP) +/- bevacizumab (BV), 4 died.
 - None in CP control arm.
 - Risk factors:
 - Squamous (4/6)
 - central lesions near pulmonary arteries or veins (5/6)
 - cavitation/necrosis (5/6)
- PHASE III EXCLUDED
SQUAMOUS CELL
HISTOLOGY



Novotny et al (2001) Proc ASCO 20: 1318a;
Johnson et al (2004) J. Clin Oncol 22 (11): 2184-91

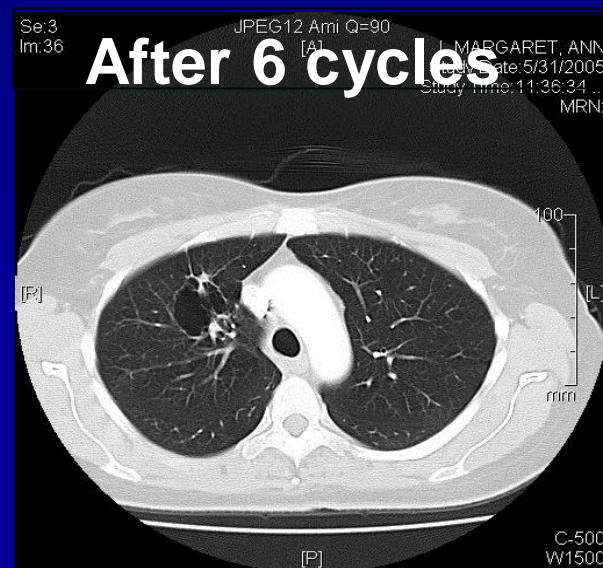
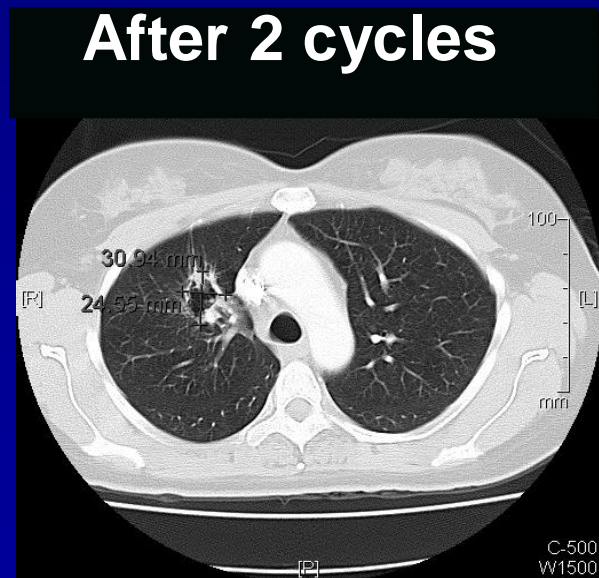
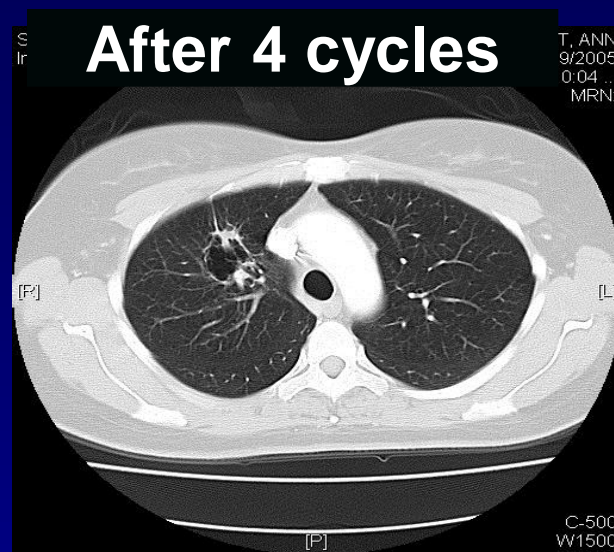
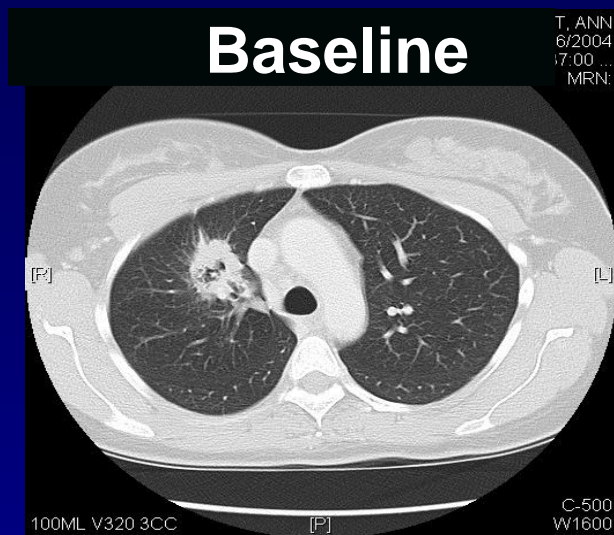
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Patient with NSCLC treated with carboplatin/paclitaxel plus AZD2171 (43 year old female)



Courtesy of Frances Shepherd

Phase III trial of sorafenib, carboplatin and paclitaxel (ESCAPE)

- N=926
- Stopped at planned interim analysis
- DMC concluded that it would not meet primary endpt of improved OS
- Higher mortality observed in patients with squamous cell carcinoma but no increase in hemoptysis was reported.

Adverse events in Phase III ZODIAC study in 2nd line NSCLC (Doc+/- Van)

- No increase in hemoptysis or CNS bleeds
- Neutropenia slightly increased

	Vandetanib+docetaxel (n=689)		Placebo+docetaxel (n=690)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Diarrhoea	289 (42%)	35 (5%)	225 (33%)	28 (4%)
Alopecia	230 (33%)	0	240 (35%)	0
Rash	291 (42%)	63 (9%)	167 (24%)	7 (1%)
Fatigue	209 (30%)	36 (5%)	215 (31%)	36 (5%)
Neutropenia	221 (32%)	199 (29%)	184 (27%)	164 (24%)
Anorexia	200 (29%)	14 (2%)	205 (30%)	10 (1%)
Nausea	159 (23%)	0	220 (32%)	0
Cough	130 (19%)	0	131 (19%)	0
Dyspnoea	119 (17%)	40 (6%)	142 (21%)	51 (7%)
Constipation	118 (17%)	0	140 (20%)	0
Pyrexia	135 (20%)	0	119 (17%)	0
Vomiting	107 (16%)	0	143 (21%)	0
Leukopenia	127 (18%)	99 (14%)	108 (16%)	77 (11%)
Asthenia	107 (16%)	21 (3%)	93 (13%)	18 (3%)
Anaemia	71 (10%)	14 (2%)	103 (15%)	29 (4%)
Myalgia	90 (13%)	0	78 (11%)	0
Insomnia	93 (13%)	0	73 (11%)	0
Stomatitis	82 (12%)	0	80 (12%)	0

Data are n (%). Adverse events are the Medical Dictionary for Regulatory Activities preferred term.

Table 2: Adverse events reported in at least 10% of patients in either group (safety population)

VEGF enhances compensatory lung growth in mice after pneumonectomy

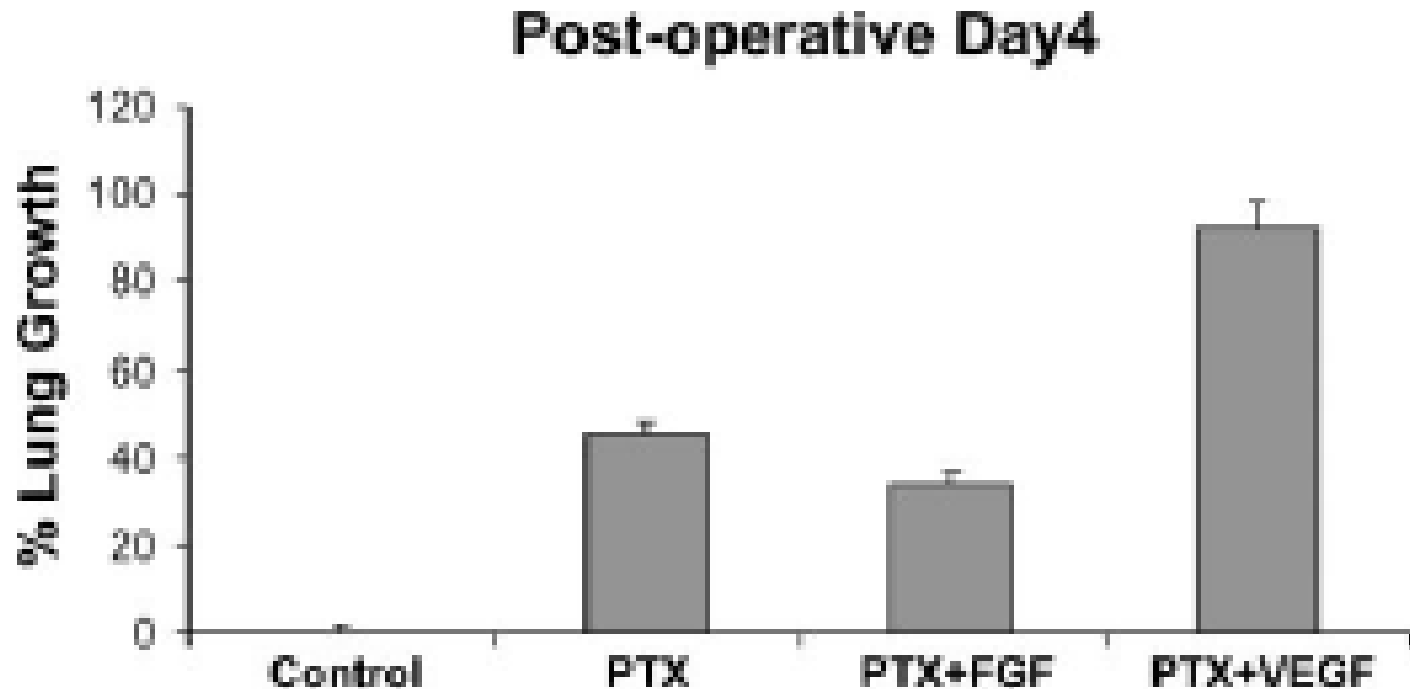


Fig. 3. Percent compensatory lung growth by LV:BW ratio on postoperative day 4 after pneumonectomy (PTX) \pm VEGF and basic fibroblast growth factor (bFGF). Error bars represent SE.

Prevention and management of hemoptysis from AI

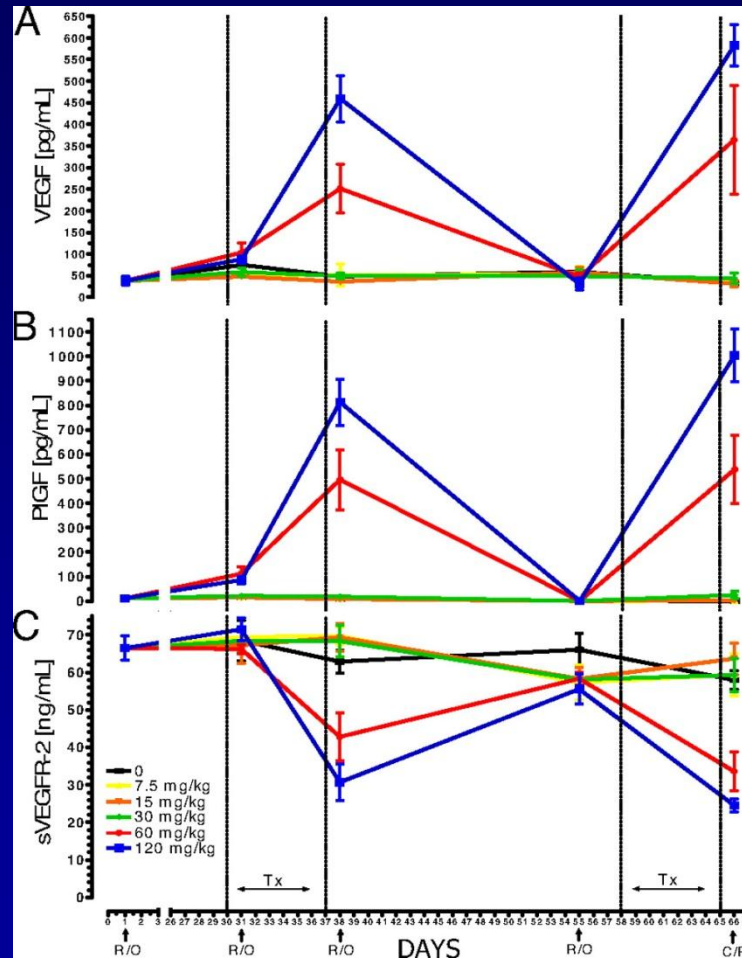
- Avoid use of BV in squamous NSCLC or with pretreatment hemoptysis (>0.5 tsp)
- Caution in patients with full-dose anticoagulation or antiplatelet therapy
- Data with TKIs mixed; it appears some can be given safely
- Novel approaches (e.g. pretreatment XRT to large central regions) are experimental

Frequency and suggested management of other toxicities

Toxicity	Approximate incidence	Suggested management
ATE	3.8% 7.1% in >65 yo 15% if h/o ATE	Discontinue if ATE Caution if >65 or h/o ATE
GI perforation	1.7-2.4% in mCRC	Discontinue Caution if intrabd. Mets or pelvic XRT
CHF	1.7%	Discontinue if ATE Caution if >65 or h/o CHF
RPLS	<0.1%	Manage BP and discontinue

Can we predict toxicities in patients treated with VEGF inhibitors?

Tumor-independent modulation of VEGF, PlGF, and sVEGFR-2 after sunitinib treatment in non-tumor bearing mice.



Ebos et al, PNAS 2007, 104(43):17069-74.

CAFs as markers of toxicity from aflibercept in GBM

- 41 CAFs in 29 patients
- Rise in GCSF, IL-13, bFGF associated with G2-G4 toxicities
 - Rise in IL-13 at 24h and 28d associated with on-target toxicities (HTN, etc)

Cytokines and angiogenic factors (CAFs) as markers of toxicity

- Randomized phase II study of vandetanib+/-CP vs CP
- 35 CAFs in 120 pts measured at BL, during treatment
- Cycle 2 rises in VEGF, GCSF, HGF, IL-2, and other CAFs associated with worsening FACT-L and TOI scores

Summary: VEGF inhibitor toxicities

- VEGF inhibitors cause toxicities distinct from that of chemotherapy
 - Class effects based on physiological role of VEGF
 - Drug- or disease-specific effects
- Typically can be managed with attention to baseline risk factors, co-morbidities, and monitoring during treatment
 - Patient education critical for avoiding preventable toxicities
 - Prophylactic strategies merit further investigation
- VEGFR TKIs may induce host-dependent changes in circulating factors that have biological consequences.

Toxicities from EGFR inhibitors

EGFR Expression and Activity Within the Skin and Hair Follicle

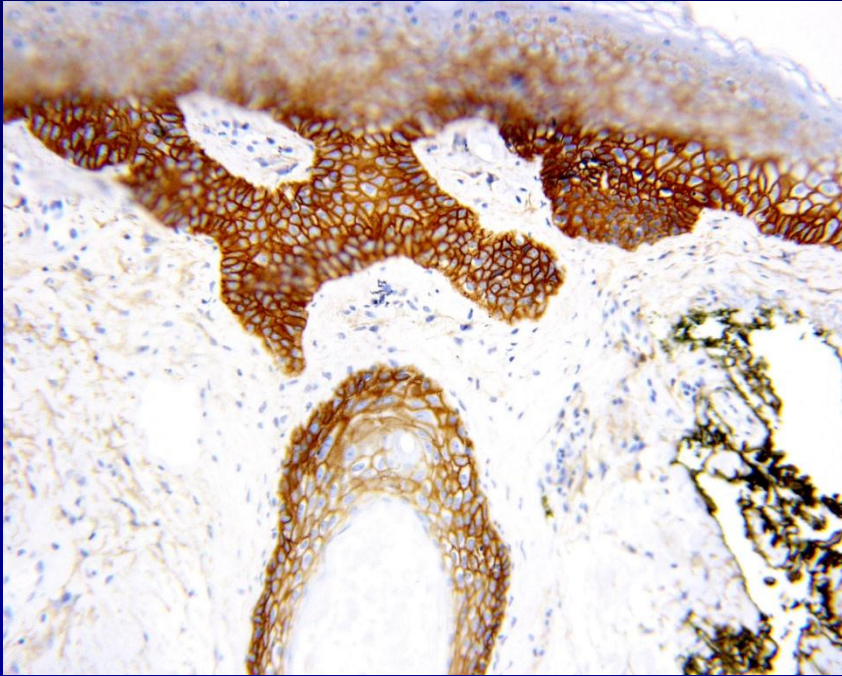
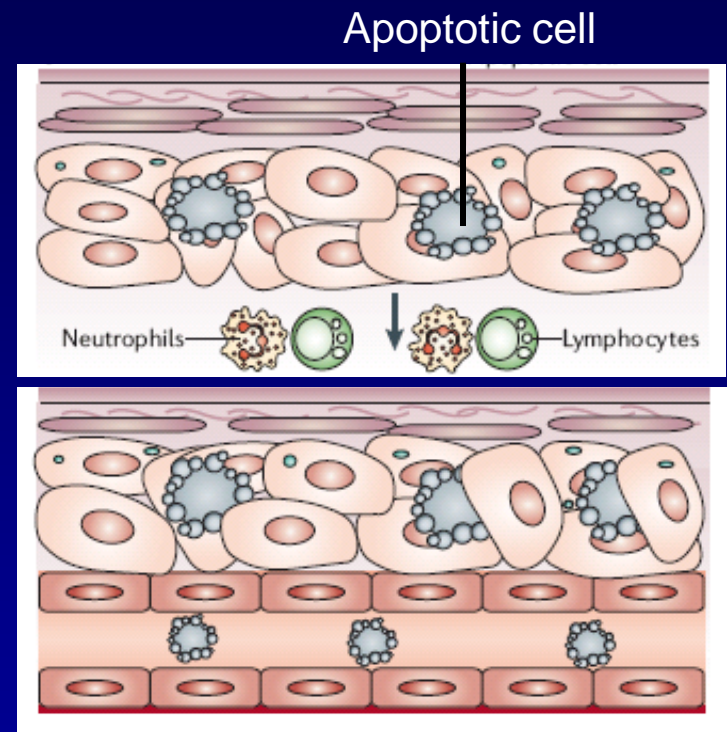


Photo courtesy of Dr. M.E. Lacouture.

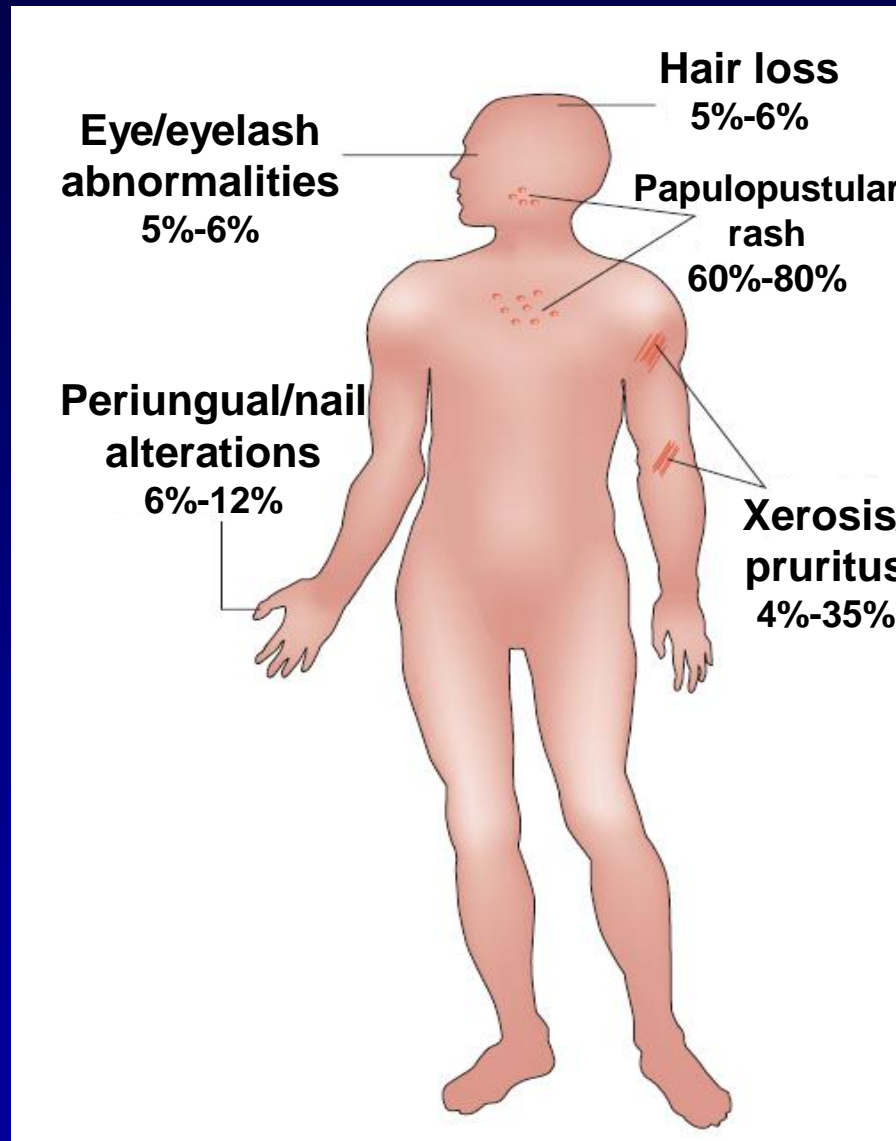
- Expressed in the epidermis, sebaceous glands, periungual tissues, and hair follicle epithelium
- Stimulates epidermal growth
- Inhibits differentiation
- Accelerates wound healing
- Stimulates keratinocyte migration
- Stimulates vasoconstriction

Proposed Mechanism of Dermatological Toxicity

- Inhibition of EGFR in keratinocytes
 - Growth arrest and apoptosis
 - Inflammation and lymphocyte infiltration
 - Abnormalities in cell attachment, differentiation, and migration
- Leads to tissue damage
 - Apoptotic keratinocytes
 - Dilated vessels
 - Decrease in epidermal thickness
 - Thin stratum corneum
- Disturbances in keratinocyte function disrupt function of other cell types, leading to clinical manifestations of EGFR-inhibitor toxicity



Cutaneous Toxicities to EGFR Inhibitors



Rash Treatment: Proposed Algorithm

Severity (CTCAE v.4)

Intervention (Reactive)

Grade 0

Prophylactic therapy with sunscreen SPF \geq 30; moisturizing creams; gentle skin-care instructions given

Continue anticancer agent at current dose and monitor for change in severity

Grade 1

Hydrocortisone 2.5% cream and clindamycin 1% gel qd

Reassess after 2 weeks (either by healthcare professional or patient self-report); if reactions worsen or do not improve proceed to next step

Continue anticancer agent at current dose and monitor for change in severity

Grade 2

Hydrocortisone 2.5 % cream
AND
Doxycycline 100mg OR minocycline 100mg bid

Reassess after 2 weeks (either by healthcare professional or patient self-report); if reactions worsen or do not improve proceed to next step

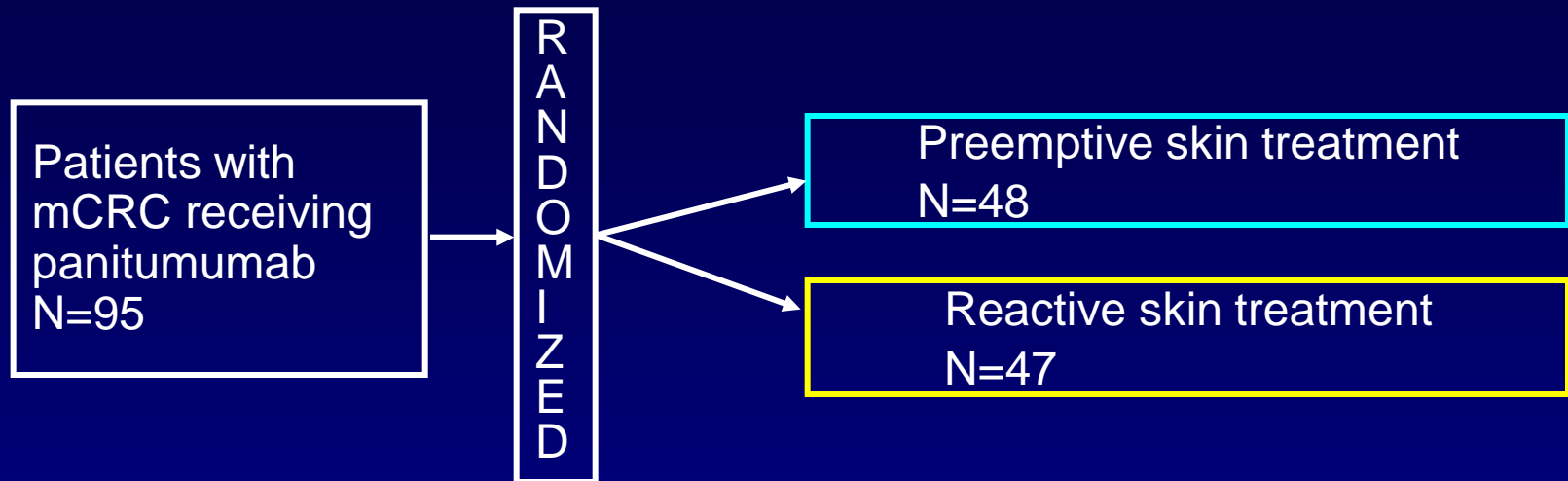
Dose modify as per package insert; obtain bacterial/viral cultures if infection is suspected and continue treatment of skin reaction with the following

Grade 3

Hydrocortisone 2.5 % cream AND
Doxycycline 100mg OR minocycline 100 mg bid AND
Prednisone 0.5mg/kg for 5 days

Reassess after 2 weeks; if reactions worsen or do not improve, dose interruption or discontinuation per package insert may be necessary

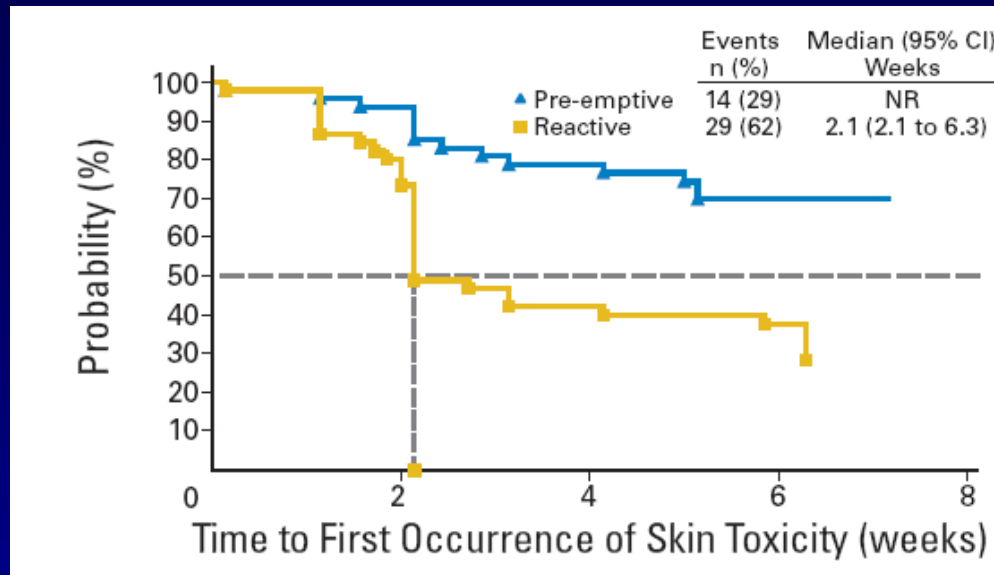
STEPP Trial: Prophylactic Skin Treatment Regimen in Patients With mCRC



- Preemptive treatment
 - Initiated on day 1 of panitumumab therapy, continued weeks 1-6
 - Daily skin moisturizer and 1% hydrocortisone cream applied to face, hands, feet, back, neck, and chest
 - Doxycycline bid
 - Sunscreen on all exposed areas
- Reactive treatment
 - Any treatments deemed necessary by investigator
 - Not prevented from using moisturizer and/or sunscreen

mCRC=metastatic CRC.

STEPP Trial: Results

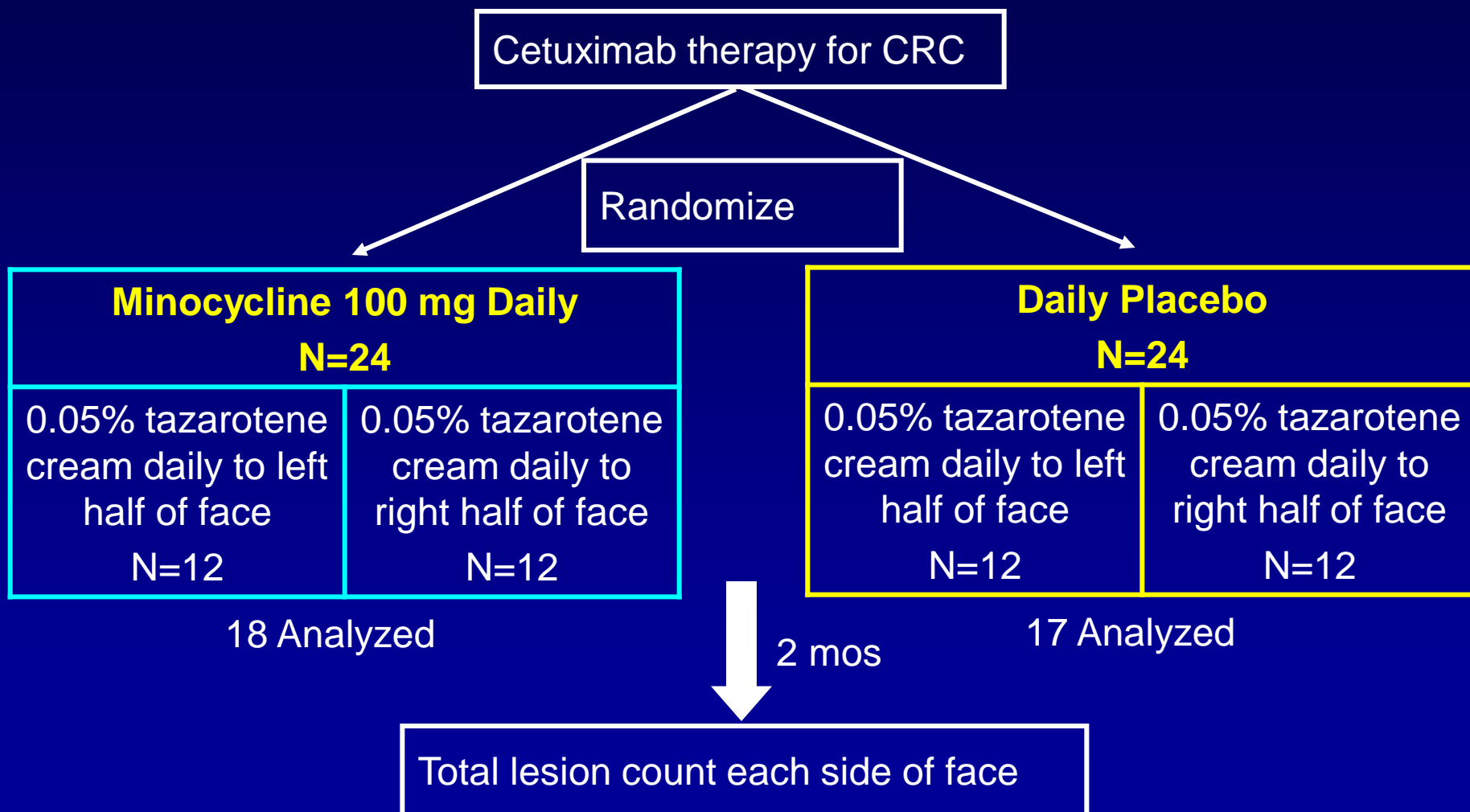


Grade of Skin Toxicity	Preemptive N (%)	Reactive N (%)
2	11 (23)	19 (40)
3	3 (6)	10 (21)
4	0	0

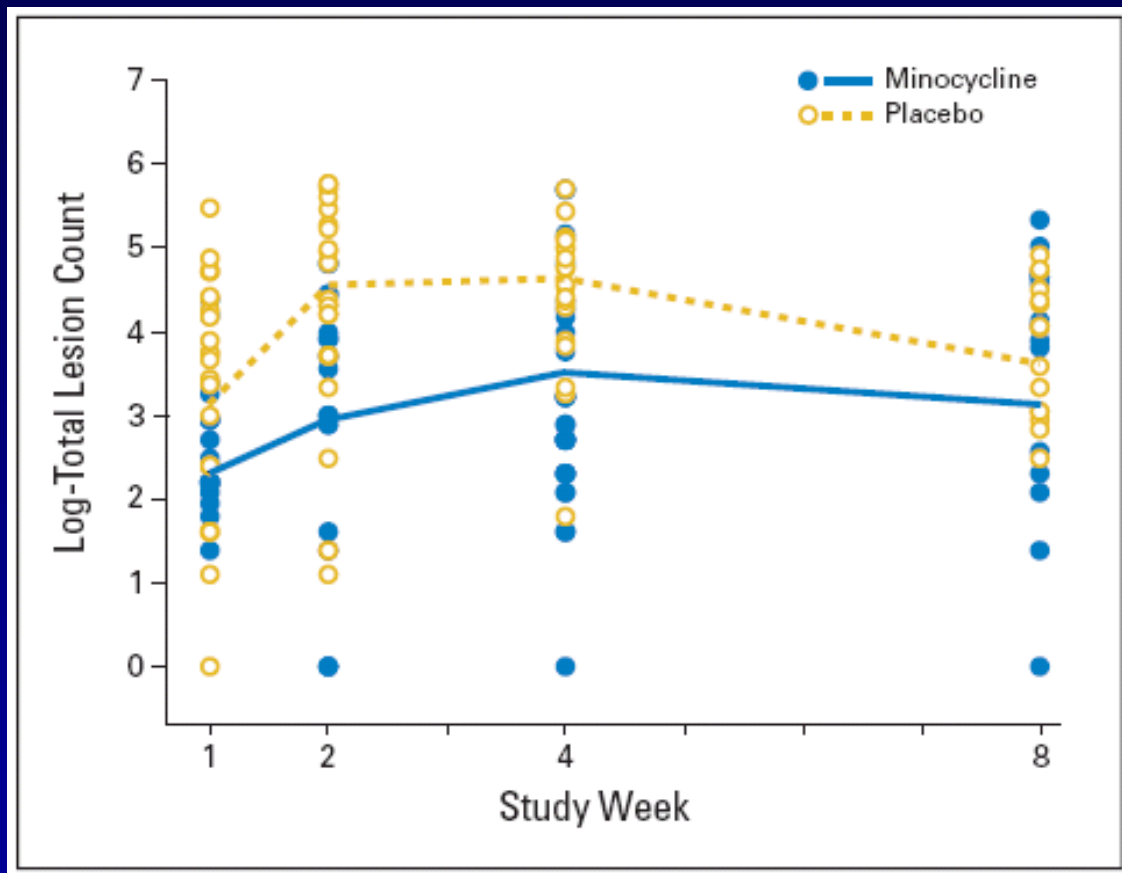
NR=not reached.

Reproduced with permission from Lacouture. *J Clin Oncol.* 2010;28:1351.

Tazarotene and Minocycline for Rash Prevention



Tazarotene and Minocycline for Rash Prevention: Total Lesion Counts



- Prophylaxis with minocycline results in decreased severity of rash in first month of cetuximab therapy

Tazarotene and Minocycline for Rash Prevention

- Prophylactic treatment with minocycline significantly decreases rash severity during the first month of cetuximab therapy
 - Prophylaxis beyond 8 weeks is not beneficial
- Application of tazarotene has no clinical benefit and, in some cases, exacerbated the rash

Patient Education

- Patient education about cutaneous toxicities is essential for optimal patient compliance and management of rash
- Information for patients
 - Rash is common, not indicative of allergy
 - Description of rash appearance aids in recognition of early symptoms
 - Inform healthcare provider at first sign of rash
- Patient education should ideally occur when
 - Appropriate family members/caregivers are present
 - The patient and/or family are calm and able to absorb new information
- Written information about dosing, schedule, and cutaneous side effects is often helpful

Summary

- Skin reactions to EGFR inhibitors are common
- Rash
 - Proactively hydrate skin and minimize sun exposure
 - Monitor closely and promptly manage
 - Associated with response
- Prophylactic minocycline or tetracycline may reduce the likelihood of severe rash
- Dry and itchy skin, paronychia inflammation, and hair changes are less common than rash
- Patient education is key to managing side effects and avoiding dose reduction or discontinuation