Chemotherapy in Non-Small Cell Lung Cancer

February 10,2018

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Aurora Cancer Care

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Outline

- Non small cell lung cancer
  - Role of adjuvant chemotherapy in resected disease
  - Management of stage III disease
  - Chemotherapy in metastatic disease
  - Is there anything new??

Non Small Cell Lung cancer

- NSCLC accounts for 80% of lung cancer cases
  - Nonsquamous (adenoCA, large cell CA)
    - Adenocarcinoma most common subtype and most frequent histology in non-smokers
  - Squamous
- Lung cancer remains the leading cause of cancer death in the U.S. – 1 in 4 cancer deaths; more women die of lung than breast cancer
- 5yr OS between 2007-13 only 23.6%
- Significant number of patients will recur with metastatic disease even after definitive treatment

NSCLC

- Cytotoxic chemotherapy remains mainstay of systemic treatment for advanced disease - approximately 50% of patients do not have a actionable mutation
- Adjuvant treatment almost exclusively cytotoxic chemotherapy
  - Targeted therapy not approved in the adjuvant setting outside clinical trial → Alchemist trial studying adjuvant targeted therapy in certain mutational subsets (EGFR/ALK)

Adjuvant Chemotherapy

Adjuvant Chemotherapy

- Chemotherapy administered after surgery with goal of prevention of recurrence
- Resected stage IA disease – chemotherapy not recommended (tumors less than 3cm)
- Data in numerous randomized trials does support consideration of adjuvant chemotherapy in resected stage IB-stage III

Meta analysis LACE (Lung Adjuvant Cisplatin Evaluation)

Table 1. Trial Description

Trial Name	Inclusion Criteria	Chemotherapy (No. of cycles, dose of cisplatin by cycle, daily dose × No. of doses for other drugs)	Radiotherapy	Inclusion Period	No. of Patients Included
JBR10	pT2pN0* or pT1-2pN1	4 cycles, cisplatin (50 × 2) mg/m^2 Vinorelbine 25 mg/m^2 × 16	No radiotherapy	1994-2001	482
Adjuvant Lung Cancer Project Italy	Stage I, II, IIIA	3 cycles, cisplatin 100 mg/m^2 Mitomycin 8 mg/m^2 × 3, vindesine 3 mg/m^2 × 6	Optional After chemotherapy	1994-1999	1,088
Adjuvant Navelbine International Trialist Association 01	Stage I, II, IIIA	4 cycles, cisplatin 100 mg/m^2 Vinorelbine 30 mg/m^2 × 16	Optional for pN+ After chemotherapy	1994-2000	840
International Adjuvant Lung Trial	Stage I, II, III	3 cycles, cisplatin 100 or 120 mg/m^2 or 4 cycles, cisplatin 80 or 100 mg/m^2 Vindesine 3 mg/m^2 × 6-8, or Vinblastine 4 mg/m^2 × 6-8, or Vinorelbine 30 mg/m^2 weekly × 13, or Etoposide 100 mg/m^2 × 9-12	Optional according to pN After chemotherapy	1995-2001	1,867
Big Lung Trial	Stage I, II, III	3 cycles, cisplatin 80 mg/m^2 (biotherapies) or 50 mg/m^2 (tritherapies) Vindesine 3 mg/m^2 × 6, or Vinorelbine 30 mg/m^2 × 6, or Mitomycin 6 mg/m^2 × 3 and ifosfamide 3 g/m^2 × 3, or Mitomycin 6 mg/m^2 × 3 and vinblastine 6 mg/m^2 × 3	Optional After chemotherapy	1995-2001	307†

Abbreviation: JBR10, National Cancer Institute of Canada Clinical Trial Group trial JBR10.
*Pathologic tumor (pT) and nodal (pN) stage.
†Patients with incomplete resection (n = 61) or neoadjuvant chemotherapy (n = 13) were excluded.

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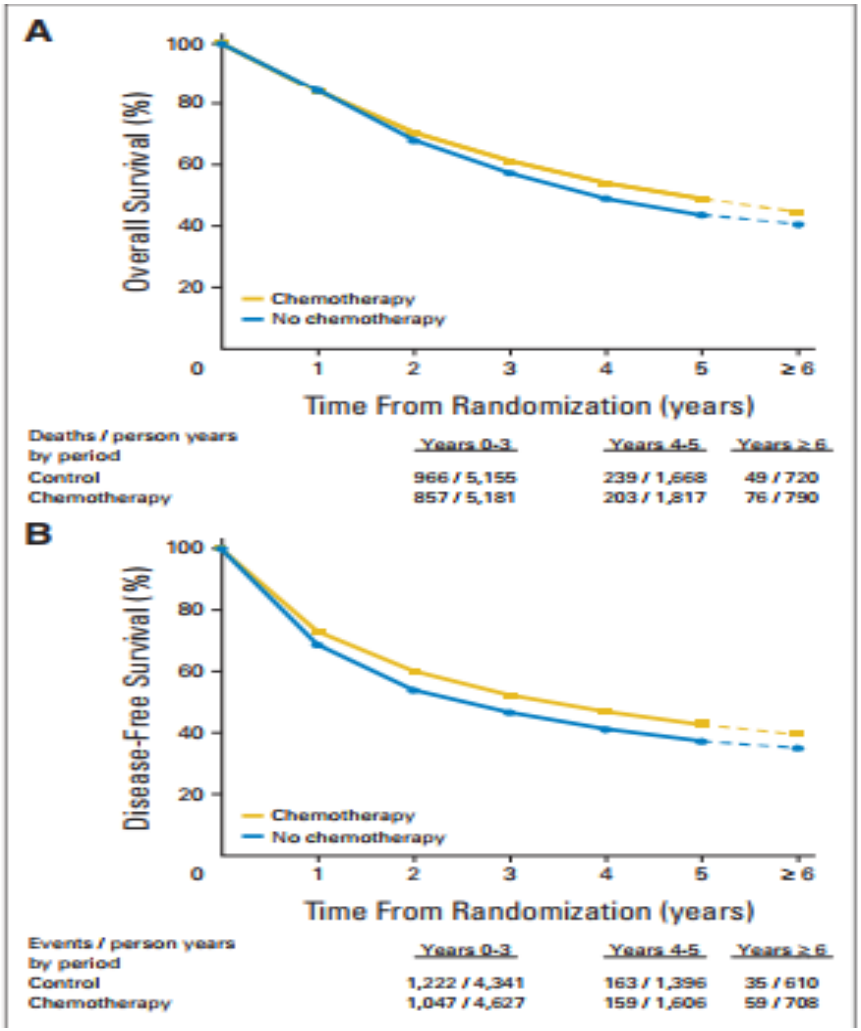
Pignon,JP et al, J Clin Oncol 2008

LACE



- Median follow up of 5.2 years decreased risk of death of 5.4%,overall HR of death was 0.89 (95% CI, 0.82 to 0.96; P = .005),
- No significant difference DFS/OS in 2nd drug in the cisplatin doublet (etoposide, vinorelbine)
- Significant benefit not seen in PS 2
- Non significant survival trend in IB disease

Adjuvant chemotherapy options

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Non-Small Cell Lung Cancer

CHEMOTHERAPY REGIMENS FOR NEOADJUVANT AND ADJUVANT THERAPY

- Cisplatin 50 mg/m² days 1 and 8; vinorelbine 25 mg/m² days 1, 8, 15, 22, every 28 days for 4 cycles[a]
- Cisplatin 100 mg/m² day 1; vinorelbine 30 mg/m² days 1, 8, 15, 22, every 28 days for 4 cycles[b,c]
- Cisplatin 75–80 mg/m² day 1; vinorelbine 25–30 mg/m² days 1 + 8, every 21 days for 4 cycles
- Cisplatin 100 mg/m² day 1; etoposide 100 mg/m² days 1–3, every 28 days for 4 cycles[b]
- Cisplatin 75 mg/m² day 1; gemcitabine 1250 mg/m² days 1, 8, every 21 days for 4 cycles[d]
- Cisplatin 75 mg/m² day 1; docetaxel 75 mg/m² day 1 every 21 days for 4 cycles[e]
- Cisplatin 75 mg/m² day 1, pemetrexed 500 mg/m² day 1 for nonsquamous every 21 days for 4 cycles[f]

Chemotherapy Regimens for Patients with Comorbidities or Patients Not Able to Tolerate Cisplatin

- Carboplatin AUC 6 day 1, paclitaxel 200 mg/m² day 1, every 21 days for 4 cycles[g]
- Carboplatin AUC 5 day 1, gemcitabine 1000 mg/m² days 1, 8, every 21 days for 4 cycles[h]
- Carboplatin AUC 5 day 1, pemetrexed 500 mg/m² day 1 for nonsquamous every 21 days for 4 cycles[i]

Adjuvant chemotherapy

- Optimal platinum regimen not established

Vinorelbine	-most studied 2nd agent -neuropathy -high rates of neutropenia/febrile neutropenia
Docetaxel	-Alopecia -febrile neutropenia -pneumonitis -neuropathy -hypersensitivity reaction (steroid pre-meds)
Gemcitabine	-thrombocytopenia -less febrile neutropenia -no alopecia
Pemetrexed	-lowest rates of febrile neutropenia -no alopecia -no neuropathy

Adjuvant chemotherapy

- Administered at least 4 weeks, at most no more than 12 weeks after definitive surgery
- Cisplatin preferred when therapy for curative intent
- Carboplatin may be preferred in patients with baseline renal dysfunction, hearing loss, pre-existing significant neuropathy or those unable to tolerate the emetogenic potential
- Stage IB high risk patients may benefit
  - Tumor greater than 4cm
  - Poorly differentiated histology
  - Visceral pleural invasion
  - Vascular invasion
- Bottom line: statistically significant survival benefit but only 5-10% depending on the trial

Management of Stage III NSCLC

Stage III NSCLC

8th Edition TNM Classification

Stage IIIA	T1a	N2	M0
	T1b	N2	M0
	T1c	N2	M0
	T2a	N2	M0
	T2b	N2	M0
	T3	N1	M0
	T4	N0	M0
	T4	N1	M0
Stage IIIB	T1a	N3	M0
	T1b	N3	M0
	T1c	N3	M0
	T2a	N3	M0
	T2b	N3	M0
	T3	N2	M0
	T4	N2	M0
Stage IIIC	T3	N3	M0
	T4	N3	M0
Stage IVA	Any T	Any N	M1a

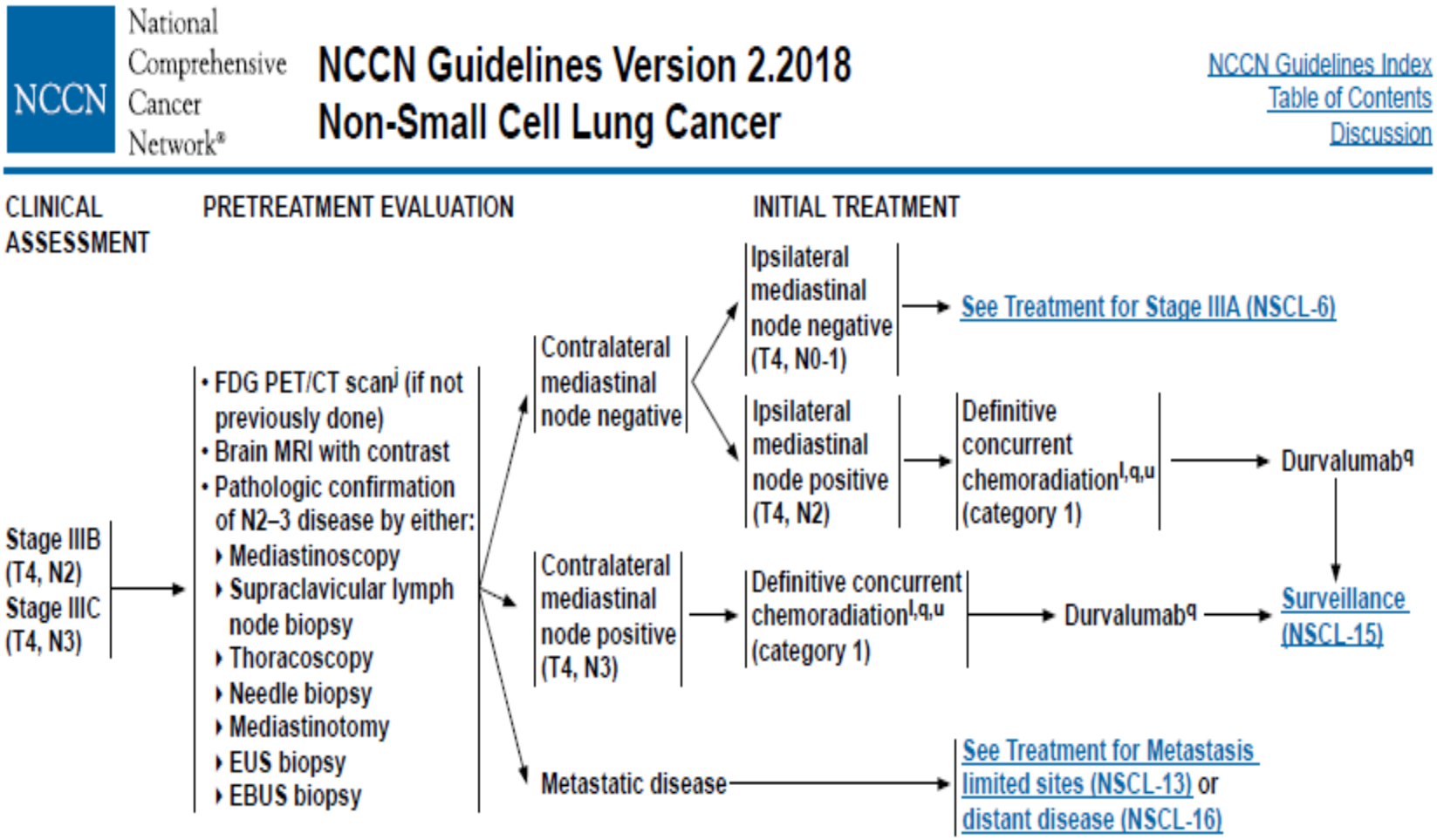
- Heterogenous group
- Multidisciplinary evaluation crucial
- Historically defined as locoregionally advanced due to tumor extension into extrapulmonary structures (T3/4) or mediastinal node involvement (N2/N3)
- 8th edition also includes > 5cm tumor (T3) with N1 nodes or >7cm tumor(T4) regardless of nodes

Stage IIIB/C NSCLC

- Includes
  - N3 nodes
  - N2 nodes but T3/T4 tumors

- Unresectable
- Definitive concurrent chemotherapy and radiation
  - Platinum agent with concurrent daily radiation
  - Concurrent chemoradiotherapy superior to sequential in randomized phase III trials
  - Optimal chemotherapy regimen?

Stage IIIB/C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CLINICAL ASSESSMENT
PRETREATMENT EVALUATION
INITIAL TREATMENT
Stage IIIB (T4, N2)
Stage IIIC (T4, N3)
• FDG PET/CT scan[j] (if not previously done)
• Brain MRI with contrast
• Pathologic confirmation of N2–3 disease by either:
Mediastinoscopy
Supraclavicular lymph node biopsy
Thoracoscopy
Needle biopsy
Mediastinotomy
EUS biopsy
EBUS biopsy
Contralateral mediastinal node negative
Ipsilateral mediastinal node negative (T4, N0-1)
See Treatment for Stage IIIA (NSCL-6)
Ipsilateral mediastinal node positive (T4, N2)
Definitive concurrent chemoradiation[l,q,u] (category 1)
Durvalumab[q]
Contralateral mediastinal node positive (T4, N3)
Definitive concurrent chemoradiation[l,q,u] (category 1)
Durvalumab[q]
Surveillance (NSCL-15)
Metastatic disease
See Treatment for Metastasis limited sites (NSCL-13) or distant disease (NSCL-16)

Stage III NSCLC

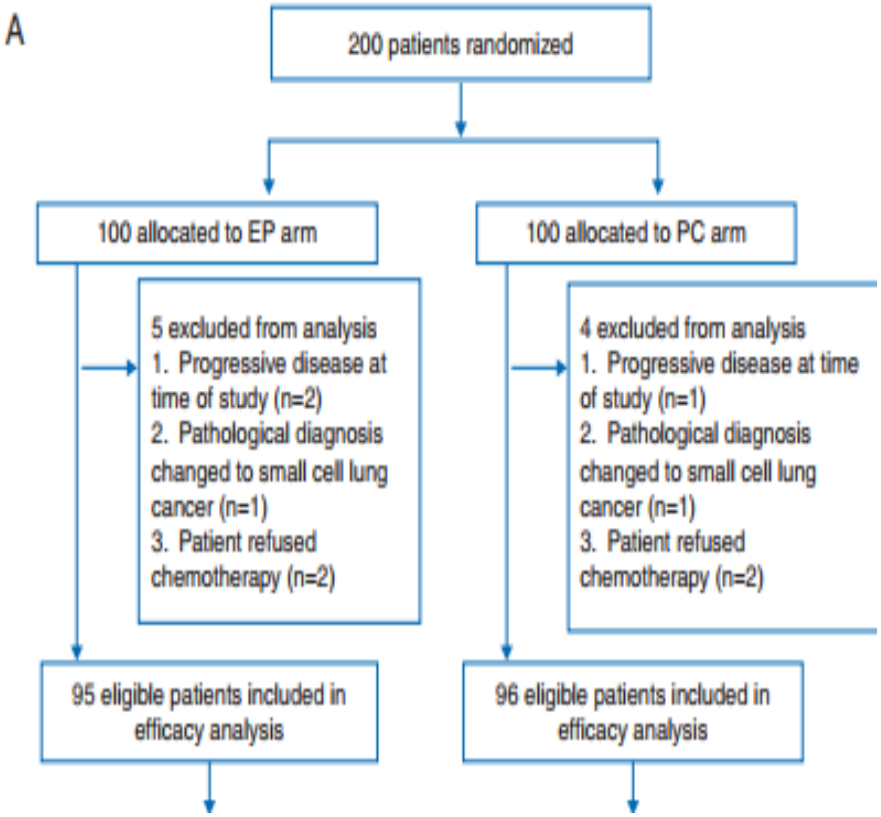
Annals of Oncology 28: 777–783, 2017
doi:10.1093/annonc/mdx009
Published online 30 January 2017

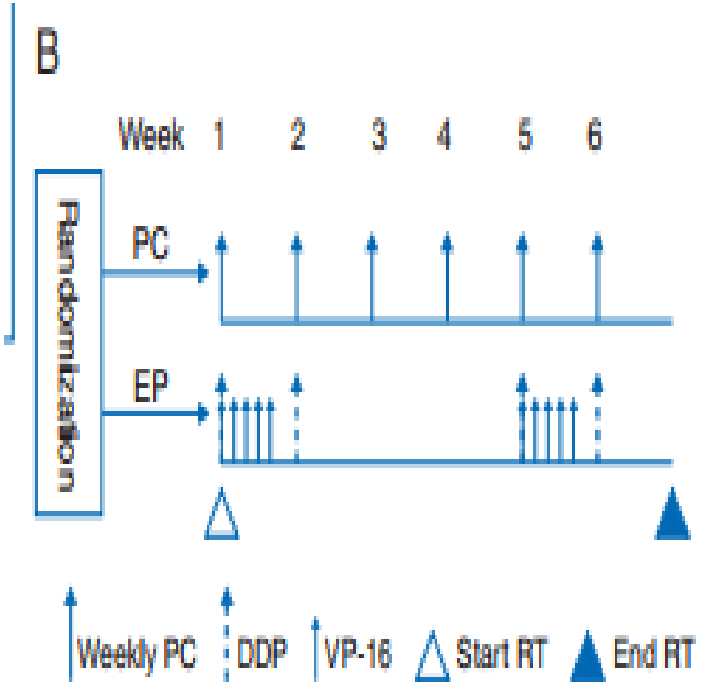
ORIGINAL ARTICLE

Etoposide and cisplatin versus paclitaxel and carboplatin with concurrent thoracic radiotherapy in unresectable stage III non-small cell lung cancer: a multicenter randomized phase III trial

J. Liang[1†], N. Bi[1†], S. Wu[2], M. Chen[3], C. Lv[4], L. Zhao[5], A. Shi[6], W. Jiang[7], Y. Xu[8], Z. Zhou[1], W. Wang[1], D. Chen[1], Z. Hui[1], J. Lv[1], H. Zhang[1], Q. Feng[1], Z. Xiao[1], X. Wang[1], L. Liu[1], T. Zhang[1], L. Du[9], W. Chen[10], Y. Shyr[9], W. Yin[1], J. Li[11], J. He[12] & L. Wang[1*]

Stage III NSCLC





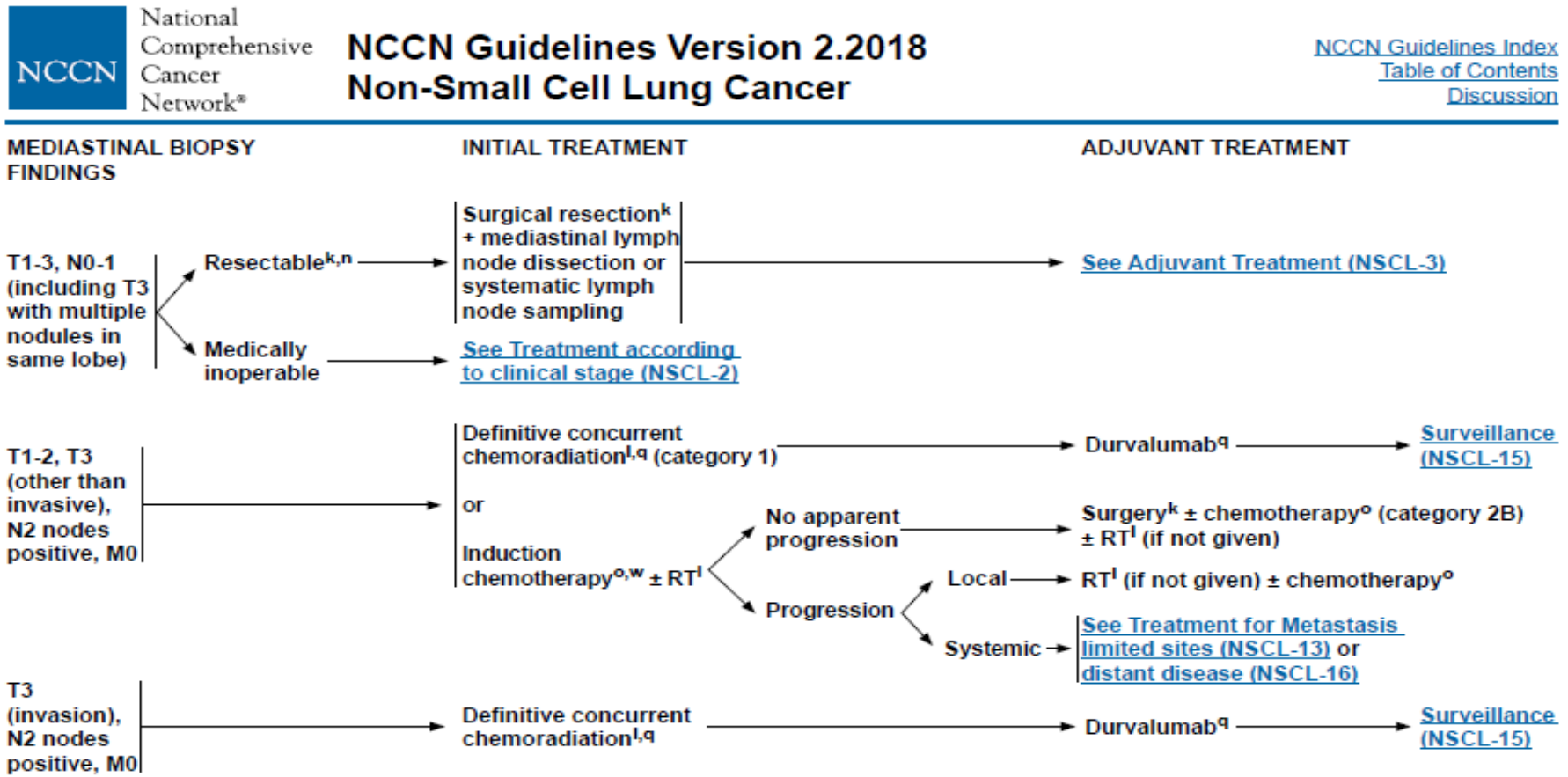
-Received radiation 60-65Gy

Results

- More grade ≥2 pneumonitis in PC arm
- More grade ≥3 esophagitis in EP arm
- Improved 3 year OS in EP arm (41 vs 26%, 0.024)
- However, patients in PC arm did NOT receive consolidation chemotherapy cycles which is standard for this regimen for systemic control
- Weekly PC with radiation + then two cycles consolidation chemotherapy (higher doses q 3 weeks) acceptable and generally more tolerable

Stage III – N2 mediastinal involvement

- N2 disease that is not resectable (eg.,T3 with invasion) – definitive chemotherapy and radiation
- Subset of patients with N2 disease will be surgical candidates
  - Contraindication to surgery include poor PS, multi-station N2 disease, T4, need for pneumonectomy
  - Single station N2 disease(<3cm), complete resection possible with lobectomy may be surgery candidates
  - Local control improved, no randomized studies have demonstrated survival benefit
- Intergroup 0139 trial
  - 400patients with N2 disease no OS survival advantage to surgery after Chemo/RT but local control increased and 5yr PFS (22 vs 11%)
    - 26% post op mortality in pneumonectomy patients (negates benefit?)



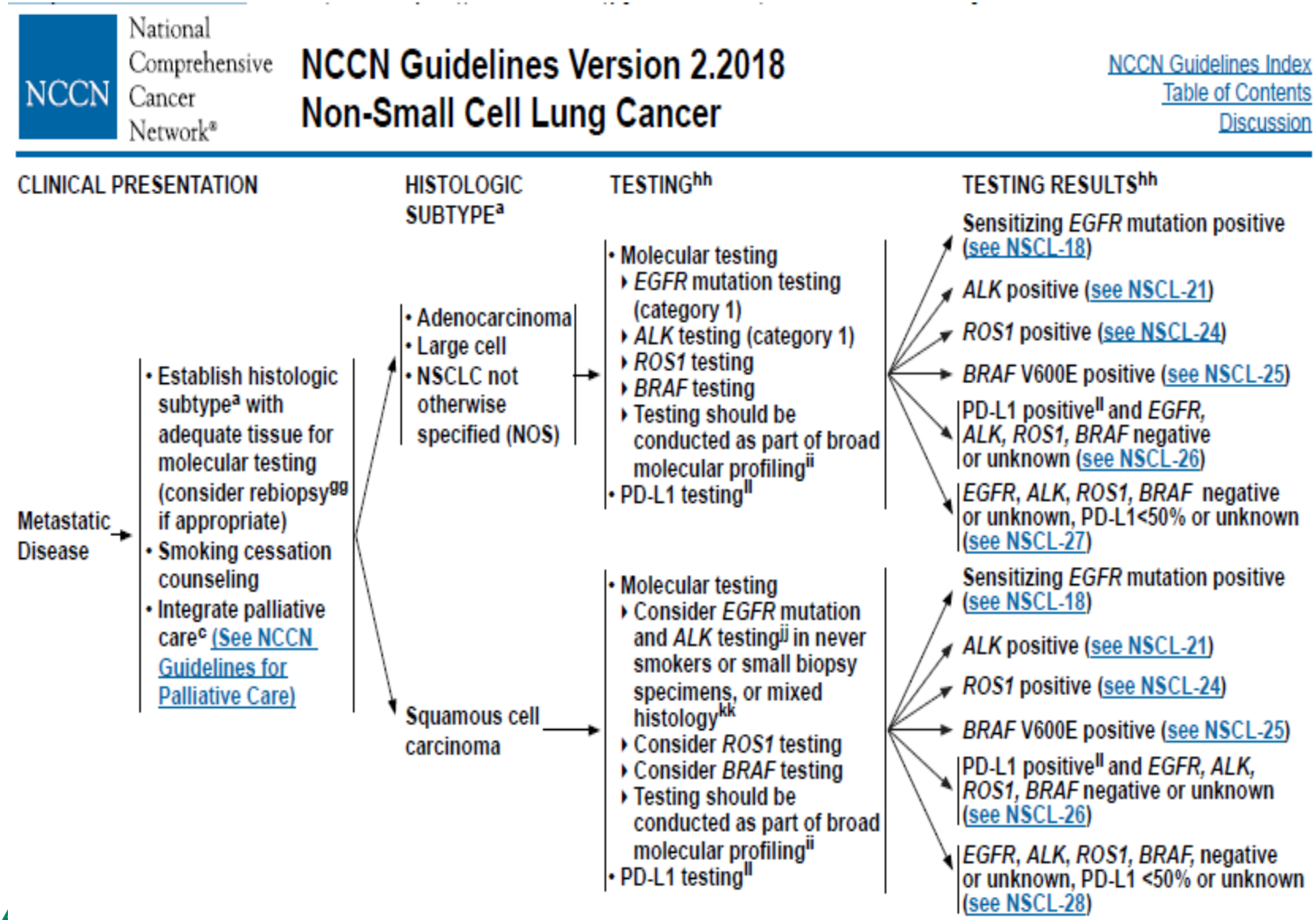
[k]See Principles of Surgical Therapy (NSCL-B).
[l]See Principles of Radiation Therapy (NSCL-C).
[n]After surgical evaluation, patients likely to receive adjuvant chemotherapy may be treated with induction chemotherapy as an alternative.
[o]See Chemotherapy Regimens for Neoadjuvant and Adjuvant Therapy (NSCL-D).
[q]See Chemotherapy Regimens Used with Radiation Therapy (NSCL-E).
[w]Chest CT with contrast and/or PET/CT to evaluate progression.

Chemotherapy in Metastatic Disease

Metastatic NSCLC

- Approximately 50% of patients are diagnosed at Stage IV and most progress/develop metastatic disease despite aggressive multi modality treatment in earlier stages.
- Therapy is palliative but has been show to improve OS vs best supportive care in patients with good PS
- Cytotoxic chemotherapy 1st line treatment for the nearly 50% of patients with no actionable mutation
- Two drugs better than one – meta analysis of 13,000pts from 65 randomized trials
  - ORR 26vs 13%
  - 1yr suvival 35vs 30%

Metastatic Disease



Metastatic disease – nonsquamous

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SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE (2 of 4)*,**

Initial Cytotoxic Therapy Options

Adenocarcinoma, Large Cell, NSCLC NOS (PS 0-1)

- Bevacizumab/carboplatin/paclitaxel (category 1)[1,†,‡,#]
- Bevacizumab/carboplatin/pemetrexed[2,†,‡,#]
- Bevacizumab/cisplatin/pemetrexed[3,†,‡,#]
- Carboplatin/albumin-bound paclitaxel (category 1)[4]
- Carboplatin/docetaxel (category 1)[5]
- Carboplatin/etoposide (category 1)[6,7]
- Carboplatin/gemcitabine (category 1)[8]
- Carboplatin/paclitaxel (category 1)[9]
- Carboplatin/pemetrexed (category 1)[10]
- Cisplatin/docetaxel (category 1)[5]
- Cisplatin/etoposide (category 1)[11]
- Cisplatin/gemcitabine (category 1)[9,12]
- Cisplatin/paclitaxel (category 1)[13]
- Cisplatin/pemetrexed (category 1)[12]
- Gemcitabine/docetaxel (category 1)[14]
- Gemcitabine/vinorelbine (category 1)[15]
- Pembrolizumab/carboplatin/pemetrexed[16,¶]

Adenocarcinoma, Large Cell, NSCLC NOS (PS 2)

- Albumin-bound paclitaxel[17]
- Carboplatin/albumin-bound paclitaxel[18,19]
- Carboplatin/docetaxel[5]
- Carboplatin/etoposide[6,7]
- Carboplatin/gemcitabine[8]
- Carboplatin/paclitaxel[9]
- Carboplatin/pemetrexed[10]
- Docetaxel[20,21]
- Gemcitabine[22-24]
- Gemcitabine/docetaxel[14]
- Gemcitabine/vinorelbine[15]
- Paclitaxel[25-27]
- Pemetrexed[28]

Metastatic disease - squamous

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SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE (3 of 4)*,,§**

Initial Cytotoxic Therapy Options

Squamous Cell Carcinoma (PS 0-1)

- Carboplatin/albumin-bound paclitaxel (category 1)[4]
- Carboplatin/docetaxel (category 1)[5]
- Carboplatin/gemcitabine (category 1)[8]
- Carboplatin/paclitaxel (category 1)[9]
- Cisplatin/docetaxel (category 1)[5]
- Cisplatin/etoposide (category 1)[11]
- Cisplatin/gemcitabine (category 1)[9,12]
- Cisplatin/paclitaxel (category 1)[13]
- Gemcitabine/docetaxel (category 1)[14]
- Gemcitabine/vinorelbine (category 1)[15]

Squamous Cell Carcinoma (PS 2)

- Albumin-bound paclitaxel[17]
- Carboplatin/albumin-bound paclitaxel[18,19]
- Carboplatin/docetaxel[5]
- Carboplatin/etoposide[6,7]
- Carboplatin/gemcitabine[8]
- Carboplatin/paclitaxel[9]
- Docetaxel[20,21]
- Gemcitabine[22-24]
- Gemcitabine/docetaxel[14]
- Gemcitabine/vinorelbine[15]
- Paclitaxel[25-27]

First line chemotherapy

Comparison of Four Chemotherapy Regimens for Advanced Non–Small-Cell Lung Cancer

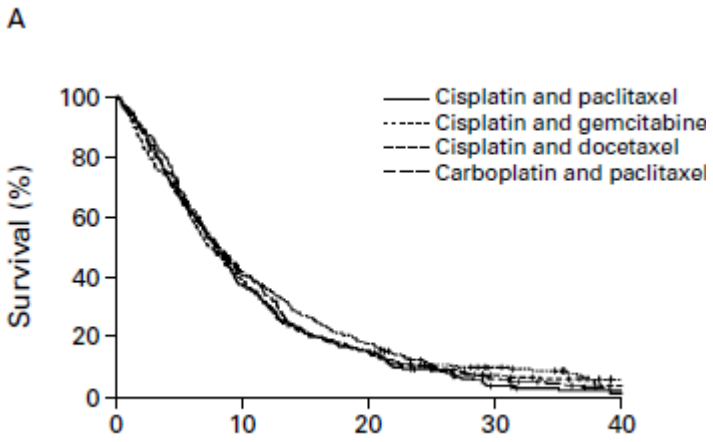
oan H. Schiller, M.D., David Harrington, Ph.D., Chandra P. Belani, M.D., Corey Langer, M.D., Alan Sandler, M.D., James Krook, M.D., Junming Zhu, Ph.D., and David H. Johnson, M.D. for the Eastern Cooperative Oncology Group

Schiller, JH, et al N Engl J Med 2002

The NEW ENGLAND JOURNAL of MEDICINE

Results

- Randomized phase III trial, 1200 patients – reference regimen cisplatin/paclitaxel
- No significant difference between regimens in first line
- Carbo/paclitaxel least toxic and became the reference regimen for ECOG



First line systemic therapy

- Platinum doublet – cisplatin increases objective response rate; toxicity outweighs benefit in most patients
  - Cisplatin increased nephrotoxicity and emetic potential
  - Carboplatin increased thrombocytopenia
- Histology matters in choosing 1st line chemo
  - Carboplatin/ paclitaxel or carboplatin/gemcitabine in squamous histology
  - Carboplatin/pemetrexed or carboplatin/paclitaxel in nonsquamous histology

First line systemic therapy

VOLUME 26 · NUMBER 21 · JULY 20 2008

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

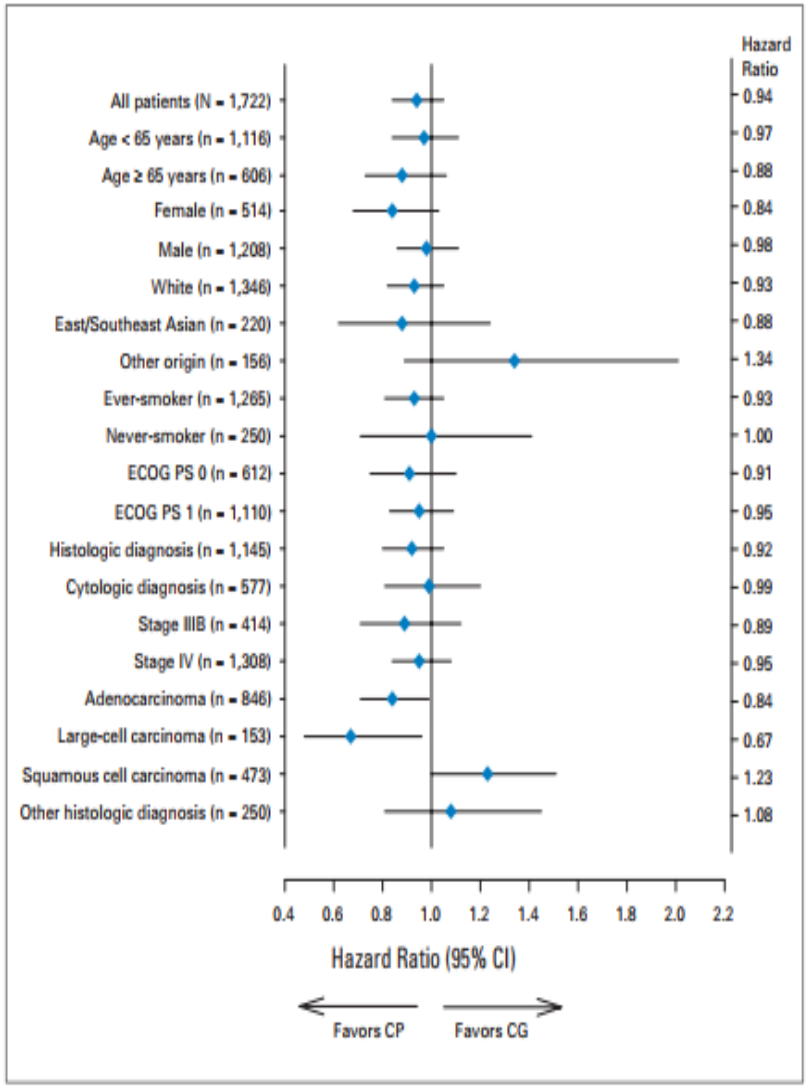
Phase III Study Comparing Cisplatin Plus Gemcitabine With Cisplatin Plus Pemetrexed in Chemotherapy-Naive Patients With Advanced-Stage Non–Small-Cell Lung Cancer

Giorgio Vittorio Scagliotti, Purvish Parikh, Joachim von Pawel, Bonne Biesma, Johan Vansteenkiste, Christian Manegold, Piotr Serwatowski, Ulrich Gatzemeier, Raghunadharao Digumarti, Mauro Zukin, Jin S. Lee, Anders Mellemgaard, Keunchil Park, Shehkar Patil, Janusz Rolski, Tuncay Goksel, Filippo de Marinis, Lorinda Simms, Katherine P. Sugarman, and David Gandara

From the University of Torino, Orbas-

- Phase III study, 1700 patients
- Non inferiority trial
- OS endpoint – noninferior between the two treatment arms

First line systemic therapy



- Pre-specified analysis of survival with respect to histology
- Statistically significant OS (12.6 vs 10.9mo) but only in nonsquamous histology
- Significantly less grade 3/4 cytopenias and febrile neutropenia in cis/pem
- Pemetrexed recommended in adjuvant and advanced NSCLC nonsquamous histology

(Scagliotti, GV et al J Clin Oncol 2008)

First line systemic therapy

- Duration of chemotherapy –
  - 4-6 cycles of initial platinum combination
  - Increase in progression free survival with longer courses of chemotherapy does not translate into significant survival advantage
- Platinum combinations have plateaued in overall RR (25-35%); MS (8-10mos) and 1 yr survival 30-40%
- Maintenance therapy after 4-6 cycles if responding disease in good PS patients may improve PFS and OS

Maintenance therapy

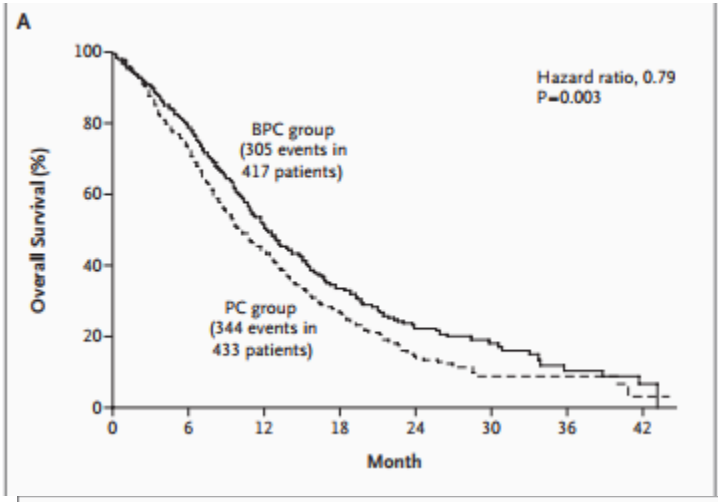
- Continuation maintenance- agent in initial chemotherapy regimen used until progression

- Switch maintenance – initiation of an agent not included in first line

Maintenance therapy- Bevacizumab

- Anti-VEGF monoclonal antibody
  - Higher VEGF levels may be associated with poorer prognosis suggesting that targeting this pathway may be useful
- Toxicity includes risk of thromboembolic events, bleeding, hypertension
- Studied in combination with first line platinum chemotherapy doublet and as maintenance

Bevacizumab



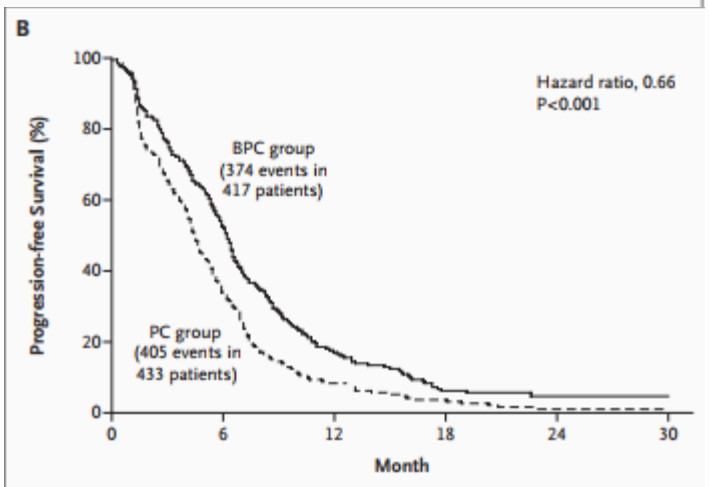


Figure 2. Kaplan–Meier Estimates of Overall Survival (Panel A) and Progression-free Survival (Panel B).

BPC denotes paclitaxel and carboplatin plus bevacizumab, and PC paclitaxel and carboplatin alone.

ECOG 4599 –

- PC vs BPC>>Bev monotherapy
- OS (12.3 vs 10.3 mo)
- PFS (6.2 vs 4.5 mo)
- RR 35% vs 15%

- Rates of clinically significant bleeding 4.4% vs 0.7% (P< 0.001)
- Bev approved in non-squamous, no hemoptysis, caution in elderly patients

Maintenance

- Non squamous histology
  - continuation maintenance with bevacizumab or pemetrexed (PARAMOUNT trial), choice depends on agents used in original combination and comorbidities
  - Bev/pem combination may improve PFS, no OS
- Squamous histology
  - Cytotoxic therapy gemcitabine and docetaxel
  - All maintenance therapy a category 2A recommendation
- Observation acceptable as well

Recent Advances – Immunotherapy!

Durvalumab after Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer

S.J. Antonia, A. Villegas, D. Daniel, D. Vicente, S. Murakami, R. Hui, T. Yokoi, A. Chiappori, K.H. Lee, M. de Wit, B.C. Cho, M. Bourhaba, X. Quantin, T. Tokito, T. Mekhail, D. Planchard, Y.-C. Kim, C.S. Karapetis, S. Hiret, G. Ostoros, K. Kubota, J.E. Gray, L. Paz-Ares, J. de Castro Carpeño, C. Wadsworth, G. Melillo, H. Jiang, Y. Huang, P.A. Dennis, and M. Özgüroğlu, for the PACIFIC Investigators*

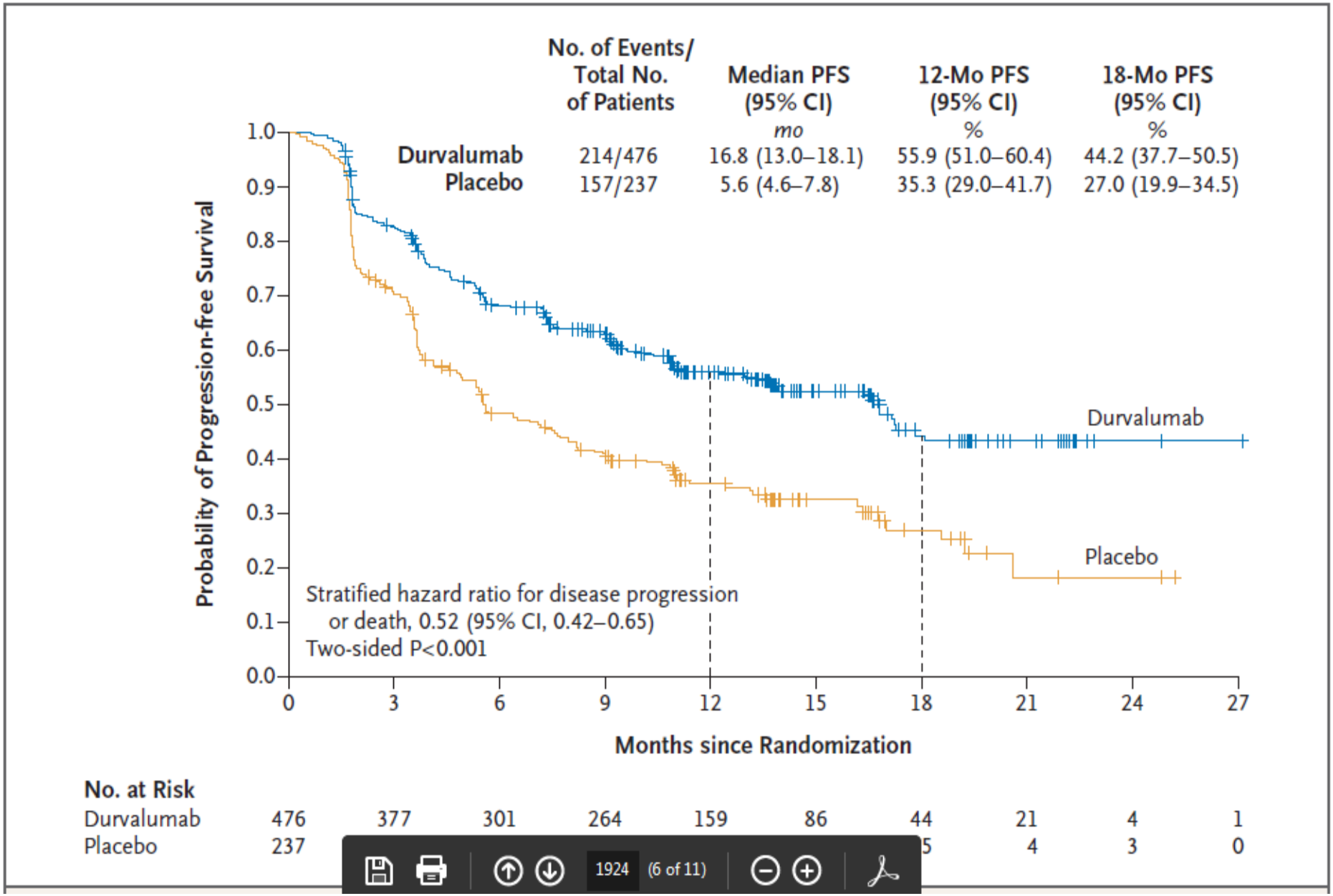
The NEW ENGLAND JOURNAL of MEDICINE

November 16, 2017

N Engl J Med 2017; 377:1919-1929

PACIFIC Trial

- Durvalumab is an anti-PDL 1 antibody
- 713 patients randomized in a 2:1 fashion to durvalumab vs placebo if stable/responding disease after concurrent chemo/radiation
- One year of durvalumab or until progression, toxicity
- Two arms were evenly matched for age, gender, smoking history and histology (squamous vs non squamous)
- Primary endpoints progression-free survival and overall survival
- Unselected population for PD-L1 expression



PACIFIC Trial

- Biomarker independent population – all levels of PD-L1 expression included in study
- All levels of PD-L1 expression benefitted vs placebo though RR and PFS increased with increasing PD-L1 levels
- FDA granted Breakthrough Therapy designation in July 2017
- Durvalumab added to most recent NCCN guidelines as category 1 recommendation for Stage III NSCLC maintenance independent of PDL1 expression

1st Line Metastatic Disease - KEYNOTE-021

Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study

Langer et al, Lancet Oncology 2016

- Pembrolizumab – PD-1 antibody
  - Approved 1st line in tumors ≥ 50% PD-L1 expression
- 123 patients with advanced nonsquamous NSCLC, unselected for PD-L1 expression
- ORR (primary endpoint) 55% vs 29% favoring pembro arm
- mPFS 13mos vs 6mos favoring pembro arm
- ORR similar in patients with or without PD-L1 expression
- FDA approved 5/2016
- Limitations: relatively small study – larger Phase III trial underway

Summary

- Adjuvant chemotherapy improves survival (magnitude of benefit?)
- Platinums still rule in all stages of disease!
  - Cisplatin preferable in curative intent, adjuvant therapy
  - First line combination in metastatic disease in patients without a driver mutations
  - Histology matters in choice of 2nd agent
- Stage III NSCLC is a heterogenous disease best treated within the context of a multidisciplinary team – chemotherapy a part of bi- or tri-modality therapy
- Addition of immunotherapy to platinum therapy in selected Stage III and Stage IV disease improves outcomes, regardless of PD-L1 status