Update on the Treatment of Small Cell Lung Cancer and Neuroendocrine Lung Cancers

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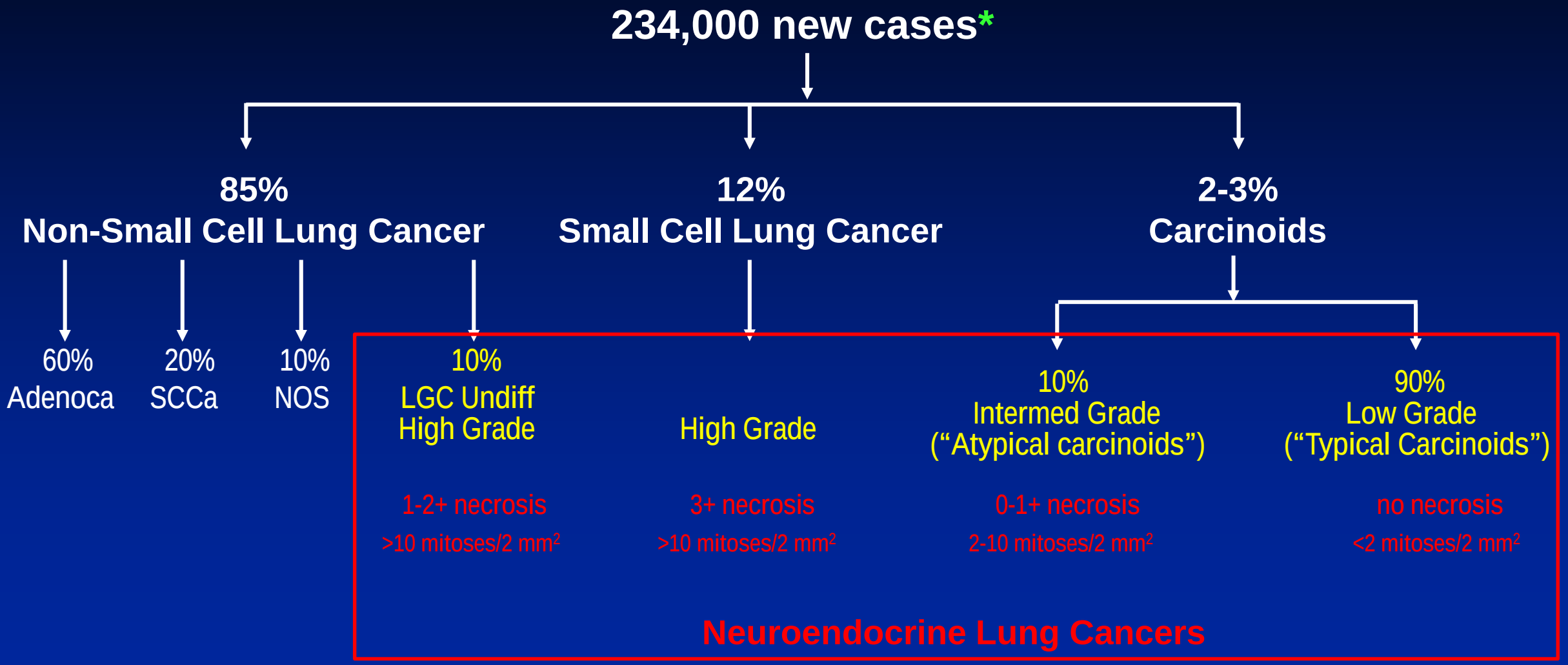
Lung Cancer in the U.S. in 2018



*Noone AM et al. SEER Cancer Statistics Review, 1975-2015, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2015, based on November 2017 SEER data posted to April 2018.

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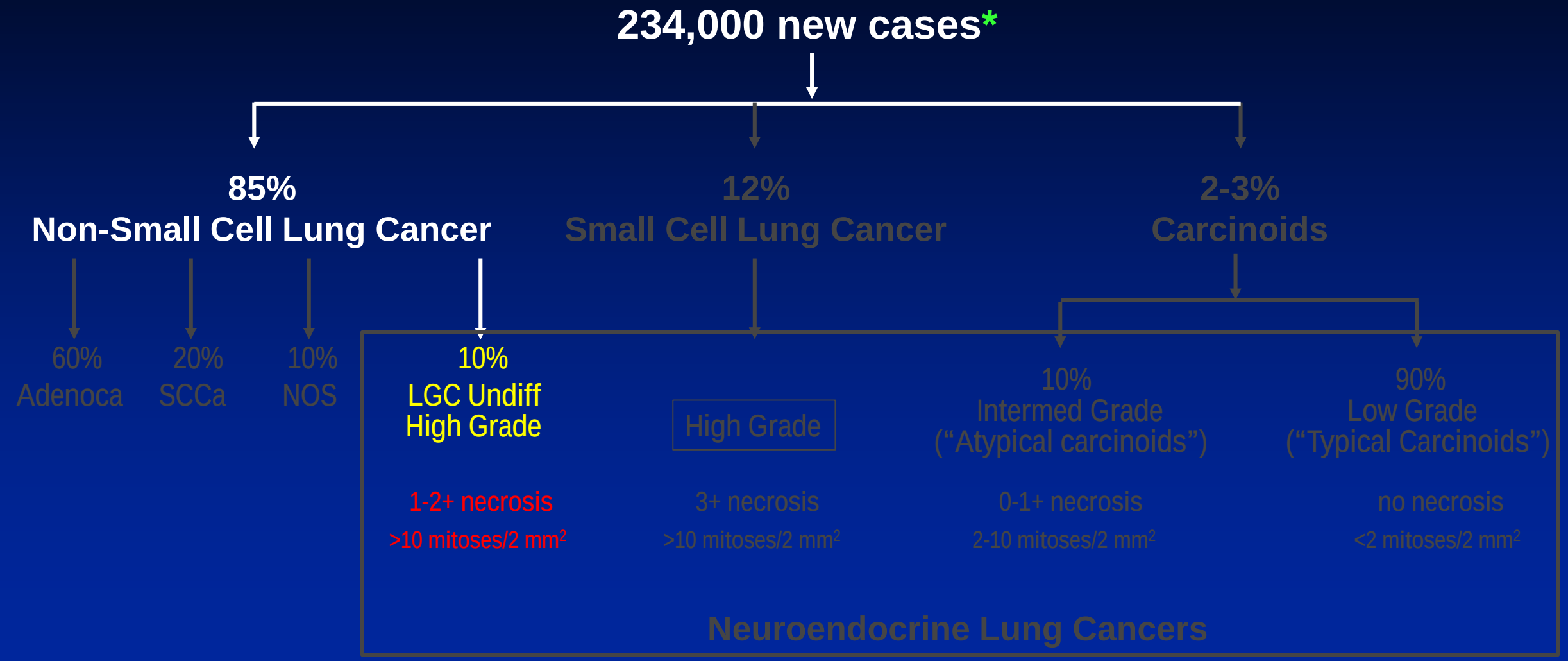

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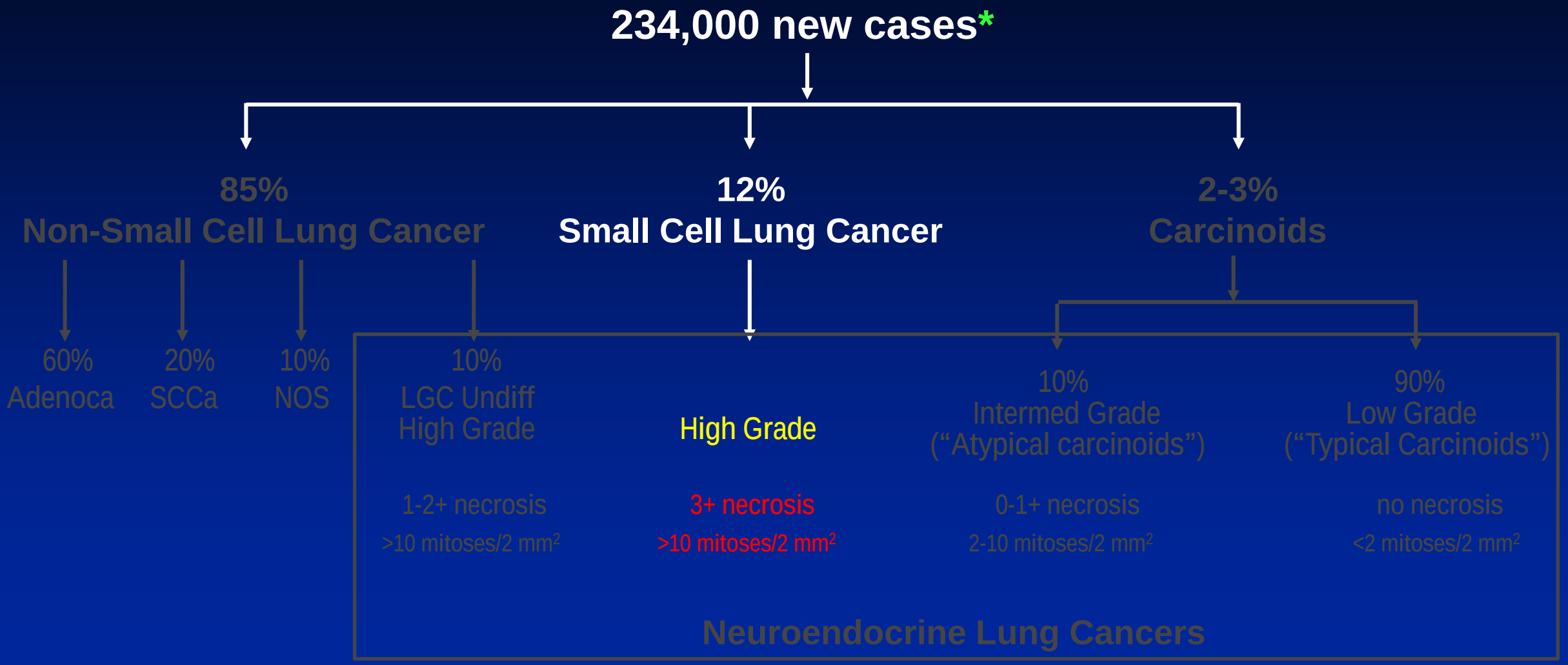
Lung Cancer in the U.S. in 2018



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Small Cell Lung Cancer: Staging

- **Limited Disease (30-35% pts)**
  - Disease confined to primary tumor, regional LNs (intrapulmonary, mediastinal and ipsilateral SCN)

  "Disease can be encompassed in a radiation field"

- **Extensive Disease (65-70% pts)**
  - Disease metastatic to contralateral lung, nodes or other organs (bones, liver, brain,etc.)
  - Pleural effusion

  "Disease can not be encompassed within a radiation field"

SCLC: State of the Art

1. **Platinum + Etoposide has been the standard 1st line treatment for SCLC for the past 35 years.**

2. **Cisplatin + etoposide / concurrent RT are the standard of care for Limited Stage SCLC.**

Cisplatin + Irinotecan Randomized Trials in Patients with E-SCLC

JCOG 9511

Noda et al. NEJM 346:85, 2002

RANDOMIZATION

- Irino 60 mg/m^2 days 1, 8, 15
  P 60 mg/m^2 day 1
  Q4 weeks x 6 cycles
- E 100 mg/m^2 days 1 to 3
  P 80 mg/m^2 day 1
  Q3 weeks x 6 cycles

North American/Australian Study

Hanna et al. JCO 24:2038, 2006

RANDOMIZATION

2:1

- Irino 65 mg/m^2 days 1 and 8
  P 30 mg/m^2 days 1 and 8
  Q3 weeks x 4 cycles
- E 120 mg/m^2 days 1 to 3
  P 60 mg/m^2 day 1
  Q3 weeks x 4 cycles

Comparison of Therapeutic Outcomes

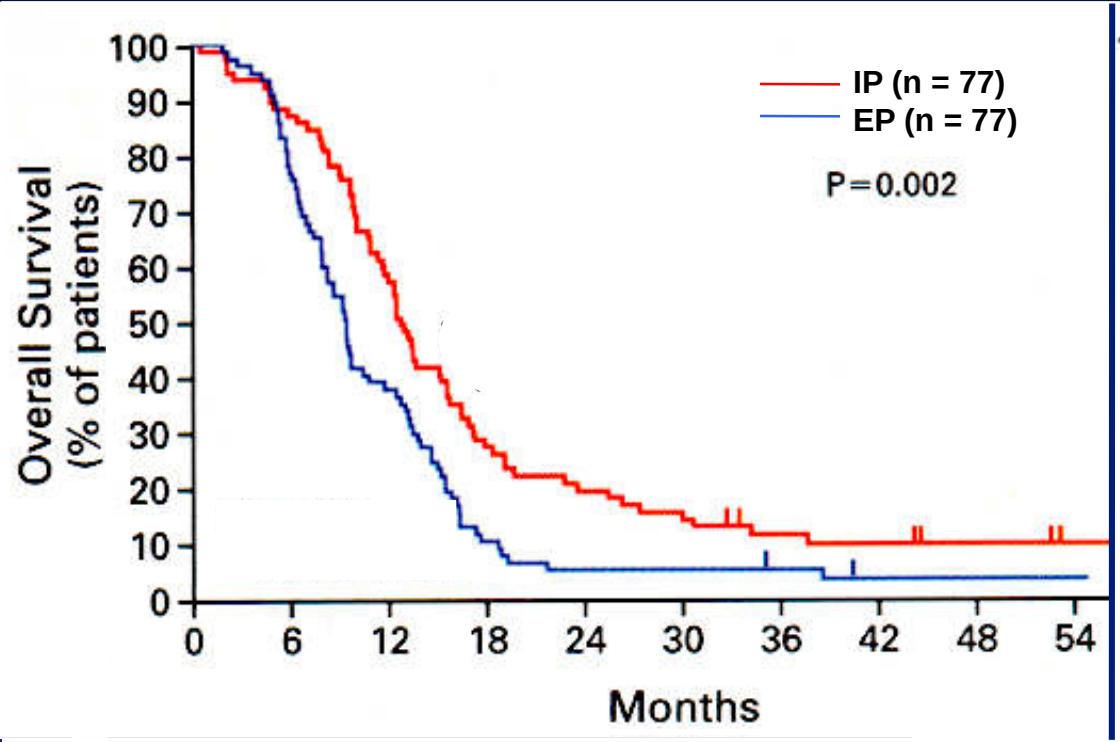
	JCOG 9511		N. American/Australian	
Result	IP (n = 77)	EP (n = 77)	IP (n = 221)	EP (n = 110)
Overall RR	84.4% * (75-92%)	67.5% * (56-78%)	48%	43.6%
Stable	2.6%	20.8%	4.1%	7.3%
Progression	3.9%	11.7%	--	--
NE for Response	9.1%	0	28.1%	29.1%
Median Survival	12.8 mos**	9.4 mos**	9.3 mos	10.2 mos
% 1 Yr Survival	58.4%	37.7%	35%	35.2%
% 2 Yr Survival	19.5%	5.2%	8%	7.9%

* p = .02

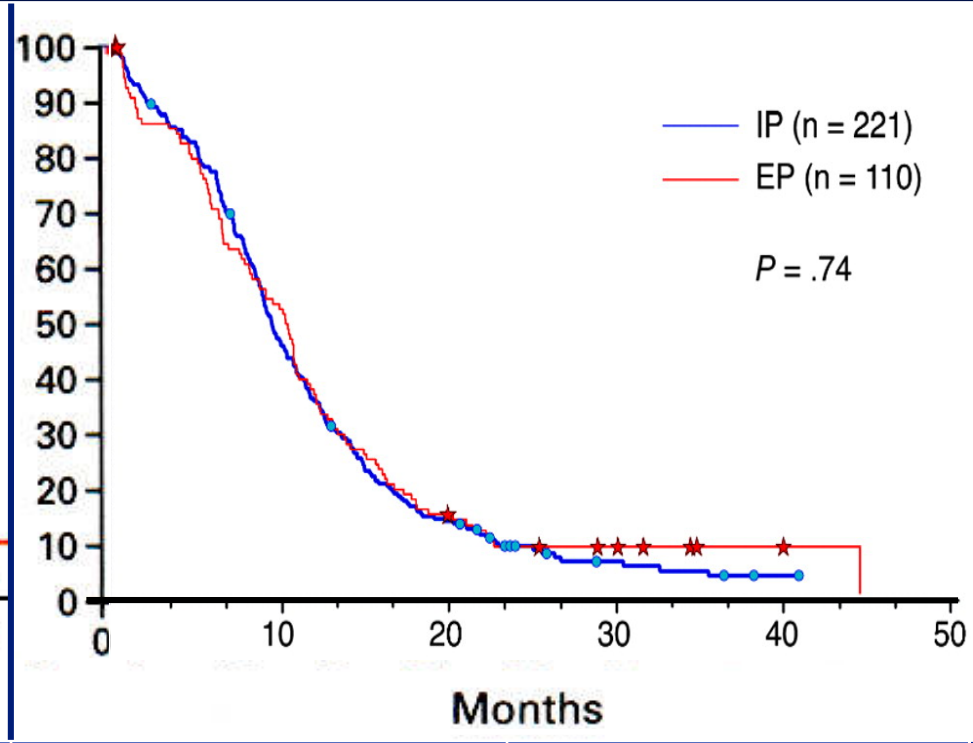
** p = .002

Comparison of Survival Outcomes

JCOG 9511



N Amer / Aus



Survival	Irino + P	Etop + CP	Irino + P	Etop + CP
Median (95% c.i.)	12.8 m	9.4 m	9.3 m	10.2 m
% 1 yr	58.4%	37.7%	35%	35.2%
% 2 yr	19.5%	5.2%	8.0%	7.9%

S0124: IP *vs* EP in E-SCLC

R.B. Natale, P.N. Lara, K.Chansky, J.Crowley, J.R Jett, J.E. Carlton, J.P. Kuebler, H. Lenz, P. Mack, D.G. Gandara, SWOG, NCCTG, CALGB. *Proc ASCO, 2008*

671 Patients

Stratified: PS 0 vs 1/2, # met sites, LDH, wght loss

Randomized

N = 336

Arm 1
Irinotecan 60 mg/m² d 1,8,15
CDDP 60 mg/m² d 1
Q 4 weeks x 4 cycles

324 evaluable for Survival (ITT)

317 evaluable for toxicity

N = 335

Arm 2
Etoposide 100 mg/m² d 1,2,3
CDDP 80 mg/m² d 1
Q 3 weeks x 4 cycles

327 evaluable for Survival (ITT)

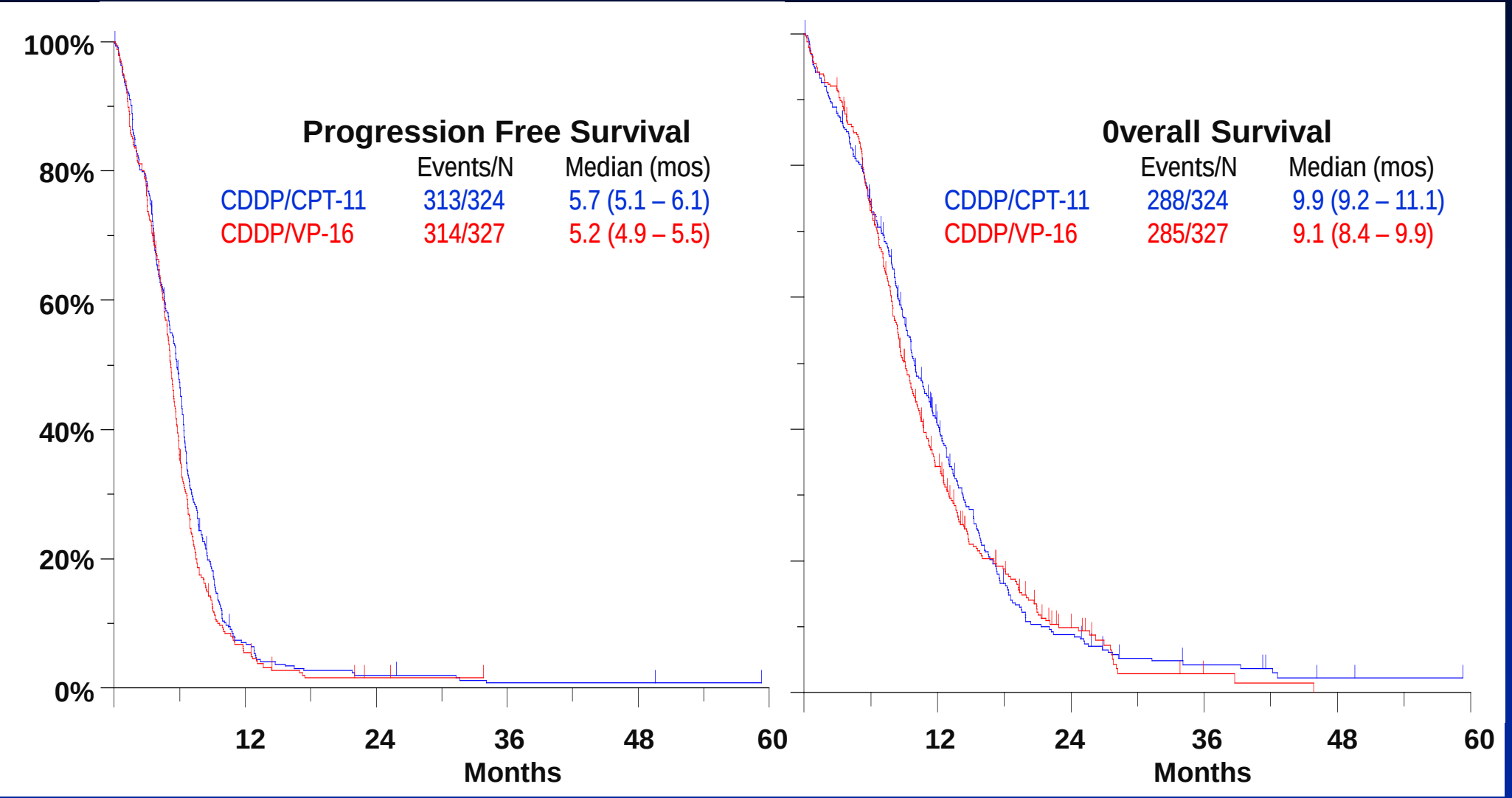
325 evaluable for toxicity

S0124: IP *vs* EP in E-SCLC
Toxicity

Toxicity Type	IP (n = 317)	EP (n = 324)
% Gr 3 / 4 ANC	19% / 15%	20% / 48%
% Gr 3 / 4 Thrombocytopenia	3.5% / <1%	12% / 3%
% Gr 3 / 4 Anemia	5% / <1%	11% / 1%
% Gr 3 / 4 Vomiting	10% / 0	9% / <1%
% Gr 3 / 4 Diarrhea	18% / 1%	3% / 0%
% Gr 3 / 4 Dehydration	15% / 1%	8% / 0
% Gr 3 / 4 Any Toxicity	42% / 22%	29% / 53%
% Treatment-Related Deaths	4.1%	4.6%

Natae RB, Lara PN, Chansky K et al. Proc ASCO, 2008.

S0124: IP *vs* EP in E-SCLC
Survival Outcome



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SCLC: State of the Art

1. Platinum + Etoposide has been the standard 1st line treatment for SCLC for the past 20 years.
2. Cisplatin + etoposide / concurrent RT are the standard of care for Limited Stage SCLC.
3. PCI is the standard of care in responding SCLC pts.

META-ANALYSIS OF PCI IN SCLC

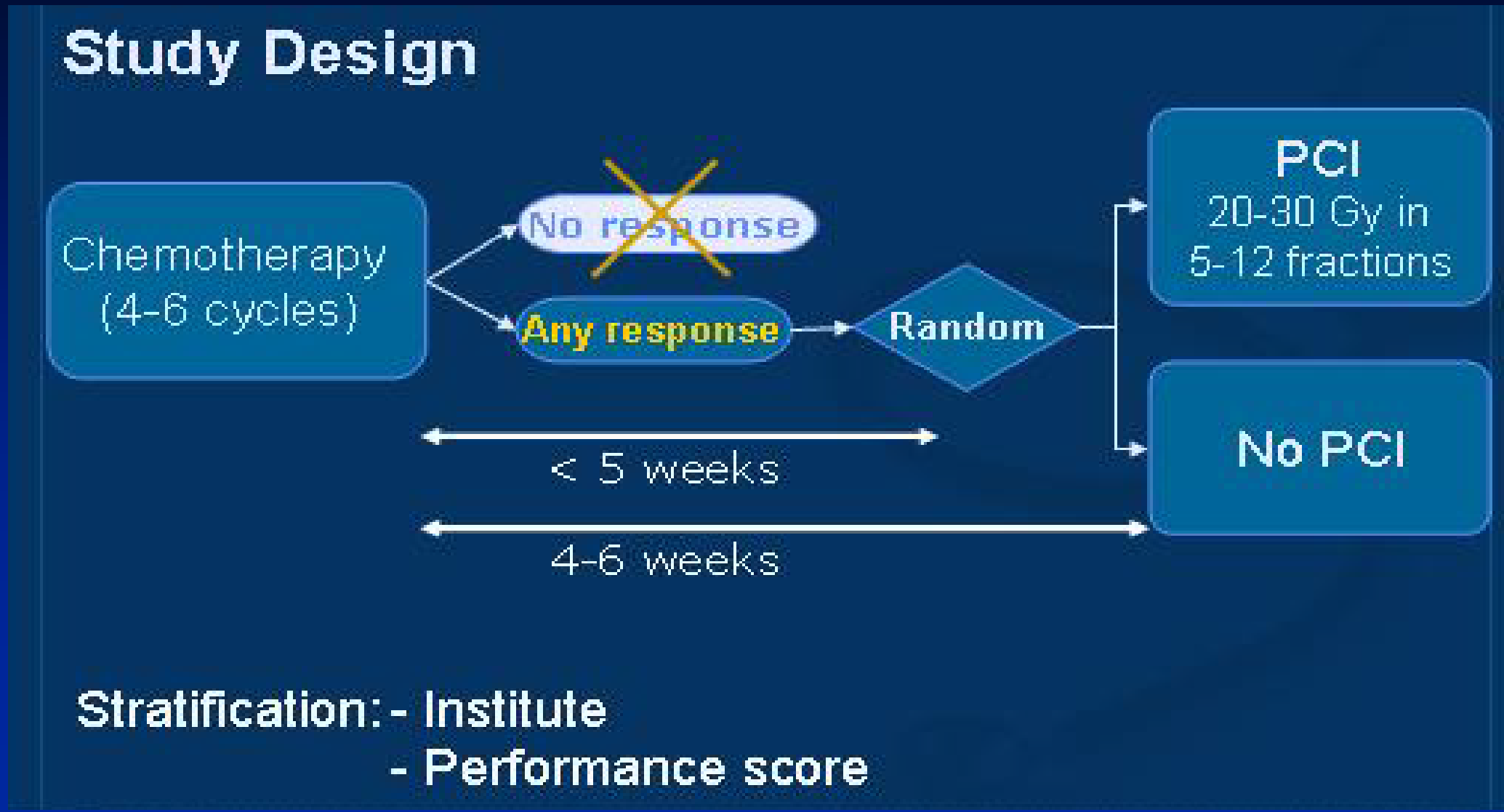
(Arriagada R et al, *Proc ASCO,* 1998)

- **7 Randomized trials**
  - 987 pts in CR (1977 to 1995)
  - PCI doses = 24 - 40 Gy in 8 - 20 fractions
  - Median follow-up = 5.9 yrs

- **Results**
  - Hazard ratio for death(PCI:Control) = 0.84
    - (16% reduction in mortality)
  - Overall survival @ 3 yrs = 20.7% *vs* 15.3%
  - Benefit (decrease in brain mets) was dose-dependent

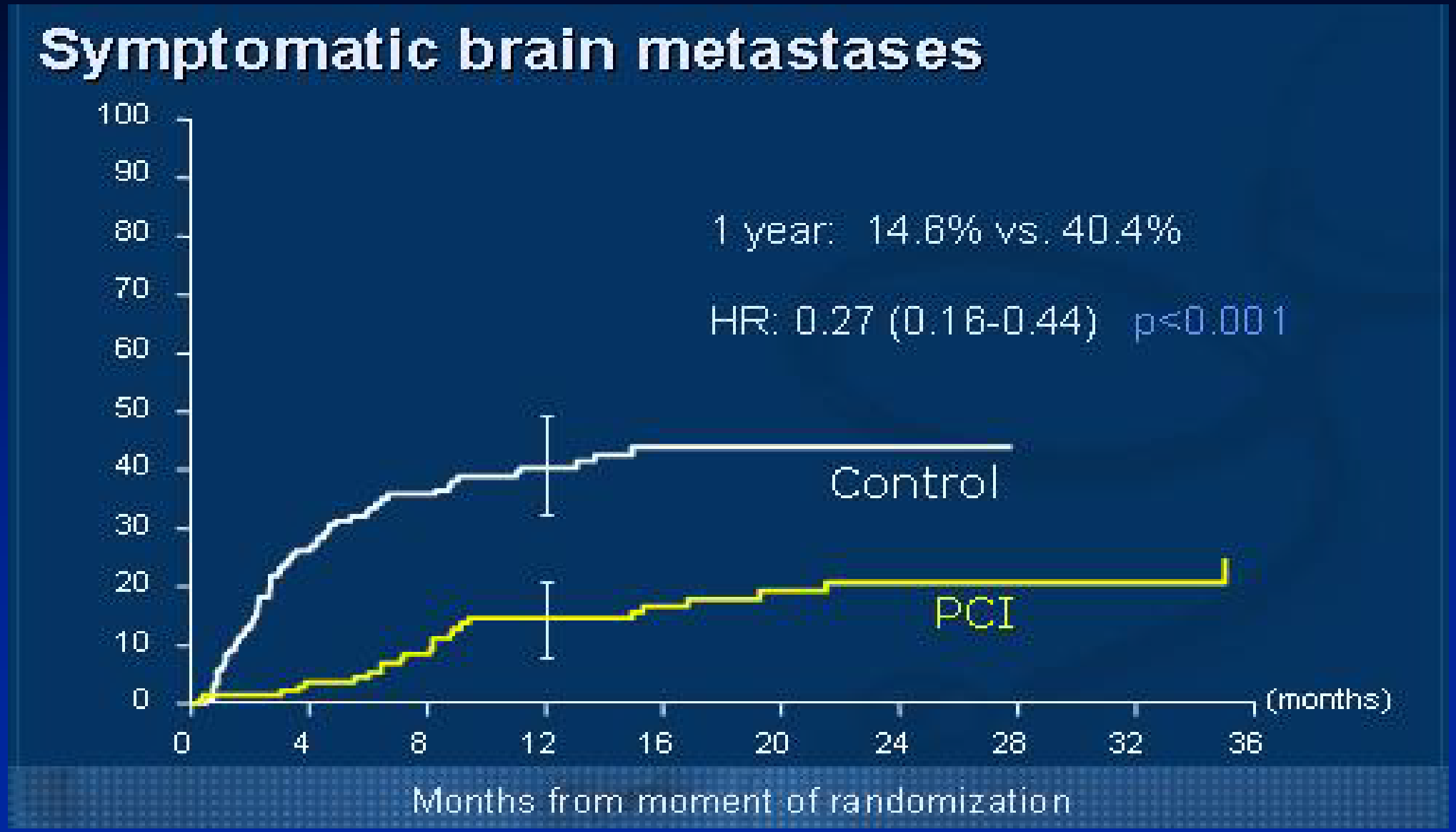
PCI in SCLC

Proc ASCO 2007



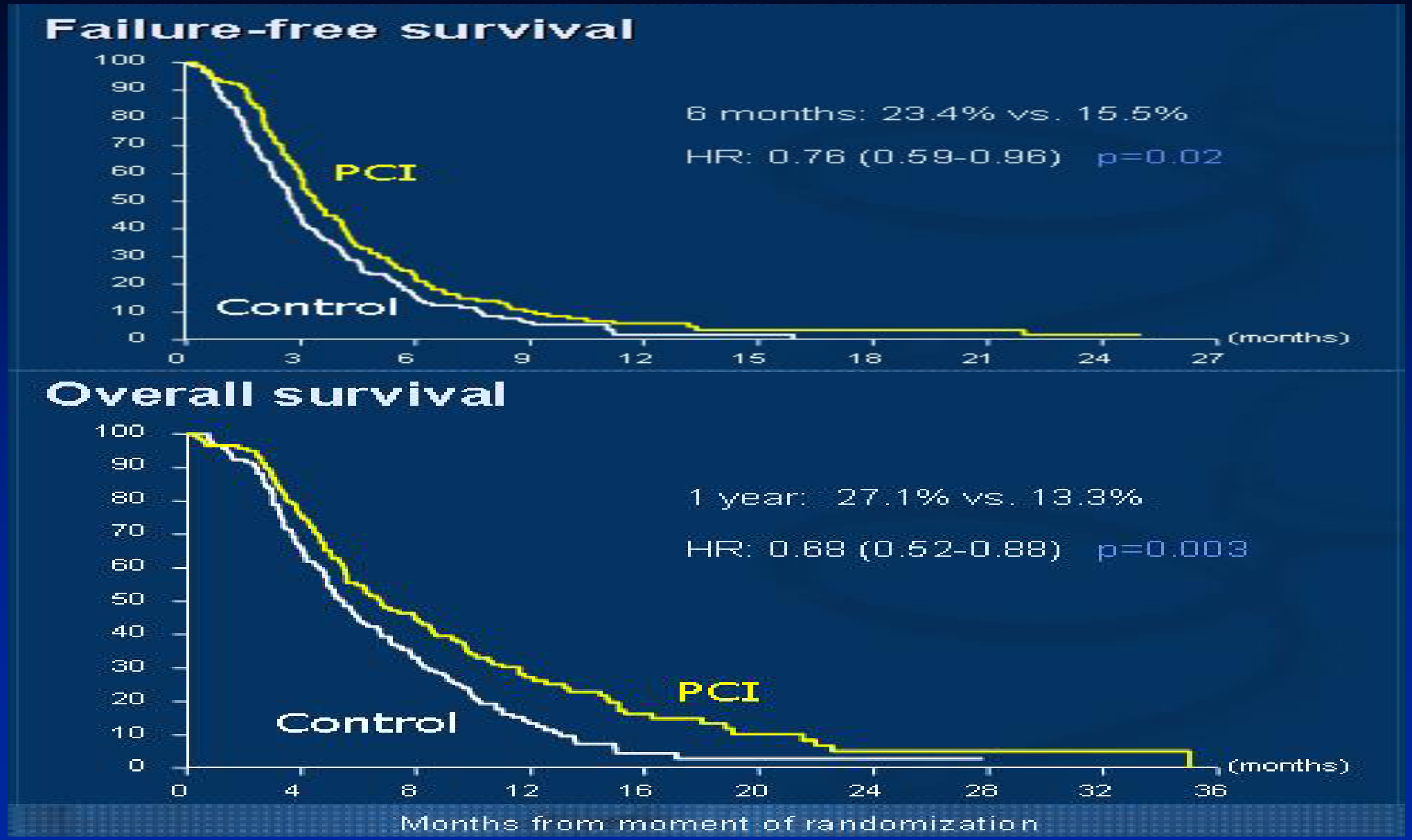
PCI in SCLC

Proc ASCO 2007



PCI in SCLC

Proc ASCO 2007



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3. PCI is the standard of care in responding SCLC pts.
4. No convincing evidence supports the substitution or addition of another cytotoxic agent, dose intensification or the addition of a biological agent (yet).

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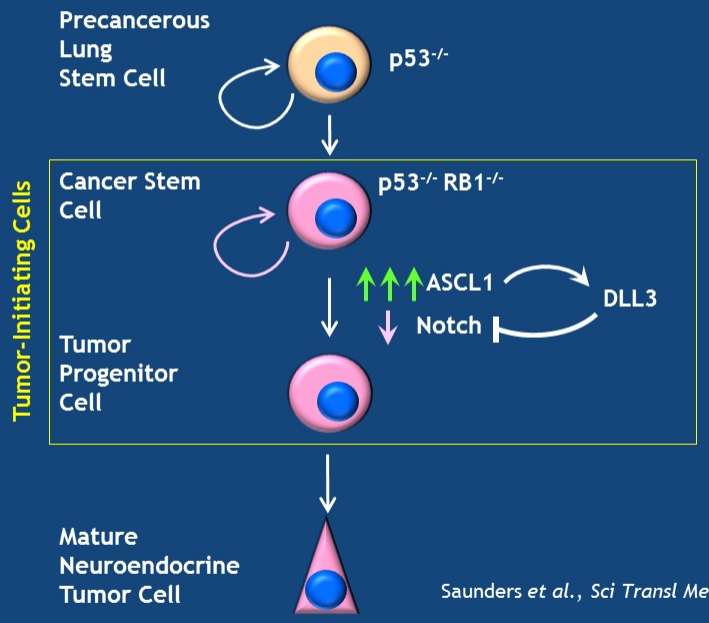
4. No convincing evidence supports the substitution or addition of another cytotoxic agent, dose intensification or the addition of a biological agent (yet).
5. Topotecan is the reference standard for 2nd line treatment.

New Treatments in Development

- **Rovalpituzumab tesirine**
- **Immunotherapy**

Delta-like Protein 3 (DLL3): A Novel Target in Neuroendocrine Tumors

- An atypical inhibitory Notch ligand
- Induced by the key neuroendocrine transcription factor, ASCL1
- Expressed on both cancer stem and tumor cells, but not normal adult tissues
- Not prognostic of SCLC outcomes on standard therapy
- >85% of SCLC express DLL3



Saunders *et al.*, *Sci Transl Med* 2015

Presented By David Carbone at 2018 ASCO Annual Meeting

TRINITY: 2, Single-Arm Study of Rovalpituzumab tesirine in DLL3-Expressing, Relapsed/Refractory SCLC

Key Eligibility Criteria
- DLL3-positive* SCLC
- Relapsed or refractory disease
- ≥ 2 previous regimens
- ≥ 1 platinum-based regimen
- ECOG Performance Status 0-1
- Stable CNS metastases allowed

→ N = 339 Rovalpituzumab tesirine 0.3 mg/kg IV Q6W x 2 →

Primary Endpoints
- Objective response rate (ORR)
- Overall survival (OS)

Secondary Endpoints
- Duration of response (DOR)
- Clinical benefit rate (CBR)
- Progression-free survival (PFS)

- Re-treatment was permitted at progression
- Study was powered to detect a 25% best overall response rate in DLL3-high Pts with a Simon's two-stage design
- Study size was increased to ensure adequate enrollment of 3L Pts

*Clinical trial mouse antibody-based immunohistochemistry assay.

CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; IHC, immunohistochemistry; IV, intravenous; q6w, every 6 weeks.

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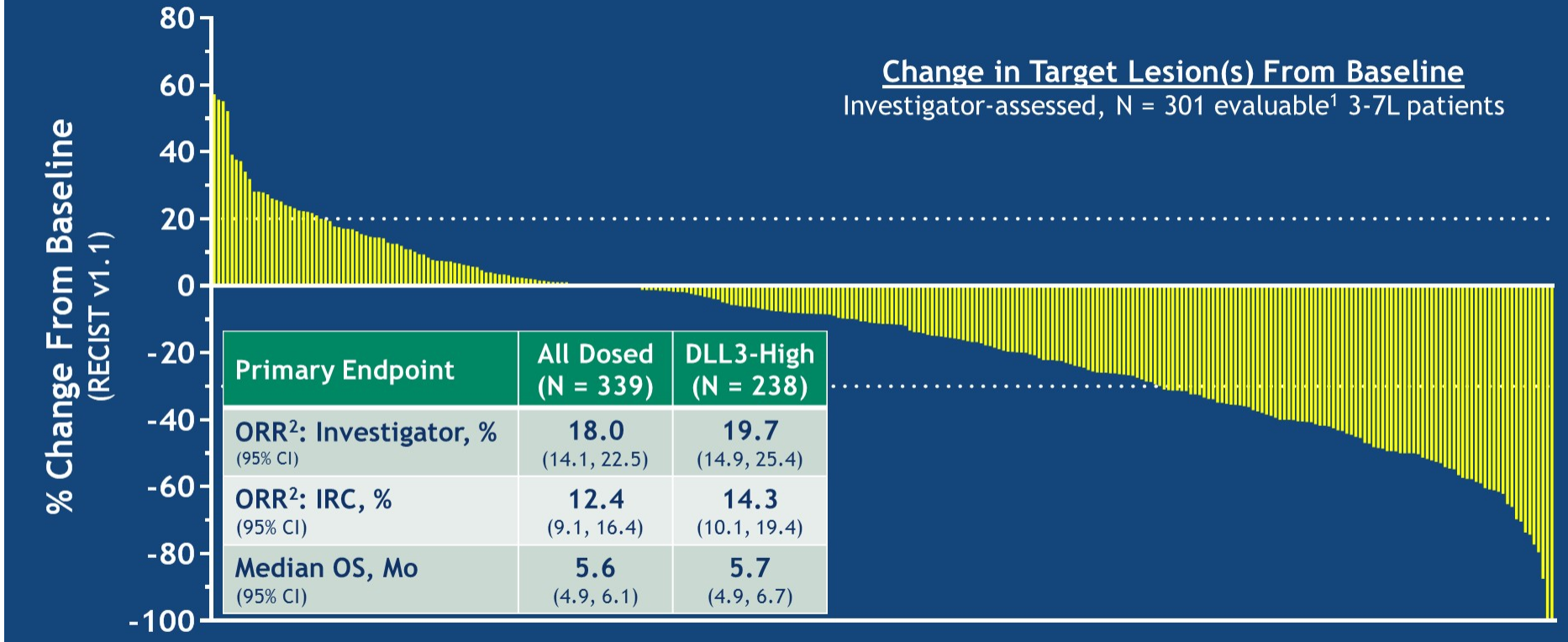
TRINITY: Primary Endpoint Analyses



Change in Target Lesion(s) From Baseline
Investigator-assessed, N = 301 evaluable[1] 3-7L patients

Primary Endpoint	All Dosed (N = 339)	DLL3-High (N = 238)
ORR[2]: Investigator, % (95% CI)	18.0 (14.1, 22.5)	19.7 (14.9, 25.4)
ORR[2]: IRC, % (95% CI)	12.4 (9.1, 16.4)	14.3 (10.1, 19.4)
Median OS, Mo (95% CI)	5.6 (4.9, 6.1)	5.7 (4.9, 6.7)

1. Patients who had a baseline scan and at least 1 follow-up scan with an evaluable response.
2. Confirmed CR+ PR per RECIST v1.1

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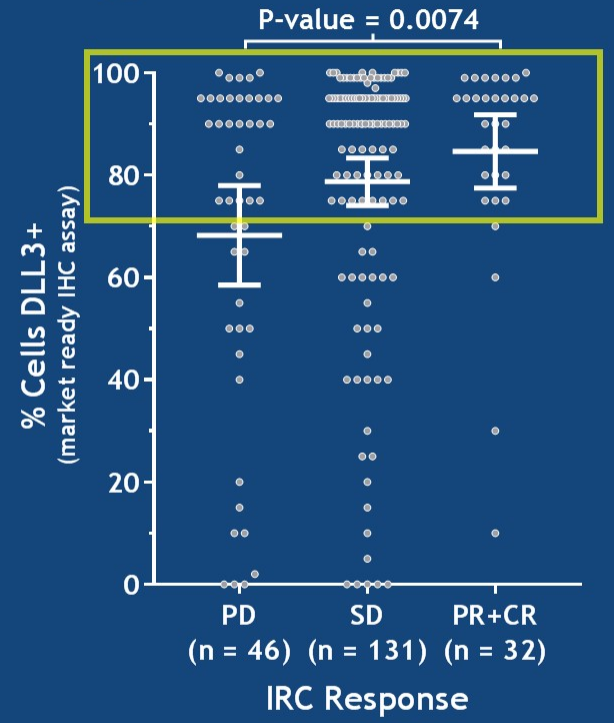
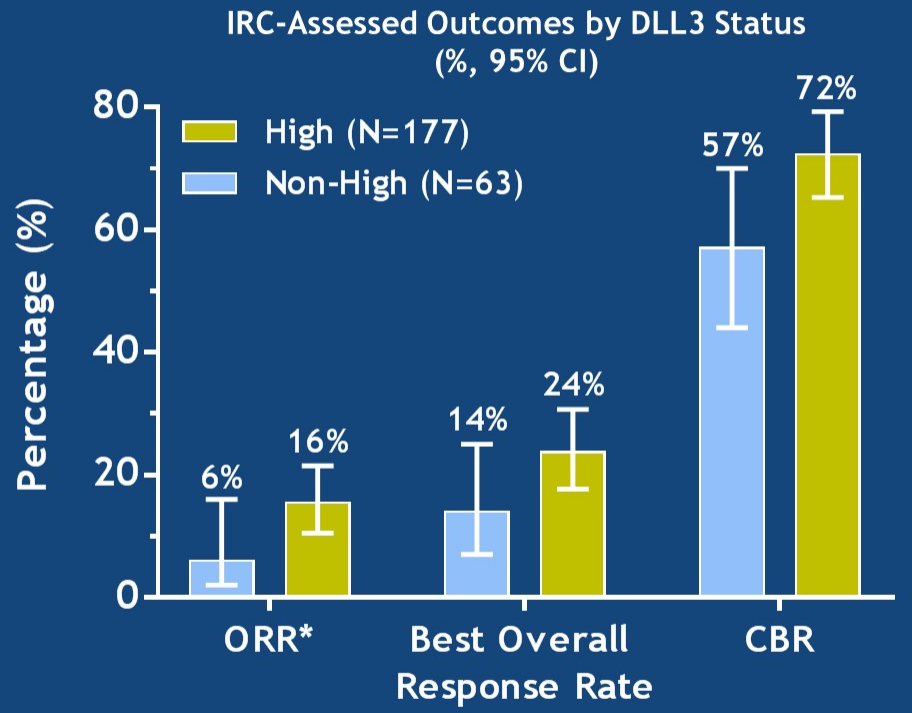
Responses are Enriched Among 3L Patients with High DLL3 Expression





P-value based on two-sample t test; not adjusted for multiple testing.
*Confirmed CR+ PR per RECIST v1.1

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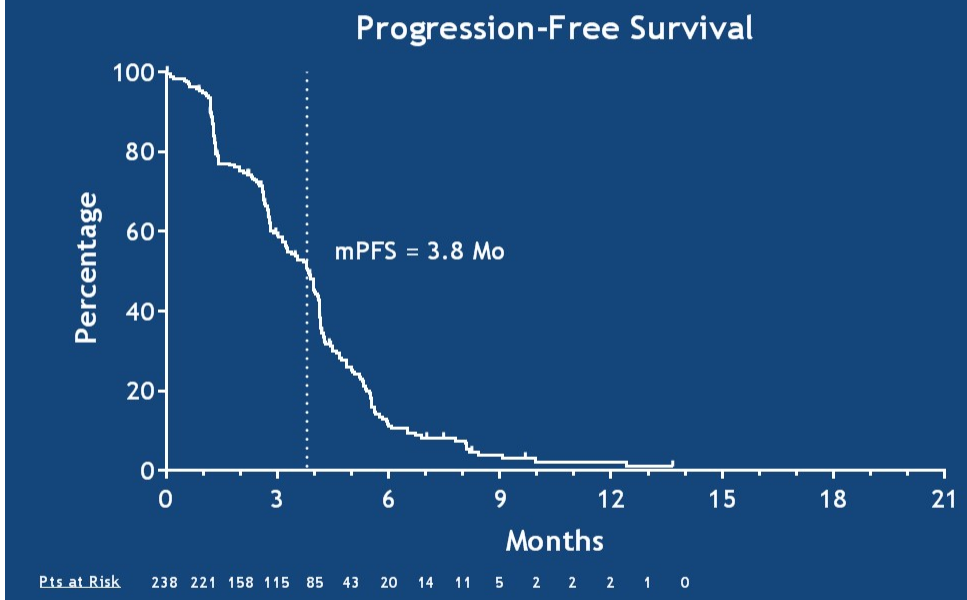
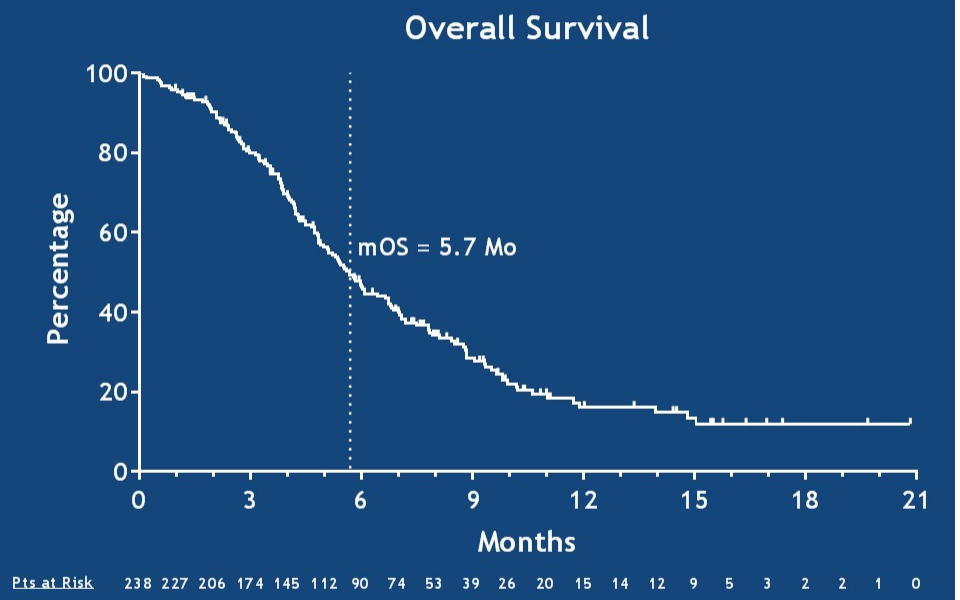
IRC-Assessed PFS & OS Among DLL3-High Patients, All Lines





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Summary of TEAEs

TEAEs, Any Grade ≥ 15% Patients	All Patients, N = 339	
	Any n (%)	Drug-Related n (%)
Fatigue	130 (38%)	96 (28%)
Photosensitivity reaction	123 (36%)	120 (35%)
Pleural effusion	109 (32%)	95 (28%)
Peripheral edema	104 (31%)	89 (26%)
Decreased appetite	103 (30%)	53 (16%)
Nausea	88 (26%)	55 (16%)
Dyspnea	84 (25%)	33 (10%)
Thrombocytopenia	83 (25%)	74 (22%)
Constipation	75 (22%)	15 (4%)
Vomiting	59 (17%)	28 (8%)
Anemia	58 (17%)	44 (13%)
Cough	55 (16%)	7 (2%)
Hypoalbuminemia	53 (16%)	40 (12%)
Pericardial effusion	50 (15%)	42 (12%)
Abdominal pain	49 (15%)	18 (5%)
Asthenia	49 (15%)	40 (12%)

TEAEs, Grade 3/4 ≥ 10 Patients	All Patients, N = 339	
	Any n (%)	Drug-Related n (%)
Thrombocytopenia	38 (11%)	37 (11%)
Photosensitivity reaction	23 (7%)	23 (7%)
Anemia	16 (5%)	12 (4%)
Fatigue	15 (4%)	12 (4%)
Pleural effusion	15 (4%)	14 (4%)

- Serosal effusions were managed primarily through standard drainage procedures; steroids, NSAIDs, and colchicine also used
- History of effusions may be identified risk factor for Gr3+ Rova-T-related effusions

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TRINITY: Conclusions

- Rovalpituzumab tesirine is active in 3L+ SCLC, where no current therapies are approved
  - ORR: 18% INV; 12% IRC
- 3L DLL3-High biomarker-selected Pts were most likely to respond and benefit
  - ORR: 20% INV; 16% IRC
  - Best Overall Response Rate: 29% INV; 24% IRC
  - Clinical Benefit Rate: 71% INV; 72% IRC
  - mOS: 5.6 Mo
- Adverse events were generally manageable
- Important identified risks were pleural/pericardial effusion, edema & photosensitivity
- Rovalpituzumab tesirine is being evaluated in 2 ongoing ph 3 studies (1st line maintenance, MERU; 2L, TAHOE), and Ph 1 studies in combination with chemotherapy (platinum/etoposide), nivolumab, and nivolumab/ipilimumab

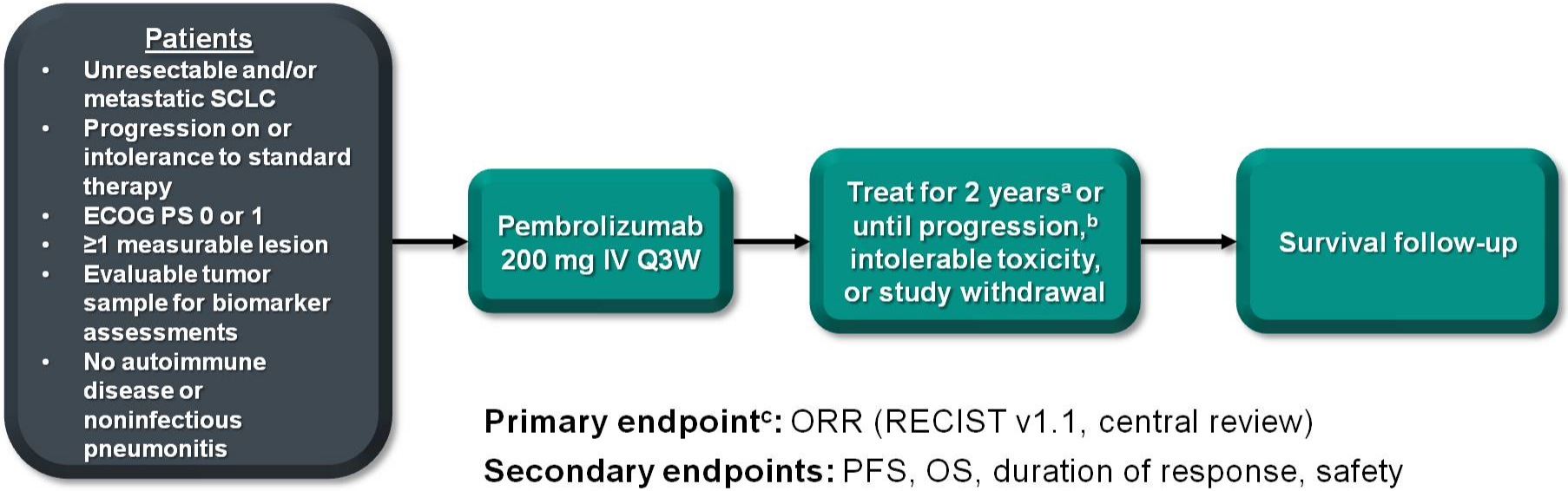
New Treatments in Development

- Rovalpituzumab tesirine
- **Immunotherapy**

Immunotherapy in SCLC

- **Pembrolizumab**
  - **Keynote 158**
- **Nivolumab**
  - Checkmate 032
- **Atezolizumab**
  - **Impower 133**

KEYNOTE-158 (NCT02628067): Phase 2 Multicohort Study of Pembrolizumab for Advanced Solid Tumors



Primary endpoint[c]: ORR (RECIST v1.1, central review)

Secondary endpoints: PFS, OS, duration of response, safety

Exploratory endpoints: Efficacy in biomarker subgroups

Response assessed every 9 weeks year 1; every 12 weeks thereafter

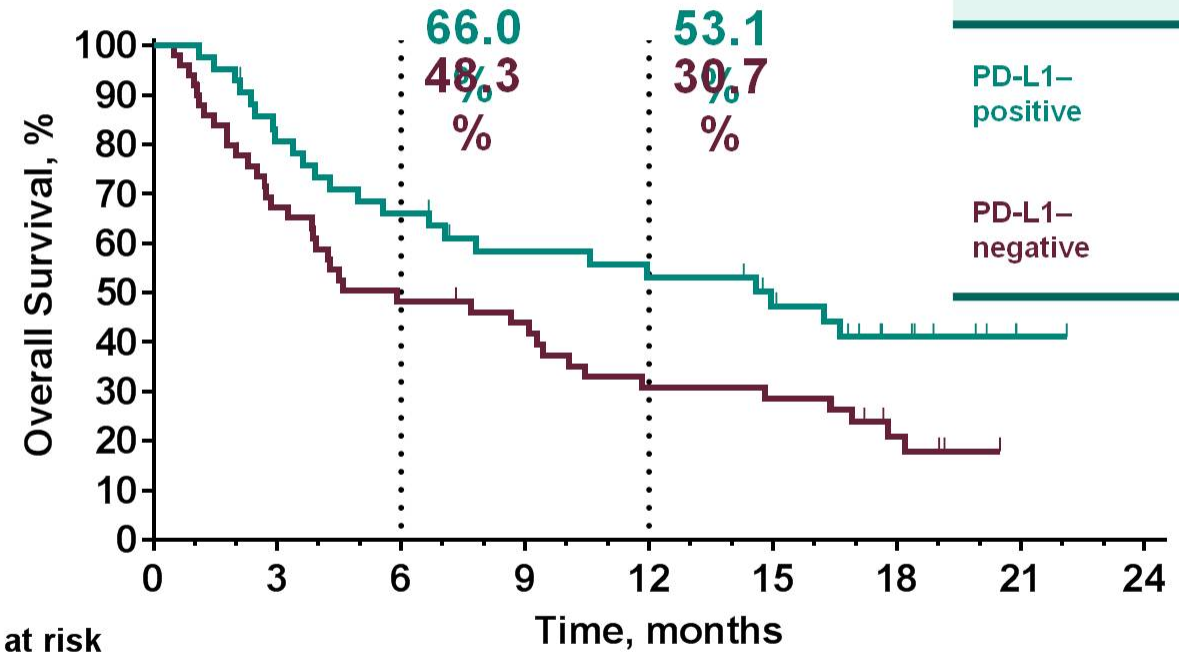
[a]If SD or better when pembrolizumab discontinued and subsequently have PD, patients may be eligible to resume pembrolizumab for ≤1 year.
[b]If clinically stable, patients are to remain on pembrolizumab until PD is confirmed on a second scan performed ≥4 weeks later.
[c]The point estimate and exact Clopper-Pearson CI were calculated.

Antitumor Activity by PD-L1 Status
(RECIST v1.1, Independent Central Review[a])

	PD-L1–Positive N = 42	PD-L1–Negative N = 50	Overall N = 107
ORR, % (95% CI)	35.7 (21.6–52.0)	6.0 (1.3–16.5)	18.7 (11.8–27.4)
Best overall response, n (%)			
Complete response	2 (5)	1 (2)	3 (3)
Partial response	13 (31)	2 (4)	17 (16)
Stable disease	3 (7)	7 (14)	12 (11)
Progressive disease	22 (52)	29 (58)	62 (58)
Disease control, n (%)	18 (43)	10 (20)	32 (30)

[a]Only confirmed responses are included.
Data cutoff date: January 15, 2018.

Overall Survival by Tumor PD-L1 Status (RECIST v1.1, Independent Central Review)



	N	Number of Events (%)	Median OS, mo (95% CI)
PD-L1–positive	42	23 (55)	14.9 (5.6–NR)
PD-L1–negative	50	38 (76)	5.9 (3.3–10.1)

No. at risk									
PD-L1–positive	42	33	27	22	20	16	9	1	0
PD-L1–negative	50	32	23	20	14	13	7	0	0

Data cutoff date: January 15, 2018.

Immunotherapy in SCLC

- **Pembrolizumab**
  - Keynote 158
- **Nivolumab**
  - Checkmate 032
- **Atezolizumab**
  - Impower 133

Checkmate 032

Stratified by TMB
(Hi v Interm v Low)

	All Pts	Hi TMB	Int TMB	Low TMB
Nivolumab 3 mg/kg Q2W				
ORR	11%	21%	7%	5%
1 Yr PFS		21%	3%	-
Nivolumab 1 mg/kg + Ipilumumab 3 mg/kg Q3W				
ORR	22%	46%	16%	22%
1 Yr PFS		30%	8%	6%

Hellmann et al. WCLC, Yokohama, Japan, 10/2017

Immunotherapy in SCLC

- **Pembrolizumab**
  - **Keynote 158**
- **Nivolumab**
  - Checkmate 032
- **Atezolizumab**
  - **Impower 133**

Atezolizumab in SCLC

- **IMpower 133: Phase III randomized, double-blind, placebo-controlled trial of carboplatin + etoposide +/- atezolizumab in ES-SCLC**
- **403 patients, randomized 1:1**
- **June 25, 2018 Press Release: Study met it's co-primary endpoints of statistically significant improvement in PFS and OS!**

Ongoing pivotal studies and emerging strategies

NRG-LU005: Phase II/III randomized study of chemoradiation versus chemoradiation plus atezolizumab

PATIENT POPULATION:
Limited stage SCLC

STRATIFICATION
- Radiation schedule (BID vs daily)
- Chemotherapy (cisplatin vs carboplatin)
- Sex
- ECOG Performance Status (0/1 vs 2)

R

Platinum/etoposide x 4 cycles
+
Thoracic RT 45 Gy bid or 66 Gy daily

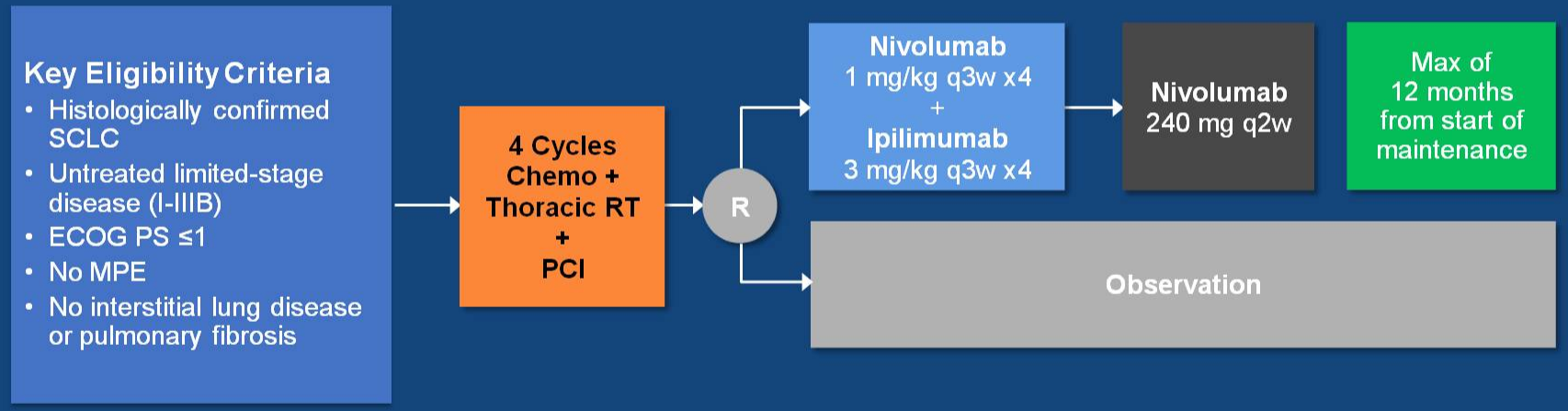
Platinum/etoposide x 4 cycles
+
Thoracic RT 45 Gy bid or 66 Gy daily
+
Atezolizumab q3 weeks beginning with cycle 2

Atezolizumab q3 weeks for 1 year

Anticipated Study Start Date: 2018

CA184-310 (STIMULI): Phase 2 trial of consolidation nivolumab and ipilimumab in limited-stage SCLC after chemo-radiotherapy

N=260



Primary Outcome Measures:
OS, PFS

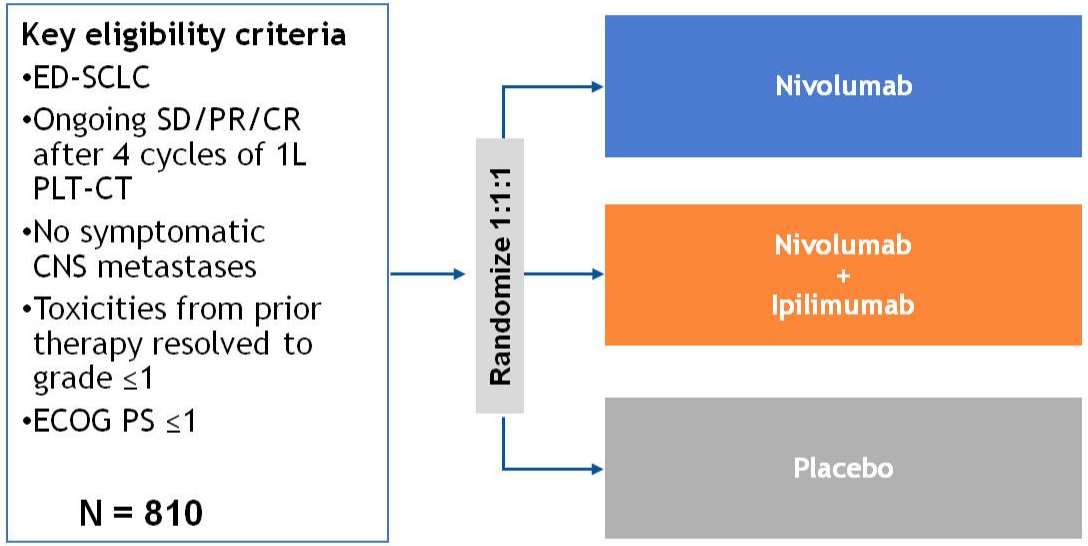
Study Start Date: July 2014
Estimated Completion Date: January 2022

Clinicaltrials.gov. NCT02046733. Accessed March 13, 2018.

Frontline immunotherapy trials in extensive stage SCLC

Study	Population	Regimen
IMpower133	Treatment naïve SCLC Phase I/III	Carboplatin/Etoposide Vs. Carboplatin/Etoposide/Atezolizumab
KEYNOTE-604	Treatment naïve SCLC Phase I/III	Pembrolizumab/Etoposide/Platinum Vs. Etoposide/Platinum
Caspian Study	Treatment naïve SCLC Phase III	Etoposide/Platinum Vs. Etoposide/Platinum + Durvalumab + Tremelimumab Etoposide/Platinum Vs. Etoposide/Platinum/Durvalumab

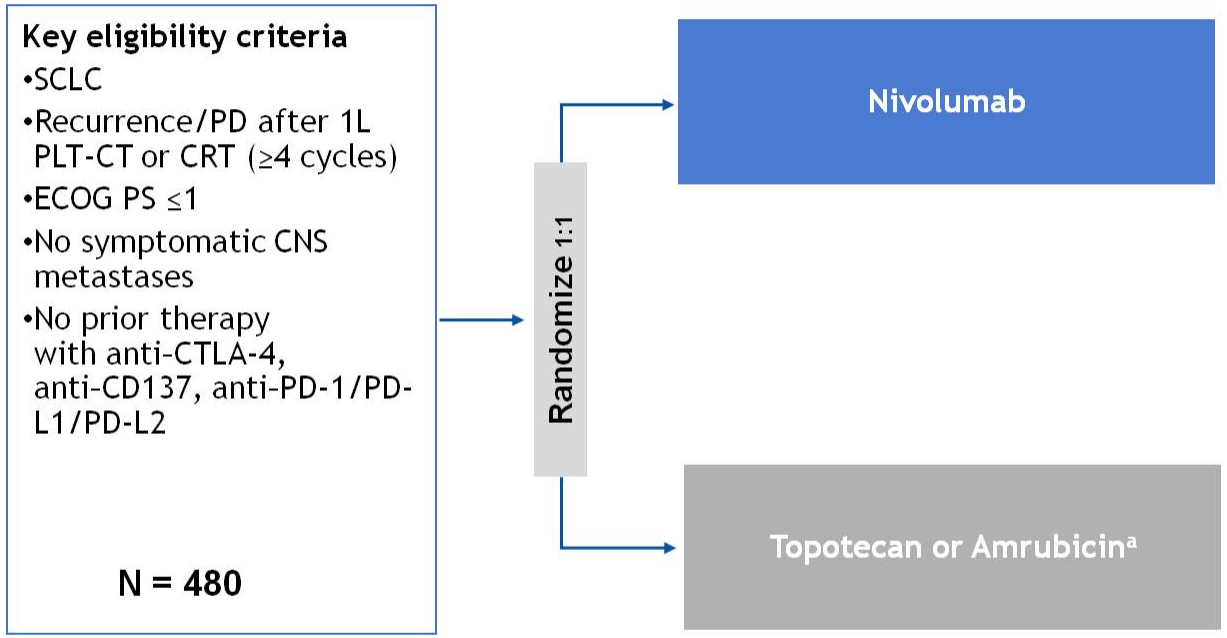
CheckMate 451: Phase 3 study of maintenance nivolumab ± ipilimumab in SCLC



- **Primary outcome measures:**
  – OS, PFS
- **Secondary outcome measures:**
  – OS and PFS descriptive analyses: nivolumab vs nivolumab + ipilimumab

1L = first-line; CT = chemotherapy; CRT = chemoradiation therapy; CTLA-4 = cytotoxic T lymphocyte antigen-4; PD-1 = programmed-death 1; PD-L2 = PD ligand 2
PLT = platinum-based; [a]Where locally approved

CheckMate 331: Phase 3 study of nivolumab versus topotecan/amrubicin in relapsed SCLC

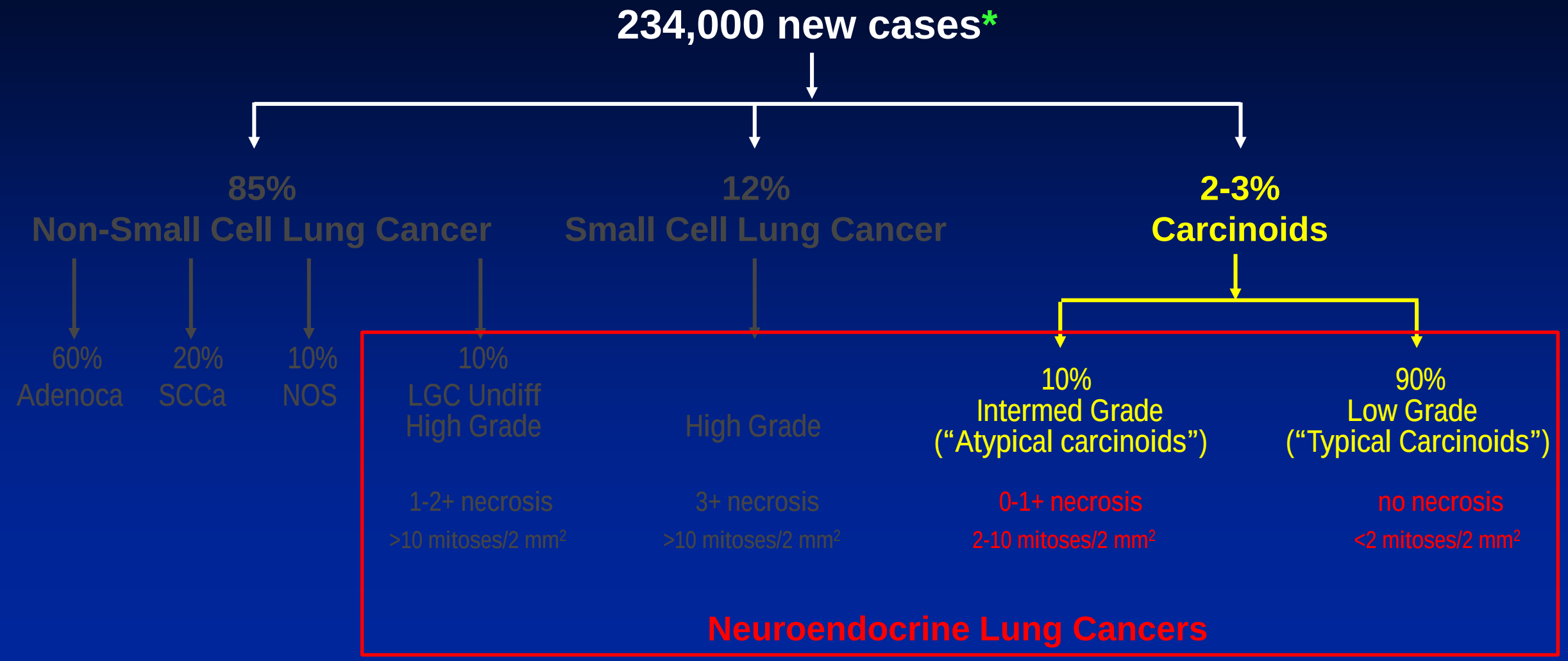


- **Primary outcome measures:** OS
- **Secondary outcome measures:** PFS, ORR

SCLC: Take Home Message

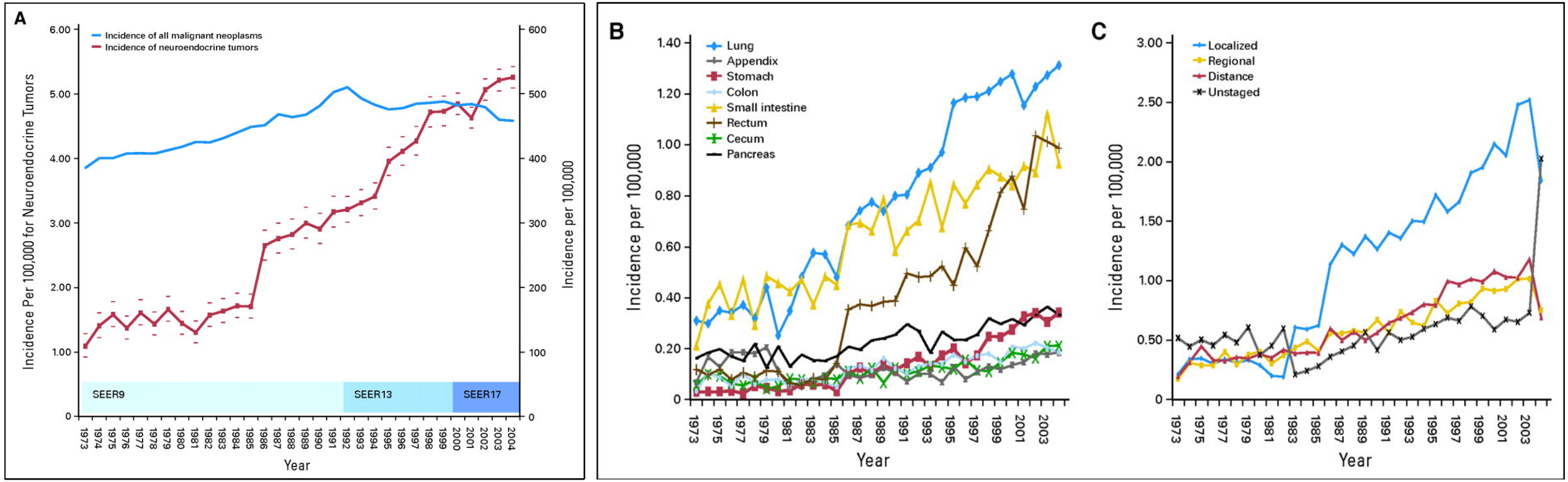
- After 30 years, the SOC for the treatment SCLC is finally about to change, perhaps dramatically
  - Immune checkpoint inhibitors will have an important role to play in ~40% of patients with high PDL-1 or high TMB
    - FDA approval of atezolizumab is imminent; others will likely follow
  - CAR-T therapy can't be much further behind
  - Targeted therapy (targeting DLL-3) is promising
    - Rovalpituzumab tesirine will likely obtain 3L FDA approval

Lung Cancer in the U.S. in 2018



*Noone AM et al. SEER Cancer Statistics Review, 1975-2015, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2015, based on November 2017 SEER data posted to April 2018.

Incidence of NETs over time by site and disease stage



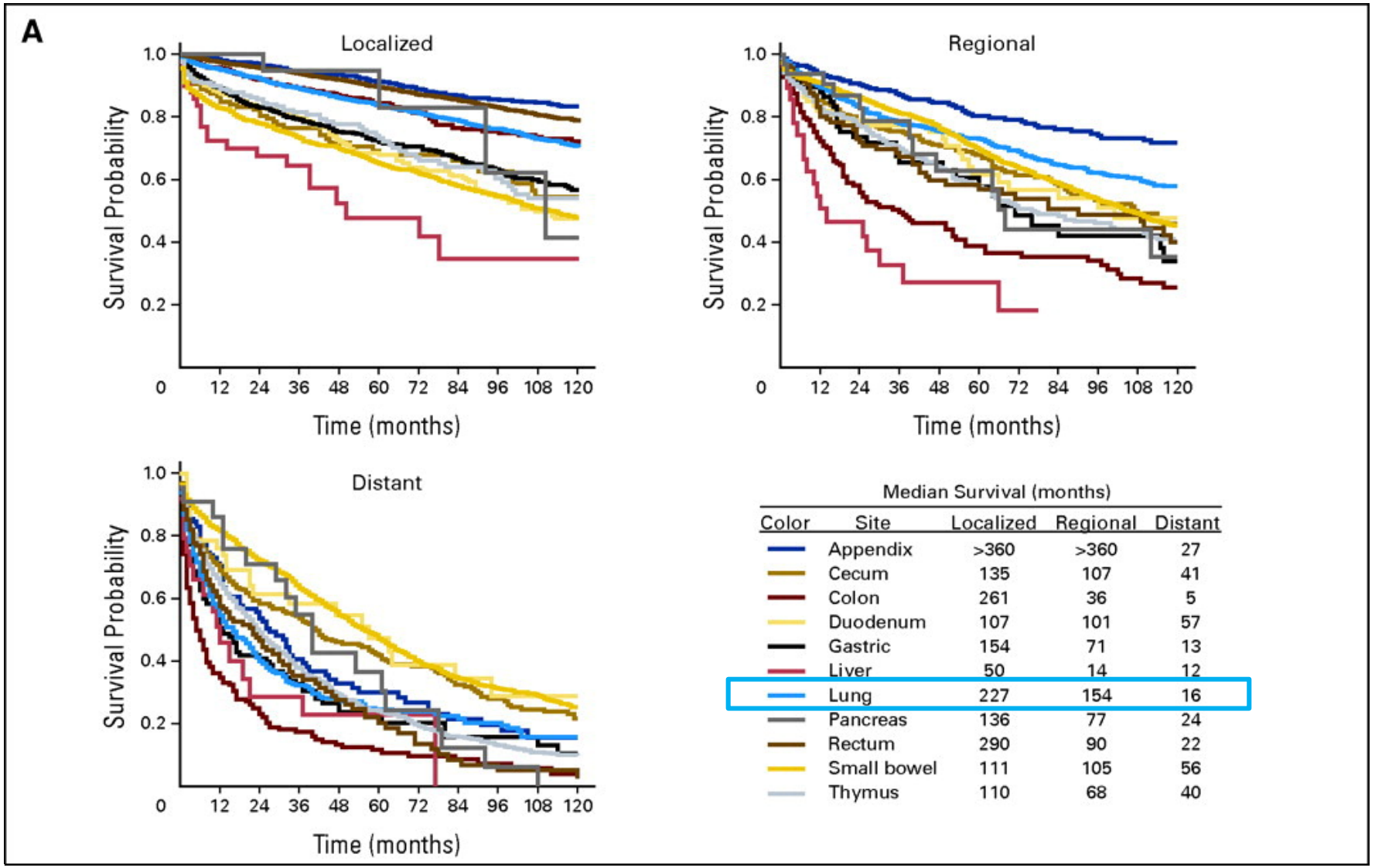
Annual age-adjusted incidence (# cases per 100,000 population), 1973-2004

Published in: James C. Yao; Manal Hassan; Alexandria Phan; Cecile Dagohoy; Colleen Leary; Jeannette E. Mares; Eddie K. Abdalla; Jason B. Fleming; Jean-Nicolas Vauthey; Asif Rashid; Douglas B. Evans; *JCO* **2008,** 26, 3063-3072. DOI: 10.1200/JCO.2007.15.4377

Treatment Options

- **Localized disease:** **surgery**

Patient Survival Dependent on Extent of Disease



Median Survival (months)

Color	Site	Localized	Regional	Distant
	Appendix	>360	>360	27
	Cecum	135	107	41
	Colon	261	36	5
	Duodenum	107	101	57
	Gastric	154	71	13
	Liver	50	14	12
	Lung	227	154	16
	Pancreas	136	77	24
	Rectum	290	90	22
	Small bowel	111	105	56
	Thymus	110	68	40

Published in: James C. Yao; Manal Hassan; Alexandria Phan; Cecile Dagohoy; Colleen Leary; Jeannette E. Mares; Eddie K. Abdalla; Jason B. Fleming; Jean-Nicolas Vauthey; Asif Rashid; Douglas B. Evans; *JCO* **2008,** 26, 3063-3072 DOI: 10.1200/JCO.2007.15.43

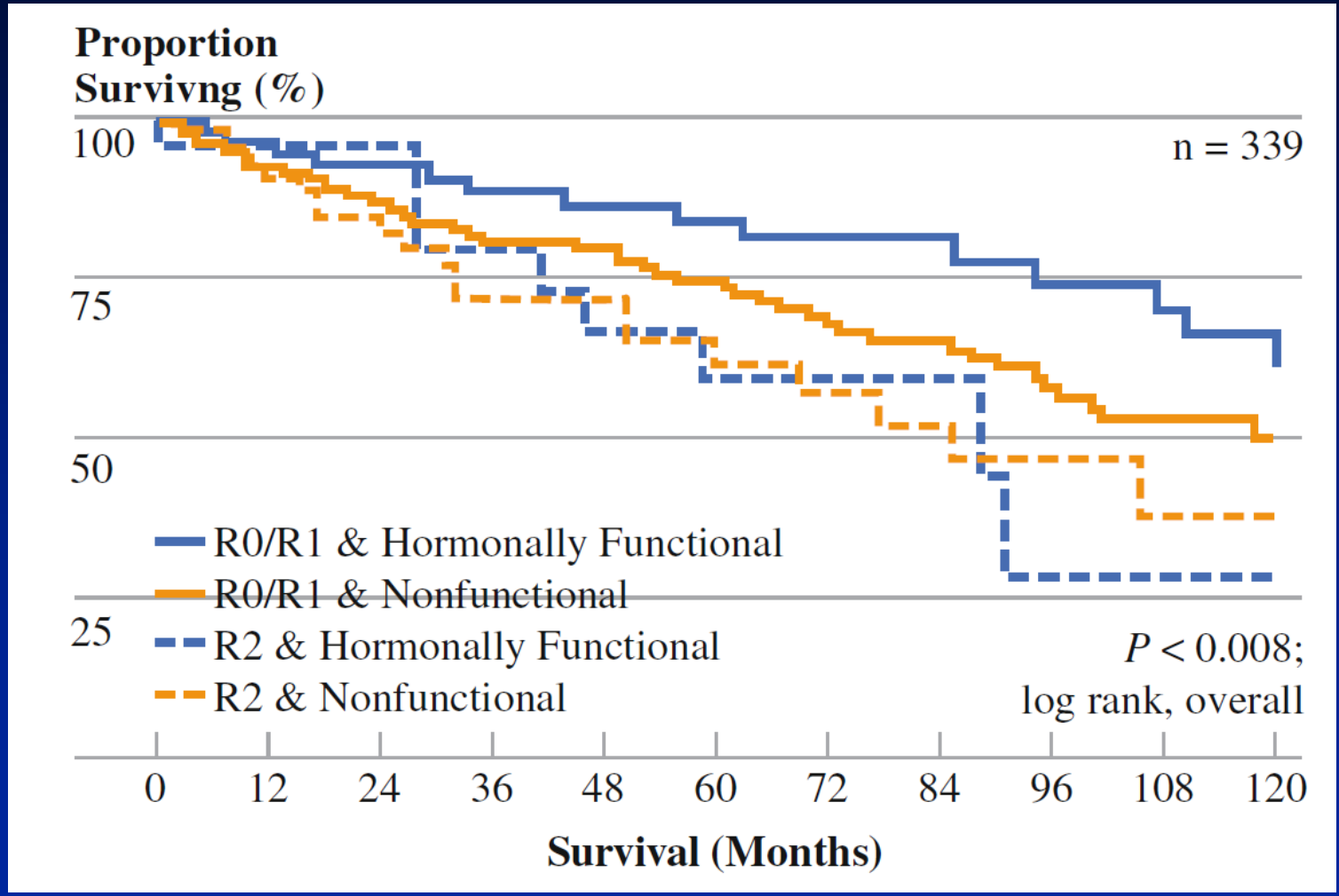
Treatment Options

- **Localized disease: surgery**
- **Locally advanced: ?Adjuvant chemotherapy +/- radiation**
  - **No good evidence supporting routine use**

Treatment Options

- Localized disease: surgery
- Locally advanced: ?Adjuvant chemotherapy +/- radiation
  - No good evidence supporting routine use
- Metastatic disease:
  - Surgery (for “oligometastases”)

Kaplan-Meier Survival following Resection of Liver Metastases (stratified by margin status and hormonal function)



Mayo SC et al. Surgical management of hepatic neuroendocrine tumor metastasis: results from an International Multi-Institutional Analysis. Ann Surg Oncol 2010; 17:3129-3136.

Treatment Options

- **Localized disease: surgery**
- **Locally advanced: ?Adjuvant chemotherapy +/- radiation**
  - **No good evidence supporting routine use**
- **Metastatic disease:**
  - **Surgery (for “oligometastases”)**
  - **SSAs (octreotide and lanreotide)**

SSAs Recommended for:

- **All TCs and ACs with ‘Carcinoid” symptoms**
  - **Recommended 1st line option**
- **70% of TCs or ACs have + SSRT status** (+Octreotide scan)
- **Randomized clinical trials in progress**

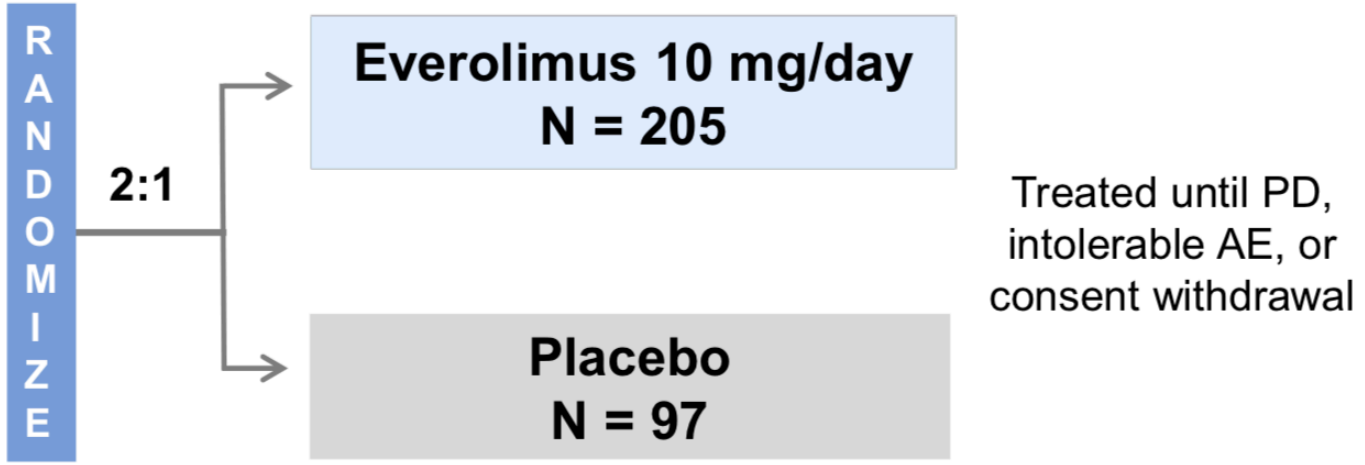
Treatment Options

- Localized disease: surgery
- Locally advanced: ?Adjuvant chemotherapy +/- radiation
  - No good evidence supporting routine use
- Metastatic disease:
  - Surgery (for “oligometastases”)
  - SSAs (octreotide and lanreotide)
  - Targeted therapy (everolimus, sunitinib, bevacizumab)
  - Interferon
  - Chemotherapy (platinum + etoposide, temozolomide)
  - PRRT (for SSTR-expressing NETs)
    - 1/26/18 FDA approved ^{177}LU-Dotatate for treatement of SSRT+ GEP-NETs

RADIANT 4 Study Design

Patients with well-differentiated (G1/G2), advanced, progressive, nonfunctional NET of lung or GI origin (N = 302)

- Absence of active or any history of carcinoid syndrome
- Pathologically confirmed advanced disease
- Enrolled within 6 months from radiologic progression



Treated until PD, intolerable AE, or consent withdrawal

Endpoints:

- **Primary:** PFS (central)
- **Key Secondary:** OS
- **Secondary:** ORR, DCR, safety, HRQoL (FACT-G), WHO PS, NSE/CgA, PK

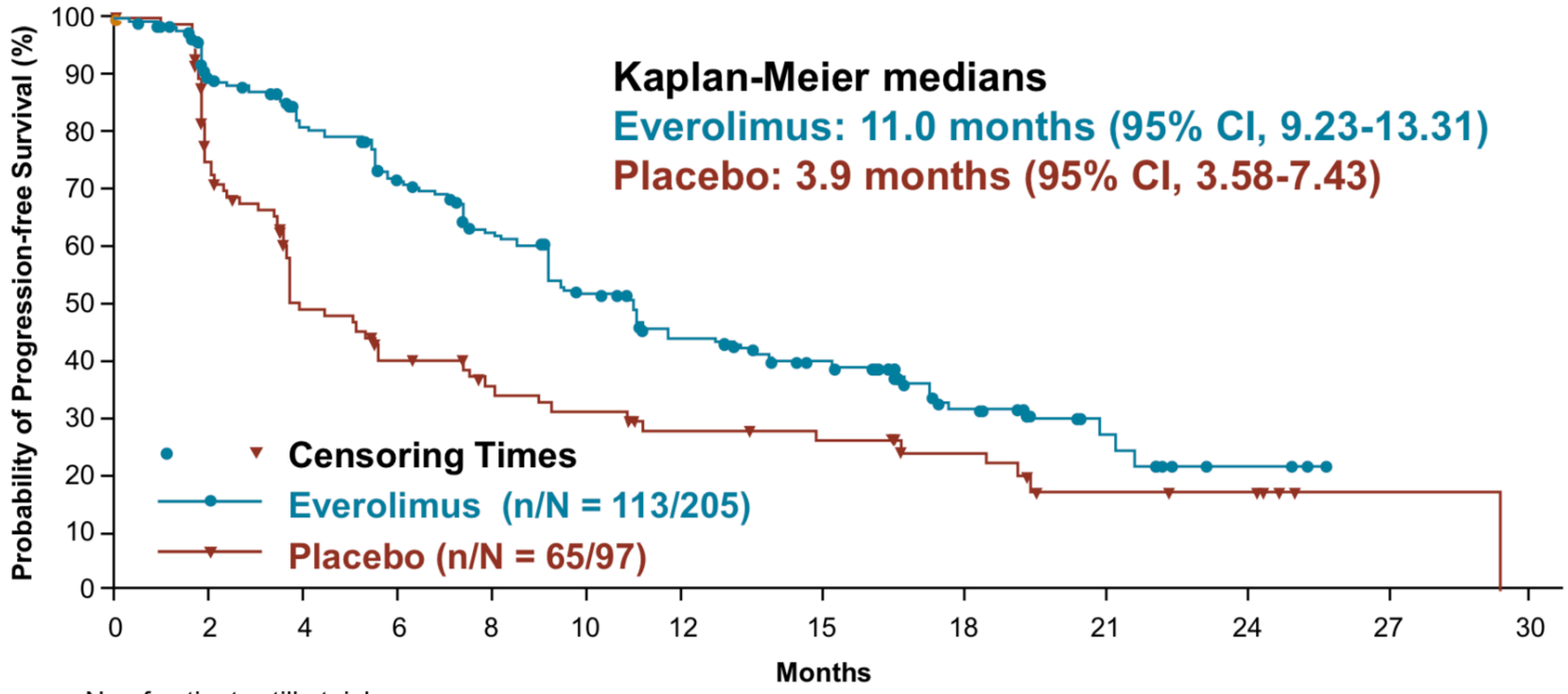
Stratified by:

- Prior SSA treatment (yes vs. no)
- Tumor origin (stratum A vs. B)*
- WHO PS (0 vs. 1)

Progression Free Survival

52% reduction in the relative risk of progression or death with everolimus vs placebo

HR = 0.48 (95% CI, 0.35-0.67); *P* < 0.00001

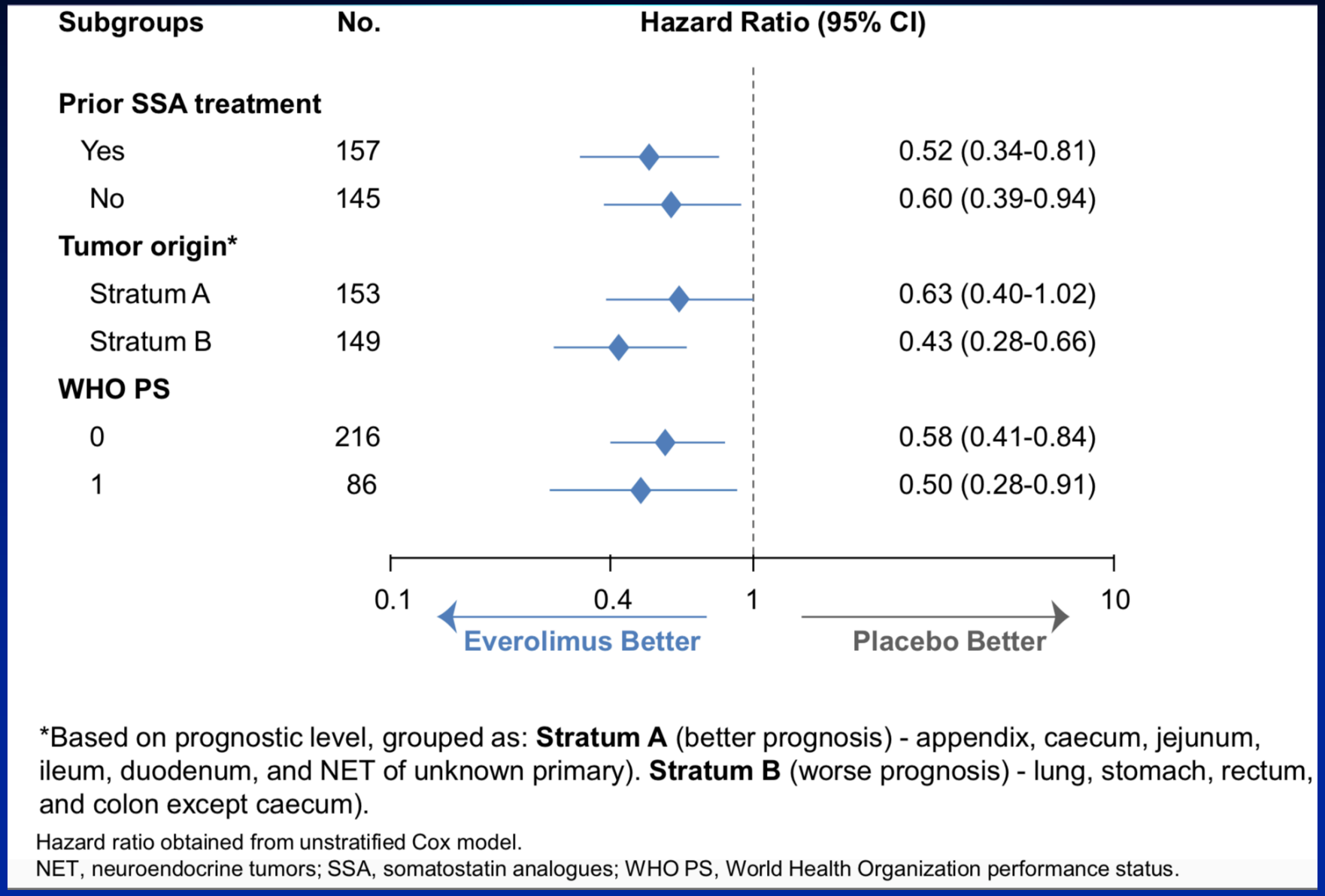


No.of patients still at risk

Everolimus	205	168	145	124	101	81	65	52	26	10	3	0	0
Placebo	97	65	39	30	24	21	17	15	11	6	5	1	0

P-value is obtained from the stratified one-sided log-rank test; Hazard ratio is obtained from stratified Cox model.

PFS Benefit Across Multiple Patient Subgroups



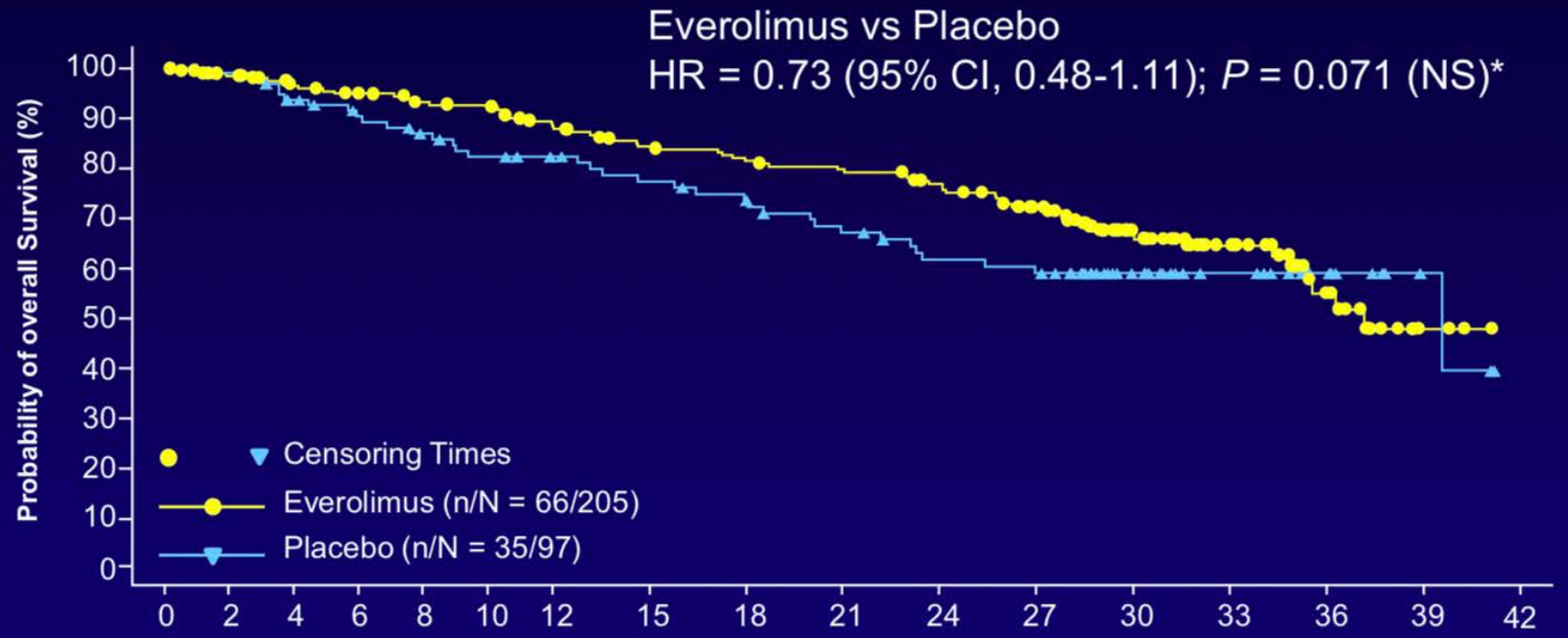
*Based on prognostic level, grouped as: **Stratum A** (better prognosis) - appendix, caecum, jejunum, ileum, duodenum, and NET of unknown primary). **Stratum B** (worse prognosis) - lung, stomach, rectum, and colon except caecum).

Hazard ratio obtained from unstratified Cox model.

NET, neuroendocrine tumors; SSA, somatostatin analogues; WHO PS, World Health Organization performance status.

Second Interim Overall Survival Analysis

Second interim OS analysis performed with 53% of information fraction favored the everolimus arm



No. of patients still at risk

Everolimus	205	195	185	180	173	171	160	148	142	138	130	115	76	42	19	3	0
Placebo	97	94	86	80	75	70	67	62	57	51	45	43	28	18	10	3	0

*P-value boundary for significance = 0.0020.
P-value is obtained from the stratified log-rank test; Hazard ratio is obtained from stratified Cox model.
Abbreviation: NS, not significant.

ADVERSE EVENTS

	Everolimus N = 202		Placebo N = 98	
Drug-related adverse events	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**
Stomatitis*	63%	9%	19%	0
Diarrhea	31%	7%	16%	2%
Fatigue	31%	3%	24%	1%
Infections†	29%	7%	4%	0
Rash	27%	1%	8%	0
Peripheral edema	26%	2%	4%	1%
Nausea	17%	1%	10%	0
Anemia	16%	4%	2%	1%
Decreased appetite	16%	1%	6%	0
Asthenia	16%	1%	5%	0
Non-infectious pneumonitis‡	16%	1%	1%	0
Dysgeusia	15%	1%	4%	0
Cough	13%	0	3%	0
Pruritus	13%	1%	4%	0
Pyrexia	11%	2%	5%	0
Dyspnea	10%	1%	4%	1%
Hyperglycemia	10%	3%	2%	0

Presented are drug-related adverse events in ≥10% of patients (safety set).
*Includes stomatitis, aphthous stomatitis, mouth ulceration, and tongue ulceration.

Treatment of Pulmonary Neuroendocrine Cancers: New Directions

- **Mutations in TC and ACs**
  - MEN1 (tumor suppressor) muationally inactivated/deleted in 30-40% of cases
  - P53 mutations (exons 5-8) in ~20%
- **Immunotherapy**
  - PDL-1 expression and tumor mutational burden generally very low
  - MMR deficiencies in ~ 10% may identify a small subset of “responsive” patients
- **ROVA-T (a DLL-3 antibody-drug conjugate)**
  - Initially promising results in SCLC failed further follow-up primarily due to low efficacy and high toxicity

PNETS: Take Home Message

- **Neuroendocrine cancers (including PNETS) are an increasing group of disease entities with an increasing need for medical oncology approaches**
- **As a group they have interesting differences from the more common medical oncology disease, but the approach is the same**
  - **Standard staging/diagnostics to define the extent of disease**
  - **Surgery remains the dominant treatment modality for localized and "oligometastatic" disease**
  - **Symptom management** (flushing, diarrhea, heart disease) **has high importance**
  - **New treatment options will be developed (keep abreast)**

Back-up Slides

Dose-Intensity with Cytokine Support

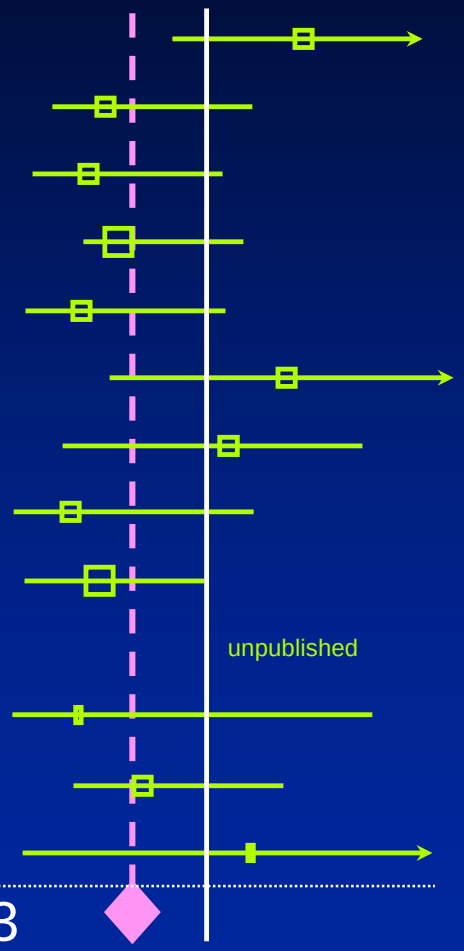
Investigators	Regimen	No. Pts.	RDI	Median Survival	
Crawford et al,1991	CAE +/- GCSF	101 110	NR	11.4 12.2	
Hamm et al, 1991	CAE +/- GCSF (10 mcg/20mcg)	NR	89% (10) 78% (0)	NS	
Fukuoka et al,1992	CODE +/- GCSF	27 26	85% 76%	14.8 8.8	p<.05
Trillet-Lenoir et al, 1993	CDE +/- GCSF	64 66	96% 88%	13.9 12.8	
Miles et al, 1994	PE/IA +/- GCSF	23 17	84% 82%	NR	
Woll et al, 1995	VICE +/- GCSF	34 31	1.34 1.13	17.2 16.2	

Small Cell Lung Cancer Treatment: Limited Disease

- **Combination chemotherapy**
  - EP (etoposide + cisplatin)
  - moderately intensive doses
  - no observed benefit of treatment >4-6 cycles
- **Radiotherapy**
  - increases survival by about 15-20%
  - most effective when given early and concurrently with chemotherapy
  - may increase morbidity/mortality of treatment
  - altered *versus* standard fractionation?
  - role of PCI?

Meta-Analysis of Thoracic Radiotherapy in SCLC

TRIAL	CT	RT	Timing	Start Day	No.Pts.
Copenhagen	CCMV	40/10,splt	Con	43	145
Sydney	CAV	40/20	Seq	63	94
NCI	CMC/VAP	40/15	Con	1-3	97
SECSG I	CAV	40/14,splt	Alt	29	295
London	VA/CM	40/20	Seq	85	138
SWOG	VME/CAV	48/22,splt	Seq	85	103
SAKK	CAE/PAE	45/25,splt	Seq	127	70
Uppsala	CAVM/CCMV	40/20	Seq	77	57
CALGB	CAE/CAV	50/24	Con	1 or 64	426
ECOG	CCM	50/25	Seq	43	264
Okayama	CVMP/AE	40/20	Seq	30	56
SECSG	CAV	45/15,splt	Con	1	322
GETCB	CAEC	32/8	Seq	224	36
Total					2103

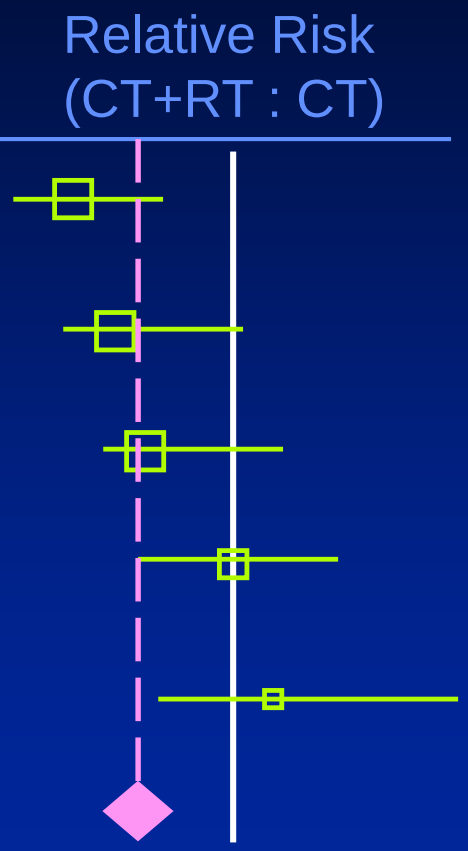


Pignon JP et al, *NEJM* 327:1618, 1992

META-ANALYSIS OF TRT IN SCLC

Relationship to Patient Age

Age	No. Pts. CT + RT	RT
< 55	309	252
55 - 59	239	233
60 - 64	257	233
65 - 69	191	181
> 70	113	86
Total	1109	985



Pilot Studies Using Cisplatin/Etoposide + TRT in SCLC

Group	No. Pts.	Sequence	No. CT *Pre*-TRT	Frctntn	% Survival 2 Yr	% Survival 5 Yr	5 Yr Local Failure(%)
SWOG	123	C	0	Daily	42	25	36
MSKCC-1	36	C	4	Daily	50	28	27
Penn	28	C	0	BID	54	36	3
ECOG-I	41	C	0	BID	36	-	-
ECOG-II	41	A	0	BID	40	-	-
NCI/Navy	36	C	0	BID	65	-	-
Mayo	27	C	3	Split/BID	39	-	20
MSKCC-2	29	S	4	BID	19	-	-

Cisplatin + Etoposide (PE) + Concurrent Thoracic Radiotherapy (TRT) [INT-0096]

(Daily *versus* BID)

Treatment Arm	No. Pts.	SURVIVAL		
		Median	2-yr	5-yr
PE x 4 + TRT 45 Gy (daily)	206	18.6 mos	40.9%	16%
		p = 0.043		
PE x 4 + TRT 45 Gy (BID)	211	22.0 mos	46.1%	26%

Cisplatin + Etoposide (PE) + Concurrent Thoracic Radiotherapy (TRT) [INT-0096]
(Daily *versus* BID)

Treatment Arm	FAILURE RATES			Brain Mets	PCI	
	Local	Local + DM	DM		+	−
PE x 4 + TRT 45 Gy (daily)	52%	23%	55%	14%		
	p=0.058	p=0.006	p=NS		15%	30%
PE x 4 + TRT 45 Gy (BID)	36%	6%	40%	31%		

META-ANALYSIS OF PCI IN SCLC

(Arriagada R et al, *Proc ASCO,* 1998)

- **7 Randomized trials**
  - 987 pts in CR (1977 to 1995)
  - PCI doses = 24 - 40 Gy in 8 - 20 fractions
  - Median follow-up = 5.9 yrs

- **Results**
  - Hazard ratio for death(PCI:Control) = 0.84
    - (16% reduction in mortality)
  - Overall survival @ 3 yrs = 20.7% *vs* 15.3%
  - Benefit (decrease in brain mets) was dose-dependent

Small Cell Lung Cancer Treatment:
Extensive Disease

- **Combination chemotherapy (4-6 cycles)**
  - EP (etoposide + cisplatin) *or* EC (carboplatin)
  - CAV (cyclophosphamide + vincristine + doxorubicin)
- **Radiotherapy**
  - no survival benefit
  - palliative only

Carboplatin + Etoposide *versus* Cisplatin + Etoposide in Previously Untreated SCLC

Kosmidis et al. (Hellenic Cooperative Oncol Group) *Semin Oncol 21:23, 1994*

Treatment Arm	No. of Pts. LD *	ED
Carboplatin 300 mg/m^2 IV x d 1 Etoposide 100 mg/m^2 IV x d 1-3	41	31
Cisplatin 50 mg/m^2 IV x d 1-2 Etoposide 100 mg/m^2 IV x d 1-3	41	30

* LD pts. received 45 Gy thoracic radiation concurrent with 4th cycle of chemotherapy.
LD pts. achieving CR received 25 Gy PCI

Carboplatin + Etoposide *versus* Cisplatin + Etoposide in Previously Untreated SCLC

Efficacy

	No. Pts.	% Overall Response	% CR	Median TTP	Median Survival	2 Yr Survival
Carboplatin Etoposide	**72** (41 LD) (31 ED)	**76%** (86%) (64%)	**29%** (37%) (16%)	**8.6 m**	**11.8 m**	**12.5%**
Cisplatin Etoposide	**71** (41 LD) (30 ED)	**63%** (73%) (50%)	**30%** (44%) (10%)	**8.4 m**	**12.5 m**	**14%**

Carboplatin + Etoposide *versus* Cisplatin + Etoposide in Previously Untreated SCLC

Toxicity

	No. Pts.	Leukopenia Gr 3	Leukopenia Gr 4	Thrombo Gr 4	N / V Gr 2	N / V Gr 3	Neuro Gr 1	Neuro Gr 2
Carboplatin Etoposide	**72**	**10.3%**	**6.8%**	**6%**	**25%**	**0%**	**18%**	**0%**
		p = .09			p = .001		p = .002	
Cisplatin Etoposide	**71**	**37.5%**	**12.5%**	**4%**	**71%**	**4%**	**41%**	**12%**