

Vascular disrupting agents in NSCLC

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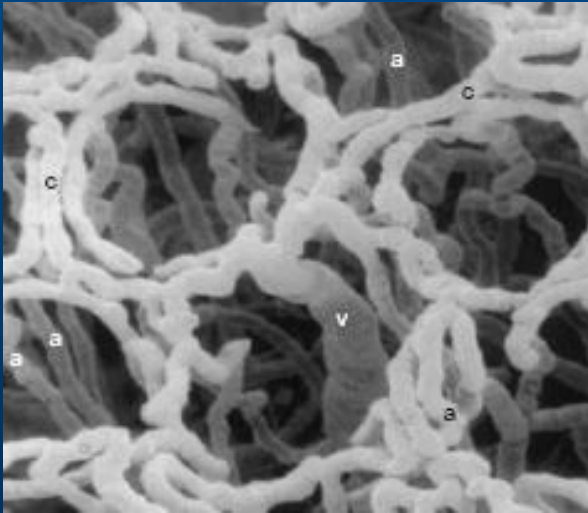
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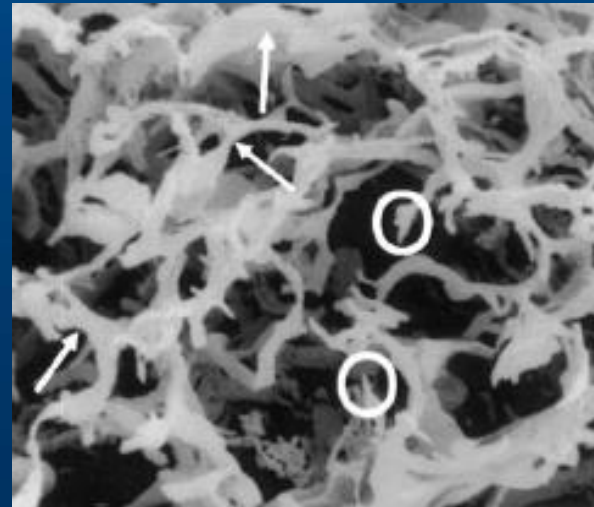
Unique Characteristics of the Tumor Vasculature

Normal tissue vasculature



- Organized hierarchy
- Homogeneous architecture
- Mature vessels with well-developed smooth muscle and pericytes

Tumor vasculature



- Lack of hierarchy
- Highly disorganized
- Heterogeneous with irregular shape
- Leaky 'sprouts'
- Immature vessels

a = arterioles; c = capillaries; v = veins; changing vessel diameters arrowed; blind ends circled

Tozer G, et al. *Nat Rev Cancer*. 2005; **5**:423–435. Patterson DM & Rustin G. *Clin Oncol (R Coll Radiol)*. 2007; **19**:443–456. Carmeliet P & Jain RK. *Nature*. 2000; **407**:249–257. Gee MS, et al. *Am J Pathol*. 2003; **162**:183–193. Images (scanning electron micrographs of polymer microvascular casts) of normal colorectal mucosa and of human sigmoidal adenocarcinoma, used with permission: Konerding MA, et al. *Br J Cancer*. 2001; **84**:1354–1362.

Rationale for Targeting the Abnormal Tumor Vasculature

- Unique features of tumor vasculature → opportunity for selective treatment^{1–8}
- Tumor vasculature abnormal → sensitive to disruption^{4–9}
- Tumor endothelium more accessible than tumor cells → improved drug delivery¹⁰
- Endothelial cells more genetically stable than cancer cells → drug resistance less likely¹⁰

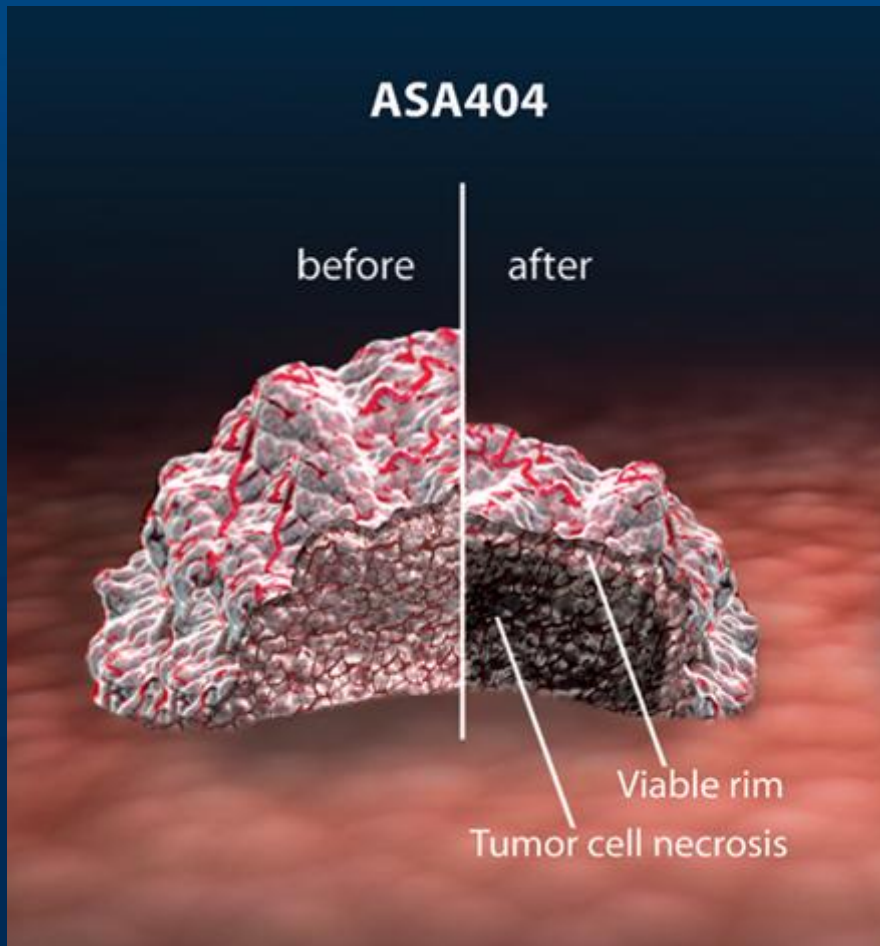
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**Tumor-VDAs:
A Novel and Promising Class
of Anti-Cancer Agents**

Tumor-VDAs: A Novel and Promising Class of Anti-Cancer Agents

- Disrupt tumor vasculature, inhibit tumor blood flow and cause extensive tumor necrosis
- Unique mechanism of action, different from anti-angiogenic agents
 - Direct disruption of existing vessels and related vascular endothelial cells rather than inhibiting development of neovessels
 - Expected to have distinct tolerability profile
- Potential to affect inaccessible tumor regions that are resistant to conventional cytotoxic therapies
 - Synergy with chemotherapeutic agents

Mechanism of Anti-Tumor Effects



- Disrupts established blood vessels
- Causes vessel occlusion and inhibition of blood flow
- Deprives tumors of necessary nutrients
- Leads to tumor necrosis, with major effect at tumor core
- Rim of viable cells remains
 - Combination with other agents may therefore provide synergistic anti-tumor activity

Conceptual anti-tumor effects of Tumor-VDA

Classes of Tumor-VDAs: Flavonoids and Tubulin-Binding Agents

Flavonoid

Tubulin-binding

Structure

- Flavonoid structure
- Aromatic stilbenes and colchicine analogues or synthetic peptides

Molecular target

- Under investigation (tubulin independent)
- Bind to β -tubulin at the colchicine or vinca alkaloid site

Key anti-vascular effects

- Direct effect: tumor endothelial cell apoptosis \rightarrow rapid inhibition of tumor blood flow
- Indirect effect: Induction of TNF- α , nitric oxide and other cytokines \rightarrow sustained inhibition of tumor blood flow (≥ 24 h)
- Direct effect: tumor endothelial tubulin depolymerization \rightarrow cytoskeletal remodeling \rightarrow inhibition of blood flow
- No known cytokine induction

Tumor-vascular disrupting agents

Drugs	TNF α	NO	Tubulin	Other
Flavonoïds				
FAA	+	-	-	-
ASA 404	+	+	-	-
Tubulin binding				
CA4P	-	-	+	-
ZD6126	-	-	+	-
ABT 151	-	-	+	-
AVE8062A	-	-	+	-
OXi4530	-	-	+	-
Dolostatin	-	-	+	-
Auristatin	-	-	+	-
OTHERS				
Thalidomide	+	-	-	-
Exherin	-	-	-	N Cadherin
Cilengitide	-	-	-	Integrin
TNP 470	-	-	-	MethAminoPeptidase
NPI 2358	-	-	+	Tubulin Dimerization

Phase I Dose-Limiting Toxicities (DLT) for Tumor-VDA Classes

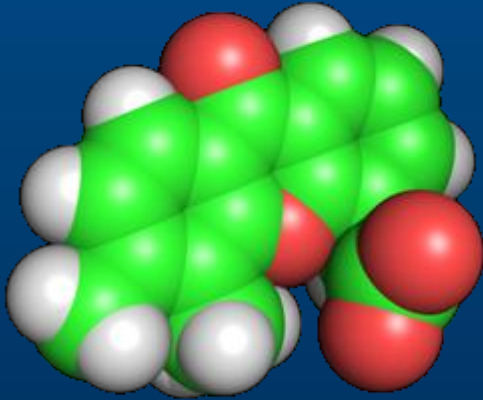
Drug	Treatment schedule	Dose range (mg/m ²)	DLT
ASA404	Weekly d 1 q3w	6–4900 IV	Urinary incontinence, visual disturbance, anxiety ^{1,2}
CA4P	d 1, 8, 15 q4w d 1–5 q3w d 1 q3w	5–114 IV 6–75 IV 18–90 IV	Bowel ischemia, tumor pain, vagal syncope, neuropathy, ataxia, cardiac ischemia ^{3–5}
AVE8062	d 1, 8, 15 q4	4.5–40 IV	Transient myocardial ischemia, hypotension ⁶
ZD6126	Weekly d 1 q3w d 1 q3w	5–28 IV 5–40 IV 5–112 IV	Myocardial infarction, pulmonary embolus, left ventricular ejection fraction decrease, fatigue ^{7–9}
MN-029	Every 3 weeks	4–180 IV	Reversible cardiac ischemia ¹⁰
ABT-751	qd 7 days q3w bid 7 days q3w	200–300 mg PO 125–175 mg PO	Ileus, constipation, fatigue, abdominal pain, neuropathy ¹¹
TZT-1027	d 1, 8 q3w d 1, 8 q3w/carbo AUC4–5 d 1 q3w	1.35–2.7 IV 1.6–2.0 IV 1.35–3.0 IV	Neutropenia, pain infusion arm, peripheral neuropathy, fatigue, ileus ^{12–13}

■ Flavonoid ■ Combretastatin family tubulin-binders ■ Other tubulin-binders

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**Tumor-VDAs in Clinical
Development for NSCLC
ASA 404 (Vadimezan)**

ASA404 (Vadimezan): A Flavonoid Tumor-VDA



- 5,6-dimethylxanthenone-4-acetic acid (DMXAA)
- Small molecule Tumor-VDA
 - Second-generation flavonoid
 - Tubulin independent
- Immediate molecular target still under investigation
- Selectively disrupts tumor vasculature via direct and indirect effects
 - Causes endothelial cell apoptosis
 - Induces cytokines

Phase IB/II: Overall Survival with First-Line ASA404 + P/C in NSCLC

Treatment on day 1 of 3-week cycle;
up to 6 cycles

Histologically confirmed
Stage IIIB/IV
NSCLC

First-line CT
naïve

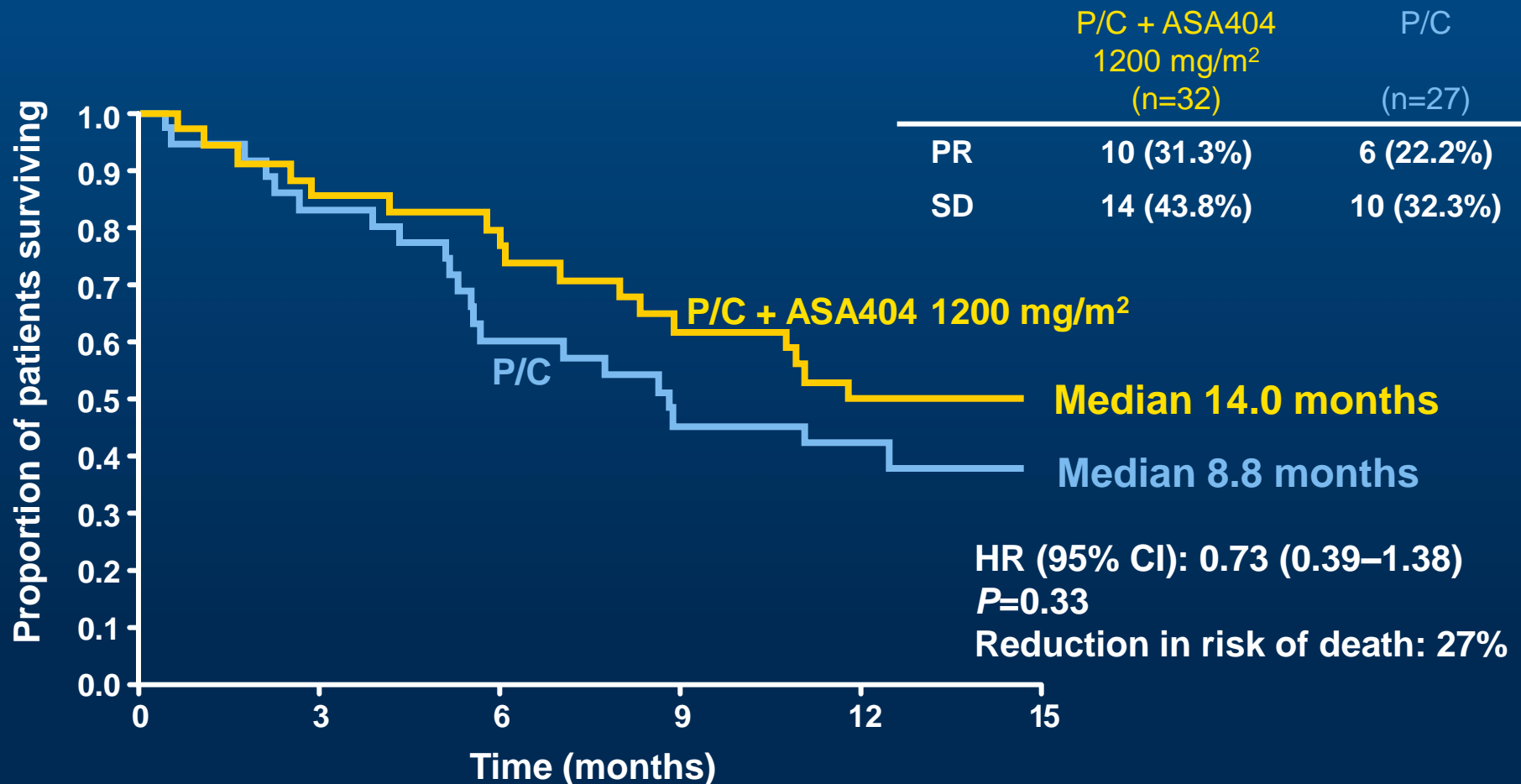
Enrolled
patients
N=73

Paclitaxel
(175 mg/m² IV x 3
h)
+
Carboplatin
(AUC 6 IV x 30
min)
+
ASA404
(1200 mg/m² IV x
20 min)

Follow-up visits
with radiologic
assessments
every
6 weeks until
disease
progression

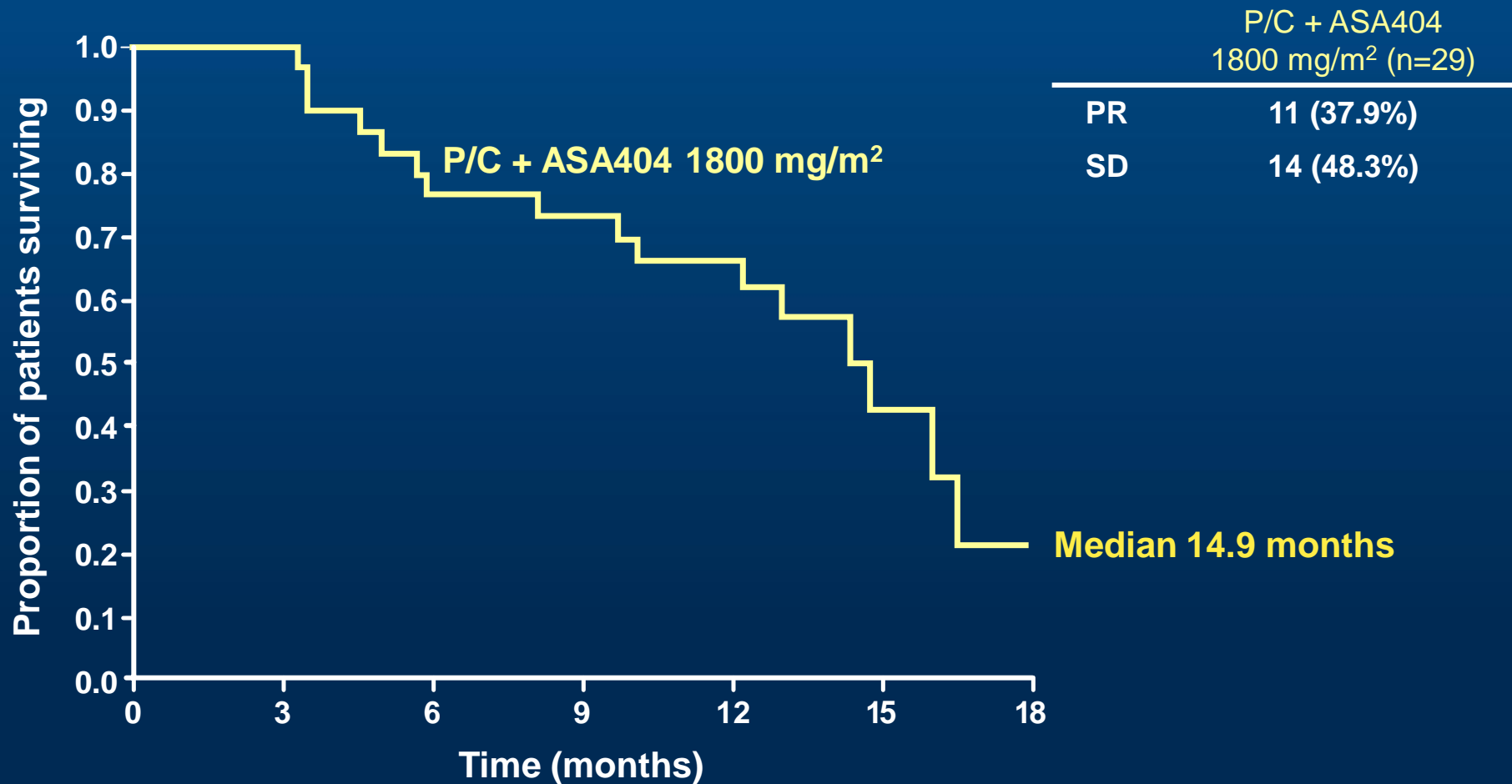
Patients
followed for
survival every
3 months after
disease
progression

Phase IB/II: Overall Survival with First-Line ASA404 + P/C in NSCLC



HR = hazard ratio; PR = partial response; SD = stable disease; P/C = paclitaxel/carboplatin

Phase II Extension: Overall Survival with First-Line P/C + ASA404 1800 mg/m²



HR = hazard ratio; PR = partial response; SD = stable disease; P/C = paclitaxel/carboplatin

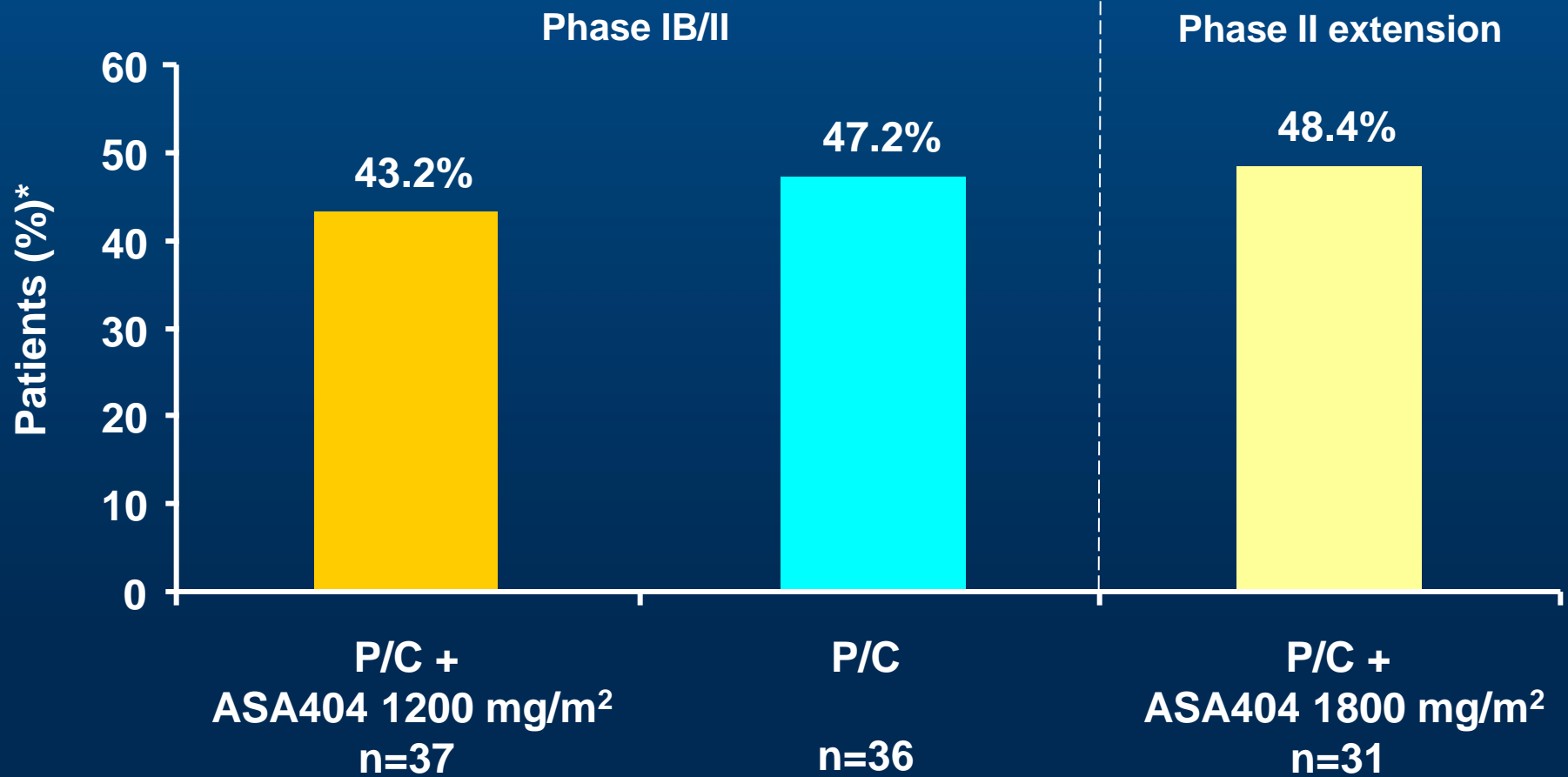
Phase IB/II Efficacy: Activity in Both Squamous and Non-Squamous NSCLC

	P/C + ASA404*		P/C		P/C + ASA404*	P/C
	Squamous	Non-squamous	Squamous	Non-squamous	All histologies	
ORR (%)	40	31.7	14.3	25.0	31.3	22.2
TTP	5.6	5.5	1.6	4.8	5.5	4.4
MST (months)	10.2 (n=21)	14.9 (n=43)	5.5 (n=11)	11.0 (n=25)	14.5 (n=64)	8.8 (n=36)

*1200/1800 mg/m² pooled data

MST = median survival time; ORR = overall response rate; P/C = paclitaxel/carboplatin; TTP = time to tumor progression

Phase II Safety: Similar Rate of SAEs with P/C + ASA404 vs P/C Alone



*Percent of patients with one or more treatment-emergent serious AEs

ATTRACT-1: First-Line Study of ASA404 in NSCLC

Phase III, randomized, double-blind,
placebo-controlled multicenter study of ASA404
in combination with paclitaxel and carboplatin as
first-line treatment for
locally advanced or metastatic
(Stage IIIB/IV) NSCLC

ATTRACT-1: Study Design

- Stage IIIB/IV NSCLC
- All histologies
- First-line CT naïve
- PS 0 or 1
- Stratification:
 - Gender
 - Squamous vs non-squamous

N=1200

Paclitaxel + carboplatin + ASA404

Primary endpoint: overall survival

Paclitaxel + carboplatin + placebo

- Study drug maintenance treatment
- After completion of 6 cycles
 - Up to progression

- Paclitaxel 200 mg/m², carboplatin AUC 6, and ASA404 1800 mg/m² or placebo
- Day 1, every 3 weeks, up to 6 cycles

ATTRACT-1: Participating Countries

Argentina
Australia
Belgium
Brazil
Canada
China
Czech Republic
France
Germany
Greece
Hong Kong
Hungary
Israel
Italy
Japan
Korea, Republic
Netherlands
New Zealand
Poland
Singapore
Spain
Sweden
Taiwan
Turkey
UK
USA



TERMINATED EARLY FOR FUTILITY

ATTRACT-2 (CASA404A2302)

A Phase III, Randomized, Double-Blind,
Placebo-Controlled Multicenter Study of ASA404 in
Combination With Docetaxel in Second-Line Treatment
of Patients With Locally Advanced or Metastatic
(Stage IIIB/IV) NSCLC

ATTRACT-2: Study Design

- Stage IIIB/IV NSCLC
- Progression on/after first-line CT
- All histologies
- WHO PS 0–2
- Stratification:
 - PS 0–1 vs 2
 - Squamous vs non-squamous
 - Prior treatment with vs without first-line paclitaxel-based regimen

N=900

Docetaxel + ASA404

Primary endpoint: overall survival

Docetaxel + placebo

- ⊗ Docetaxel 75 mg/m² and ASA404 1800 mg/m² or placebo
- ⊗ Day 1, q3w, one cycle = 21 days
 - Continue until progression, unacceptable toxicity or withdrawal of consent
- ⊗ Study drug maintenance treatment
 - Optional following completion of 6 cycles of protocol treatment and no disease progression
 - OR
 - No earlier than cycle 3 following one dose reduction of docetaxel and if persistent docetaxel-related toxicities occur

ATTRACT-2: Participating Countries

Argentina
Belgium
Brazil
Canada
China
France
Germany
Hungary
Italy
Japan
Mexico
Netherlands
Poland
South Africa
Spain
Switzerland
Thailand
Turkey
UK
USA



-Still on going

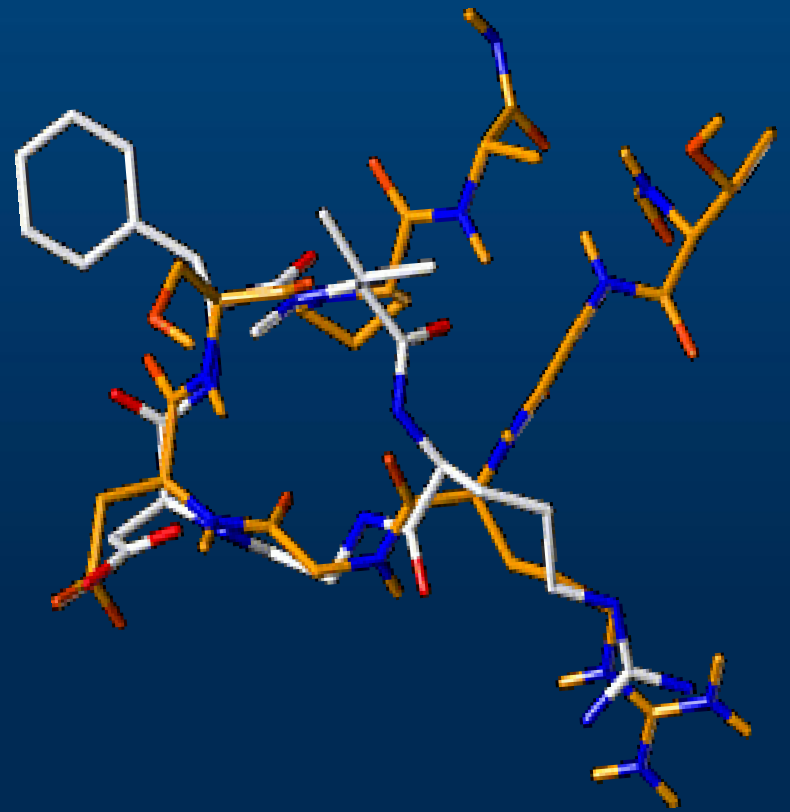
-End of accrual planned late 2010

**Tumor-VDAs in Clinical
Development for NSCLC
Cilengitide**

Cilengitide: Integrin Inhibitor

Cilengitide (EMD 121974, NCE)

- RGD-containing pentapeptide
- Inhibitor of integrins
- Cyclized Arg-Gly-Asp ($\alpha\text{v}\beta\text{3}$, $\alpha\text{v}\beta\text{5}$)
- Angiogenesis inhibition demonstrated in preclinical trials
- Thought to have direct anti-tumor and anti-invasive properties
- Potential for synergistic anti-tumor effect with XRT and chemotherapy



Cyclo-(Arg-Gly-Asp-DPhe-NMeVal)

Single Agent Activity in Glioblastoma and Anaplastic Astrocytoma

Integrin Inhibitors Reaching the Clinic

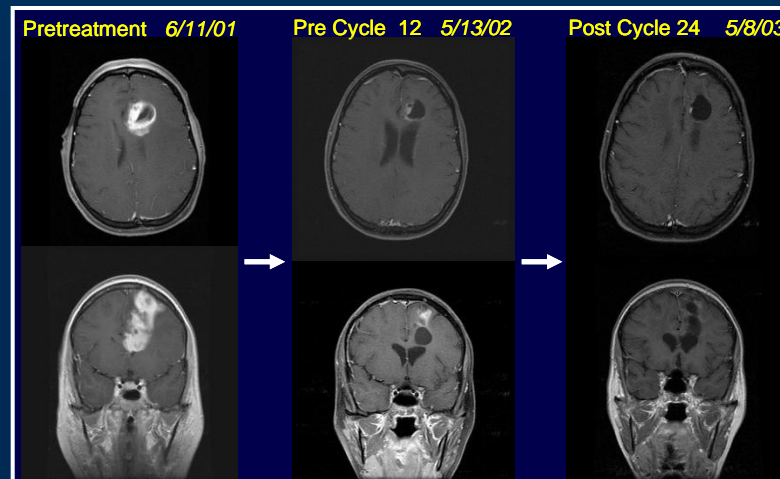
JOURNAL OF CLINICAL ONCOLOGY

Roger Stupp, *Multidisciplinary Oncology Center, University of Lausanne Hospitals, Lausanne, Switzerland*
Curzio Ruegg, *Multidisciplinary Oncology Center, University of Lausanne Hospitals, and the Swiss Institute for Experimental Cancer Research, National Center of Competence in Research Molecular Oncology, Epalinges, Lausanne, Switzerland*

Phase I and Correlative Biology Study of Cilengitide in Patients With Recurrent Malignant Glioma

L. Burt Nabors, Tom Mikkelsen, Steven S. Rosenfeld, Fred Hochberg, Narasimha S. Akella, Joy D. Fisher, Gretchen A. Cloud, Yu Zhang, Kathryn Carson, Sabine M. Wittemer, A. Dimitrios Colevas, and Stuart A. Grossman
J Clin Oncol 25:1651-1657. © 2007

51 pts: 120–2400mg/m²
no MTD
2CRs, 3PRs (4SD)



Study 003

Randomized, phase II study of three doses of the integrin inhibitor cilengitide versus docetaxel as second-line treatment for patients with advanced non-small cell lung cancer

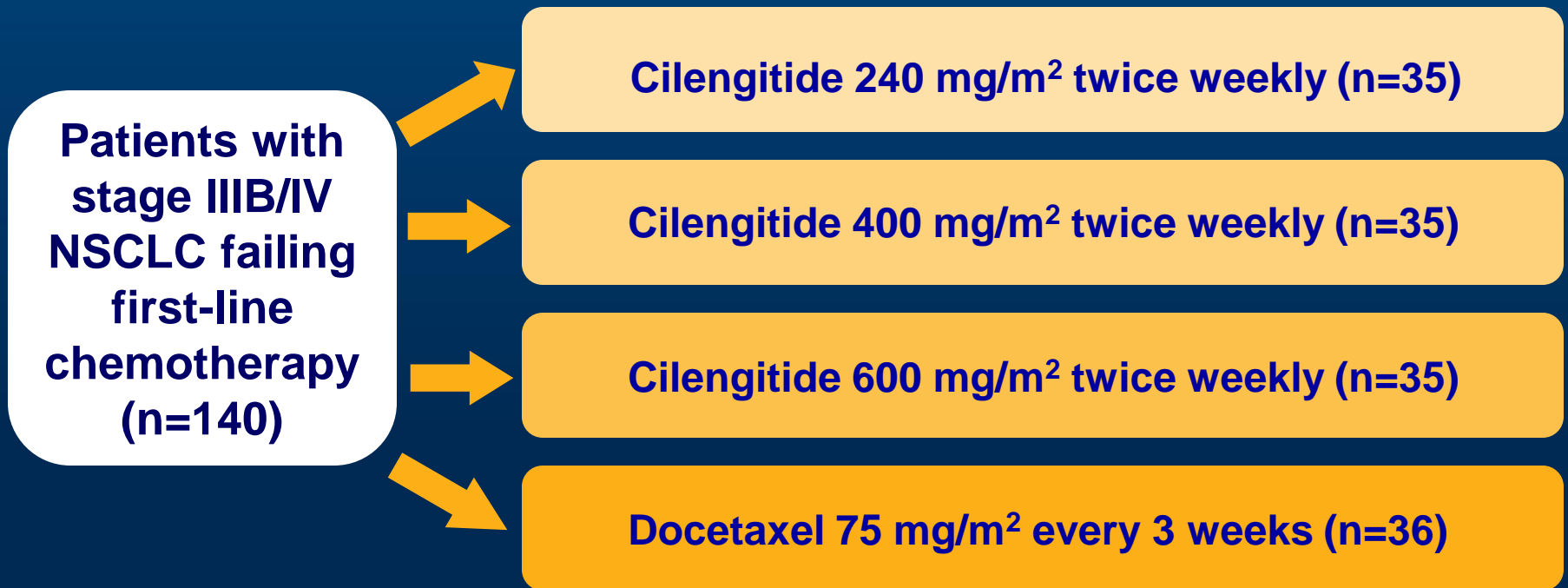
Manegold C, et al. WCLC 2009; Abstract No: D2.2

CERTO-IM - Lyon 15/16.06.2010

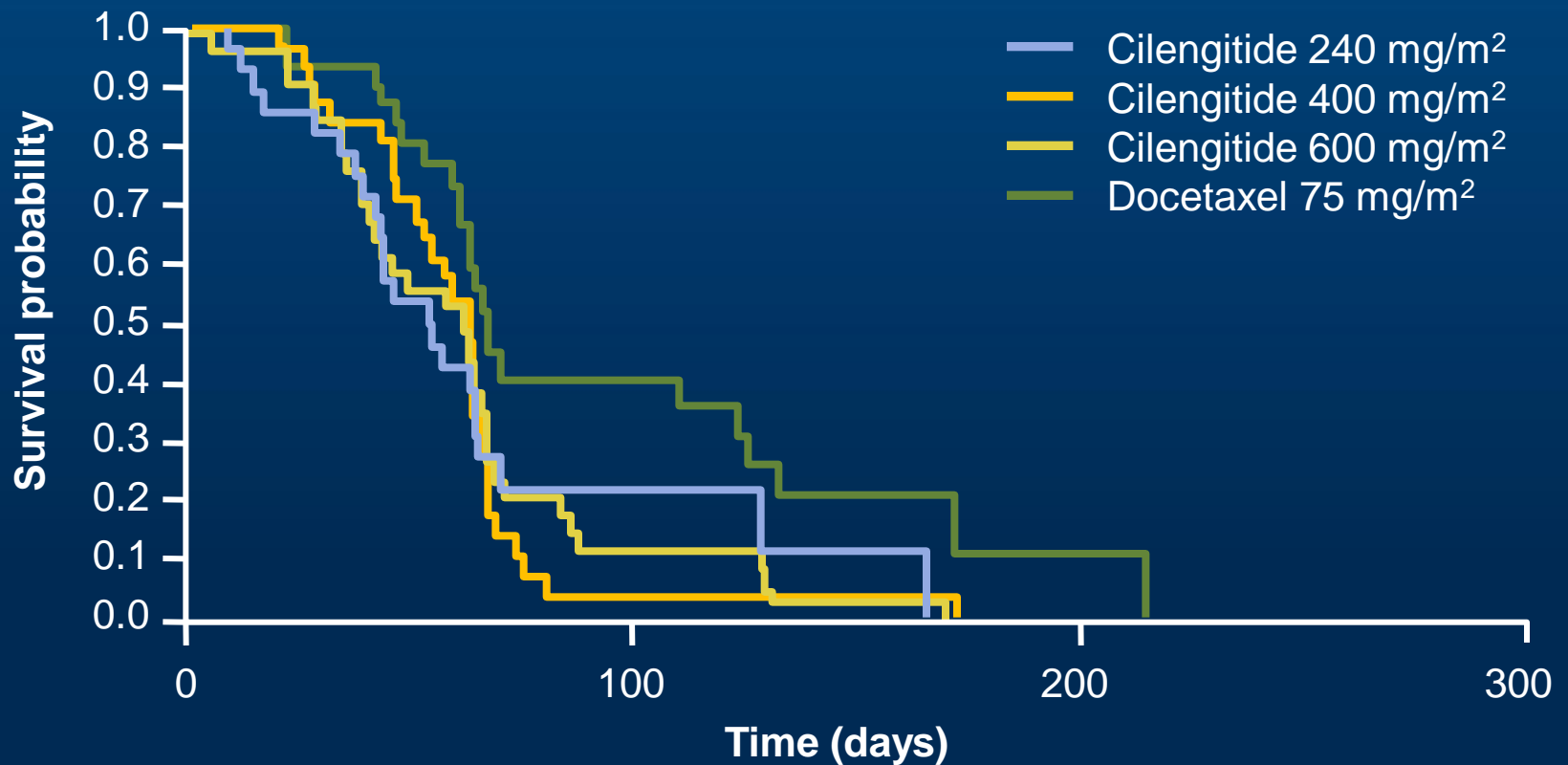
Study Design

- Randomized, multinational (7 countries), multicenter (30 centers), open-label, phase II study

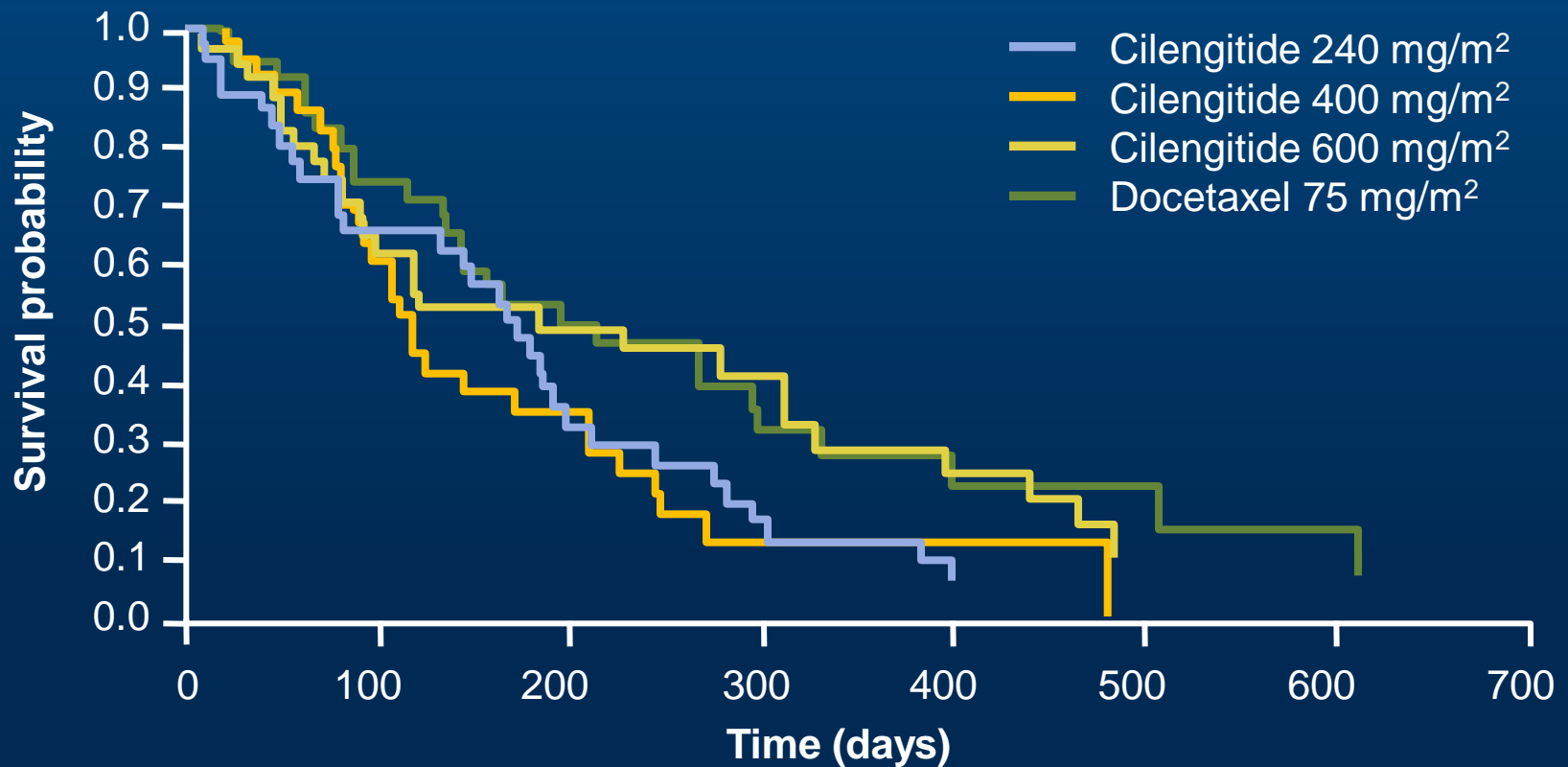
Primary endpoint: progression-free survival (PFS)



Primary Endpoint: Progression-Free Survival



Overall Survival



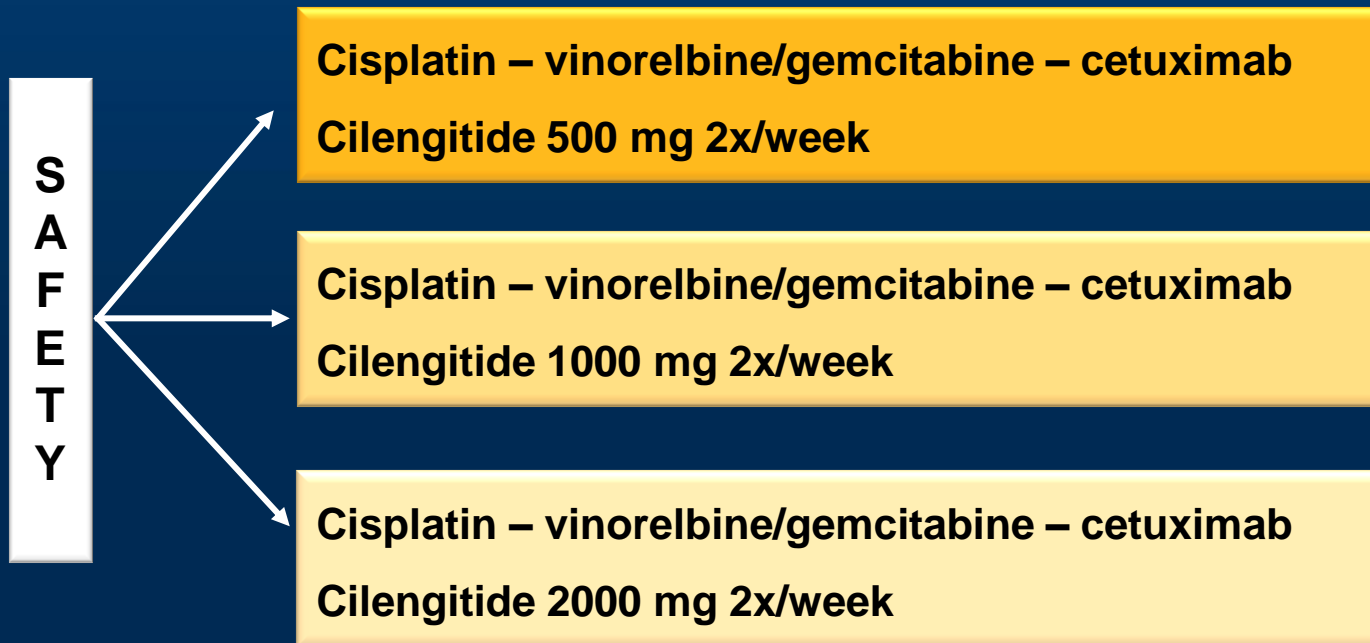
Study EMR 200037-014

Cilengitide and cetuximab in combination with cisplatin and vinorelbine/gemcitabine as first-line treatment for subjects with advanced NSCLC

Open-label, randomized, controlled, multicenter phase II study

CERTO: Safety Run-In

- Formal Safety Monitoring Committee
- Regimen intensified in stepwise manner, 3+3 design, for both platinum-based chemotherapy regimens
- Maintenance with cetuximab and cilengitide after 6 cycles of chemotherapy



Safety Run-In: Cilengitide-Related Adverse Events (Grade 3)

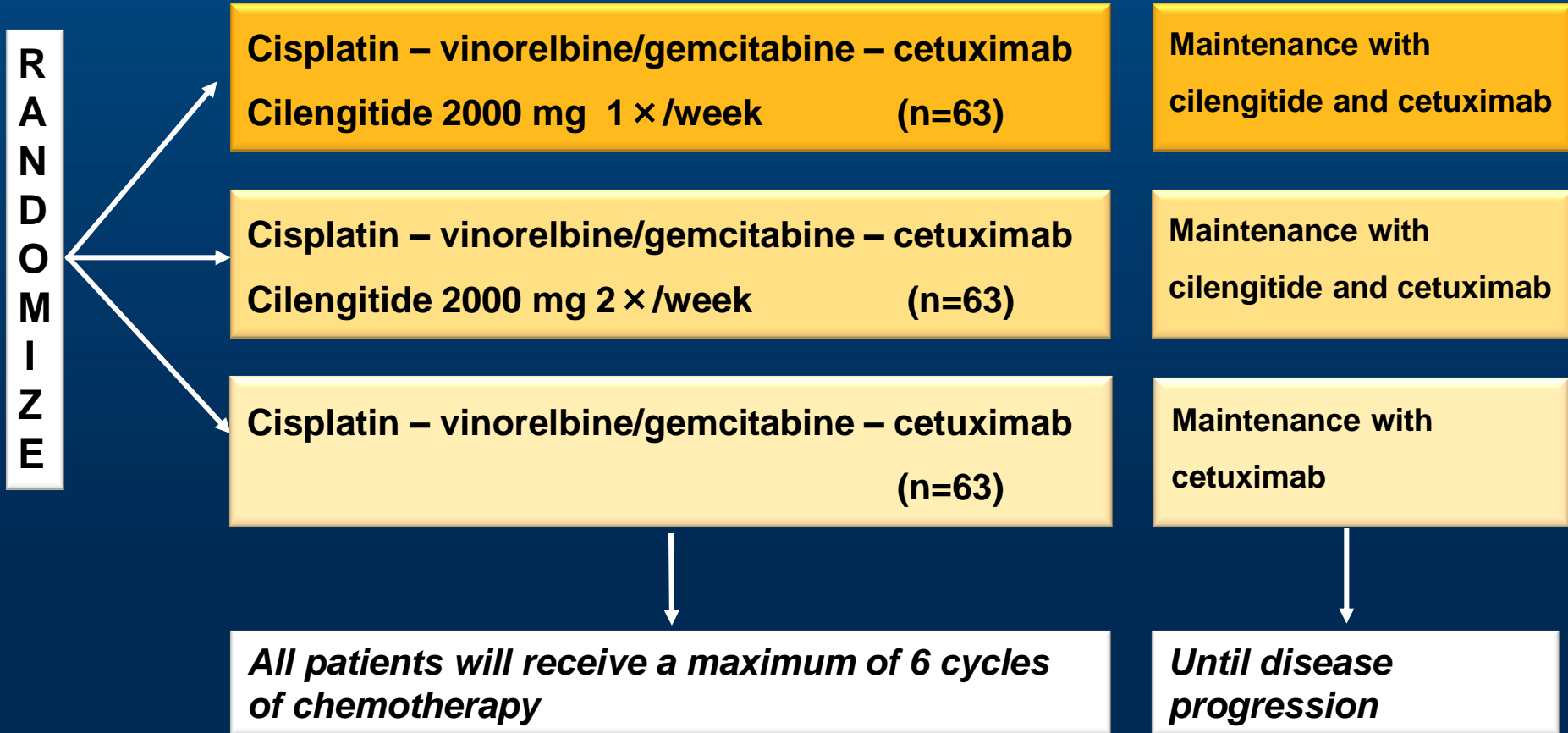
	Cohort 1 Gem (n=3)	Cohort 1 Vin (n=3)	Cohort 2 Gem (n=3)	Cohort 2 Vin (n=3)
Subjects with grade 3 AE	–	1	–	–
GI bleeding	–	1	–	–

- No grade 4 AEs assessed as related to cilengitide

Conclusion: Safety Run-In

- No DLTs observed
 - The observed adverse events are in line with the subjects' underlying cancer disease or reflect the toxicities known for cetuximab and/or the concomitant chemotherapies
 - No relevant differences with regard to frequency and severity of the adverse events across dose levels
 - No unexpected safety findings
- ⇒ Definite dose is 2000 mg cilengitide once/twice weekly for the randomized part

CERTO: Randomized Section



CURRENTLY RECRUITING

Vascular-disrupting agents: a new class for anti-angiogenesis in NSCLC?

- ASA 404 failed in 1st-line, 2nd-line data expected
- Cilengitide has shown promising activity in GMB (Phase I&II)
- Mechanisms of action differ between the 2 drugs
- Tolerance profile is very acceptable in combination with CT
- Numerous other compounds with promising pre-clinical activities are in their early development phase.