Early Stage NSCLC:
Imprimatur of Adjuvant Therapy

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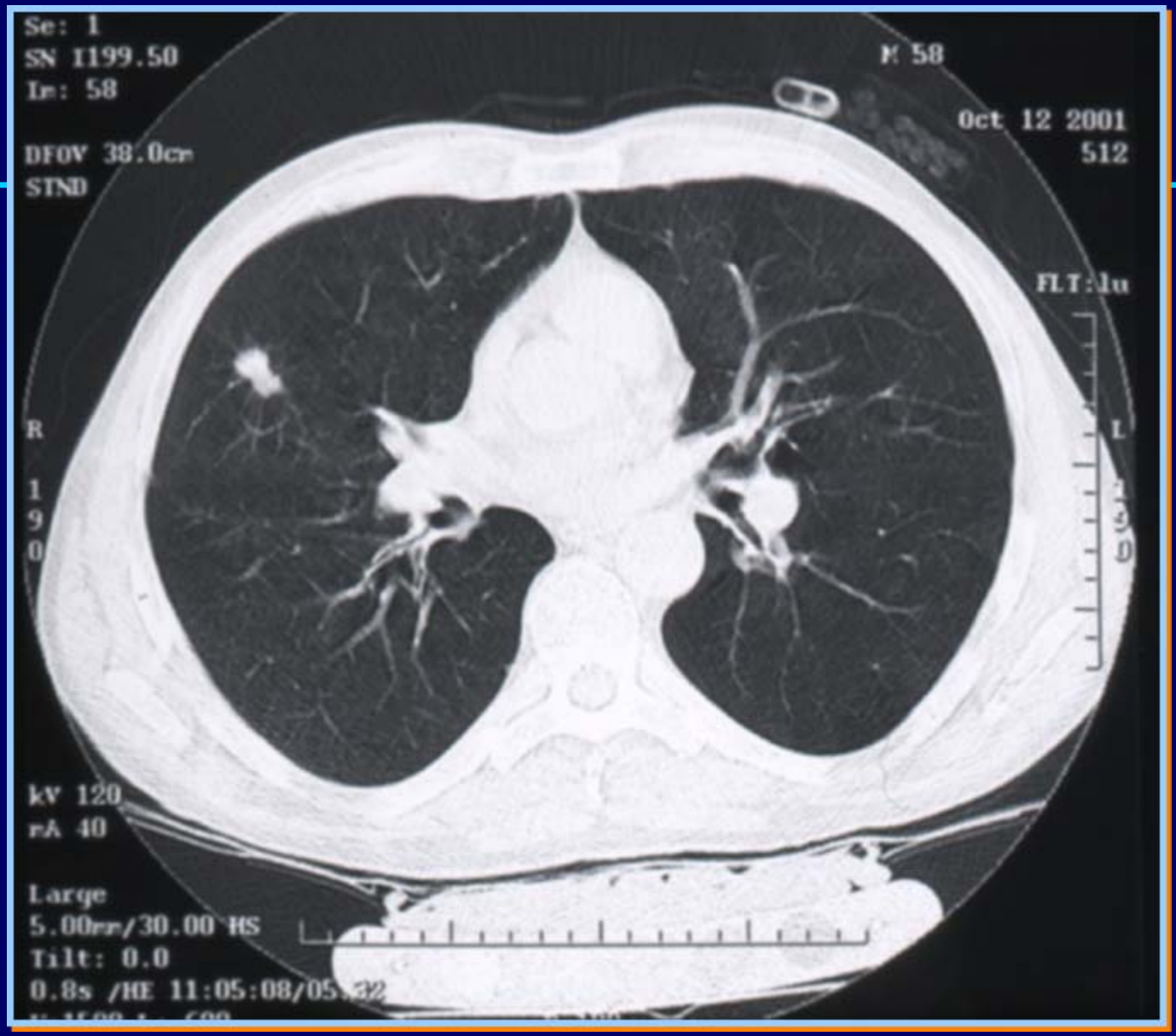
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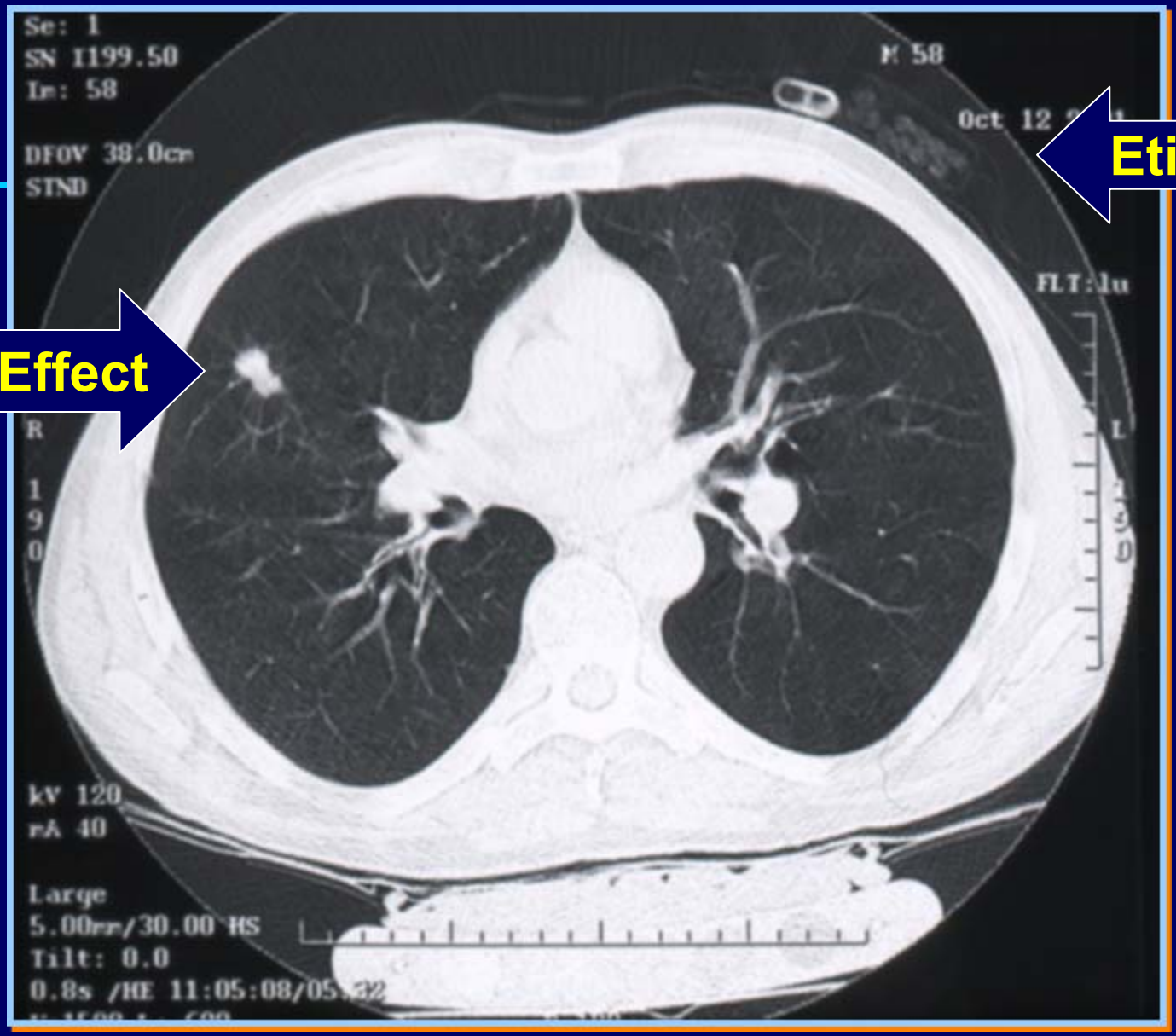


End Effect

Etiology

Adjuvant Therapy for Lung Cancer

- Adjuvant therapy – treatment (e.g. chemotherapy) after surgery to eradicate microscopic residual cancer and prevent cancer recurrence

- 4 Large Studies have shown that Adjuvant Chemotherapy can increase cure rate in lung cancer

Stage-Specific Hazard Ratios
Recent Adjuvant Trials

Trial	IB	II	IIIA
IALT	0.95	0.93	0.79
BR-10	0.94	0.59	N/A
ANITA	1.10	0.71	0.69
CALGB	0.8	N/A	N/A
LACE	0.92	0.83	0.83

Negative

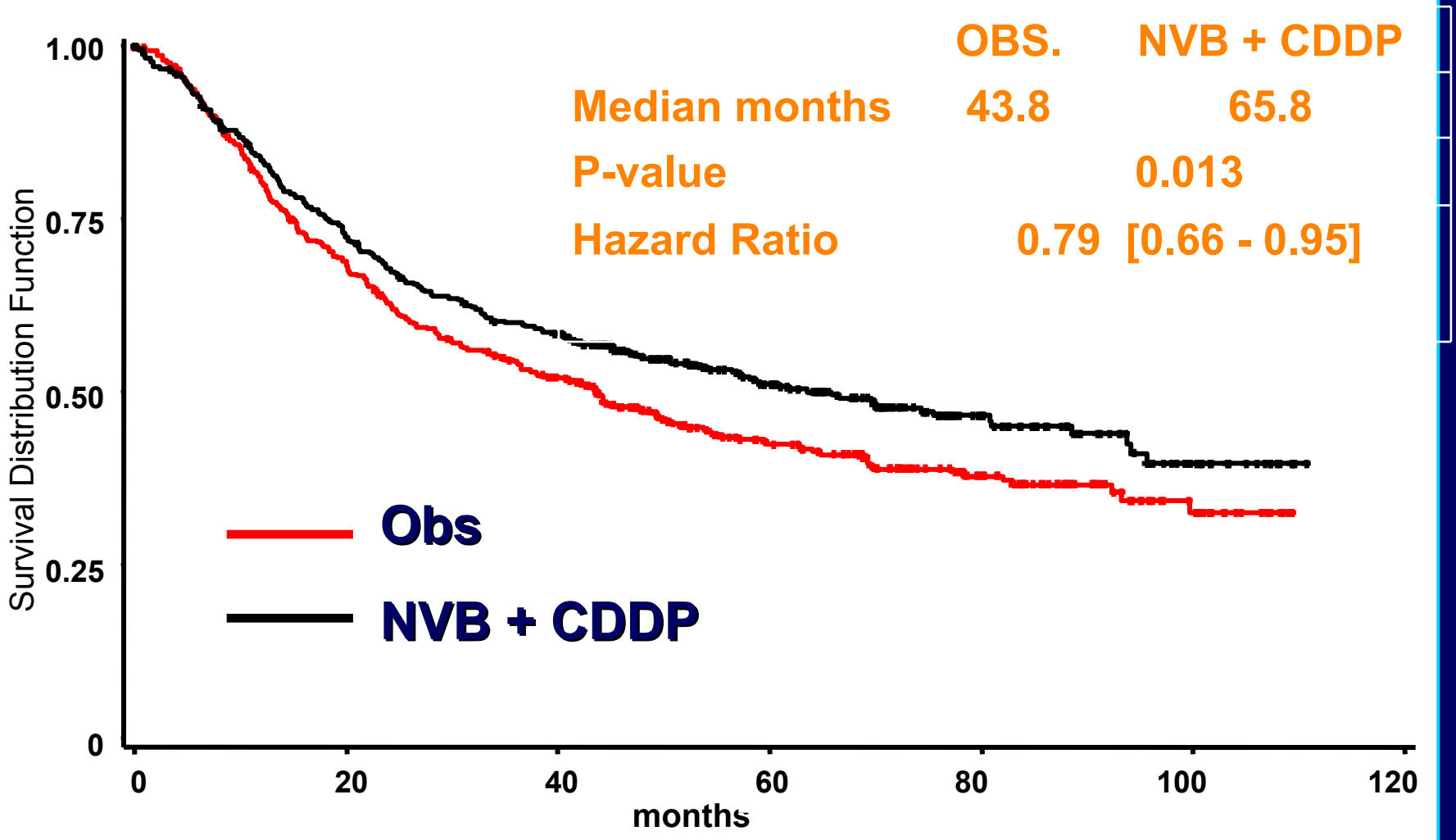
Positive

Indeterminate

Not studied

Abstract #7013: ANITA Trial

Overall survival - ITT population



ANITA: Randomized Phase III Trial of Vinorelbine and Cisplatin vs Observation in resected stage I-III NSCLC

Arm	Observation	Adjuvant
No	433	407
RFS (mo)	21	36
Median Surv (mo)*	44	66
2 yr OS	63	68
5 yr OS	43	51
7 yr OS	37	48
5 yr OS		
Stage I	62	63
Stage II	39	52
Stage III	26	42

* P =0.002, HR 0.76

Douillard et al ASCO 2005, A-7013, p624

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Stage IB Analysis

	T < 4 cm		T ≥ 4 cm	
	HR OS	p	HR OS	p
CALGB 9633	1.02	.51	0.66	.04
JBR.10	1.73	.07	0.66	.13
	No Chemo Benefit		Potential Chemo Benefit	

Stage-Specific Hazard Ratios

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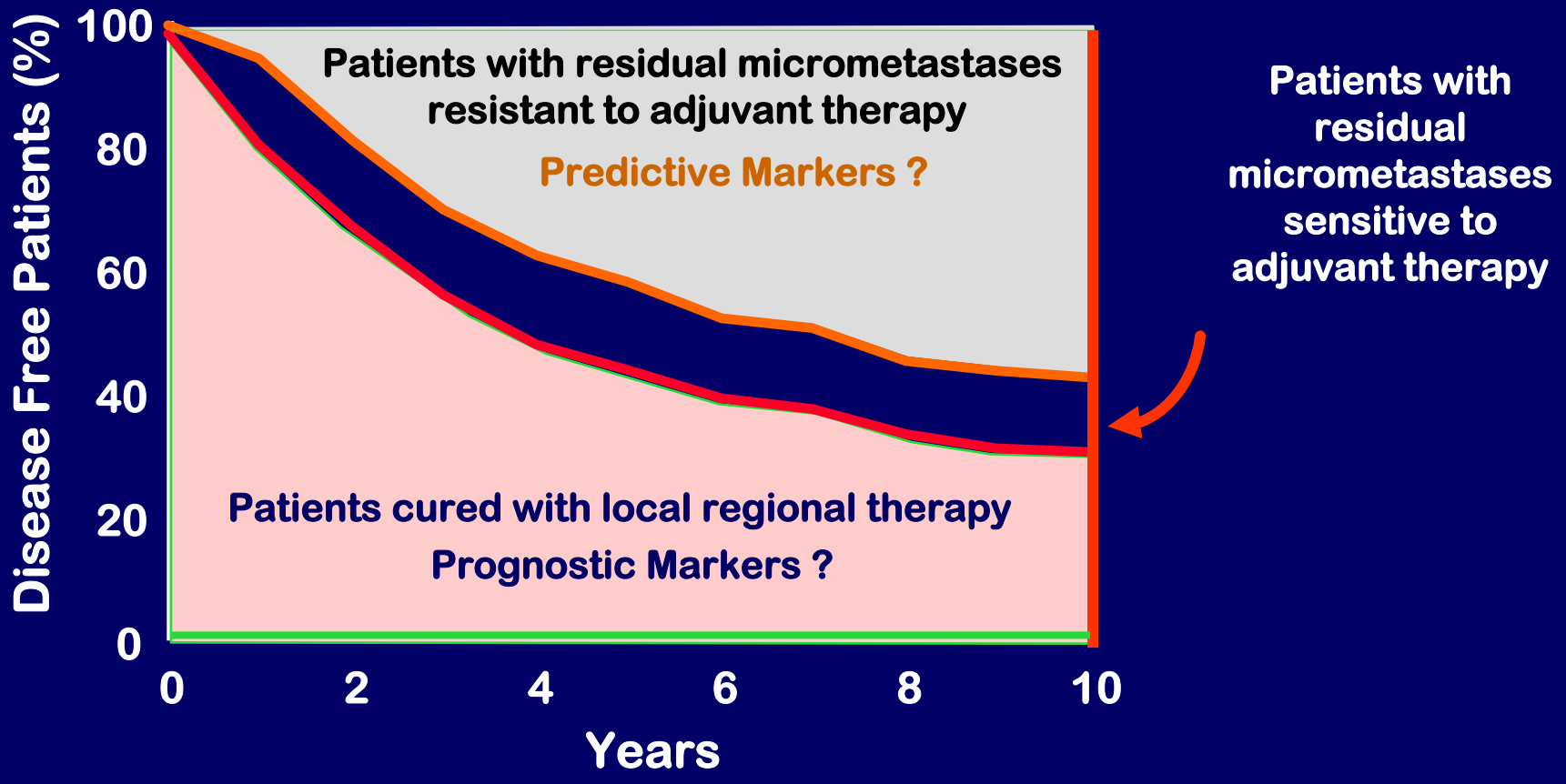
Therapeutic Implications
Adjuvant Therapy

- Short course adjuvant, platinum-based therapy has emerged as standard practice in resected stage Ib-IIIa NSCLC
  - Clear indication in patients with Node (+) disease, i.e. N1 (stage II) and N2 (stage IIIA)
  - Emerging data supporting use in stage IB (≥4 cm)
- If a patient can make it through surgery, he/she can make it through adjuvant chemo

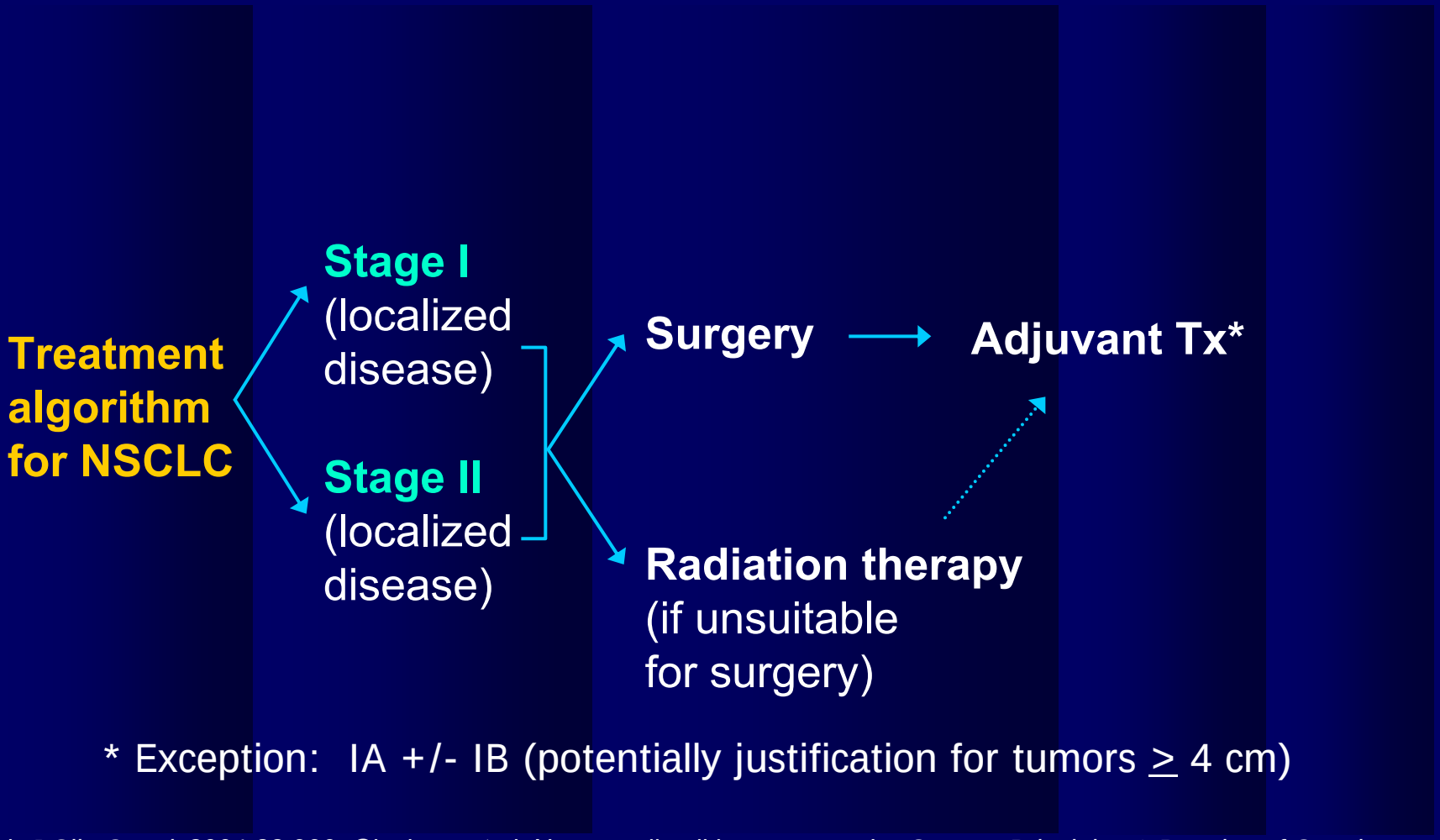
Therapeutic Implications
Adjuvant Therapy

- Ongoing controversies re:
  - Ideal platinating agent: carbo vs cisplatin
  - Choice of partner agent
  - Molecular Selection
  - Influence of Age on Outcome
  - Impact of Stage
  - Role of targeted agents
  - Utility of radiation in IIIA (N2)

Potential Benefit from Adjuvant Systemic Therapy



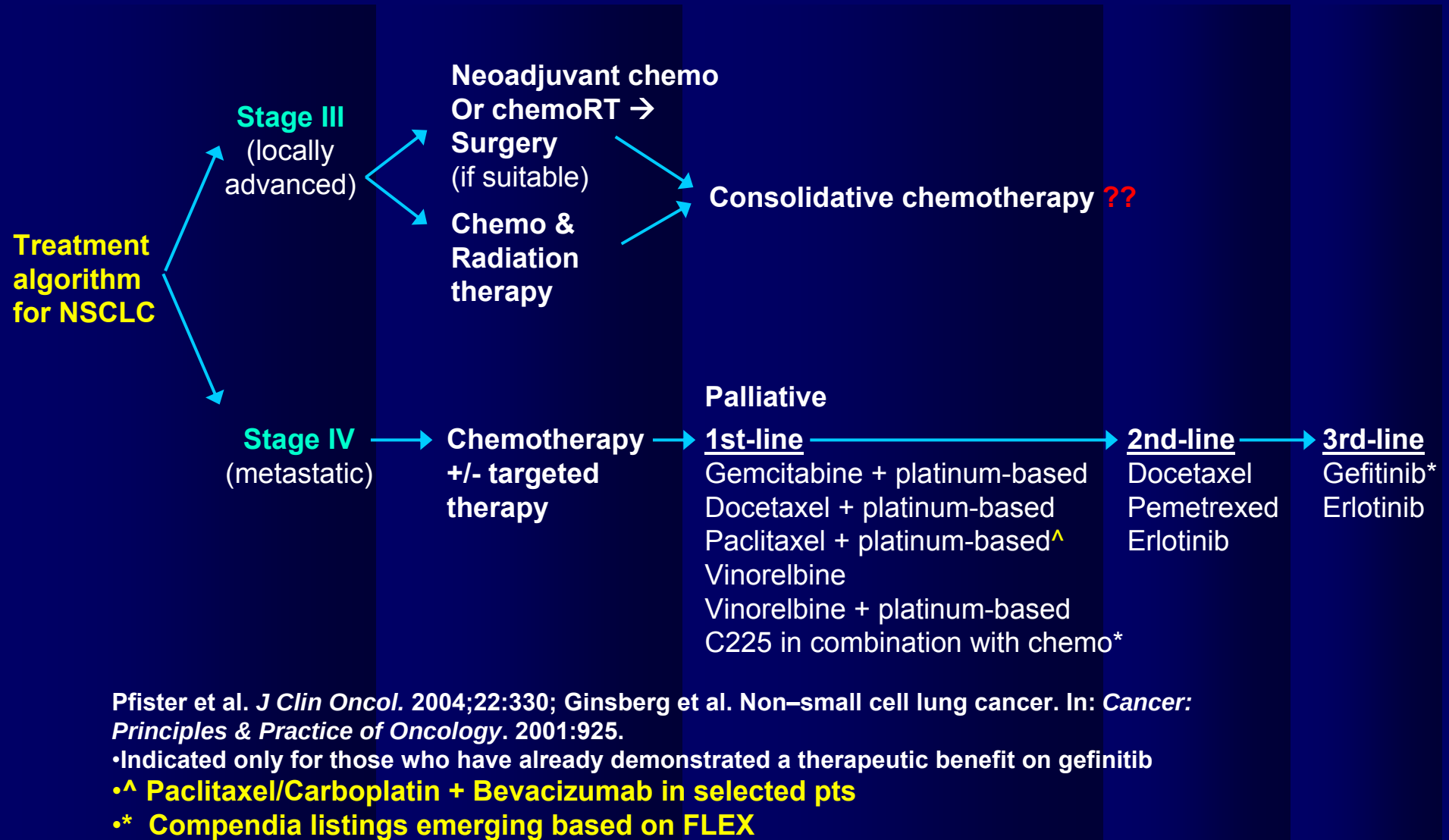
Current Systemic Treatment NSCLC – ASCO and NCCN Guidelines



* Exception: IA +/- IB (potentially justification for tumors ≥ 4 cm)

Pfister et al. *J Clin Oncol.* 2004;22:330; Ginsberg et al. Non–small cell lung cancer. In: *Cancer: Principles & Practice of Oncology*. 2001:925.

Current Treatment Options for NSCLC (cont'd)



Pfister et al. *J Clin Oncol.* 2004;22:330; Ginsberg et al. Non–small cell lung cancer. In: *Cancer: Principles & Practice of Oncology*. 2001:925.

- Indicated only for those who have already demonstrated a therapeutic benefit on gefinitib
- ^ Paclitaxel/Carboplatin + Bevacizumab in selected pts
- * Compendia listings emerging based on FLEX

Treatment for Advanced Non-small Cell Lung Cancer

- For patients with advanced (metastatic) disease, chemotherapy improves survival and quality of life (but does not cure)
- More effective and less toxic options are clearly needed
- Proving ground for agents that can be exported into the adjuvant setting

Drugs Recently Approved for Advanced Non-small Cell Lung Cancer

- Pemetrexed (ALIMTA): February 2004
- Erlotinib (Tarceva): November 2004
- Bevacizumab (Avastin): Fall 2006

Bevacizumab:
Targeting Tumor Blood Vessels

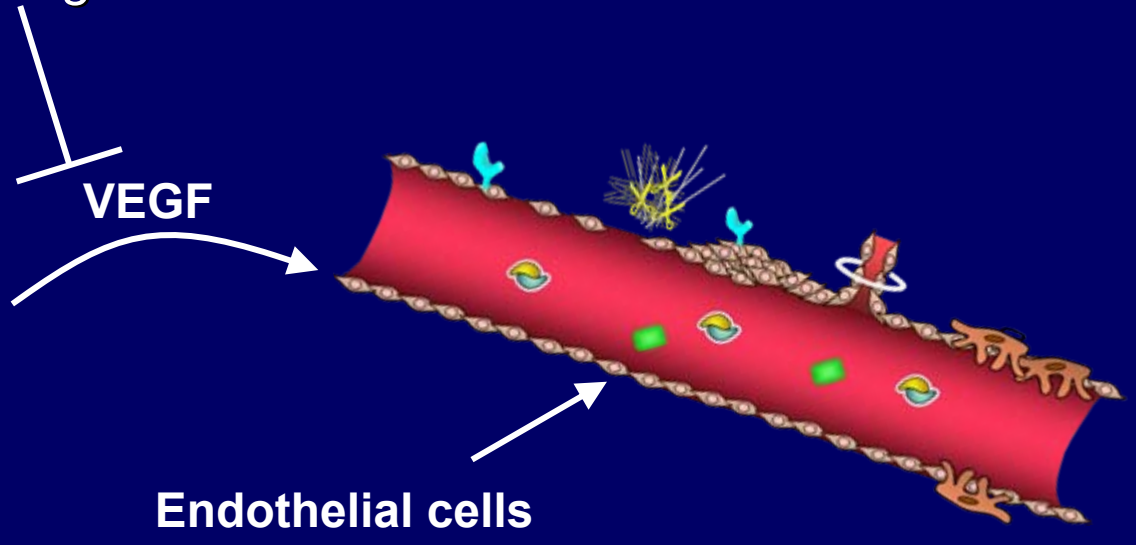
- Monoclonal antibody to VEGF
- Given IV every 3 weeks
- Prevents cancers from developing their blood supply, deprives cancer cells of nutrients, forcing them to wither and die off
- Improves survival in combination with chemo compared to chemo alone (Lesson learned from E4599)

Avasting Shrinks Blood Supply to Tumors

Direct blockade

Bevacizumab

Prevents endothelial cells from responding to multiple angiogenic proteins, by binding VEGF



VEGF = vascular endothelial growth factor; bFGF = basic fibroblast growth factor; IL-8 = interleukin-8; PDGF = platelet-derived growth factor.

Personal communication, Roy Herbst, MD, PhD.

Pemetrexed (Alimta)

- Chemotherapy, approved for lung cancer
  - Equivalent to Docetaxel in second line setting
  - Superior to Gemcitabine in first line setting
  - Survival Advantage as Maintenance (vs placebo)
- Given IV
- Does not cause hair loss, less N/V
- Vitamin B12 and folic acid need to be taken with it – help mitigate side effects

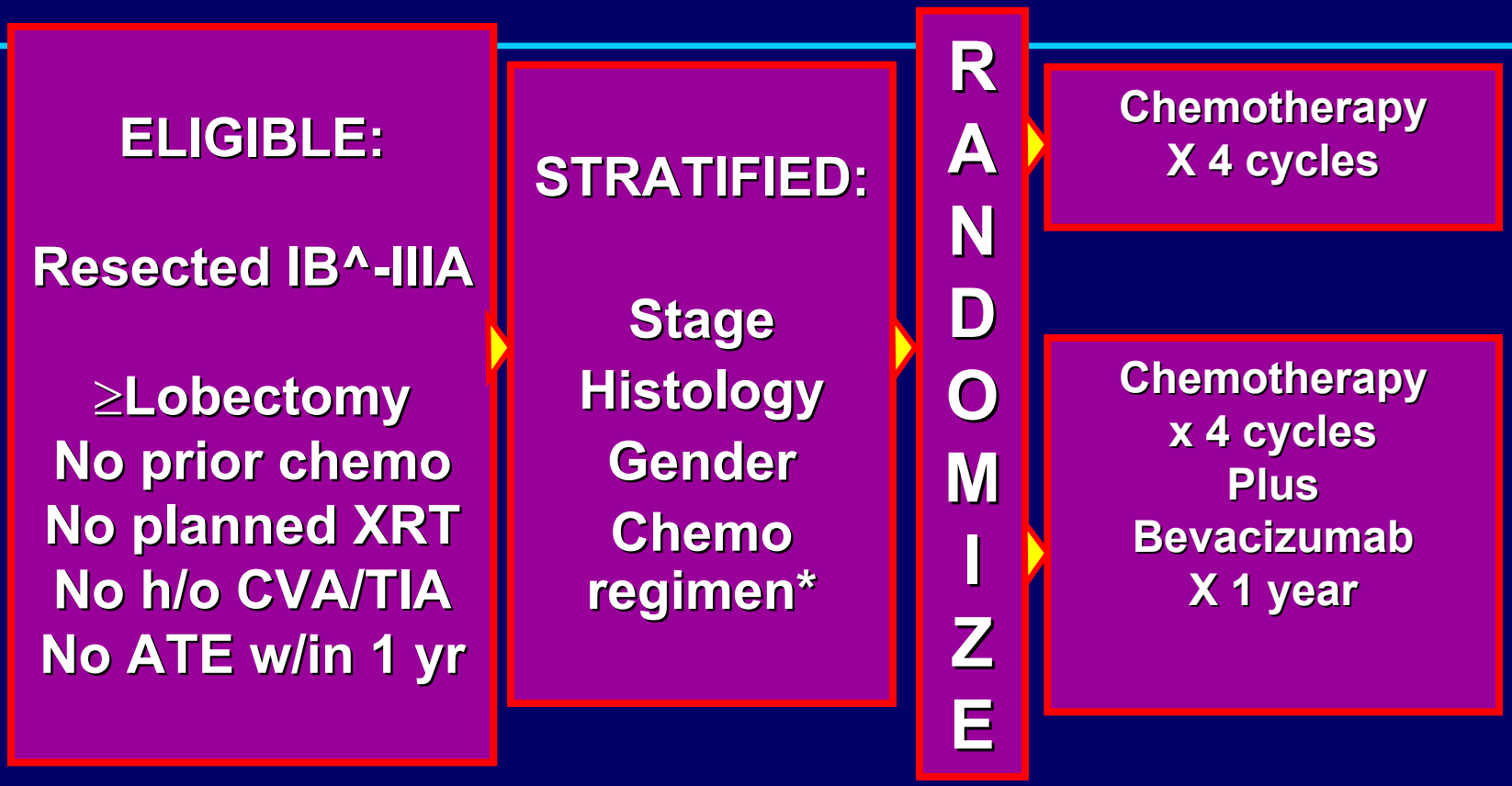
Erlotinib (Tarceva)

- Oral EGFR tyrosine kinase inhibitor
- Activity in non-small-cell lung cancer
  - ~10-15% of tumors will shrink
  - ~30-40% will be stable
- Erlotinib improves survival in patients with metastatic disease whose cancer has progressed after first-line or second line chemotherapy
- Occasional dramatic and durable tumor responses are seen, especially in patients whose tumors harbor the EGFR mutation

Erlotinib (Tarceva)

- Targets a receptor found in lung cancer
- Taken by mouth
- Less side effects (no hair loss or drop in blood counts)
- Rash and diarrhea are the most common side effects

ECOG 1505: Adjuvant Bevacizumab

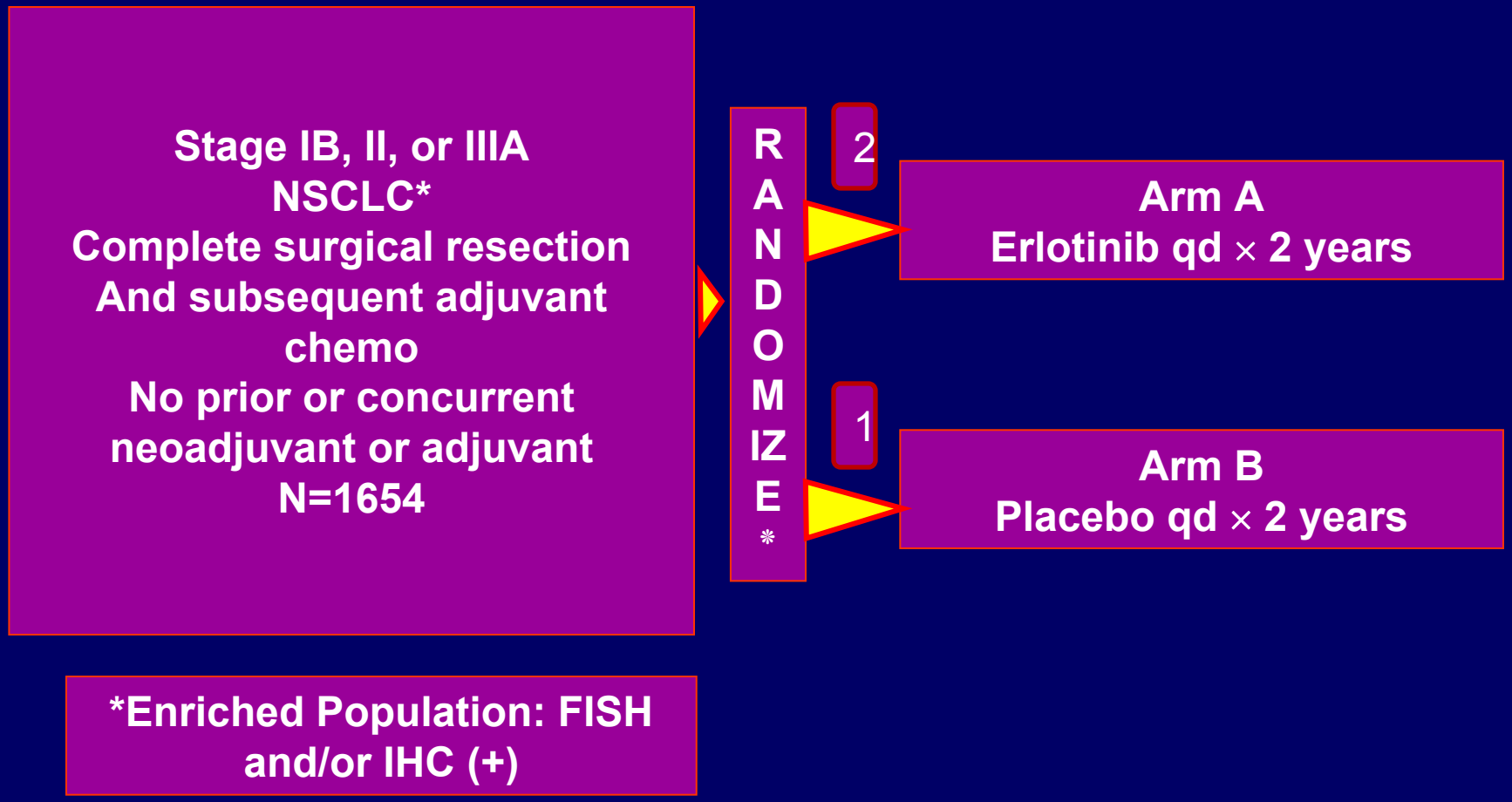


*Investigator Choice of 4 chemo regimens
^ Now revised to exclude IB < 4cm

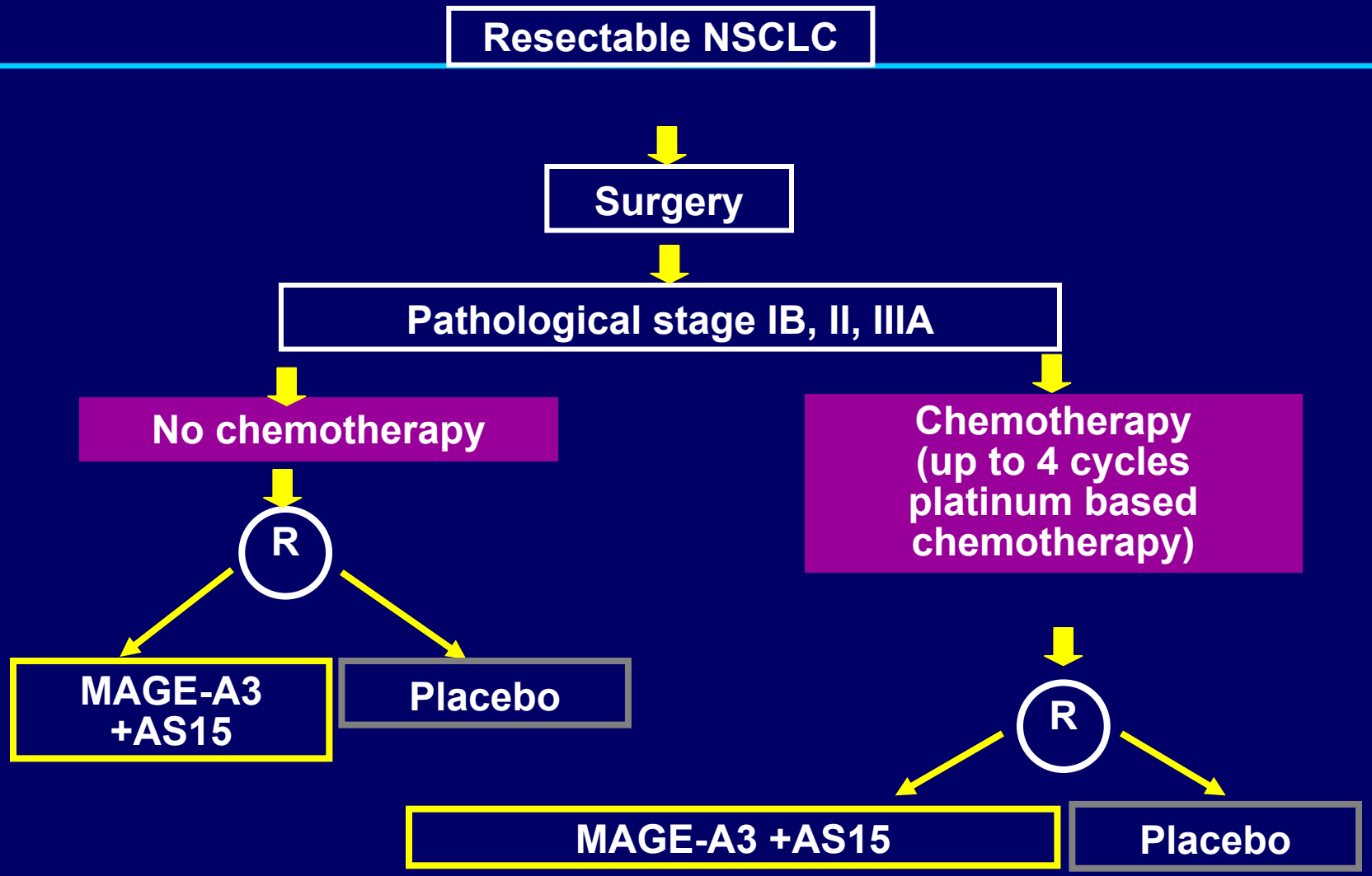
Chemotherapy Regimens

- Therapy to start 6-12 weeks post-operatively
  - Investigator Choice of Chemo - 4 cycles (12 wks)
- Cisplatin/Pemetrexed
  - Cis 75 mg/m2 d1, Pemetrexed 500 mg/m2 d1
- Cisplatin/Vinorelbine
  - Cis 75 mg/m2 d 1, Vin 25 mg/m2 d1,8 q21 d
- Cisplatin/Docetaxel
  - Cis 75 mg/m2 d 1, Docetaxel 75 mg/m2 d 1 q21 d
- Cisplatin/Gemcitabine
  - Cis 75 mg/m2 d 1, Gem 1250 mg/m2 d1,8 q 21 d
- +/- Bevacizumab 15 mg/kg q 21 days x 12 mos

RADIANT Trial: Adjuvant Trial of Erlotinib in NSCLC



MAGE Trial Design (GSK sponsored)



Ongoing Clinical Trials at PENN

- Stage IA and IB (< 4 cm)
  - Selenium
    - Randomized [2:1] phase III vs placebo
    - Must be > 6 mos, < 3 yrs from surgery
  - Telomerase Vaccine
    - Phase II

Ongoing Clinical Trials at PENN

- Stages IB (> 4 cm), II and IIIA
  - Phase II Erltoinib if EGFR mutation (+)
  - MAGE if antigen present at screening
  - RADIANT: Erlotinib (must be screened for EGFR by either IHC or FISH)
  - E1505: Bevacizumab
  - Telomerase Vaccine Trial
- Trials addressing RT in resected IIIA
  - None currently
  - Horizon: Lung d'ART; AMORE

CLINICAL TRIAL HIERARCHY

- PHASE I (EXPERIMENTAL)
  - New agent(s) or new combination of established agents
  - Establish top, safe dose (MTD ~ maximally tolerated dose) or optimal biologic dose
  - *May* require tumor biopsies or frequent blood draws (PKs)
  - Usually reserved for tumors for which no standard treatment exists or after "standard" treatments have been exhausted
- PHASE II
  - Systemic agent(s) applied to multiple patients with a specific disease type
  - Gauge side effects (toxicity); feasibility
  - Determine activity (response rate); freedom from progression; survival
- PHASE III
  - Randomized comparison of standard established treatment (control arm) vs. new(er) promising regimen (investigational arm)
  - Computerized coin toss (neither patient nor physician chooses)
  - Placebo controls used only if observation is standard

IMPEDIMENTS TO CLINICAL TRIALS

- TIME (labor-intensive)
- FUNDING (third party payer)
- PERCEPTION: physician; patient

WHAT PATIENTS (and CLINICIANS)SHOULD KNOW ABOUT CLINICAL TRIALS

1. Carefully conducted protocols mandate IRB approval, intensive monitoring, and close follow-up.
2. Informed consent is required.
3. Alternative options must be discussed. You cannot be coerced.
4. Total accrual is limited; statisticians oversee results/analysis.
5. Serious adverse events (AEs) are reported to IRB. Excessive AEs can result in a trial's early closure.
6. All clinical trials subject to FDA audit.
7. Enrollees on clinical trials do as well, if not better, than patients treated off protocol or empirically; costs are $\leq$ 10% higher than standard care.
8. You are not a guinea pig; you can opt out of clinical trial at will, without compromise to subsequent care.
9. Your physician may halt your participation if you are not benefiting, if superior therapies emerge, or if toxicity proves intolerable.

10 QUESTIONS to ASK YOUR HEALTH CARE TEAM

1. What are the most common side effects of my treatment?
2. What causes the side effects?
3. How can I prevent or minimize the side effects?
4. Do you have any printed material on the treatment?
5. Can I take other medicines while I am receiving treatment?
6. How will I know if my treatment is working?
7. Can I speak with someone on a one-to-one basis who has had a similar treatment experience?
8. What other options do I have regarding therapy?
9. Can I get financial assistance with medications or transportation?
10. How can I help other patients once I've completed my own treatment?

OTHER QUESTIONS

- Expectations of treatment
- What do we do if treatment doesn't work?
  What are the options?
- Can I stop treatment early?
  What are the consequences?

FOUR RULES FOR BEING A HAPPY DOCTOR

… adapted from Michael Greenberg, M.D., Elk Grove Village, IL
American Medical News, 2000; offped@aol.com

1. *Golden Rule*
   Treat patients as if they are members of your own family. Would the treatment you suggest for your patient be the same if it were your child or parent? What would you do if the person sitting across from you in your exam room were yourself or a member of your immediate family and, even more important, what would you not do?

2. *Honesty*
   Always tell patients the truth – no matter how scary, but do it respectfully and supportively. Occasionally, a patient will leave your practice rather than face the truth, but in the long run, honesty is the only sure route to happiness.

3. *Use Available Resources*
   If another physician does something better than you do or has the capacity to do something you feel is indicated but cannot accomplish, send your patient to that physician. You have a sacred duty to ensure your patients obtain the best care; sometimes a referral is the appropriate action.

4. *Acknowledge Fallibility/Limits*
   Learn to say, "I don't know." All of us hate to expose our ignorance, but patients (and colleagues) respect us when we admit our fallibility. Patients understand that we don't know everything. The purpose of our education is to give us the basic language of our profession and to teach us how to obtain the information we need.