Disclosures

- Financial Relationships with Relevant Commercial Interests
  - Post Marketing Royalties for *EGFR* mutation testing from DFCI
  - Paid Consultant to Novartis, Checkpoint Therapeutics, Daichi Sankyo, GSK, Hengrui Therapeutics, Boston Pharmaceuticals, Genentech
  - 1-Day Advisory Boards: Chugai, Foundation Medicine, Lilly, G1 Therapeutics, Jazz Pharmaceuticals, Janssen Scientific Affairs
  - Unpaid Member of Steering Committee for Pfizer
  - Research Support from Novartis, Cannon Medical Imaging
- Resolution
  - Reviewed and found to be unbiased

GW 2

Small Cell Lung Cancer

- **Pathology and molecular pathogenesis**
- Presentation
- Staging
- Treatment
- Prophylactic cranial irradiation
- Relapsed small cell lung cancer

GW 3

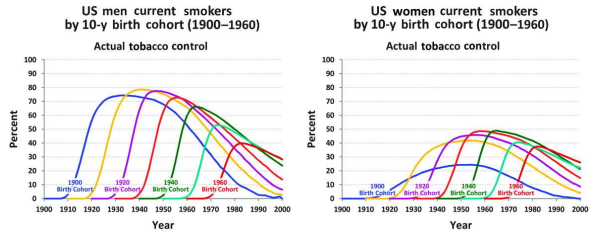
Small Cell Lung Cancer: 2015

- The Recalcitrant Cancer Research Act of 2012 (H.R. 733) requires the National Cancer Institute (NCI) to "develop scientific frameworks" that will assist in making "progress against recalcitrant or deadly cancers."
- Small cell lung cancer (SCLC) is a recalcitrant cancer as defined by its five-year relative survival rate of less than 7 percent and the loss of approximately 30,000 lives per year. While it is true that the outcomes for the other common forms of lung cancer (squamous cell and adenocarcinoma) need to be greatly improved, each of the three major types of cancer that originate in the lung present very different problems, requiring different solutions.

http://deainfo.nci.nih.gov/advisory/ctac/workgroup/SCLC/SCLCCongressionalResponse

4

Epidemiology



Moolgavkar, et al. *JNCI.* 2012

5

Epidemiology of Smoking (U.S.)

- **Median Prevalence (2019):** 14% (15% for men, 13% for women)
- **Prevalence Range (2018):** 9% (Utah) to 25% (West Virginia)
- **Smoking by Age Group**
  - 8% age 18-24
  - 17% age 25-64
  - 8% older than 65
- **Smoking by Socioeconomic Status**
  - 21% <$35,000/year
  - 7% +$100,000/year

https://www.cdc.gov/tobacco/data_statistics/fact_sheets/adult_data/cig_smoking/index.htm

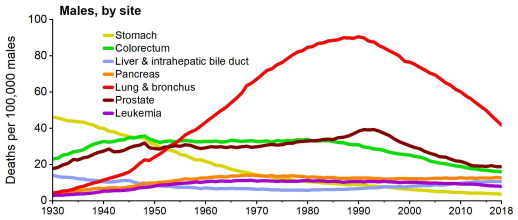
6

Epidemiology of Smoking (U.S.)

- **Smoking by Race/Ethnicity**
  - 20.9% Non-Hispanic American Indians/Alaska Natives
  - 15.5% Non-Hispanic Whites
  - 14.9% Non-Hispanic Blacks
  - 8.8% Hispanics
  - 7.2% Non-Hispanic Asians

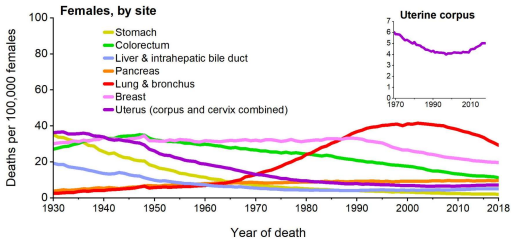
https://www.cdc.gov/tobacco/data_statistics/fact_sheets/adult_data/cig_smoking/index.htm

U.S. Cancer Death Rates 1930-2018: Males



Siegel et al. *CA Cancer J Clin.* 2021 71:7-33

U.S. Cancer Death Rates 1930-2018: Females



Siegel et al. CA Cancer J Clin. 2021 71:7-33

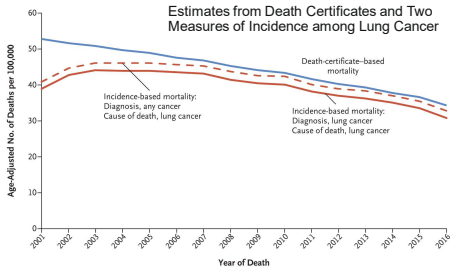
Epidemiology of Lung Cancer (U.S.)

- 235,760 people will be diagnosed at a median age of 70 (119,100 men, 116,660 women)
- 131,880 individuals will die of cancer of the lung and bronchus in 2021 (69,410 men and 62,470 women)
- Overall 5-year relative survival from 9 SEER geographic areas is 22% (2008-2014)
- Percentage with localized disease at time of presentation is 18%, regional is 22%, and distant is 56% (5% are unstaged)

Siegel et al. *CA Cancer J Clin.* 2021 71:7-33; http://seer.cancer.gov/statfacts/html/lungb.html#survival

10

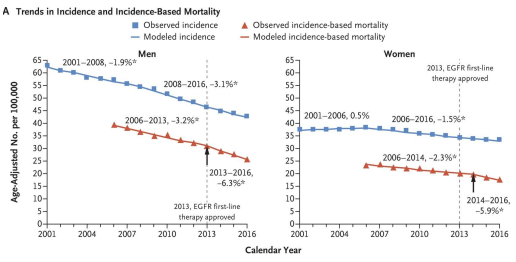
Incidence & Mortality



Howlader et al. *N Engl J Med* 2020; 383:640-649

11

Incidence & Mortality: NSCLC



Howlader et al. *N Engl J Med* 2020; 383:640-649

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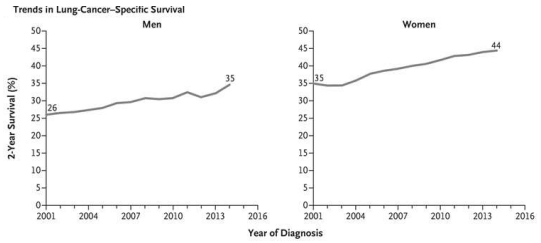
Cancer-Specific Survival: NSCLC



Howlader et al. *N Engl J Med* 2020; 383:640-649

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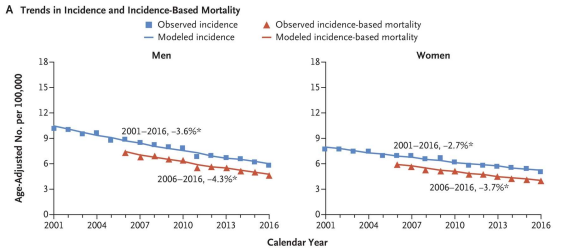
Incidence & Mortality: Small Cell Lung Cancer



Howlader et al. *N Engl J Med* 2020; 383:640-649

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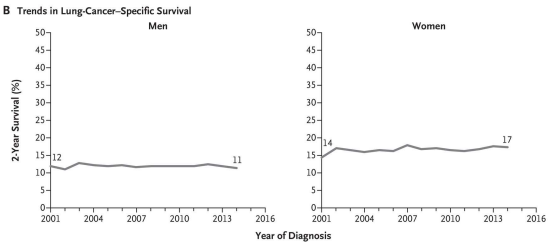
Cancer-Specific Survival: Small Cell Lung Cancer



Howlader et al. *N Engl J Med* 2020; 383:640-649

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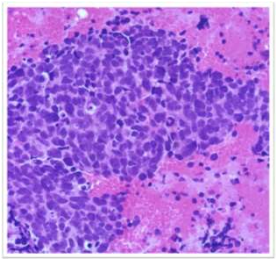
Pathology & Molecular Pathogenesis

- **Non-Small Cell Lung Cancer** **87%**
- **Small Cell Carcinoma** **13%**
  - Small Cell Carcinoma >90%
  - Variant (Combined Small Cell Carcinoma) < 10%

Pathology & Molecular Pathogenesis: Smoking

- Small cell lung cancer is the most closely linked with cigarette smoking.
  - >97% of patients have a history of cigarette smoking
- Squamous cell carcinoma and large cell carcinoma are intermediately linked with cigarette smoking
  - Approximately 80% of patients have a history of cigarette smoking
- Adenocarcinoma is least closely linked to cigarette smoking.
  - 70% of patients have a history of cigarette smoking
- Pulmonary carcinoid tumors are not associated with cigarette smoking.

Small Cell Lung Cancer

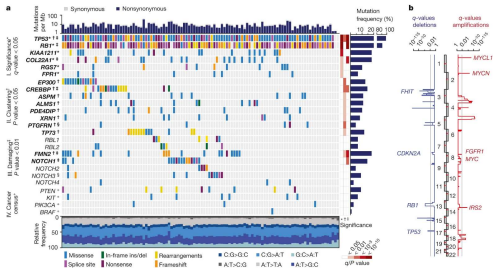


Pathology & Molecular Pathogenesis

- Markers of neuroendocrine differentiation
  - Chromogrannin A
  - Synaptophysin
  - CD56 or Neural Cell Adhesion Molecule (NCAM)

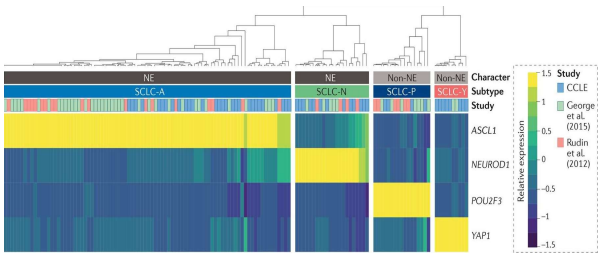
Yatabe et al. *J Thorac Oncol.* 2019 Mar;14(3):377

SCLC: Genomic Characterization



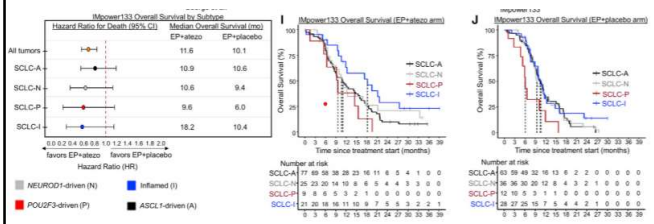
J George et al. *Nature* 524, 47–53, 2015

SCLC: Transcriptional Characterization



Rudin, et al. *Nat Rev Cancer* 2019:289-

SCLC: Transcriptional Characterization



Byers, et al. *Cancer Cell*. 2021 Mar 8;39(3):346

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Small Cell Lung Cancer

- Pathology and molecular pathogenesis
- **Presentation**
- Staging
- Treatment
- Prophylactic cranial irradiation
- Relapsed small cell lung cancer

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Paraneoplastic Syndromes

Syndrome	Protein	Pts with SCLC
Hyponatremia of Malignancy	Arginine Vasopressin and Atrial Natriuretic Peptide	15%
Hypercalcemia of Malignancy	Parathyroid Hormone Related Peptide	<1%
Ectopic ACTH Syndrome	Adrenocorticotrophic Hormone	3%
Acromegaly	Growth Hormone Releasing Hormone	<1%

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Small Cell Lung Cancer

- Pathology and molecular pathogenesis
- Presentation
- **Staging**
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- Relapsed small cell lung cancer

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SCLC Staging

The staging classification for these patients is a simple two-stage Veterans Administration Lung Study Group System, updated in 1989 by International Association for the Study of Lung Cancer.

- Limited stage: Disease confined to 1 hemithorax with regional lymph nodes including either ipsilateral or bilateral hilar, mediastinal, and supraclavicular lymph node metastases and without ipsilateral pleural effusion that fit within a tolerable chest radiation field
- IASLC now recommends staging them using TNM; stage I-III and IV is roughly equivalent to limited or extensive stage disease.1
- Extensive stage: Disease beyond these boundaries

(ClinicalTrials.gov NCT #03811002)-NRG-Chemotherapy plus Chest RT with or without Atezolizumab

Stage Definition-Pathologically (histologically or cytologically) proven diagnosis of limited stage small cell lung cancer (Stage Tx, T1-T4, N0-3, M0)

Vallières, et al. *Journal of Thoracic Oncology.* 2009;4:1049-1059

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Small Cell Lung Cancer

- Pathology and molecular pathogenesis
- Presentation
- Staging
- **Treatment**
- Prophylactic cranial irradiation
- Relapsed small cell lung cancer

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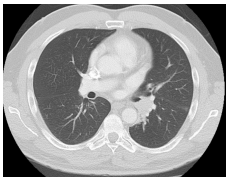
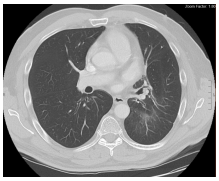
Limited Stage SCLC Treatment

Pre-treatment
April 2010



Post-treatment
July 2020

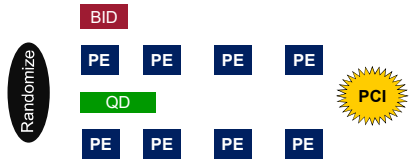


GW 28

Limited Stage SCLC Treatment

BID-QD Radiotherapy: Schema

Platinum - 60; Etoposide - 120 / Cycle Q 21 days PCI: 25 Gy

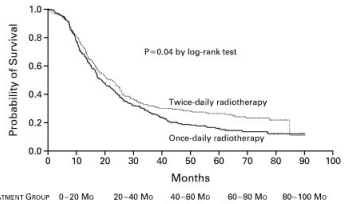


Turrisi AT 3rd, et al. *NEJM*. 1999;340(4):265-271.

GW 29

Limited Stage SCLC Treatment

BID-QD Radiotherapy: Survival



Treatment Group	0–20 Mo	20–40 Mo	40–60 Mo	60–80 Mo	80–100 Mo
	no. of deaths/no. at risk				
Once daily	108/206	48/96	15/47	4/21	0/5
Twice daily	100/211	47/109	7/62	5/42	1/14

Turrisi AT 3rd, et al. *NEJM*. 1999;340(4):265-271.

GW 30

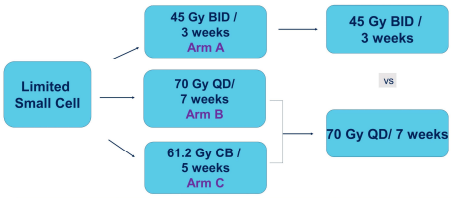
Limited Stage SCLC Treatment

Phase 3 High-Dose Radiotherapy

2021 ASCO ANNUAL MEETING

#8505: Phase 3 comparison of high-dose once-daily thoracic radiotherapy (TRT) with standard twice-daily TRT in limited stage small cell lung cancer: CALGB 30610 (Alliance)/RTOG 0538.

Initial Schema



- **Chemotherapy** : Cisplatin 80 mg/m2 day 1 and etoposide 100mg/m2 day 1-3 q 21 days x 4 cycles
- **TRT to begin with the first cycle of chemotherapy**

Bogart, et al. 2021 ASCO Annual Meeting #8505

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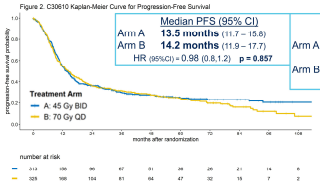
Limited Stage SCLC Treatment

Phase 3 High-Dose TRT: Progression-free Survival

Figure 2. C30610 Kaplan-Meier Curve for Progression-Free Survival



	Median PFS (95% CI)	2-yr PFS	5-yr PFS
Arm A	**13.5 months** (11.7 – 15.6)	Arm A **36%** (31, 42)	**25%** (20, 31)
Arm B	**14.2 months** (11.9 – 17.7)	Arm B **36%** (31, 0.42)	**24%** (20, 30)

HR (95%CI) = 0.98 (0.8,1.2) **p = 0.857**

Arm A = 45 Gy BID
Arm B = 70 Gy QD

2021 ASCO ANNUAL MEETING

Bogart, et al. 2021 ASCO Annual Meeting #8505

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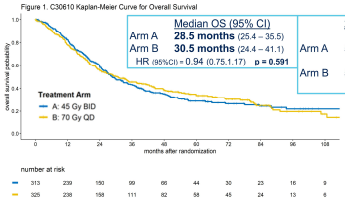
Limited Stage SCLC Treatment

Phase 3 High-Dose TRT: Overall Survival

Median follow-up = 4 years

Figure 1. C30610 Kaplan-Meier Curve for Overall Survival



	Median OS (95% CI)	2-yr OS	5-yr OS
Arm A	**28.5 months** (25.4 – 35.5)	Arm A **58%** (53, 64)	**29%** (23, 35)
Arm B	**30.5 months** (24.4 – 41.1)	Arm B **56%** (51, 62)	**34%** (23, 35)

HR (95%CI) = 0.94 (0.75,1.17) **p = 0.591**

Arm A = 45 Gy BID
Arm B = 70 Gy QD

2021 ASCO ANNUAL MEETING

Bogart, et al. 2021 ASCO Annual Meeting #8505

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Limited Stage SCLC Treatment

Phase 3 High-Dose TRT: Adverse Events

Overall Maximum:	Arm	N(%)
Grade 3	A	93 (31.5%)
	B	78 (25.9%)
Grade 4	A	149 (50.5%)
	B	161 (53.5%)
Grade 5	A	4 (1.4%)
	B	11 (3.7%)
Hematologic Adverse Events (no Grade 5 AEs)		
Grade 3	A	66 (22.4%)
	B	70 (23.3%)
Grade 4	A	140 (47.5%)
	B	157 (52.2%)

Non-hematologic Adverse Events		
	Arm	N(%)
Grade 3	A	130 (44.1%)
	B	128 (42.5%)
Grade 4	A	36 (12.2%)
	B	49 (16.3%)
Grade 5	A	4 (1.4%)
	B	11 (3.7%)

Arm A = 45 Gy BID
Arm B = 70 Gy QD

2021 ASCO ANNUAL MEETING

Bogart, et al. 2021 ASCO Annual Meeting #8505

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Limited Stage SCLC Treatment

Summary

- Patients with limited stage SCLC should be treated with concurrent chest radiotherapy with etoposide plus cisplatin. These patients lived longer than patients treated with chemotherapy alone.
- Chest radiotherapy should start with cycle 1 or 2.
- Chest radiotherapy can be given twice daily over 3 weeks to 4500 cGy or at higher dose (7000 cGY) given once daily for 35 fractions which gives similar results.

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Limited Stage SCLC Treatment

Outcomes

- Demographic information for patients with L-SCLC diagnosed between 2004 and 2014 was obtained from the National Cancer Database.
- The follow-up end point is death or last follow-up (date of last contact).
- Patients were divided into 5 mutually exclusive cohorts by race.
- Data analysis was performed in October 2019.

Zhou, et al. *JAMA* Netw Open. 2021 Jan 4;4(1):e2032276

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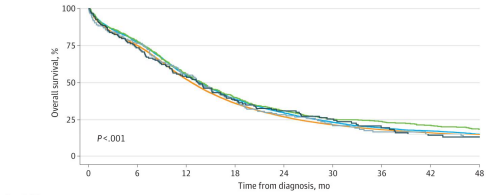
Limited Stage SCLC Treatment

Survival by Race/Ethnicity



No. at risk

White	47379	34916	23889	16077	11437	8596	6788	5556	4580
African American	4191	3199	2219	1533	1102	796	617	510	408
Asian	603	452	310	214	158	118	105	82	63
Native American	147	109	77	51	37	25	19	15	13
Hispanic	152	106	74	50	35	28	17	12	10

Zhou, et al. *JAMA Netw Open*. 2021 Jan 4;4(1):e2032276

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Extensive Stage SCLC: Metastatic Sites

- 35% Bone
- 25% Liver
- 20% Bone marrow
- 20% Brain
- 5% Extrathoracic lymph nodes
- 5% Subcutaneous masses

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Extensive Stage SCLC Treatment

Etoposide-Carboplatin with/without Atezolizumab

IMpower133: Global Phase randomized, placebo-controlled trial evaluated atezolizumab + carboplatin + etoposide in 1L ES-SCLC

Patients with (N = 403):
- Measurable ES-SCLC (RECIST v1.1)
- ECOG PS 0 or 1
- No prior systemic treatment for ES-SCLC
- Patients with treated asymptomatic brain metastases were eligible

Stratification:
- Sex (male vs. female)
- ECOG PS (0 vs. 1)
- Brain metastases (yes vs. no)[a]

1:1

Induction (4 x 21-day cycles)

Atezolizumab (1200 mg IV, Day 1) + carboplatin + etoposide

Placebo + carboplatin + etoposide

Carboplatin: AUC 5 mg/mL/min IV, Day 1
Etoposide: 100 mg/m² IV, Days 1–3

Maintenance

Atezolizumab

Placebo

Treat until PD or loss of clinical benefit

PCI per local standard of care

Survival follow-up

Co-primary end points:
- Overall survival
- Investigator-assessed PFS

Key secondary end points:
- Objective response rate
- Duration of response
- Safety

Liu, et al. *J Clin Oncol*. 2021 Feb 20;39(6):619

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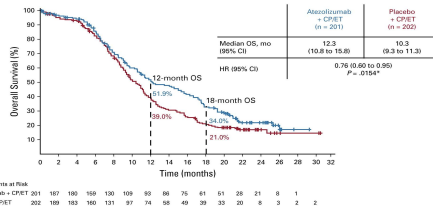
Extensive Stage SCLC Treatment

Etoposide-Carboplatin with/without Atezolizumab



FDA APPROVED
March 2019
1st Line Treatment

Liu, et al. *J Clin Oncol.* 2021 Feb 20;39(6):619

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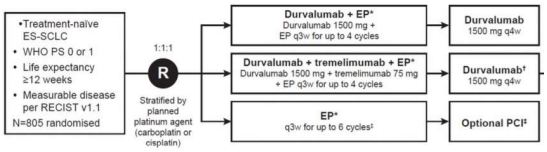
Extensive Stage SCLC Treatment

Etoposide-Carboplatin with/without Durvalumab



Paz-Ares, et al. *Lancet.* 2019; 394(10212):1929

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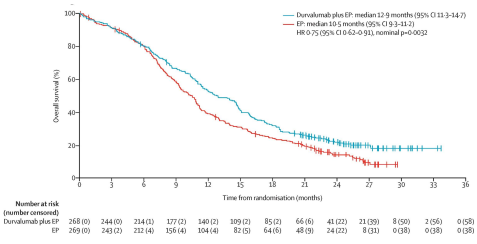
Extensive Stage SCLC Treatment

Etoposide-Carboplatin with/without Durvalumab



FDA APPROVED
March 2020
1st Line Treatment

Goldman, et al. *Lancet Oncol.* 2021 Jan;22(1):51

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Extensive Stage SCLC Treatment

Thoracic Radiation

- 498 patients with extensive stage SCLC with response to 4 to 6 cycles of chemotherapy
- Thoracic treatment volume considered treatable using acceptable radiation fields; prophylactic cranial RT was used as well
- Patients were followed for time to progression and survival

Slotman BJ, et al. *Lancet* .2015;385:36

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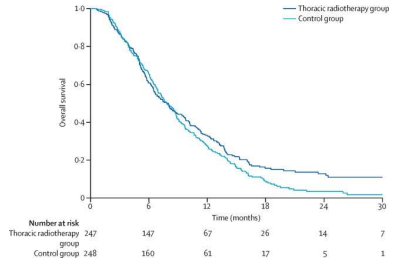
Extensive Stage SCLC Treatment

Thoracic Radiation



Slotman BJ, et al. *Lancet* .2015;385:36

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Extensive Stage SCLC Treatment

- Fit patients with extensive stage SCLC should be treated with etoposide carboplatin with atezolizumab or durvalumab
- Patients with residual chest masses after chemotherapy should be referred to radiation oncologists for consideration of chest RT

Slotman BJ, et al. *Lancet* .2015;385:36

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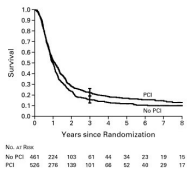
Small Cell Lung Cancer

- Pathology and molecular pathogenesis
- Presentation
- Staging
- Treatment
- **Prophylactic cranial irradiation**
- Relapsed small cell lung cancer

Prophylactic Cranial Irradiation

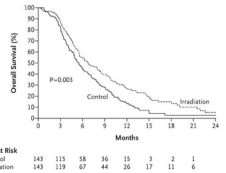
Survival: Limited & Extensive Stage SCLC

Limited & Extensive Stage
N = 987



Auperin, et al. *NEJM*. 1999;341-476

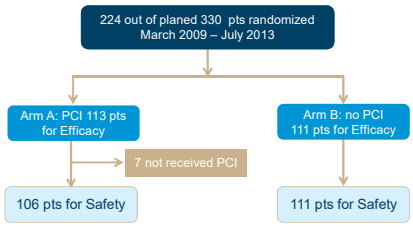
Extensive Stage
N = 286



Slotman B, et al. *NEJM*. 2007;357:664

Prophylactic Cranial Irradiation

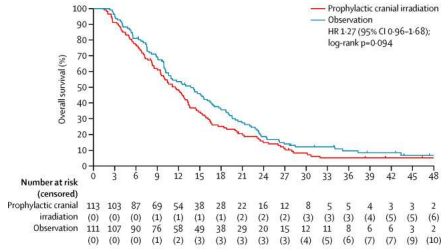
Multicenter, Randomized, Open-label, Phase 3 Trial



Takahashi T, et al. *Lancet Oncol* .18:663, 2017

Prophylactic Cranial Irradiation

Survival by PCI Arm



Takahashi T, et al. *Lancet Oncol.*18:663, 2017

Prophylactic Cranial Irradiation

In Summary

- Patients with SCLC have a 60-80% actuarial risk of developing brain metastases within 2 years after the start of treatment
- PCI has been shown to prolong survival for patients with limited stage SCLC with a response to chemotherapy
- PCI (2500 cGy) administered at the time of complete remission can reduce the chance of developing brain metastases by 50-67%
- The data recently published does not support administering PCI to patients with extensive stage disease

Arrigada R, et al. *J Natl Cancer Inst.* 1995;87(3):183-190. Auperin A, et al. *NEJM.* 1999;341(7):476-484. Slotman B, et al. *NEJM.* 2007;357(7):664-672. Le Pechoux C, et al. *Lancet Oncol.* 2009;10:467 Takahasi T, et al. *Lancet Oncol.* 2017;18:663

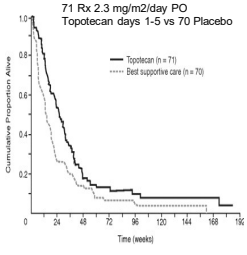
Small Cell Lung Cancer

- Pathology and molecular pathogenesis
- Presentation
- Staging
- Treatment
- Prophylactic cranial irradiation
- **Relapsed small cell lung cancer**

Relapsed SCLC

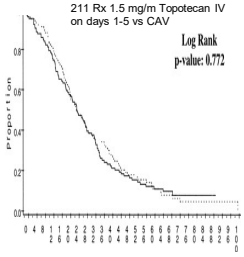
Topotecan

71 Rx 2.3 mg/m2/day PO
Topotecan days 1-5 vs 70 Placebo



O'Brien ME, et al. *J Clin Oncol.* 2006;24:5441

211 Rx 1.5 mg/m Topotecan IV
on days 1-5 vs CAV



von Pawel et al. *J Clin Oncol.* 1999;17:658

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Relapsed SCLC

Temozolomide

- Previously treated patients with sensitive relapse SCLC (48) or refractory SCLC (16)
- 24 had brain metastases including 13 with target lesions assessable by RECIST
- Treated with 21/28 days of 75 mg/m2 of temozolomide
- Followed for toxicity, response, time to progression, and survival

Pietanza, et al. *Clin Cancer Res.* 2012; 18:1138

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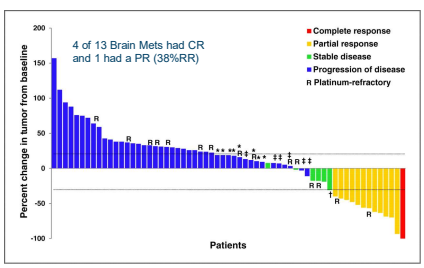
Relapsed SCLC

Temozolomide



Pietanza, et al. *Clin Cancer Res.* 2012; 18:1138

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Relapsed SCLC

Pembrolizumab & Nivolumab for Previously Rx SCLC

- FDA approved in 2019 for SCLC patients treated with at least two regimens
- **Pembrolizumab approval withdrawn in 2021**
  - KEYNOTE-604 (Chemo with or without Pembro HR 0.80 in favor of Pembro)
- **Nivolumab approval withdrawn in 2021**
  - Checkmate 331(Nivolumab versus Topotecan or Amrubicin in Relapse Setting HR 0.86)
  - Checkmate 451 (Nivolumab, Nivolumab/Ipilumumab, placebo in Maintenance Setting HR 0.84 and 0.92 Respectively)

Rudin, et al. *J Clin Oncol.* 2020 Jul 20;38(21):2369
Owonikoko. *J Clin Oncol.* 2021 Apr 20;39(12):1349
Spigel, et al. *Ann Oncol.* 2021 May;32(5):631

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Relapsed SCLC

Lurbinectedin for Previously Rx SCLC

- 105 Patients with Previously SCLC
- One Previous Regimen
- ECOG Performance Status of 0-2
- Treated with 3·2 mg/m2 of lurbinectedin administered as a 1-h intravenous infusion once every 3 weeks

Trigo, et al. *Lancet Oncol.* 2020; 21:645

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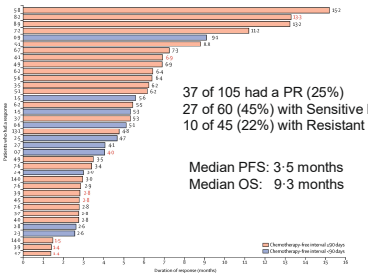
Relapsed SCLC

DOR of Lurbinectedin for Previously Rx SCLC



37 of 105 had a PR (25%)
27 of 60 (45%) with Sensitive Disease
10 of 45 (22%) with Resistant Disease

Median PFS: 3·5 months
Median OS: 9·3 months

FDA APPROVED
Accelerated
Jun 15, 2020
For patients with metastatic SCLC progression on or after platinum-based chemotherapy

Trigo, et al. *Lancet Oncol.* 2020; 21:645

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Thank You