JADPRO CE Regional Education

From Inquiry to Investigation to Insight: Clinical Clarity in Non–Small Cell Lung Cancer

Managing Early-Stage and Locally Advanced NSCLC

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- **Ms. Eaby-Sandy** has served as a consultant and on speakers bureaus for AstraZeneca, Helsinn, Merck, and Takeda.
- **Dr. Beardslee** has served as a consultant for AstraZeneca and Herron, and on the speakers bureau for AstraZeneca.
- **Dr. Davies** has served on speakers bureaus for AstraZeneca, Bristol-Myers Squibb, Genentech, and Merck.
- **Ms. Gilbert** has no conflicts of interest to disclose.
- **Ms. Persinger** has served on speakers bureaus for Genentech and Guardant Health, and on the advisory board for AstraZeneca.

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Learning Objective

- Devise treatment plans for patients with locally advanced NSCLC

Outline

- Surgical approaches to early-stage NSCLC
  - Workup and staging
  - Surgical approaches
  - Nonsurgical candidates
- Stage III NSCLC
  - Workup
  - Treatment considerations
  - Controversies: surgery vs. chemo/radiation

Audience Response Question

A 60-year-old gentleman has just completed chemotherapy and radiation for his stage III NSCLC with weekly paclitaxel and carboplatin. He is here to discuss what would offer him the best survival advantage. Which would you counsel is the optimal option based on the patient's goals?

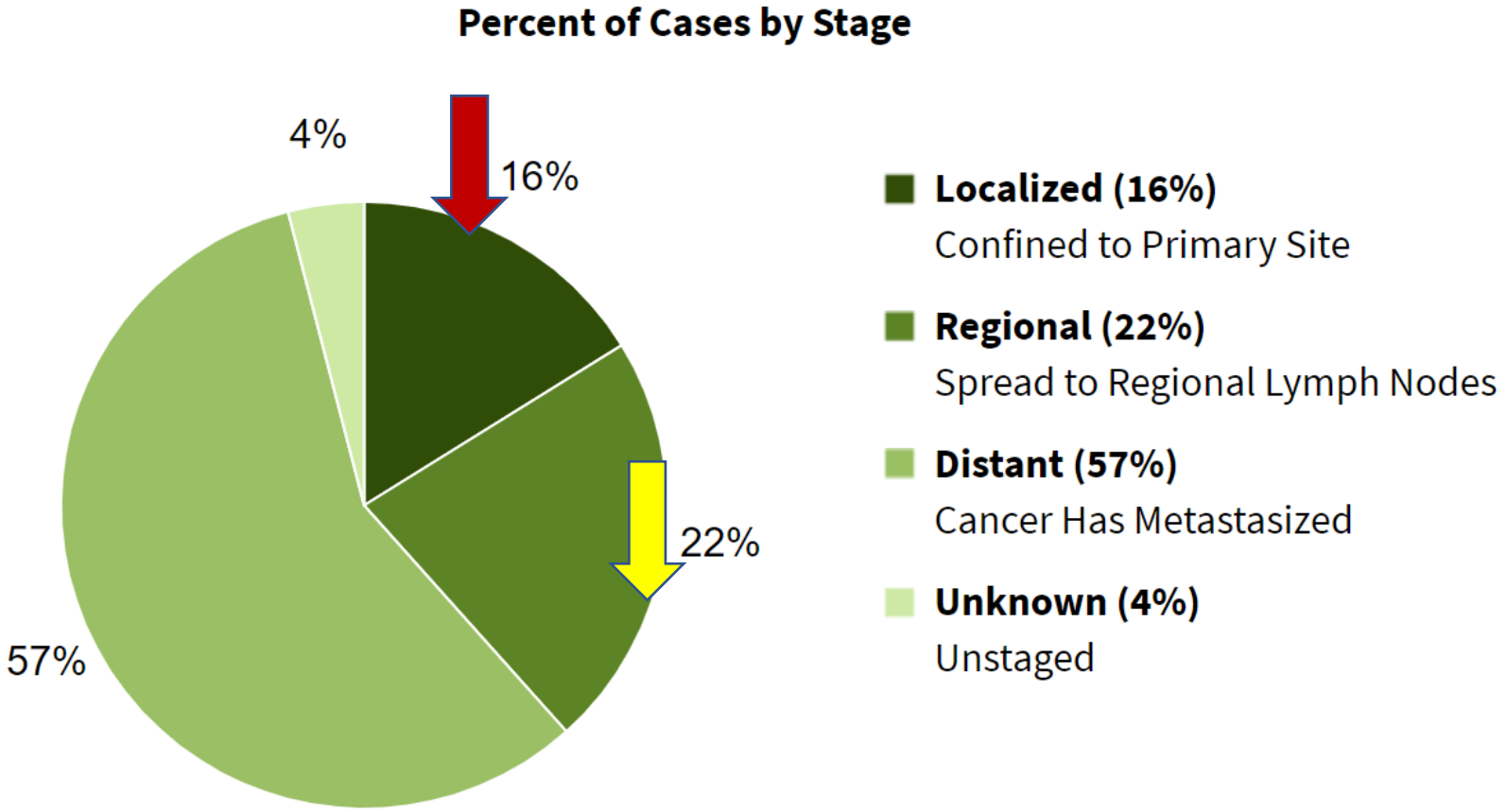
A. Immunotherapy for a year post concurrent chemotherapy and radiation
B. Full-dose consolidation chemotherapy followed by immunotherapy for 1 year
C. Stop with concurrent chemo/radiation and go onto a surveillance imaging schedule of every-3-month CT scans
D. Full-dose chemotherapy after the weekly chemo/radiation and then go onto surveillance imaging every 3 months
E. Unsure

Audience Response Question

Which drug(s) are approved for locally advanced NSCLC after completion of concurrent chemo/radiation when the cancer has not progressed?

A. Pembrolizumab
B. Durvalumab
C. Nivolumab
D. A and B
E. Unsure

Lung Cancer



https://seer.cancer.gov/statfacts/html/lungb.html

Early-Stage NSCLC

- Refers to stage I and stage II
- Generally considered surgery the best option
- If not surgical candidate
  - Stereotactic body radiation
  - Radioablative procedures

Primary Tumor (T) Classification

T1 Tumor 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus

T1a Tumor 2 cm or less in greatest dimension

T1b Tumor more than 2 cm but 3 cm or less in greatest dimension

T2 Tumor more than 3 cm but 7 cm or less or tumor with any of the following features (T2 tumors with these features are classified T2a if 5 cm or less): involves main bronchus, 2 cm or more distal to the carina; invades visceral pleura (PL1 or PL2); associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung

T2a Tumor more than 3 cm but 5 cm or less in greatest dimension

T2b Tumor more than 5 cm but 7 cm or less in greatest dimension

Regional Lymph Node (N) Classification

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastases

N1 Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension

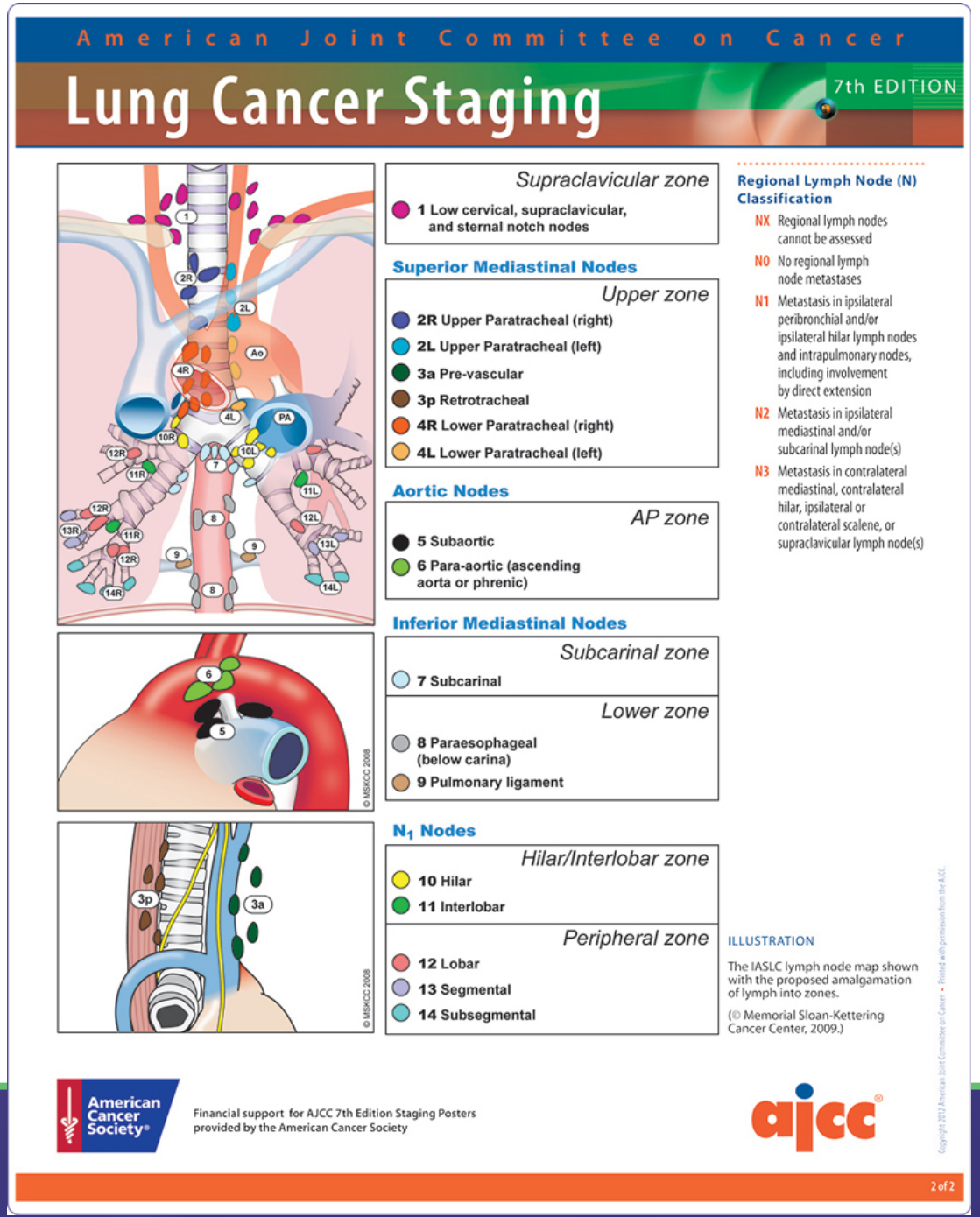
N2 Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)

N3 Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

ANATOMIC STAGE/PROGNOSTIC GROUPS			
Occult Carcinoma	TX	N0	M0
Stage 0	Tis	N0	M0
Stage IA	T1a	N0	M0
	T1b	N0	M0
Stage IB	T2a	N0	M0
Stage IIA	T2b	N0	M0
	T1a	N1	M0
	T1b	N1	M0
	T2a	N1	M0
Stage IIB	T2b	N1	M0
	T3	N0	M0
Stage IIIA	T1a	N2	M0
	T1b	N2	M0
	T2a	N2	M0
	T2b	N2	M0
	T3	N1	M0
	T3	N2	M0
	T4	N0	M0
	T4	N1	M0
Stage IIIB	T1a	N3	M0
	T1b	N3	M0
	T2a	N3	M0
	T2b	N3	M0
	T3	N3	M0
	T4	N2	M0
	T4	N3	M0
Stage IV	Any T	Any N	M1a
	Any T	Any N	M1b

Management of Early-Stage NSCLC

- Need to stage the mediastinum
  - PET/CT vs. bronch/EBUS
- Definitive surgery for stage I or stage II NSCLC is lobectomy with full mediastinal nodal sampling
- Bilobectomy or pneumonectomy if needed
- Only wedge resection in patients with limiting factors
  - ie, poor pulmonary function



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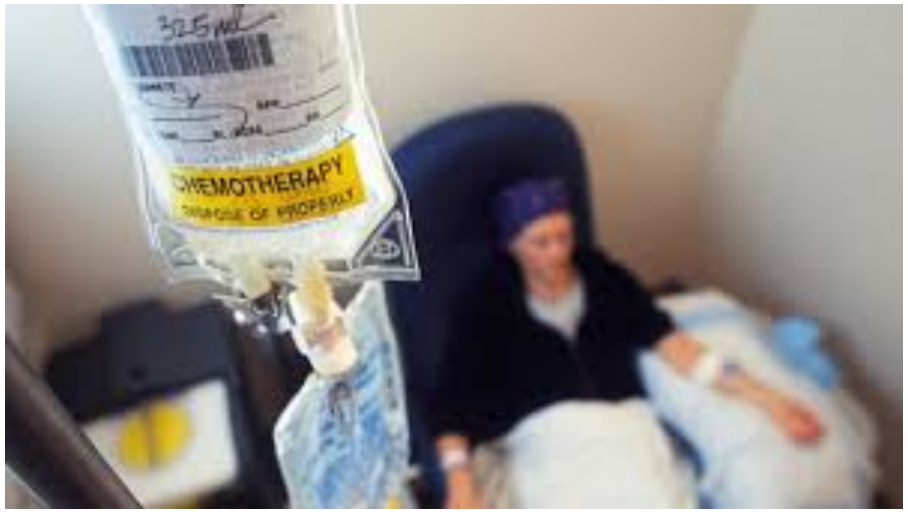
What's New in Thoracic Surgical Oncology?

- Early detection with CT screening
  - Age 55–77, asymptomatic, at least 30 pack/years smoking history
  - Current smoker or quit in past 15 years
  - Must have extensive counseling visit first
- Trials looking at intraoperative "glow" to look for subcentimeter nodules
- Robotic surgery approaches; but so far not shown to affect the post operative course

Principles of Adjuvant Chemotherapy Post Surgery

- Stage II and stage III
- Cisplatin-based chemotherapy best
- 4 cycles
- Concurrent with radiation for N2 disease



Adjuvant Therapy in Resected NSCLC

- Adjuvant chemo with cisplatin-based doublet established as standard for patients with completely resected NSCLC
  - Increases 5-year survival rate

Trial	No. pts	Stage	Chemo	OS			
				5-year survival, %			
				Chemo	Control	HR	*p* value
IALT	1,867	I-III	Cis/Vinca	44.5	40.4	0.86	< .03
JBR. 10	482	IB-II	Cis/Vino	69	54	0.69	.04
ANITA	840	IB-IIIA	Cis/Vino	51.2	42.6	0.80	.02
LACE meta-analysis	4,584	I-IIIA	Cisplatin-based	48.8	43.5	0.89	.004

Pirker, R et al. *Clinical Lung Cancer* 2018;20(1):1–6. https://doi.org/10.1016/j.cllc.2018.09.016

Adjuvant Therapy in Resected NSCLC: Targeted Therapy

- Adding bevacizumab to adjuvant chemo did not improve outcome
- EGFR TKIs did not improve outcome
  - Except gefitinib among Chinese EGFR+ patients

Trial	No. pts	Stage	Drug	HR
ECOG 1505	1501	IB–IIIA	CT ± bevacizumab	OS 0.99
NCIC CTG BR19	503	IB–IIIA	Gefitinib vs. placebo	OS 1.24
RADIANT	973	IB–IIIA	Erlotinib vs. placebo	DFS 0.90
ADJUVANT	483	II–IIIA	Gefitinib vs. placebo	DFS 0.60
MAGRIT	2312	IB–II	MAGE-A3 vs. placebo OS	1.04

Pirker, R et al. *Clinical Lung Cancer* 2018;20(1):1–6. https://doi.org/10.1016/j.cllc.2018.09.016

Adjuvant Therapy in Resected NSCLC: ICIs (Phase III Trials)

- ICIs being evaluated in phase III trials

Trial	Drug	No. patients	Stage	Primary endpoint	NCT #
PEARLS	Pembrolizumab	1,380	IB–IIIA	DFS	NCT02504372
BR31	Durvalumab	1,360	IB–IIIA	DFS	NCT02273375
IMpower010	Atezolizumab	1,127	IB–IIIA	DFS	NCT02486718
ANVIL	Nivolumab	714	IB–IIIA	OS/DFS	NCT02595944

Pirker, R et al. *Clinical Lung Cancer* 2018;20(1):1–6. https://doi.org/10.1016/j.cllc.2018.09.016

Locally Advanced NSCLC

Case Study: TC is a 60 y/o Male With Stage III NSCLC

- Oncologic diagnosis: NSCLC (squamous cell lung cancer)
- Stage: IIIA (pT2b, pN2, cM0), right suprahilar mass
- Molecular/IHC markers: PD-L1 TPS 2%
- 6/16/18
  - Staging brain MRI was negative
- 6/18/18
  - PET/CT: biopsy-proven malignancy in the right suprahilar region is markedly FDG-avid. Mildly increased uptake in a nonenlarged right paratracheal lymph node suspicious for nodal metastatic involvement. There was no evidence of distant metastatic disease.
- 7/18/18
  - Mediastinoscopy: Right paratracheal mass; squamous cell carcinoma, PD-L1 2%

IHC = immunohistochemistry; TPS = tumor proportion score; FDG = fluorodeoxyglucose.

Case Study: TC is a 60 y/o Male With Stage III NSCLC (cont.)

- Current smoker, has smoked 1 PPD x 40 years
- Lives in “safe house” or with sister at times, has some long-standing cognitive deficits, bipolar disorder, lacks insight
- HTN, COPD, not open to quitting smoking
- Comes with his sister who is supportive
- Comes in wheelchair, chronic joint pains, but walks around at home
- How should we manage this patient?

PPD = pack per day; HTN = hypertension; COPD = chronic obstructive pulmonary disease.

Stage III NSCLC: Surgery vs. Chemo/Radiation

Stage IIIA

- Controversial management strategies
  - Generally standard of care: IIIA disease, definitive concurrent chemotherapy and radiation without surgery best option
  - If surgery considered, should involve induction treatment with chemotherapy or chemotherapy plus radiation prior to surgery
  - Proper staging prior to surgery should limit patients who are found to be stage IIIA at time of surgery

Stage IIIB

- Really never surgical approach
- Should always be concurrent chemotherapy and radiation for curative intent treatment in eligible candidates

Stage IIIA NSCLC: To Do Chemo/Rad or Surgery Plus Chemo/Rad?

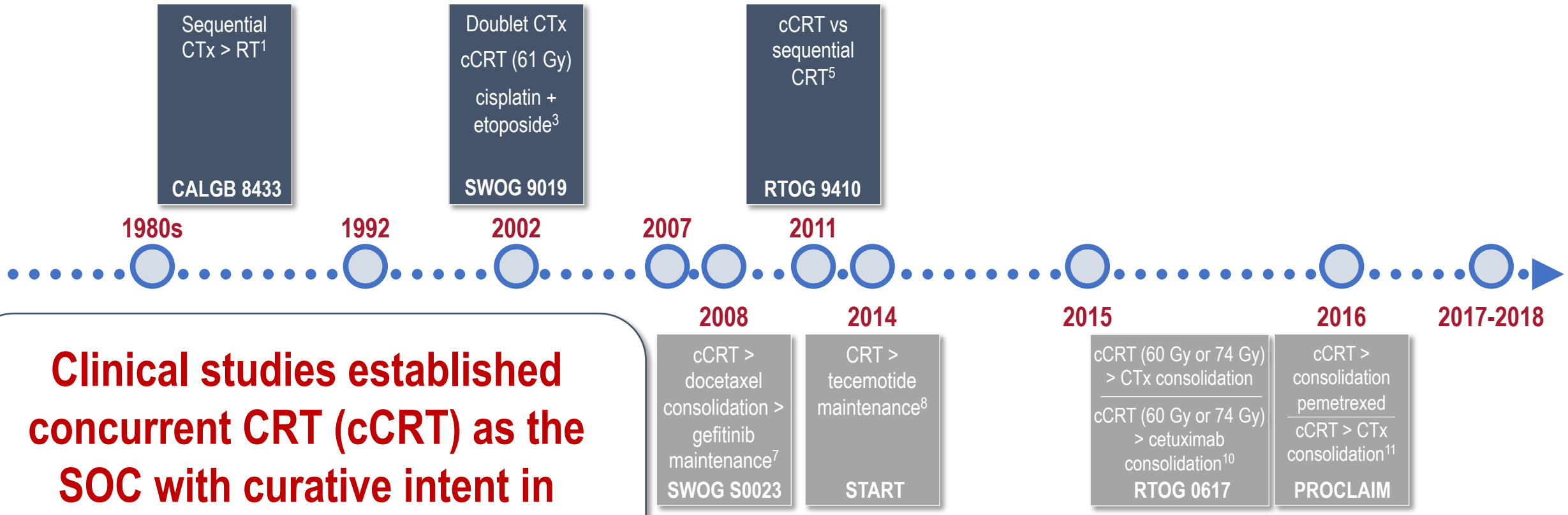
- Many of these trials could not accrue well
- P-value not significant
- Median OS and long-term survival almost the same
- Increased morbidity and mortality due to treatment in the surgical arms

Table 1: Randomized studies comparing induction treatment followed by surgery with definitive radio(chemo)therapy.

Trial (Period of Recruitment)	Inclusion Criteria	Treatment		median OS [mo]	long-term OS	Hazard Ratio	*P*
RTOG 89-01 (1990-1994)	IIIA N2	[R]*	(1) 2x CDDP/VBL (MMC) → S (2) 2x CDDP/VBL (MMC) → RT [64 Gy]	19.4 17.4	22.0% [4Y] 22.0%	n.g.	0.46
NCI Canada (closed 1995)	IIIA N2	[R]	(1) 2x CDDP/VBL → S (2) ---------- → RT [60 Gy]	18.7 16.2	n.g.	n.g.	NS
MRC (1995-1999)	IIIA	[R]	(1) 4x CDDP/MMC/IFO or VBL → S (2) ---------- → RT [40-60 Gy]	13.8 11.2	n.g.	0.91 [0.49-1.72]	0.78
EORTC 08941 (1994-2002)	IIIA N2	(1) 3x CDDP/ 3rd gen drug →[R]° (2) 3x CDDP/ 3rd gen drug	→ S [+PORT 56 Gy] → RT [60-62.5 Gy]	16.4 17.5	15.7% [5Y] 14.0%	1.06 [0.84-1.35]	0.596
Nordic TOG (1998-2009)	IIIA N2	[R]	(1) 3x carboplatin/paclitaxel → S [+PORT 60 Gy] (2) 3x carboplatin/paclitaxel → RT [60 Gy]	17.3 14.9	19.0% [5Y] 17.0%	0.866	0.218
INT 0139 (1994-2001)	IIIA N2	[R]	(1) 2x CDDP/ETOII45 Gy/1.8 Gy qd → S → 2x CDDP/ETO (2) 2x CDDP/ETOII45 Gy/1.8 Gy qd → RT [61 Gy]→2x CDDP/ETO	23.6 22.2	27.0% [5Y] 20.0%	0.87 [0.7-1.1]	0.24
ESPATUE (2004-2012)	IIIA N2 selected IIIB	(1) 3x CDDP/paclitaxel→CDDP/VINII45 Gy (AHF)→[R]→ S (2) 3x CDDP/paclitaxel→CDDP/VINII45 Gy (AHF) → RT [20-26 Gy→65-71 Gy] +CDDP/VIN		49.3 34.8	44.0% [5Y] 40.0%	0.81 [0.5-1.3]	0.34

Pottgen C, et al. Definitive radiochemotherapy *versus* surgery within multimodality treatment in stage III non-small cell lung cancer (NSCLC) - a cumulative meta-analysis of the randomized evidence *Oncotarget,* 2017, Vol. 8, (No. 25), pp: 41670-41678

Limited Advancements in Systemic Treatment of Unresectable Stage III NSCLC in the Last 10 Years



Clinical studies established concurrent CRT (cCRT) as the SOC with curative intent in unresectable stage III NSCLC[6]

1. Dillman RO, et al. *J Natl Cancer Inst*. 1996;88(17):1210-1215. 3. Albain KS, et al. *J Clin Oncol*. 2002;20(16):3454-3460 5. Curran WJ Jr, et al. *J Natl Cancer Inst*. 2011;103(19):1452-1460. 6. Hanna N. *Am Soc Clin Oncol Educ Book*. 2015:e442-e447. 7. Kelly K, et al. *J Clin Oncol*. 2008;26(15):2450-2456. 8. Butts C, et al. *Lancet Oncol*. 2014;15(1):59-68. 10. Bradley JD, et al. *Lancet Oncol*. 2015;16(2):187-199. 11. Senan S, et al. *J Clin Oncol*. 2016;34(9):953-962. 12. Antonia SJ, et al. *N Engl J Med*. 2017;377(20):1919-1929. 13. Antonia SJ, et al. *N Engl J Med*. 2018;379(24):2342-2350.

Most Common Regimens in Stage III Concurrent Chemotherapy/Radiation

- Usually daily fractions of XRT to around 54–66 Gy over a span of 6–7 weeks (Monday through Friday)
- Weekly paclitaxel/carboplatin likely best tolerated
- q3 week pemetrexed/platinum (cisplatin or carboplatin): full dose, can be toxic
- Etoposide/cisplatin: Advantage gets full dosing of chemo, given
  - Etoposide 50 mg/m^2 D1 to D5
  - Cisplatin 50 mg/m^2 D1 and D8
  - Total of 2 cycles 28 days apart

Toxicity Concerns of Concurrent Chemotherapy/Radiation

- XRT: esophagitis, radiation dermatitis, visceral organ damage
- Chemotherapy: pancytopenias, neuropathy, hearing loss/tinnitus, CINV, good renal function, alopecia, several others
- Pneumonitis: Due to XRT, some studies show up to 25% rates of pneumonitis
- In ECOG PS of 2 or higher patients, likely a sequential approach or radiation alone a better option

XRT = radiation therapy; CINV = chemotherapy nausea and vomiting; ECOG = Eastern Cooperative Oncology Group; PS = performance score.

Stage III NSCLC

- Unresectable: Most are unresectable. Standard of care is concurrent chemotherapy and radiation
- Resectable: minority of cases, single station N2 node, small tumor size
- What to do after concurrent chemotherapy and radiation?
  - Prior to 2018
    - Sometimes consolidation chemotherapy, although no good evidence to support this
      - **Now in NCCN guidelines: You should NOT do consolidation chemotherapy post chemo/radiation**
    - Nothing, surveillance scans every 3 months, majority of patients recurred, around 80% recurrence rate, usually in the first year
    - Data in late 2017 showed immunotherapy improves PFS

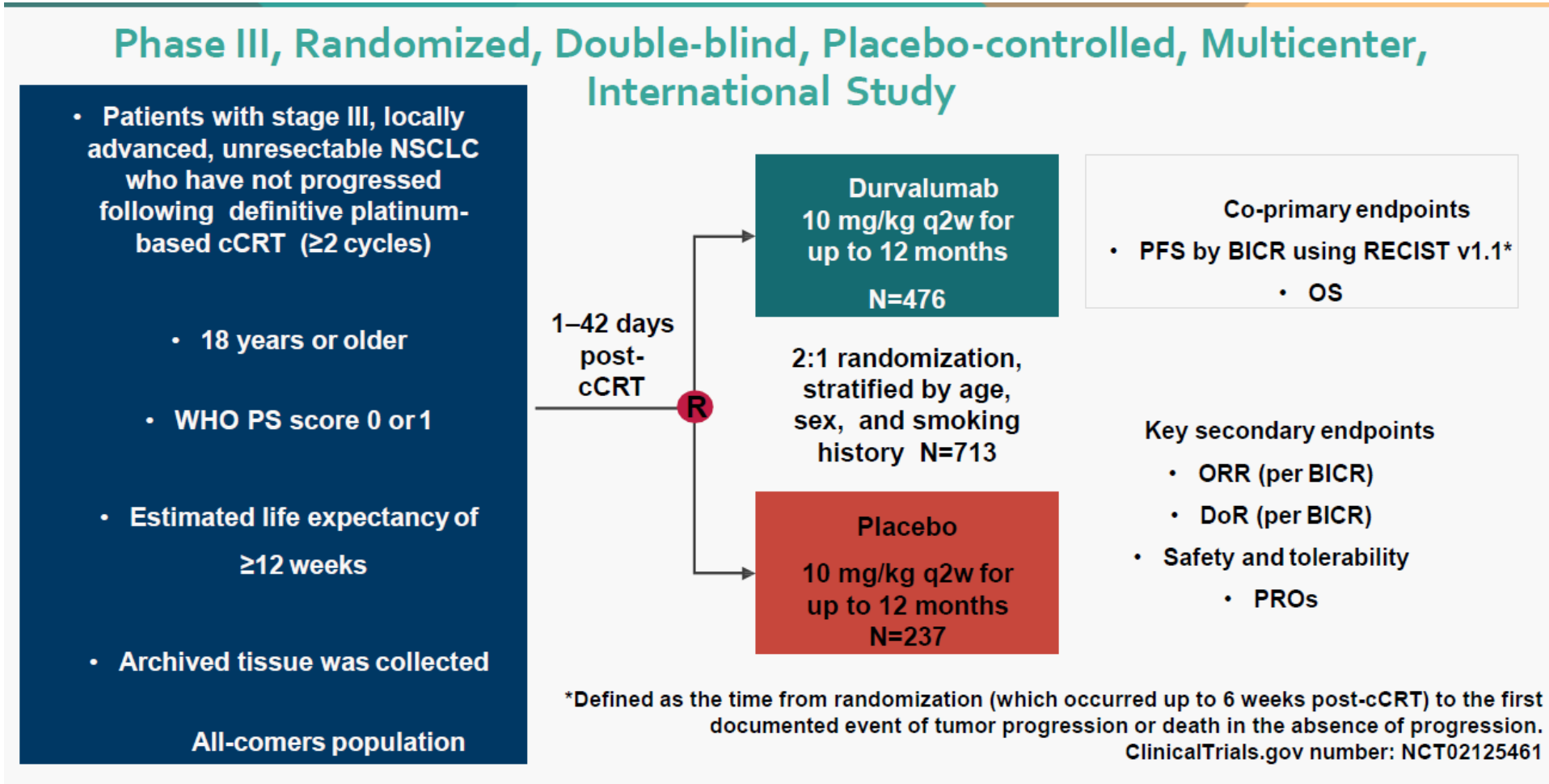
Case Study: TC is a 60 y/o Male With Stage III NSCLC (cont.)

- TC receives weekly paclitaxel and carboplatin with radiation x 7 weeks and tolerates generally well. Finishes 10/2018.
- CT chest with IV contrast 11/8/18:
  1. **No evidence of progressive disease in the chest.**
  2. **Interval marked decrease in the right perihilar mass 14 x 23 mm, previously 26 x 43 mm** with relief of the right mainstem bronchial tumor invasion. Persistent obstruction of the right upper lobe bronchus with associated mucous plugging. Probable associated lymphangitic carcinomatosis in the right upper lobe, stable to slightly improved.
  3. Mediastinal and right hilar adenopathy, overall stable to minimally increased in the interval
  4. Probable esophageal dysmotility.
- What would you do with this patient next?

Consolidation Treatment in Stage III Unresectable NSCLC: First Drug to Show PFS and OS Benefit

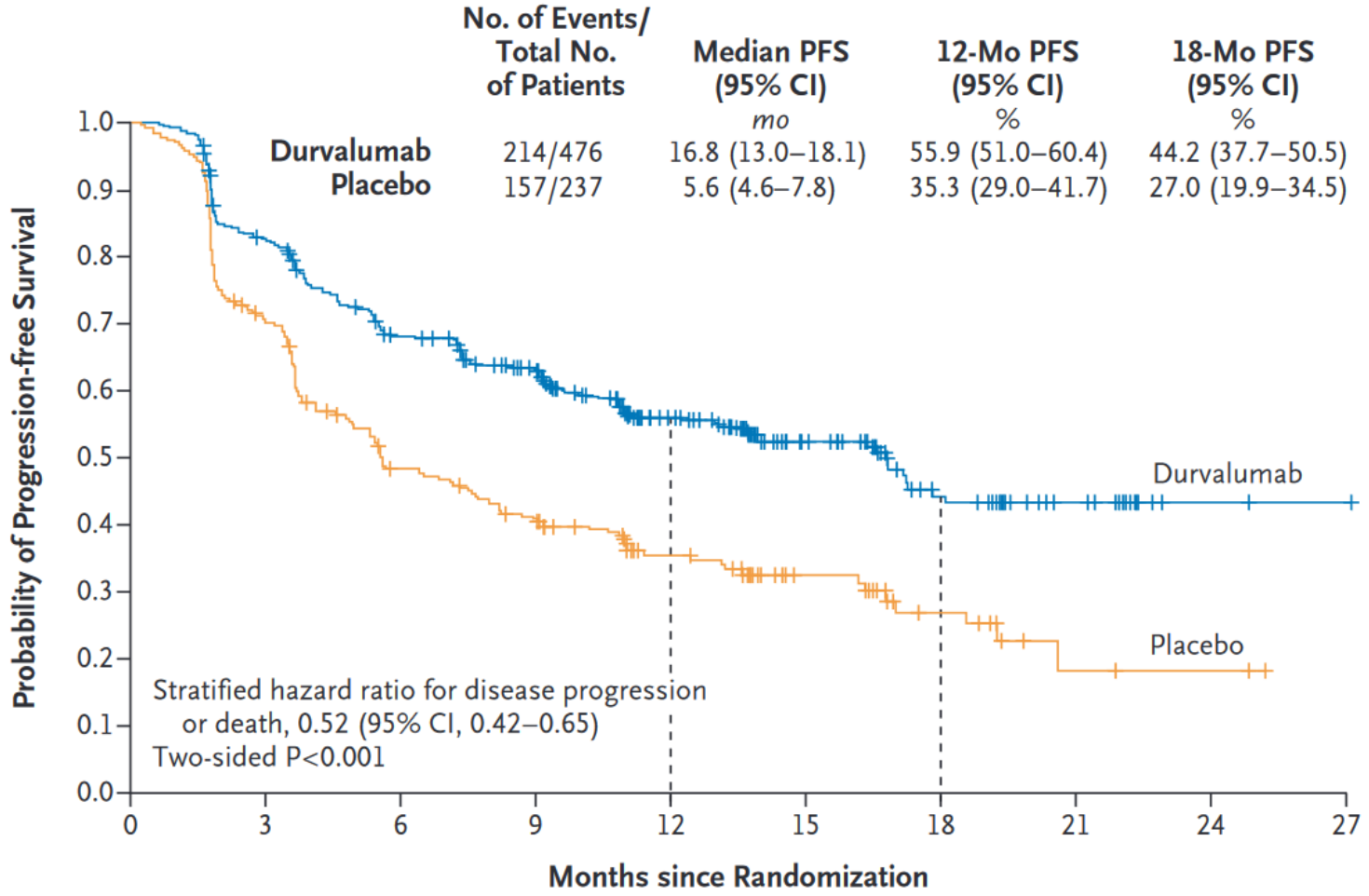
Durvalumab: Approved in February 2018

Trial of Durvalumab Post Chemo/Radiation



Antonia SJ, et al. *NEJM* 2017;377:1919-29.

Durvalumab PFS in PACIFIC Trial



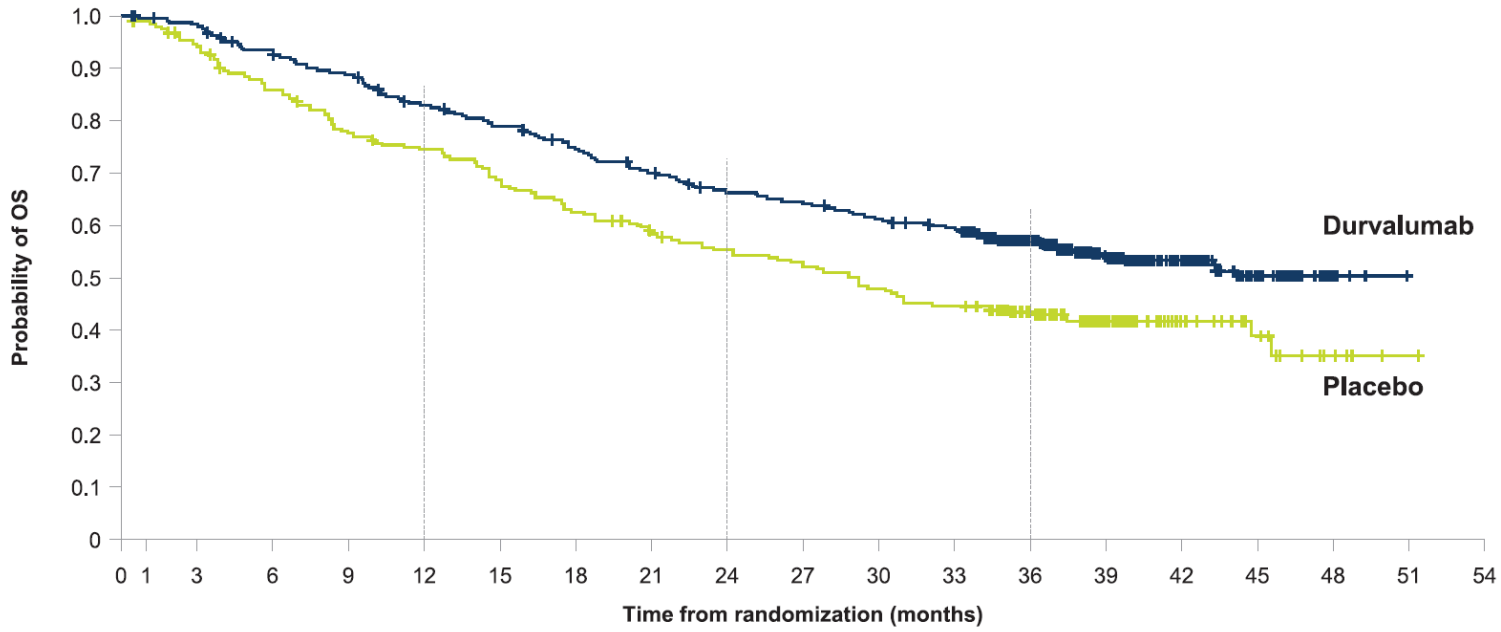
Antonia SJ, et al. *NEJM* 2017;377:1919-29.

Durvalumab OS in PACIFIC trial

Figure 3. Updated OS in the ITT population

	No. of events/ total no. of patients (%)	Median OS (95% CI) months	12-month OS rate (95% CI) %	24-month OS rate (95% CI) %	36-month OS rate (95% CI) %
Durvalumab	210/476 (44.1)	NR (38.4–NR)	83.1 (79.4–86.2)	66.3 (61.8–70.4)	57.0 (52.3–61.4)
Placebo	134/237 (56.5)	29.1 (22.1–35.1)	74.6 (68.5–79.7)	55.3 (48.6–61.4)	43.5 (37.0–49.9)

Stratified hazard ratio for death, 0.69 (95% CI, 0.55–0.86)
Stratified hazard ratio for death from the primary analysis,[9] 0.68 (95% CI, 0.53–0.87)



Gray JE, Villegas AE, Daniel DB, et al. Three-year overall survival update from the PACIFIC trial. Poster presented at: 2019 ASCO Annual Meeting; May 31-June 4, 2019; Chicago, IL

Toxicity Concerns IO Post Chemo/Radiation

- Toxicity concern
- Pneumonitis
  - All grades 34% vs. 25% in placebo arm
  - Grade 3/4 was 3.4% vs. 3.0% in placebo arm

Pembrolizumab in Locally Advanced NSCLC

- New indication as of 4/2019 for patients with stage III NSCLC with TPS score of 1% or greater.
- Patients in study had stage III NSCLC; however, they were not candidates for or refused concurrent chemo/radiation or surgery.
- So really, these patients were treated as stage IV, even though they were clinically/pathologically diagnosed at stage III.
  - This happens in reality, poor PS, not candidate for surgery/radiation, etc.

Case Study: TC is a 60 y/o Male With Stage III NSCLC (cont.)

- Continues durvalumab as of 8/2019
- q2 weeks with no evidence of disease progression
- Only toxicity has been the development of psoriasis on arms and trunk of body. Treating with topicals and has consulted dermatology. Not bothersome enough to hold treatment.

Clinical Pearls

- Surgery in early-stage NSCLC stages I and II, rarely in stage III
- Chemo/radiation standard of care in stage III NSCLC in eligible patients
- Durvalumab immunotherapy for 1 year after chemo/radiation improves PFS and OS in stage III patients.

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Questions?