XXII Riunione Nazionale I.T.M.O.

ONCOLOGIA:
EVOLUZIONE
DELLE
CONOSCENZE

Coordinatore:
Prof. Emilio Bajetta

Monza, 1 luglio 2016

Sede:
Aula Padiglione "Faggi"
Istituto di Oncologia Policlinico di Monza
Via Carlo Amati, 111

Adjuvant Therapy in NSCLC

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Agenda

- **What do we expect today from new adjuvant chemotherapy**
- **Which data do we have with targeted agents in the adjuvant setting**

  ….according to molecular predictors
- **What we expect with Immunotherapy agents**

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- **What do we expect today from new adjuvant chemotherapy**
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  ….according to molecular predictors
- **What we expect with Immunotherapy agents**

Recent meta-analyses of surgery (+/- RT) + CT vs surgery (+/- RT)

Author	Type of data	Number of trials	Number of patients	Outcome	Hazard Ratio (95% CI)
Hotta 2004	Published data	11*	5716	Survival	0.87 (0.81 to 0.94)
Sedrakyan 2004	Published data	19	7200	Survival	0.87 (0.81 to 0.93)
Berghmans 2005	Published data	17	7644	Survival	0.85 (0.79 to 0.91)
Bria 2005	Published data	11 + 1 meta-analysis	6494	Survival	0.93 (0.89 to 0.95)
Hamada 2005	Individual participant data	6**	2003	Survival	0.74 (0.61 to 0.88)
Pignon 2008	Individual participant data	5†	4584	Survival Event-free survival	0.89 (0.82 to 0.96) 0.84 (0.78 to 0.91)

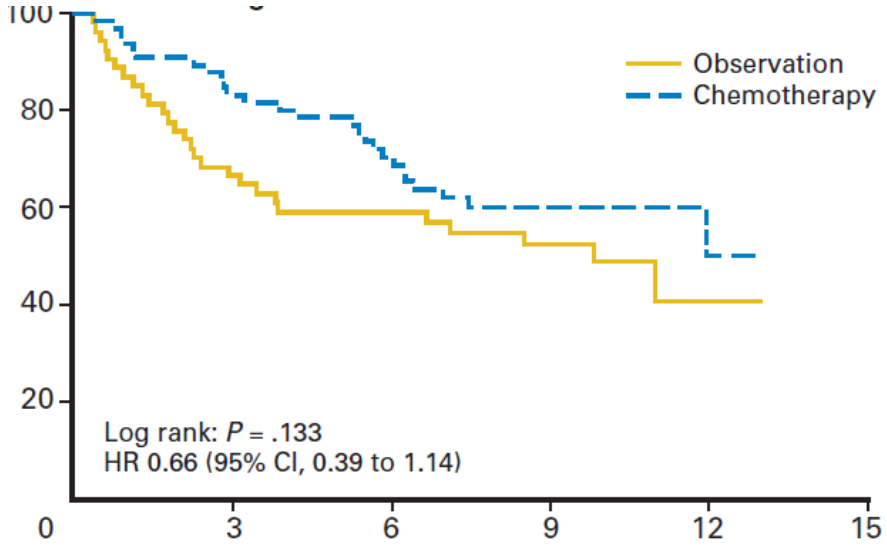
* Recent trials only
**UFT trials only
† Large (> 300 patients) and recent cisplatin trials only

Burdett S, The Cochrane Collaboration 2015

Absolute improvements in 5-year survival of 3% for stage IA (from 70% to 73%), 5% for stage IB (from 55% to 60%), 5% for stage II (from 40% to 45%), and 5% for stage III disease (from 30% to 35%).

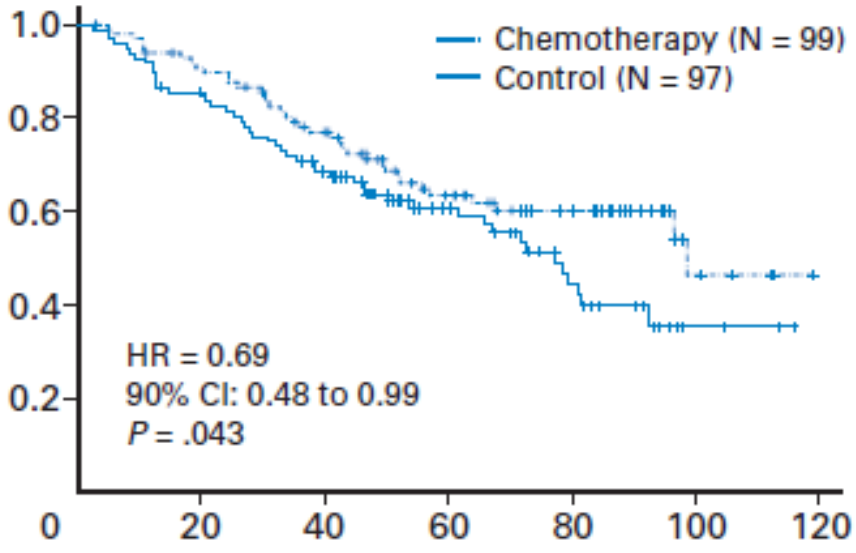
‘Big/High-Risk’ Stage I [NCCN]?

JBR.10



Butts, JCO 2010

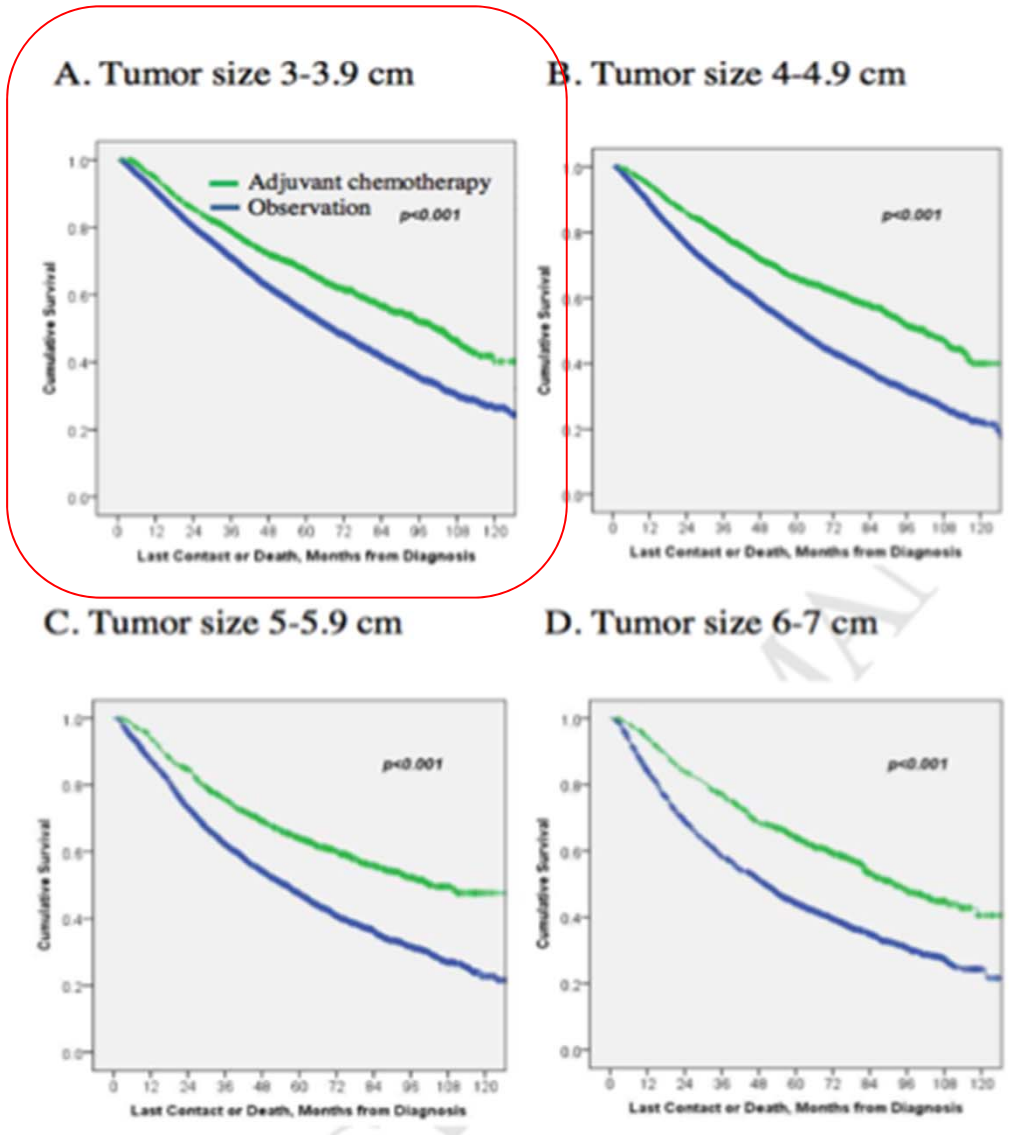
CALGB 9633



Strauss G, JCO 2008

T-size ≥ 4 cm

Adjuvant Chemotherapy for Patients with T2N0M0 NSCLC

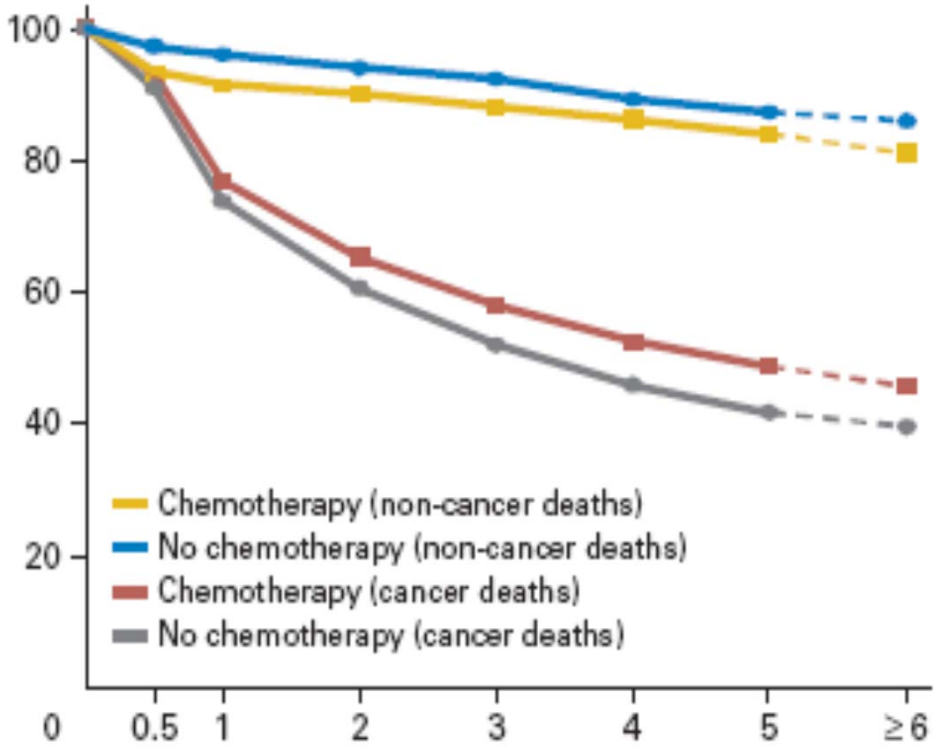


The current exclusion of stage IB tumors < 4 cm in the adjuvant NSCLC trials should be revisited.

Morgensztern, et al, JCO May 2016

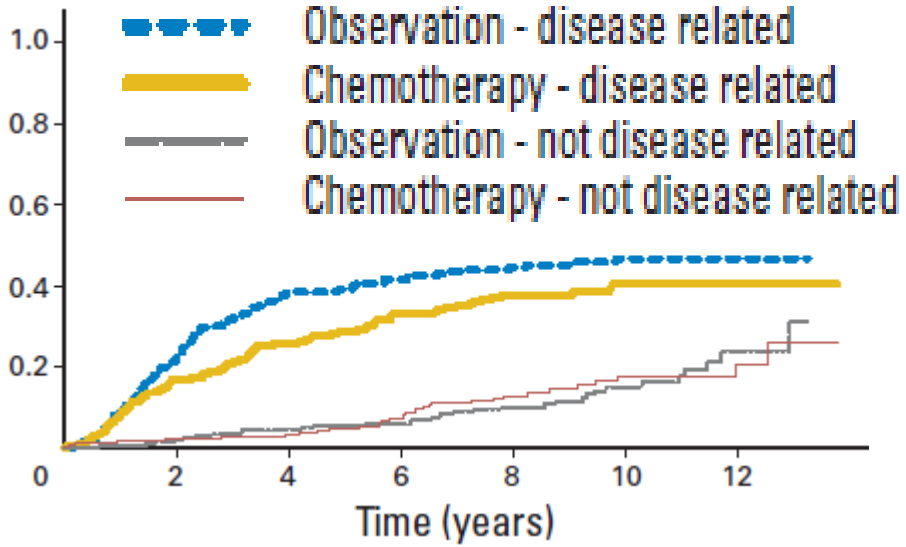
‘Late events’ at longer F.U.

LACE



Pignon, JCO 2008

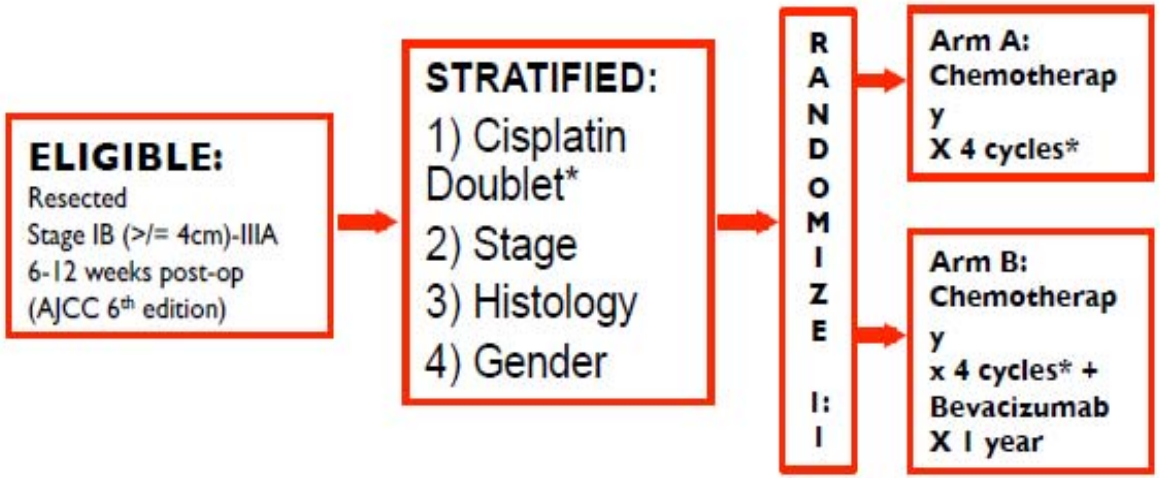
JBR.10



Test for Non-Disease–Related Deaths
Log-rank $P = .660$
Fine-Gray test $P = .622$
Test for Disease-Related Deaths
Log-rank $P = .027$
Fine-Gray test $P = .023$

Butts, JCO 2010

Randomized phase III trial of adjuvant chemotherapy with or without bevacizumab in resected NSCLC: Results of E1505



***Investigator Choice of 4 chemotherapy regimens**
21 day cycles all with Cisplatin given at 75 mg/m^2 on day 1
Cisplatin /**Vinorelbine**: 30 mg/m2 day 1, 8
Cisplatin /**Docetaxel** 75 mg/m2 day 1
Cisplatin /**Gemcitabine** 1200 mg/m2 day 1,8
Cisplatin /**Pemetrexed** 500 mg/m2 day 1 (2009 amendment)

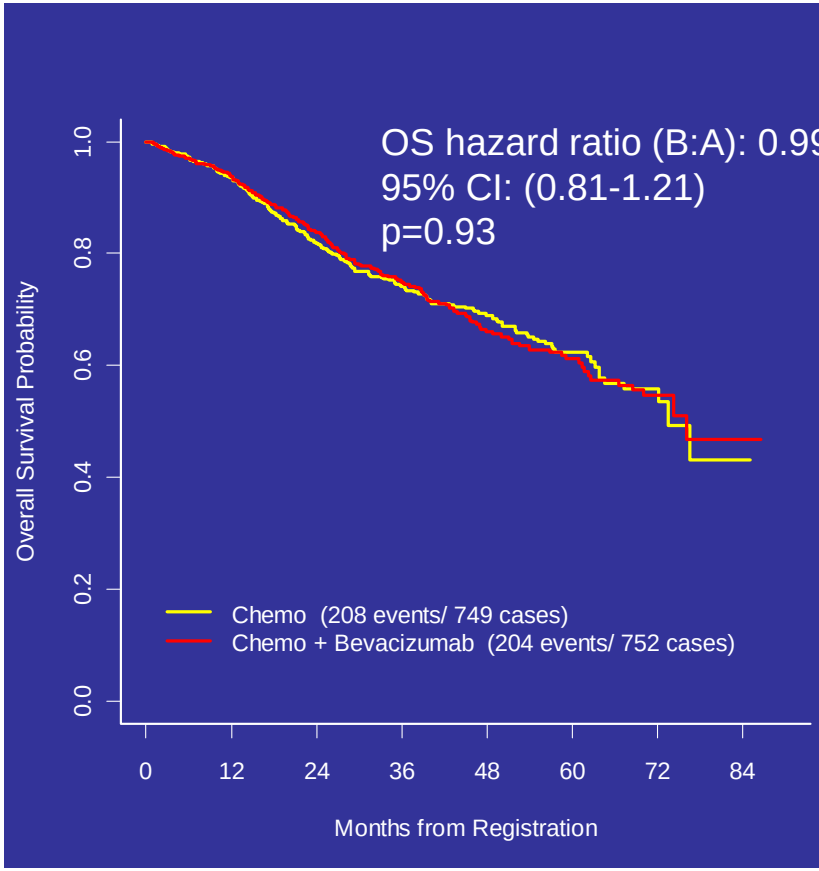
Bevacizumab 15 mg/kg IV q 3 weeks for up to 1 year

- From July 2007 to September 2013, 1501 patients were enrolled
- Spring 2015: 6th planned interim analysis at 60.9% information
- Independent DSMC recommended releasing the trial results due to futility
- 230 of 1501 (15.3%) of patients were ineligible

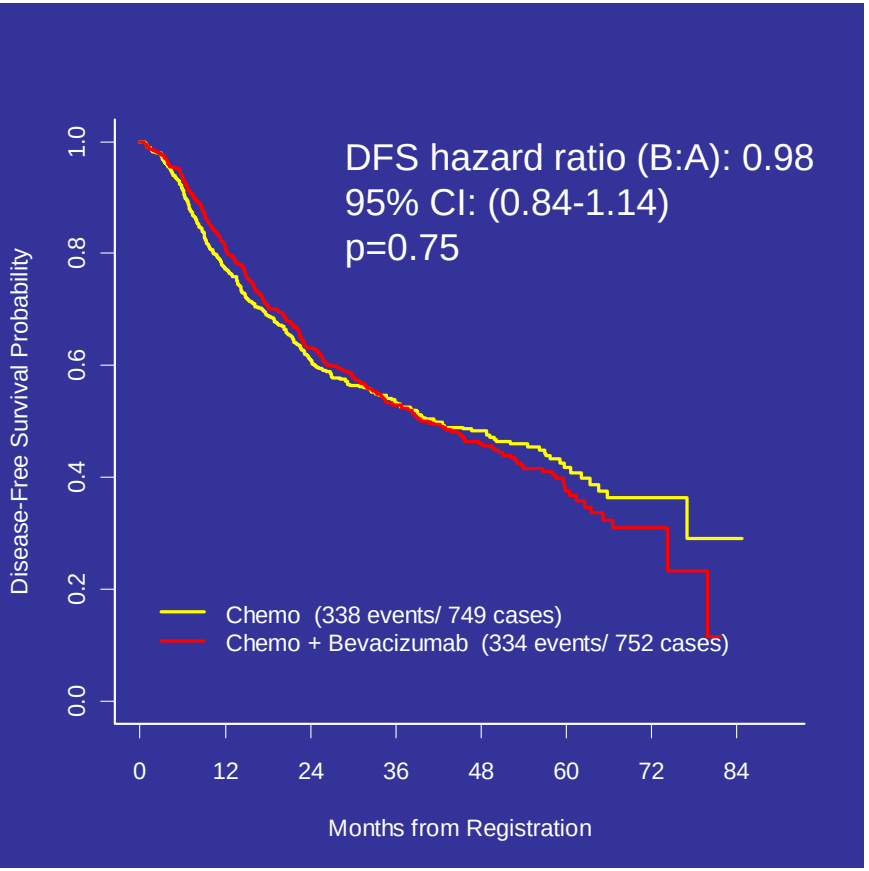
Wakelee HA, WCLC 2015

The addition of bevacizumab to adjuvant chemotherapy DOES NOT improve survival for patients with surgically resected early stage NSCLC

Overall Survival

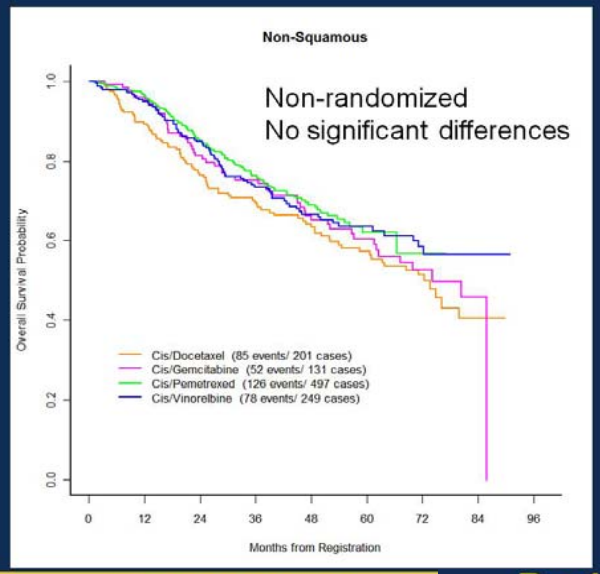


Disease Free Survival

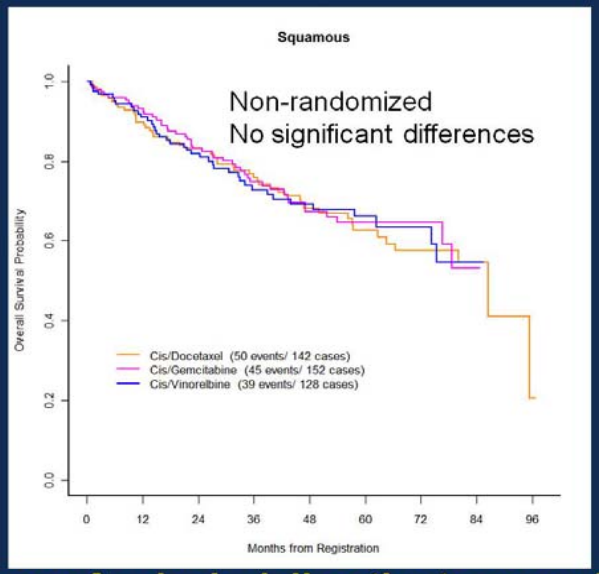


Pooled Chemo Analysis (all patients regardless of treatment arm)

OS by chemo group
Non-squamous : Logrank p=0.18



OS by chemo group
Squamous: Logrank p=0.99



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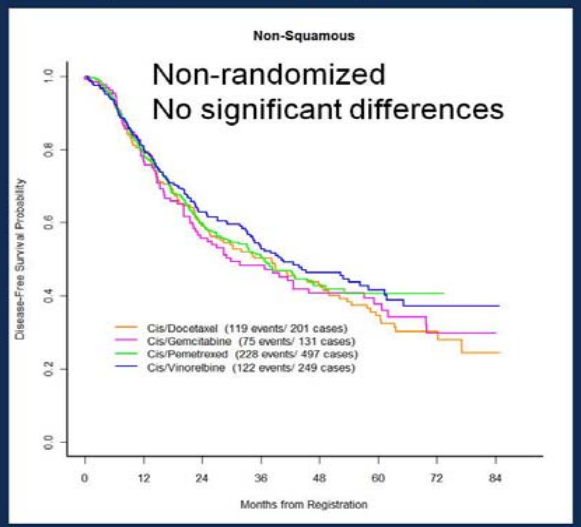
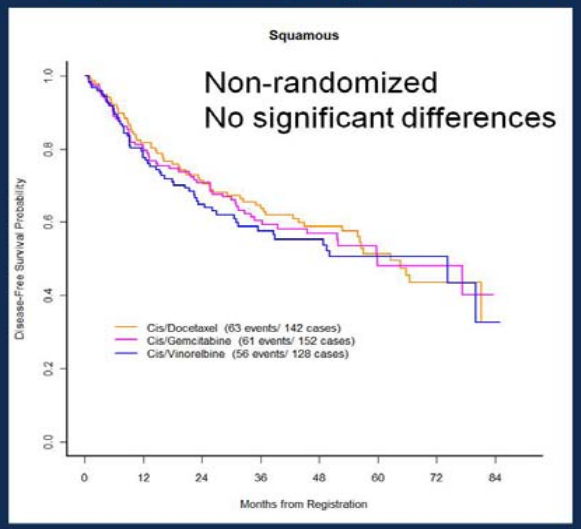
Pooled Chemo Analysis (all patients regardless of treatment arm)

DFS by chemo group
Non-squamous : Logrank p=0.58



DFS by chemo group
Squamous : Logrank p=0.83



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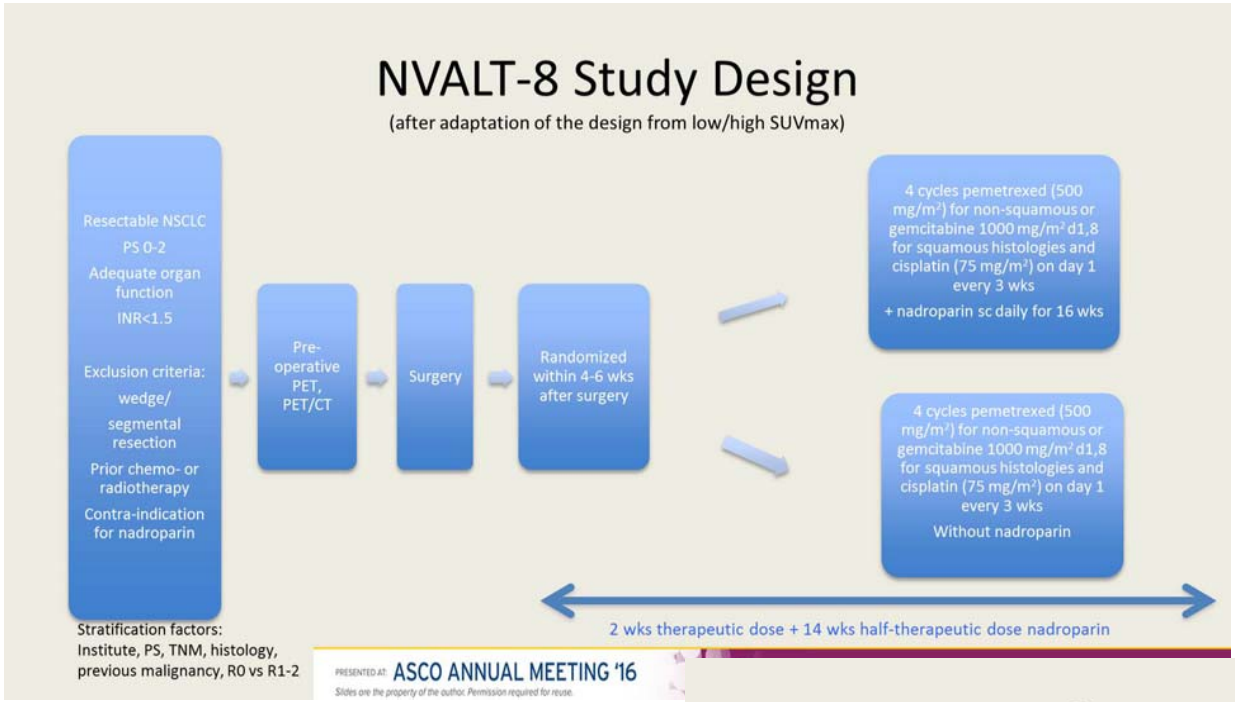
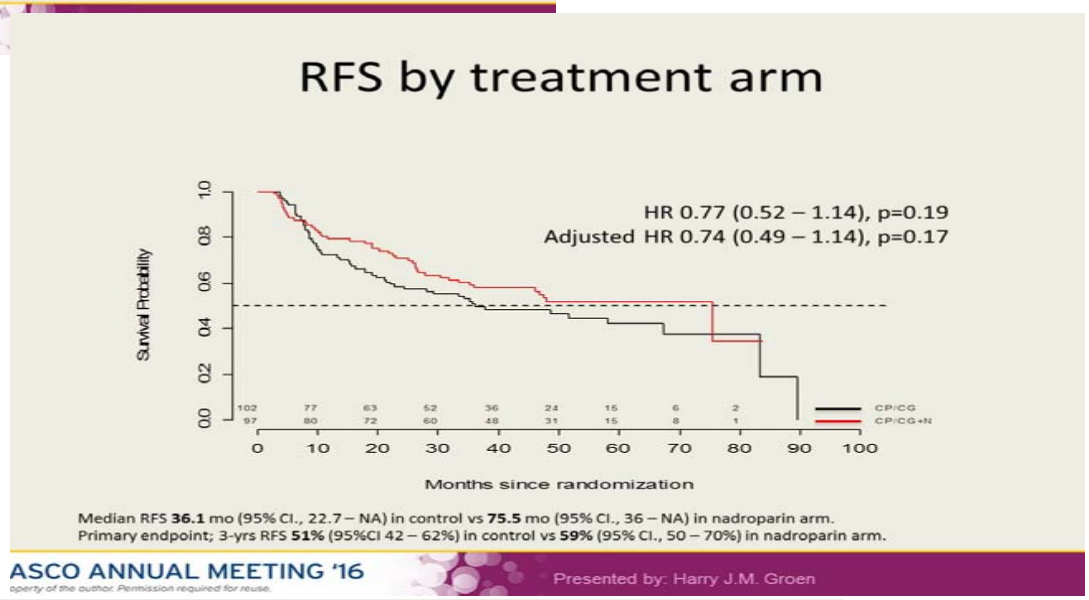




Adjuvant nadroparin in patients with resected NSCLC added to adjuvant chemotherapy does not improve RFS.

Agenda

- What do we expect today from adjuvant chemotherapy
- **Which data do we have with targeted agents in the adjuvant setting**

  ….according to molecular predictors
- What we would expect with immunotherapy agents

Prognostic and predictive biomarkers for ACT (adjuvant chemotherapy) in resected non-small cell lung cancer (R-NSCLC): LACE-Bio

While a number of biomarkers were identified in single studies that could have predictive or prognostic value, cross-validation with the other studies did not confirm the utility of the majority of markers

Marker	Trial 1st tested in	Predictive?	Prognostic?	Validated?
ERCC1	IALT	Yes	Yes	No
Lymphocyte infiltrate	**IALT**	**No**	**Yes**	**Prognostic (OS/DFS)**
Mucin	CALGB	No	Yes	No
β-tubulin	**JBR10**	**Trend**	**Yes**	**Prognostic (OS/DFS)**
P27	IALT	Yes	No	No
FASL	**IALT**	**Trend**	**No**	**Predictive (OS)**
FAS/FASL	IALT	Yes	Yes	No
BAX	IALT	Trend	No	No
Cyclin E/P16*	IALT, JBR10	No	No	No
P53*	IALT, JBR10, CALGB	Yes**	Yes**	No

- **Conclusion**
  - IHC assays from single trials may be misleading and should be validated before being implemented

Seymour et al, ESMO 2014

A Single Biomarker Can Have Both Prognostic and Predictive Values

The Case of EGFR-M+

Prognostic marker

Influences clinical outcomes regardless of the therapy received

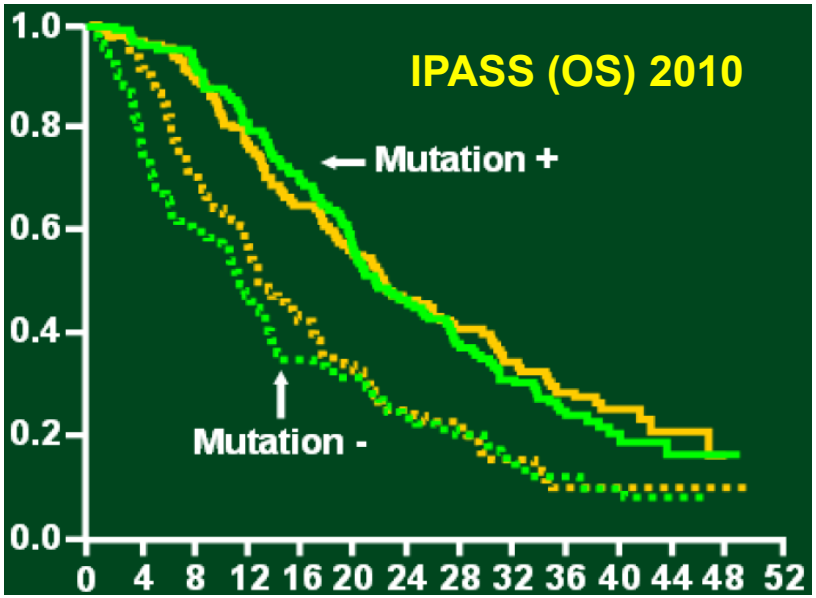
→ Does not help to personalise treatment

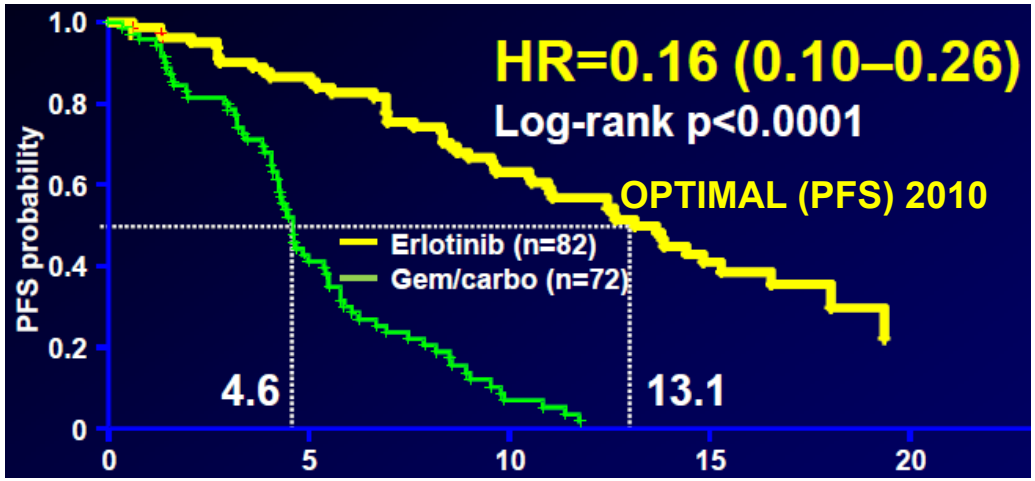
Predictive marker

Influences clinical outcomes with a specific therapy

→ Select patients who are likely to benefit

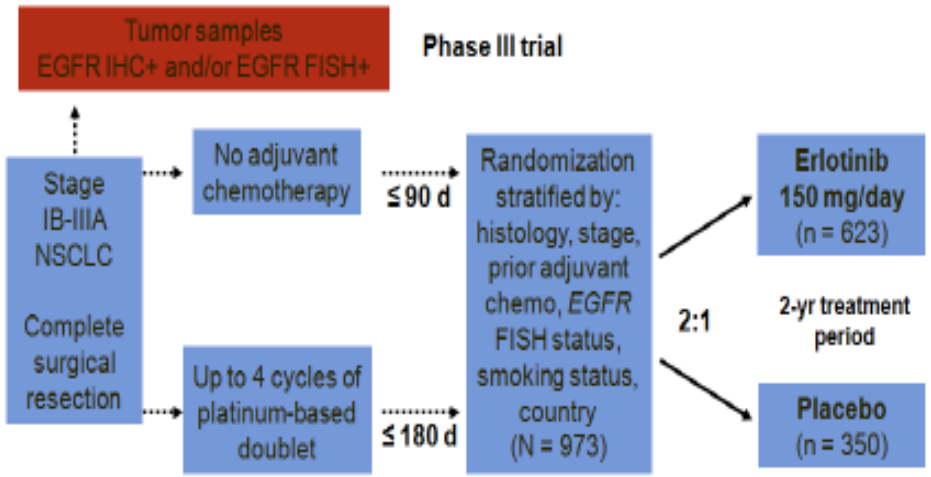
→ Exclude patients who are not likely to benefit





Courtesy of Zhou & Soria, ESMO 2010; Wolf J, PeerView Press 2010

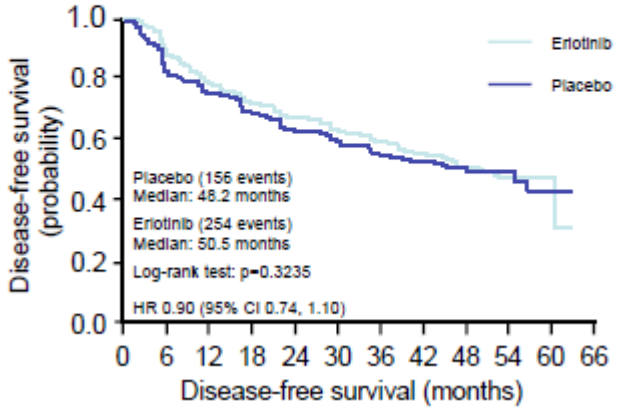
RADIANT: Adjuvant Erlotinib vs Placebo in stage Ib-IIIA



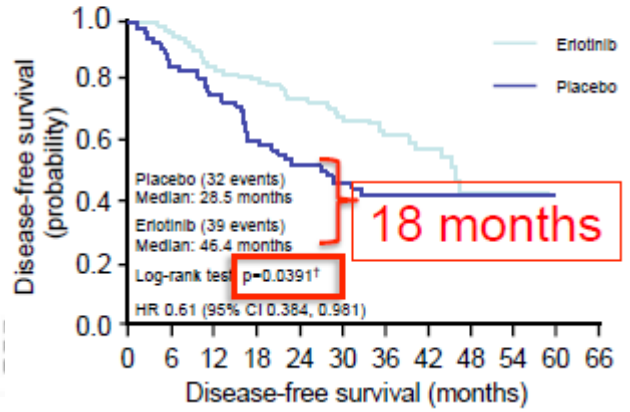
Primary endpoint: DFS

Secondary endpoints: OS; DFS and OS in pts with del(19)/L858R (*EGFR* M+)

DFS (overall population)

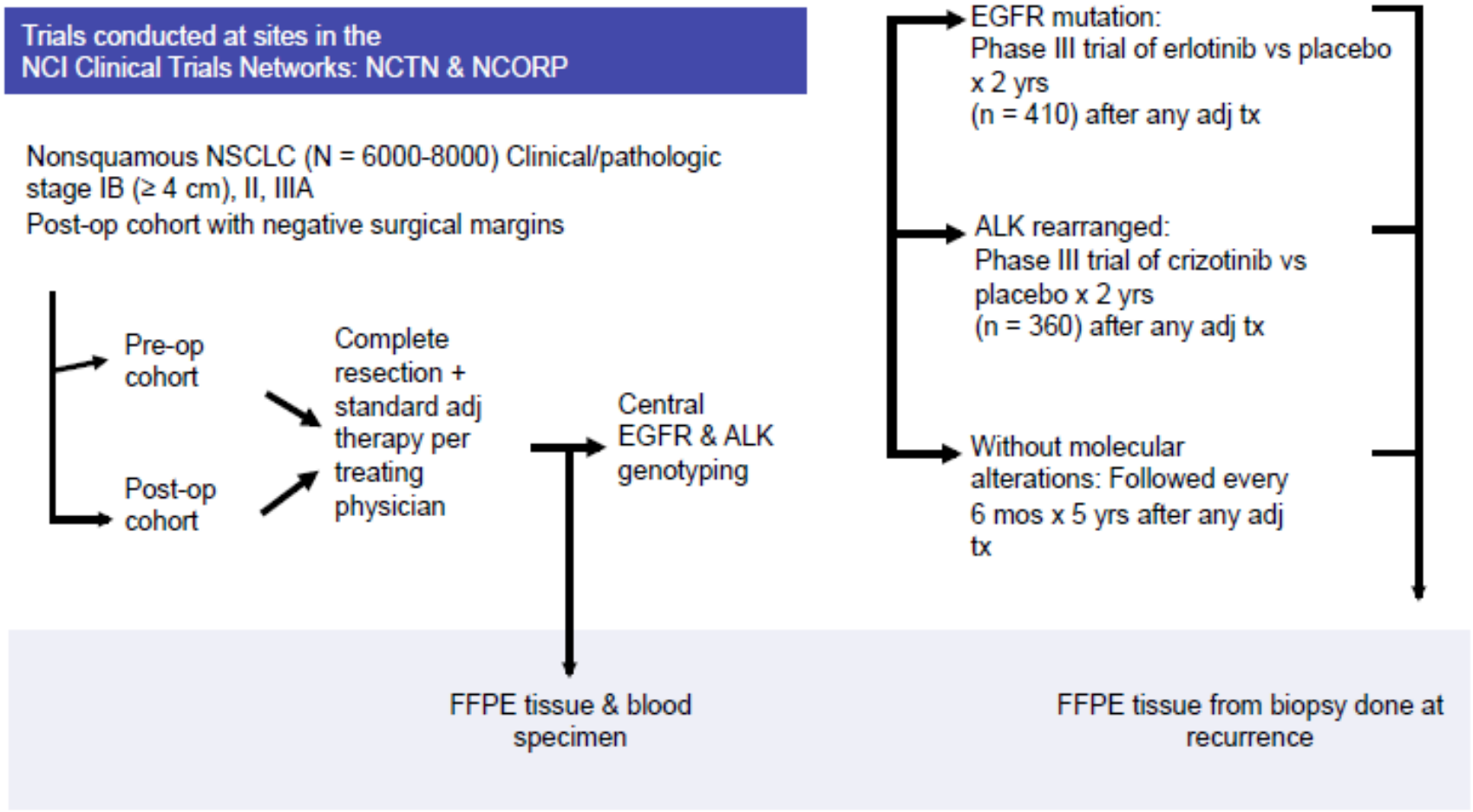


DFS (del19 and L858R)

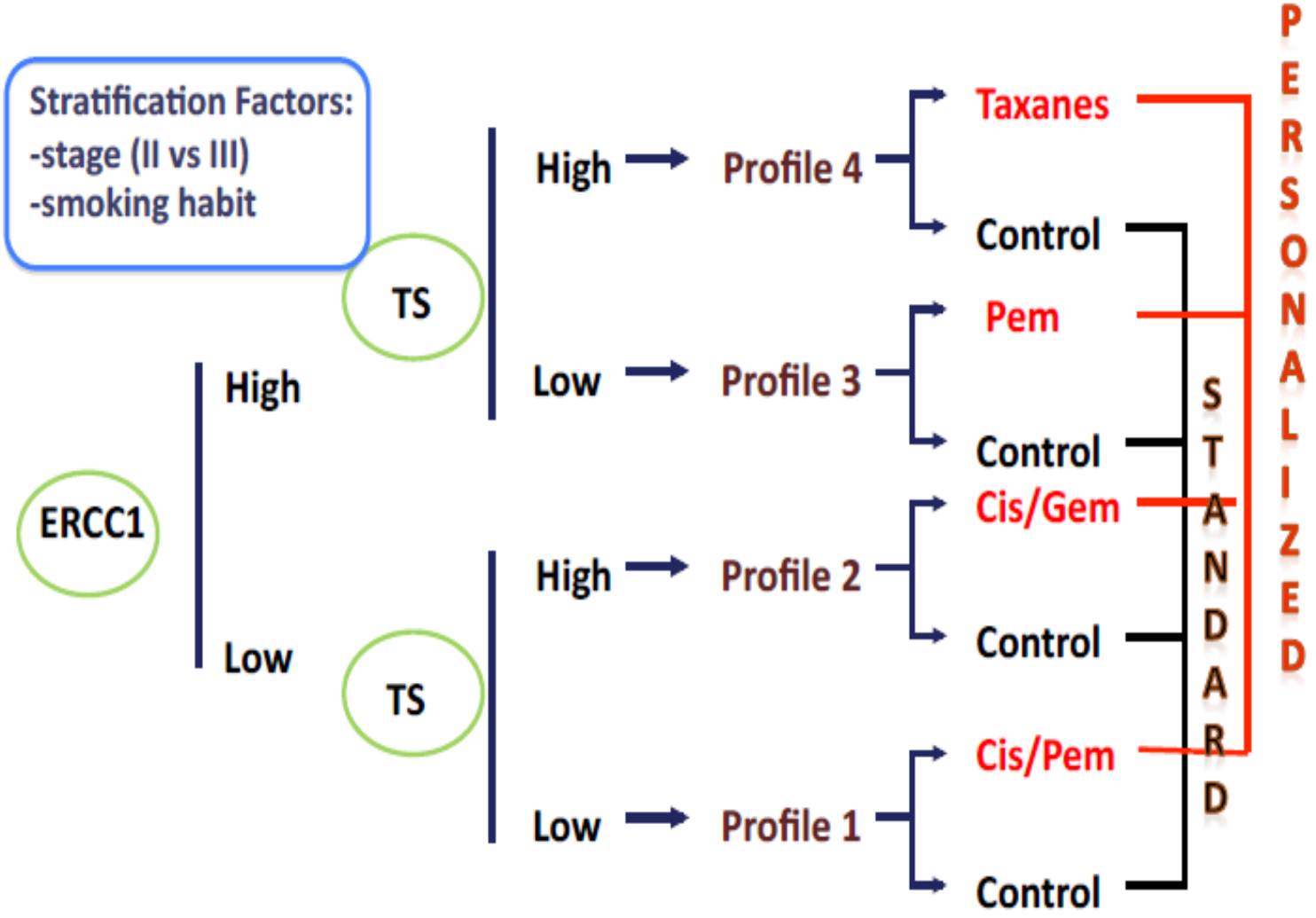


Kelly K, *JCO* 2015

Phase III ALCHEMIST Study: genetic testing in resectable stage IB-IIIA NSCLC



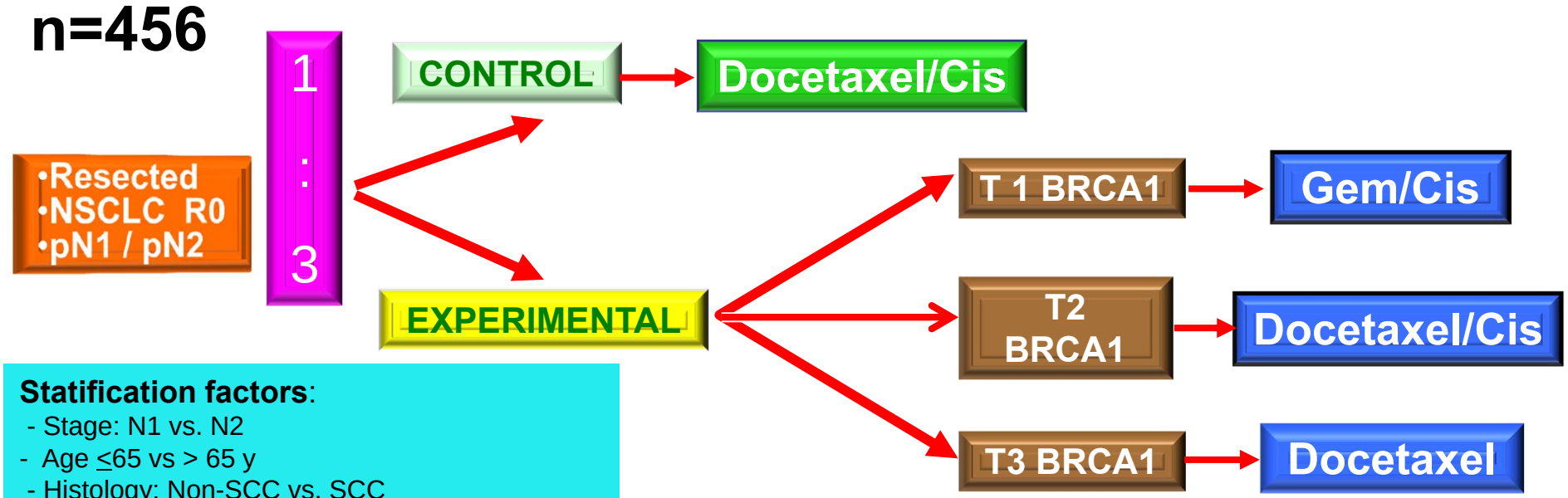
ITACA: trial design



Control = investigators' choice of cisplatin-based doublet
Trial was amended with the new Staging System (7 th) on December 2010

Novello S, WCLC 2015

Results Ph III trial customized adjuvant CT after resection of NSCLC with lymph node metastases SCAT :A Spanish Lung Cancer Group trial



Statification factors:
- Stage: N1 vs. N2
- Age ≤65 vs > 65 y
- Histology: Non-SCC vs. SCC
- Type of resection: Lobectomy vs Pneumonectomy

Planned number of patients: 432 (amended)

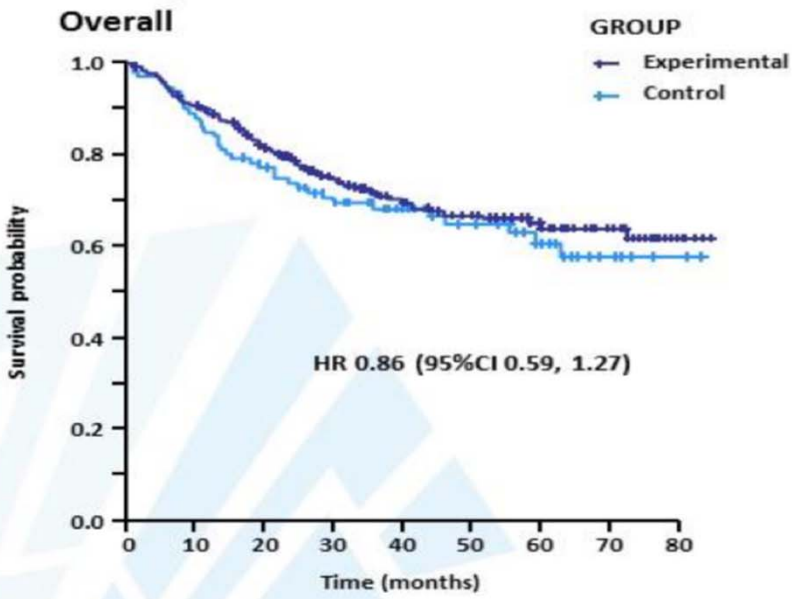
CT should be started before 8 weeks after surgery

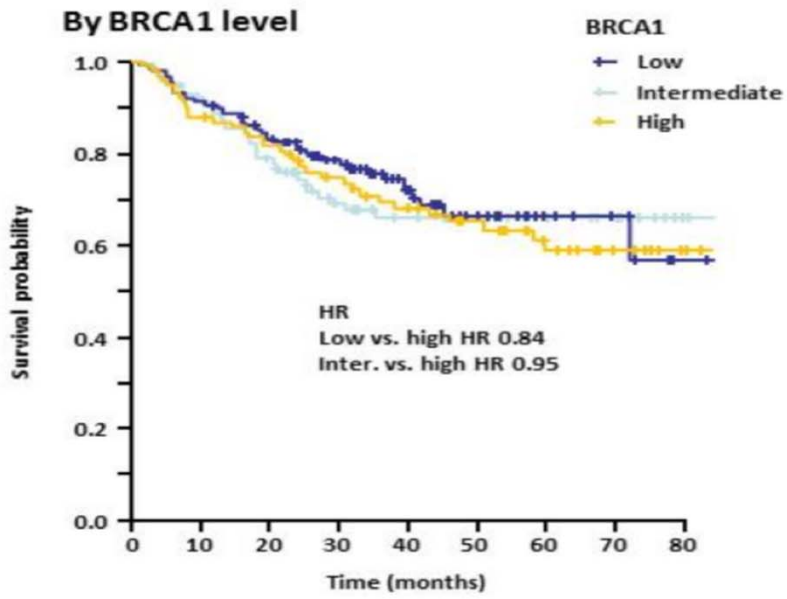
PORT in N2 patients

Primary end-point: **OS**

Early stage NSCLC

> ph3 Spanish Lung Cancer Group trial





Massuti et al, J Clin Oncol 33 Suppl: abstr 7507, 2015

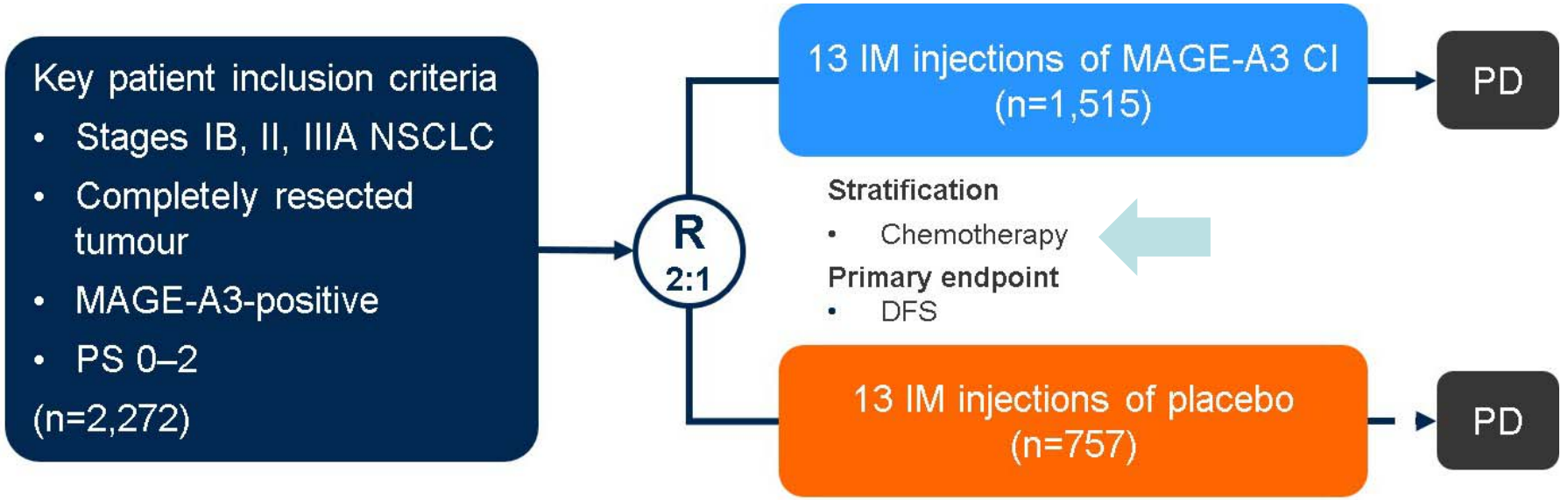
Low BRCA1 : Cis-Gem regimen is superior to Cis-Doc (HR = 0.50; p= 0.016)
High BRCA1: treatment without platinum is inferior to Cis-Doc (HR = 1.24)

Agenda

- What do we expect today from adjuvant chemotherapy
- Which data do we have with targeted agents in the adjuvant setting
- ….according to molecular predictors
- **What we expect with Immunotherapy agents**

MAGRIT: Phase III Study - MAGE-A3 as Adjuvant Non-Small Cell LunG CanceR ImmunoTherapy

MADRID 2014 ESMO congress



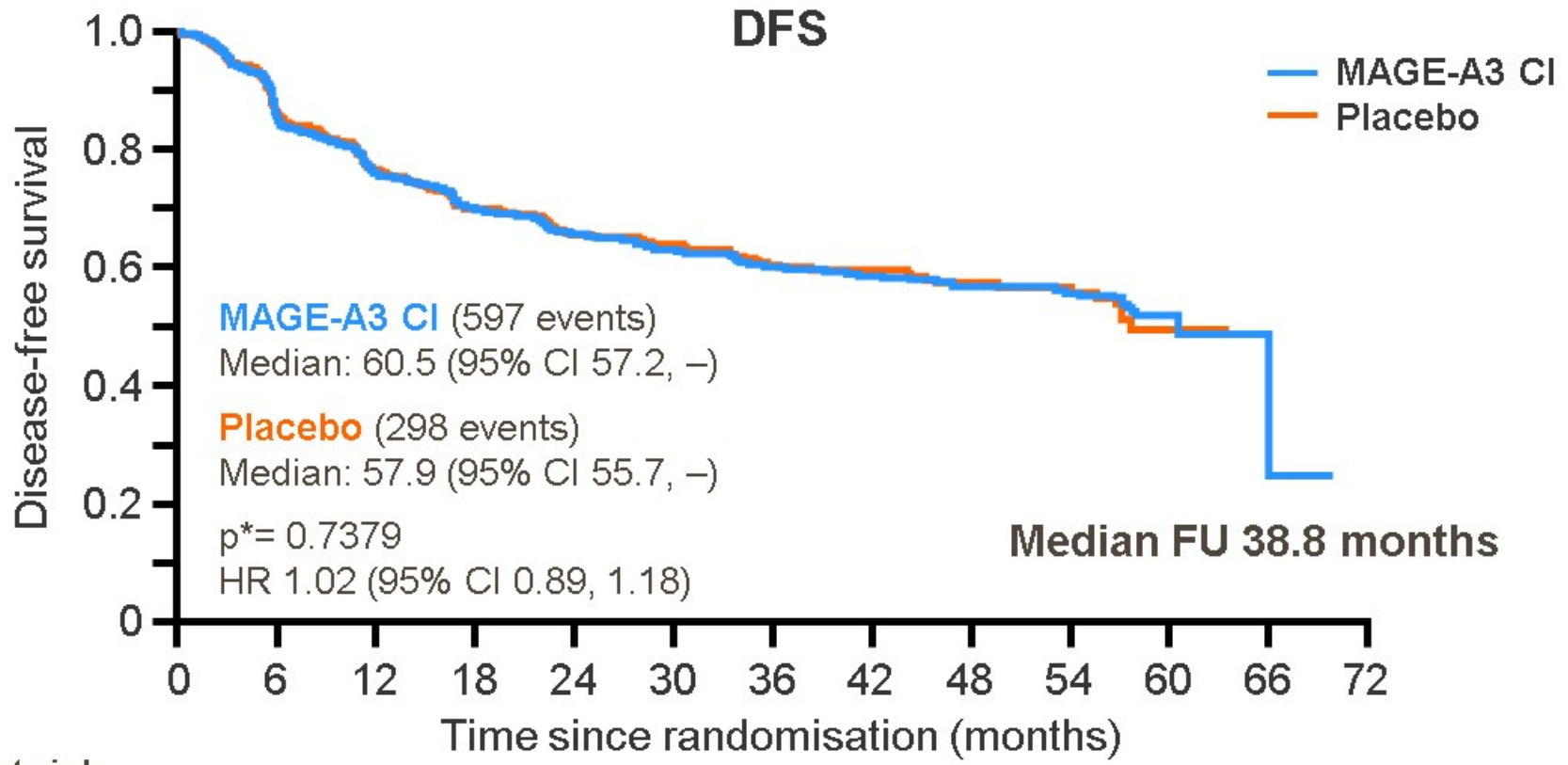
Screened	MAGE-A3 Valid test	MAGE-A3 (+) n (%)	Randomized	Treated
13,849	12,820	4,210 (33%)	2,312	2,272

Main protocol amendment: addition of DFS in Gene Signature positive (GS+) patients as co-primary endpoint

Vansteenkiste et al. ESMO 2014

MAGRIT: Phase III Study - MAGE-A3 as Adjuvant Non-Small Cell LunG CanceR ImmunoTherapy

MADRID 2014 ESMO congress

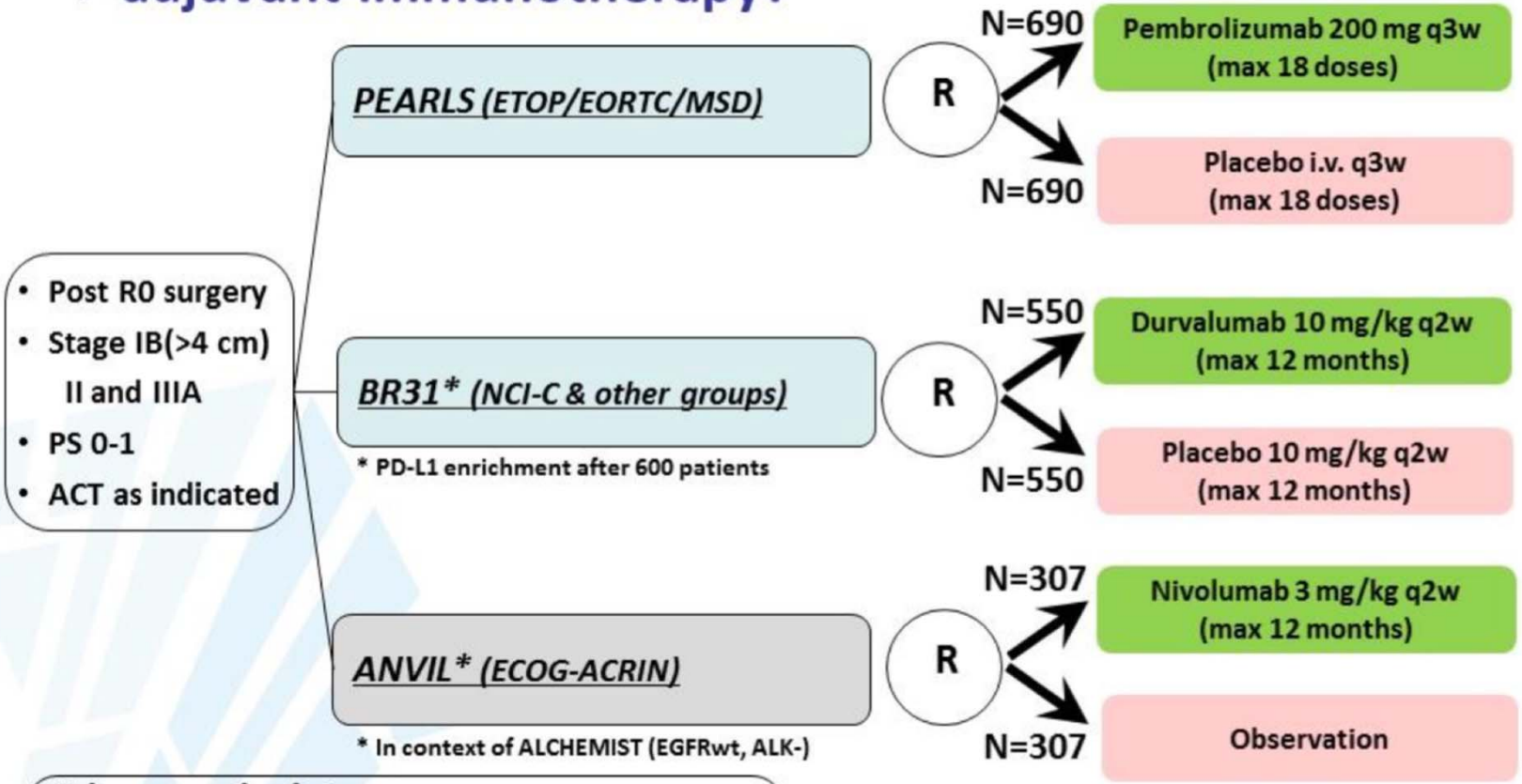


Number at risk												
MAGE-A3 CI	1,515	1,257	1,115	1,013	887	656	476	339	220	127	19	2
Placebo	757	639	562	514	448	328	253	180	114	62	6	0

Vansteenkiste et al. ESMO 2014

Early stage NSCLC

> adjuvant immunotherapy?



Take Home Messages
Early Stage Adjuvant Therapy

- Standard adjuvant therapy remains cisplatin-based doublet
  [for resected stage II/IIIA, controversy upon stage IB]

- Progress in stage IV is NOT translated to curative setting
  [In the current state of knowledge, the choice of adjuvant therapy should not be guided by molecular analyses]

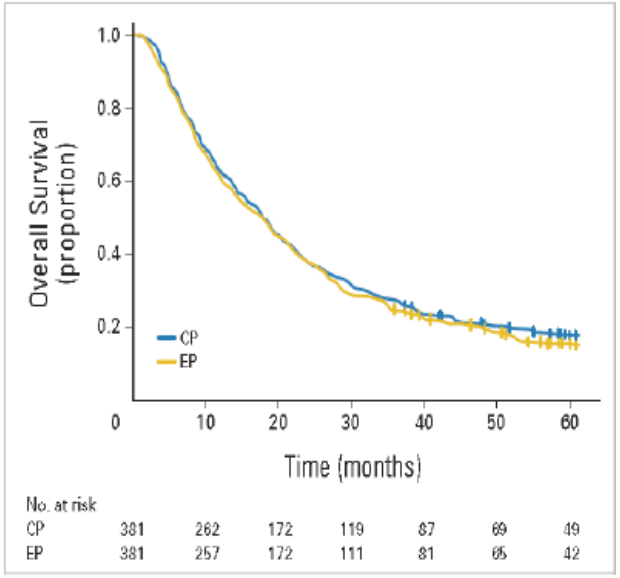
- In the current state of knowledge, targted agents should not be used as adjuvant therapy in any patient (unless into a clinical trial)

- Therapeutic vaccination with current technology does not work as adjuvant tx for lung cancer

Locally Advanced NSCLC: Concurrent chemoradiation, if tolerable, is recommended vs sequential approach or Rt alone [Chemo: cispl/etop and Carb/pacl; RT: 60 Gy in 2 Gy fractions, over 6 weeks]

No role for the **induction chemotherapy** before chemoradiation, neither **consolidation chemotherapy**

Bezjak, JCO 2015

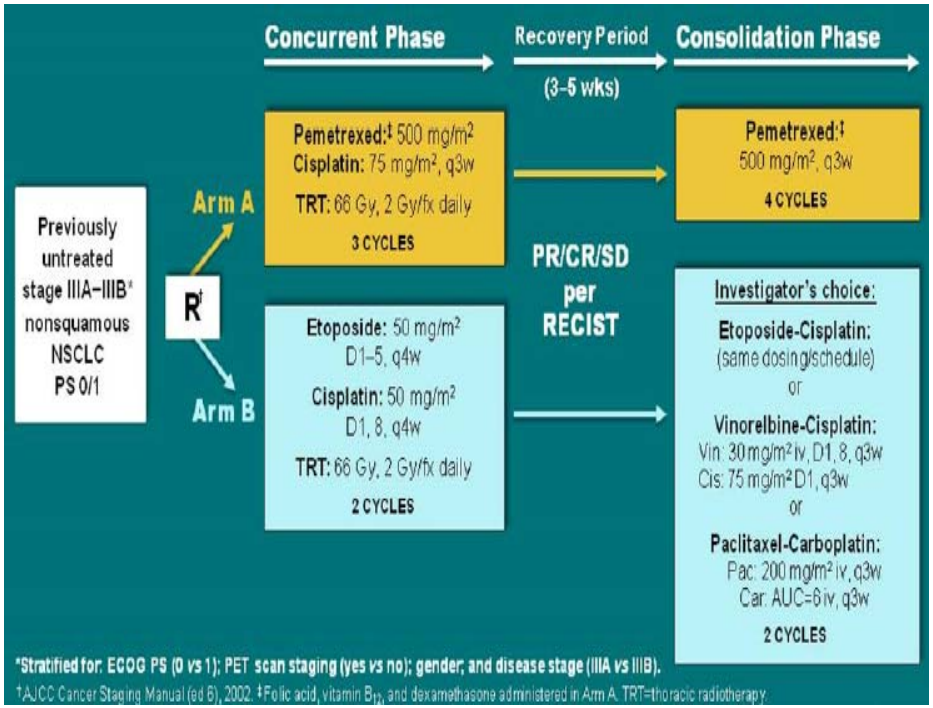


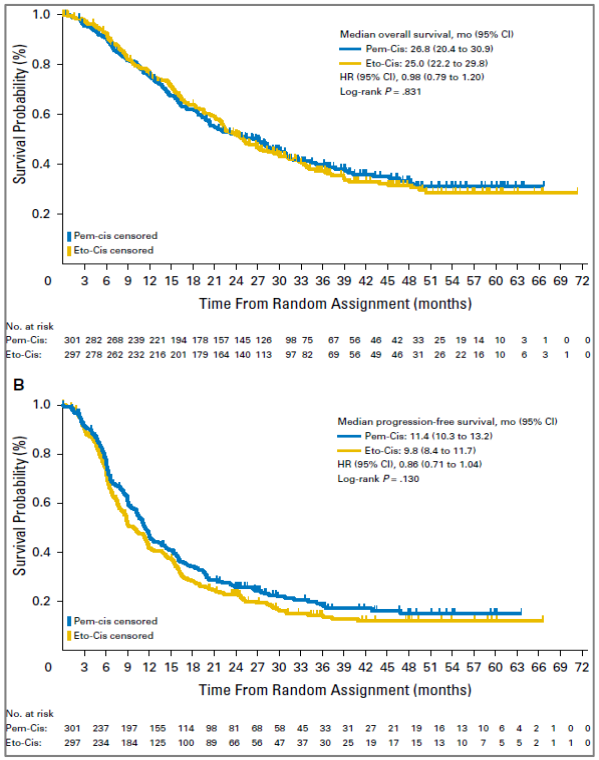
Santana-Davila R, JCO 2015

	CISPLATIN/ETOPOSIDE	CARBOPLATIN/PACLITAXEL	
Overall Response Rate	58% (CI 55%-61%); N=1457	56% (CI 54%- 58%);N=2385	(p=0.28)
3 years survival rates	30% (CI 27%-34%), N=763	25% (CI 22%-28%), N=951	(p=0.5)
Overal survival	Weighted median survival = **19.4 months (N=2770)**	Weighted median survival = **18.4 months (N=3602)**	p=0.35

Steuer CE, WCLC 2015

Locally Advanced NSCLC: Concurrent chemoradiation, if tolerable, is recommended vs sequential approach or Rt alone [Chemo: cispl/etop and Carb/pacl; RT: 60 Gy in 2 Gy fractions, over 6 weeks]





PROCLAIM, Senan S et al, JCO 2016


Thank you !