WVU Cancer Institute

Medical Oncology Therapy for Early Stage Lung Cancer

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Disclosure

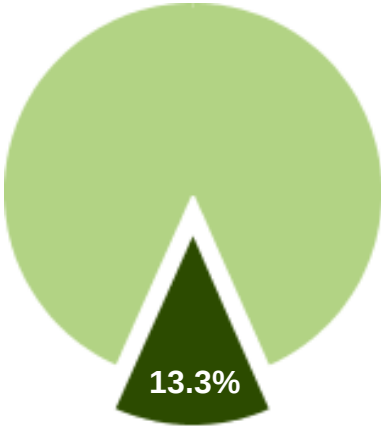
Speakers Bureau – Merck, ARIAD-Takeda

Clinical Research – AbbVie, AstraZeneca, Bristol-Myers Squibb, EpicentRx, Incyte, Loxo, Medimmune, Merck, Pfizer, Spectrum, Tesaro, Xcovery

Advisory Committee - Caris Precision Oncology Alliance (POA)

Lung Cancer – Stats and Harsh Facts

- Estimated New Cases in 2016 – **Incidence**: **224,390**
- **13.3%** of All ***New*** Cancer Cases
- Estimated (Lung Cancer) Deaths in 2016 – Lung Cancer-Specific **Mortality**: **158,080**
- ***68% Death rate in women with lung cancer!! 75% in men with lung cancer!!!!***
- % of All Cancer ***Deaths*** – **26.5%**
- **Prevalence**: In 2013, an estimated **415,707** living with lung cancer in the U.S.

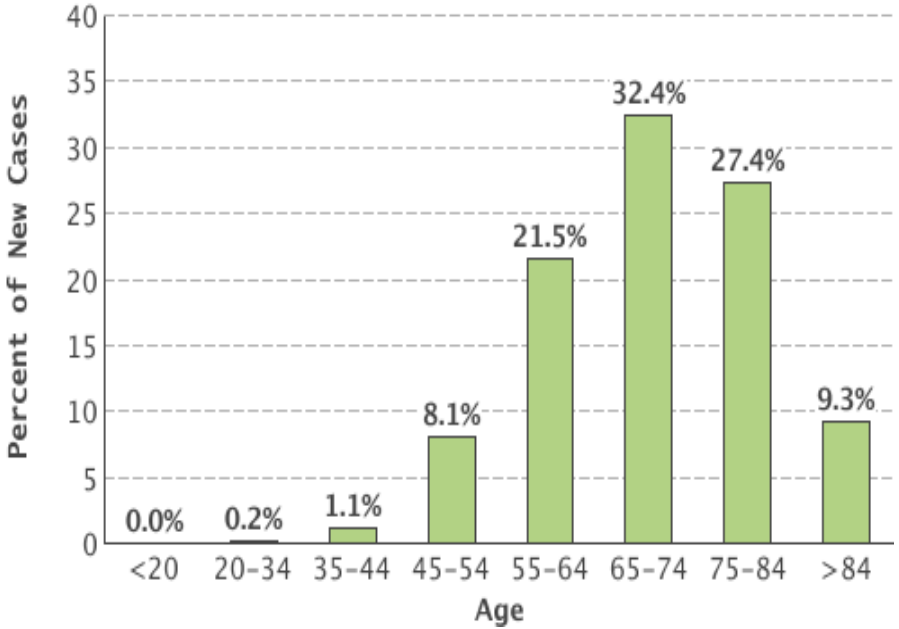


New Lung Cancer Cases in 2016

- Percent **Surviving 5 Years**: **17.7%** (2006-2012)
- **Lifetime Risk of Developing Cancer**:

  ~ **6.6 percent** of men and women will be diagnosed with lung and cancer at some point during their lifetime, based on 2010-2012 data.

New Cases by Age Group: Lung Cancer



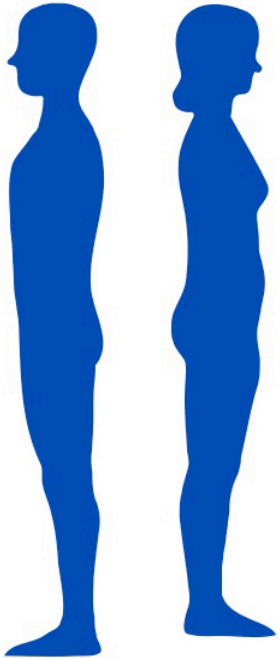
- Lung cancer is most frequently diagnosed among people aged 65-74.
- Median Age At Diagnosis: **70**

SEER 18 2009-2013, All Races, Both Sexes

2010 Estimated US Cancer Deaths*

Men 299,200	
Lung & bronchus	29%
Prostate	11%
Colon & rectum	9%
Pancreas	6%
Liver & intrahepatic bile duct	4%
Leukemia	4%
Esophagus	4%
Non-Hodgkin lymphoma	4%
Urinary bladder	3%
Kidney & renal pelvis	3%
All other sites	23%

Source: American Cancer Society, 2010.



Women 270,290	
26%	Lung & bronchus
15%	Breast
9%	Colon & rectum
7%	Pancreas
5%	Ovary
4%	Non-Hodgkin lymphoma
3%	Leukemia
3%	Uterine corpus
2%	Liver & intrahepatic bile duct
2%	Brain/Other nervous system
24%	All other sites

Source: American Cancer Society, 2010.

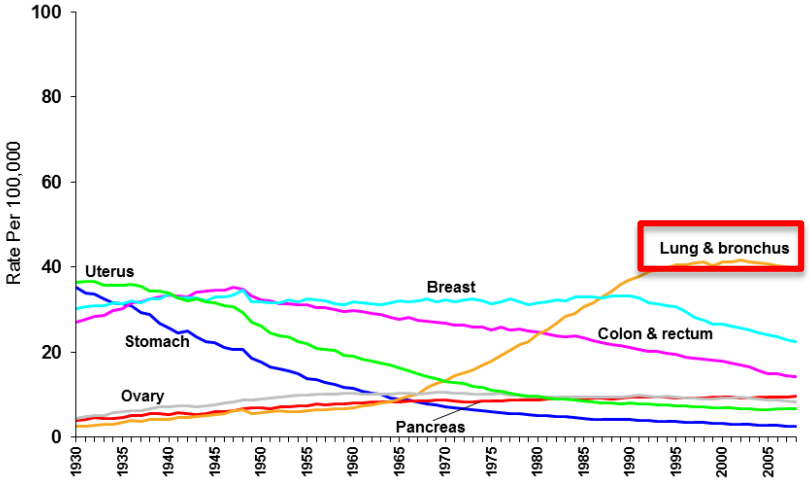
Five-Year Survival Rates in Lung Cancer (2006 – 2012)

Percent Surviving
5 years:
17.7%

Based on data from SEER 18 2006-2012.
Gray figures represent those who have died from lung and bronchus cancer.
Green figures represent those who have survived 5 years or more.

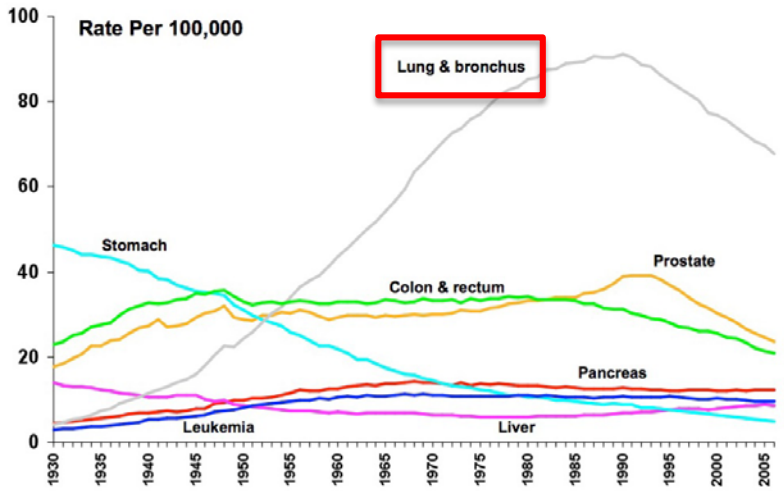
U.S. Cancer Death Rates Historic Trends

Cancer Death Rates* Among Women, US,1930-2008



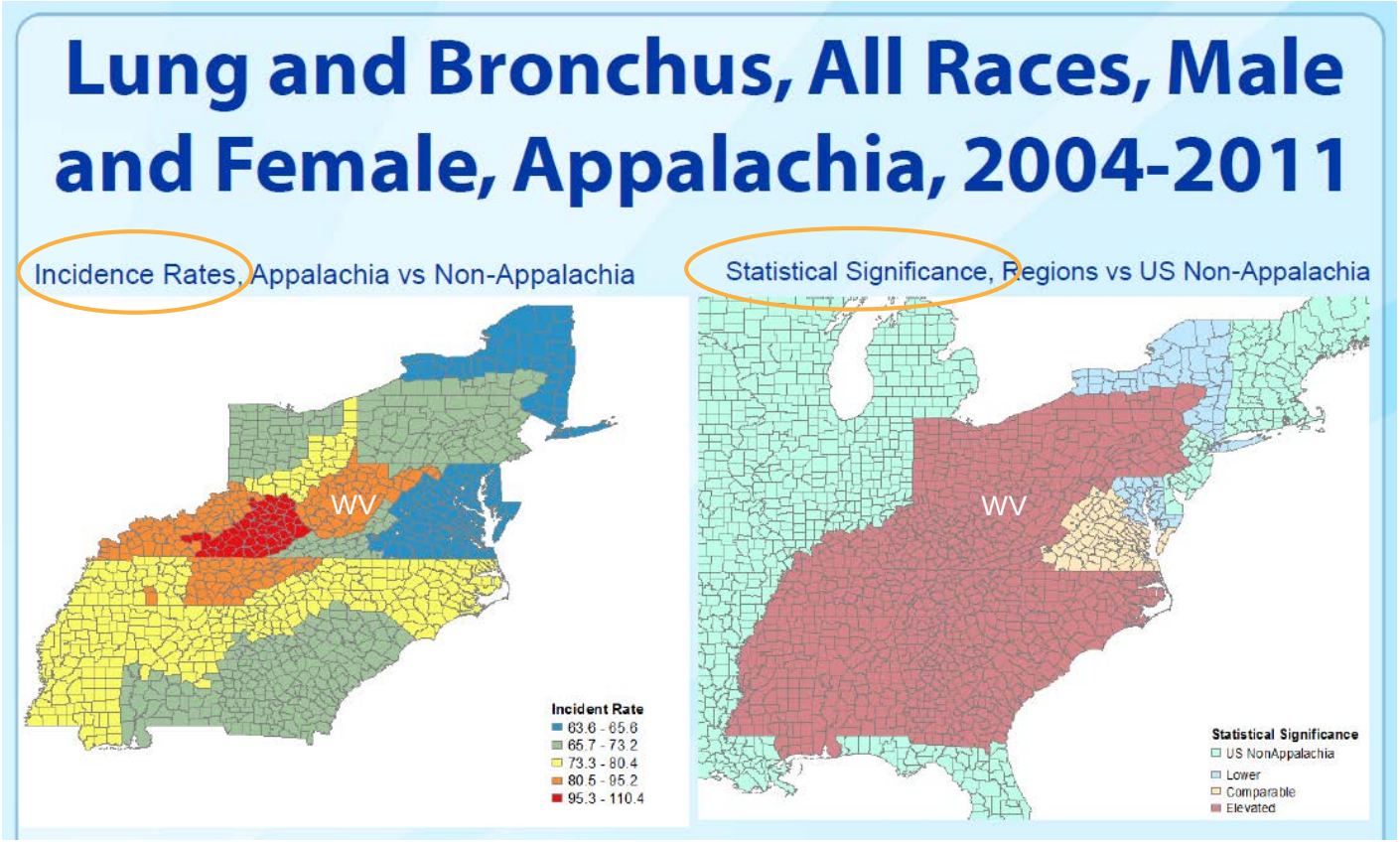
*Age-adjusted to the 2000 US standard population.
Source: US Mortality Data 1960-2008, US Mortality Volumes 1930-1959,
National Center for Health Statistics, Centers for Disease Control and Prevention.

Cancer Death Rates* Among Men, US,1930-2006



*Age-adjusted to the 2000 US standard population.
Source: US Mortality Data 1960-2006, US Mortality Volumes 1930-1959,
National Center for Health Statistics, Centers for Disease Control and Prevention, 2009.

Appalachian Lung Cancer Disparity: West Virginia

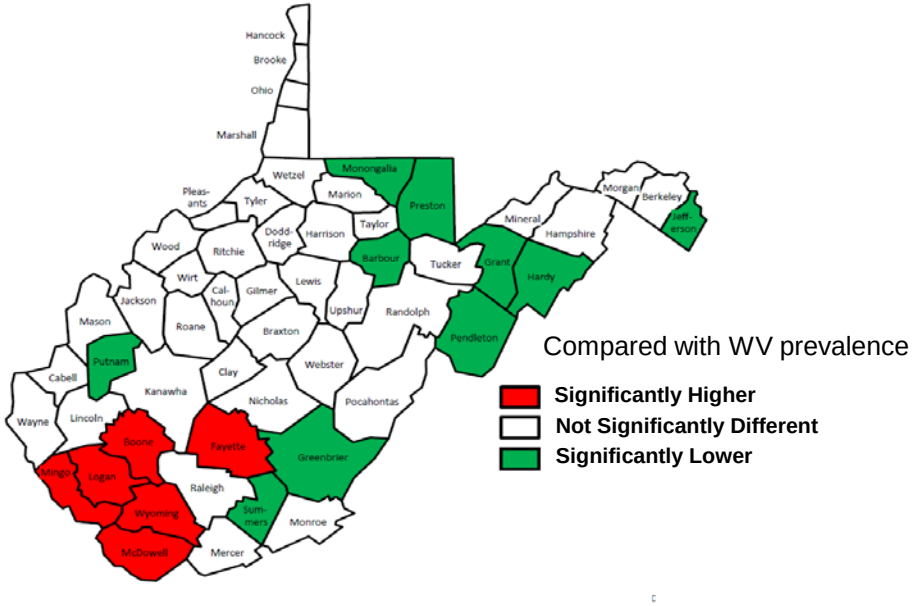


CDC Nov. 2014: National Program of Cancer Registries

Appalachian Lung Cancer Disparity: WV

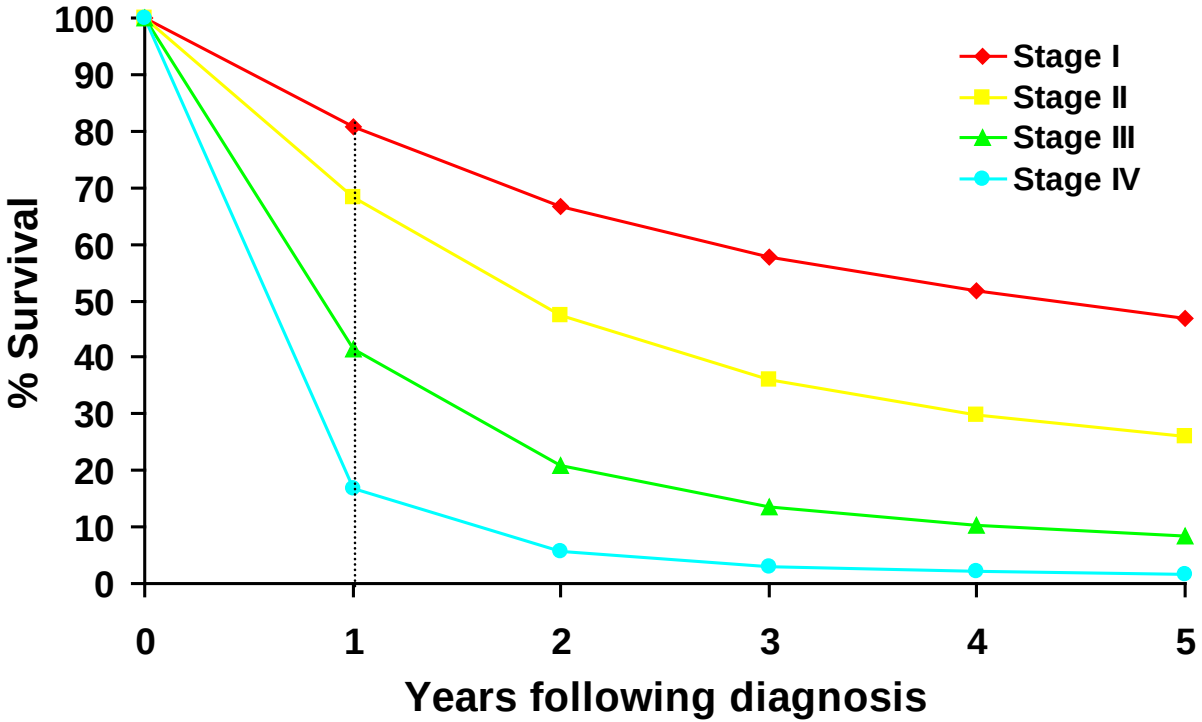
- Lung cancer has the highest cancer-mortality nationally, with **45.0** deaths/100,000 (2012);
- West Virginia has a mortality disparity with

  59.6 deaths/100,000.



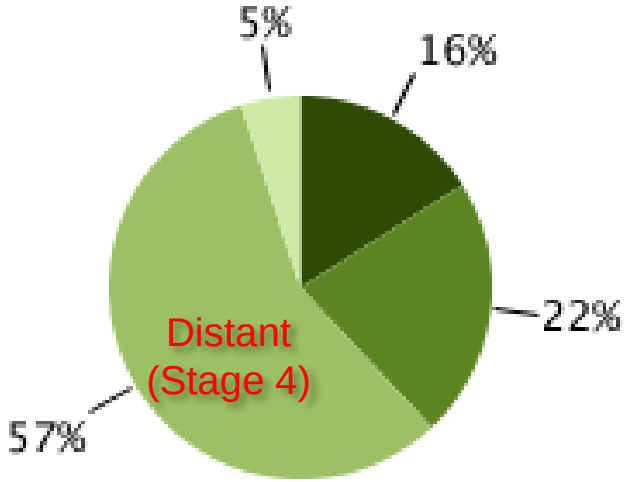
West Virginia Lung Cancer Mortality (2009-2013): 61.8/100,000

NSCLC: U.S. Survival by Stage at Diagnosis



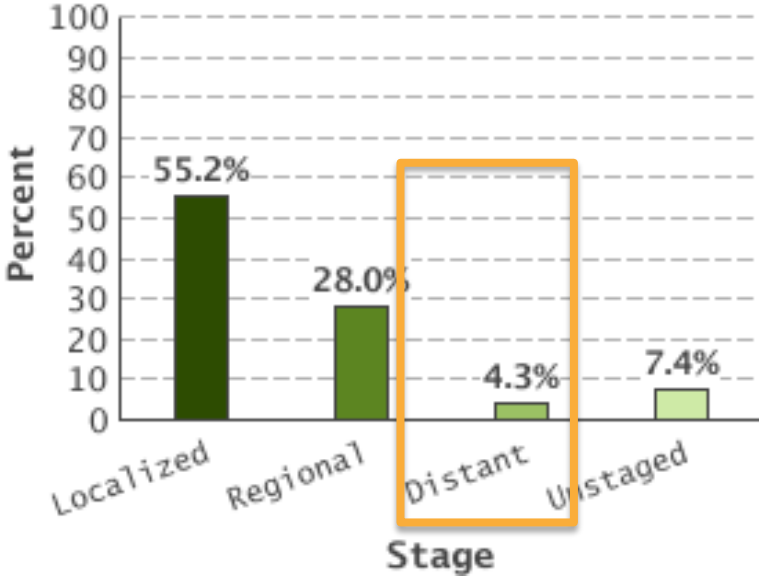
Greene et al, eds.
AJCC Cancer Staging Manual. 6th ed. 2002.

Percent of Cases and 5-Year Survival by Stage at Diagnosis



Percent of **Cases** by Stage

5-Year **Survival** by Stage



SEER 18 2006-2012, All Races, Both Sexes by SEER Summary Stage 2000

NSCLC Treatment by Stage

- **Stage I:** Resection (Lobectomy); SBRT

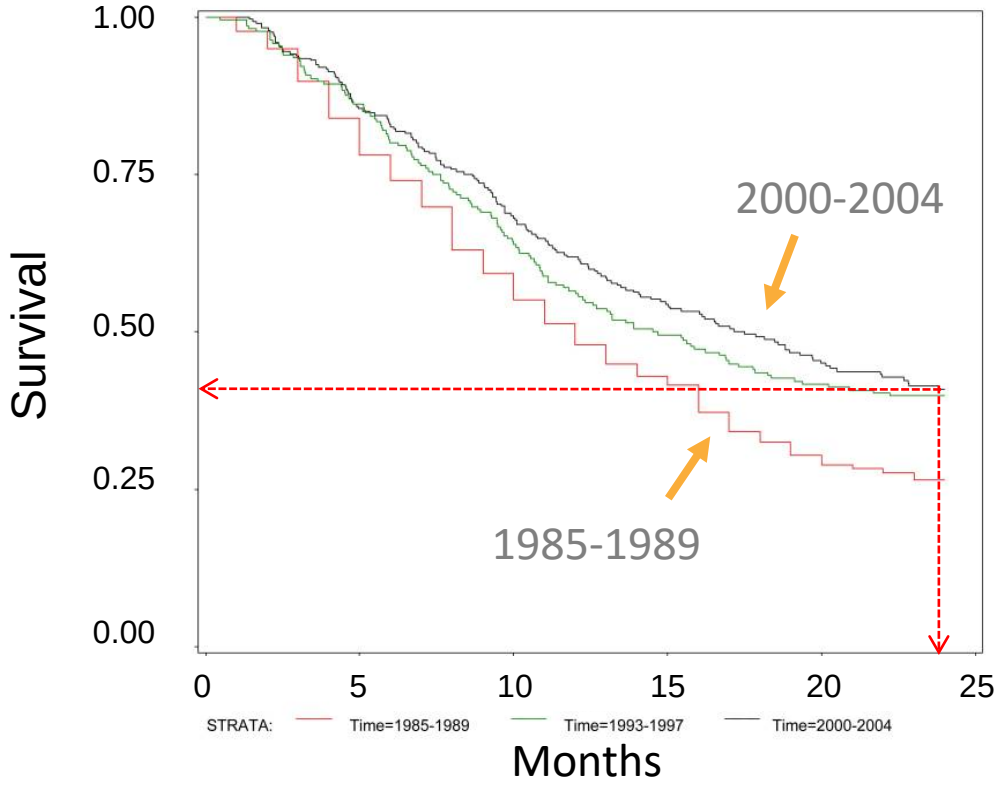
- **Stage II:** Resection (Lobectomy/Segmentectomy/Pneumonectomy); SBRT

- **Stage III:** most heterogeneous group
  (Resectable: **IIIA** vs ?Unresectable: **IIIB**).
  Neoadjuvant Chemo-(Radiation) → Surgery
  Definitive Chemoradiation.

  – Stage II – III: **Adjuvant Chemotherapy** !!! (Survival Benefits)

- **Stage IV:** <5% 5-year survival.
  Chemotherapy, Targeted therapy, Biologics therapy, Immunotherapy.

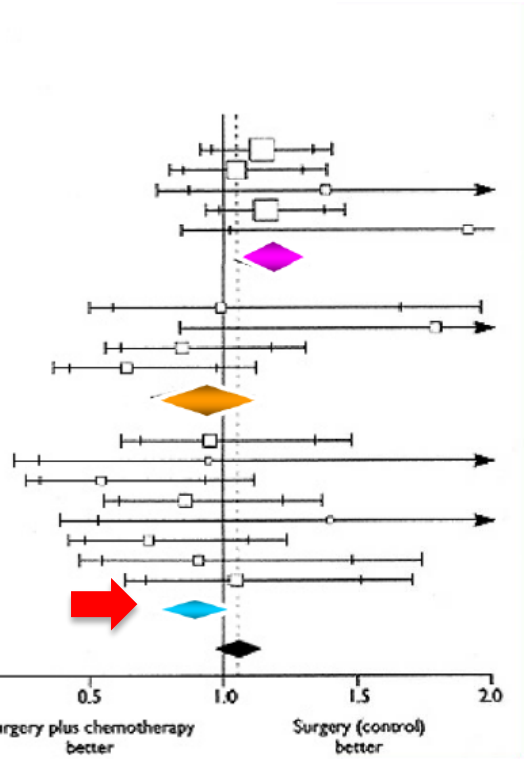
Historical Survival Outcome in Lung Cancer



Cancer Detect Prev. 2008;32(2):101-8. doi: 10.1016/j.cdp.2008.05.009. Epub 2008 Jul 17

Meta-Analysis of Adjuvant Chemotherapy 1995: Early indication suggesting benefits with Cisplatin-based chemotherapy

Trial	No of events/ No of patients entered: Surgery plus chemotherapy	Surgery	Observed − expected deaths	Variance
Long term alkylating agents:				
MRC LUO2	415/428	209/215	18.22	143.32
VASAG	251/291	128/152	4.50	86.00
EORTC 08741	38/71	36/75	5.82	18.06
VASOG 5	292/424	261/417	20.63	137.53
WPL 7351	25/36	15/36	6.36	9.83
Subtotal	1021/1250	649/895	55.53	394.74
Other drugs:				
OLCSG Ia	30/163	28/158	-0.09	14.47
OLCSG Ib	27/41	21/42	6.59	11.36
SGACLC ACTLC 1	70/154	75/152	-6.10	36.12
WJSG 2 (2 and 3)	38/108	49/100	-9.79	21.49
Subtotal	165/466	173/452	9.39	83.44
Cisplatin based:				
LCSG 801	66/140	71/143	-1.81	34.21
OLCSG Ic	5/12	7/16	-0.19	2.93
FLCSG 1	20/54	30/56	-7.79	12.21
SGACLC ACTLC2	64/165	68/167	-4.80	32.88
IPCR Chiba	11/15	7/14	1.33	4.07
WJSG 2 (1 and 3)	44/115	49/100	-7.66	22.94
LCSG 853	29/94	32/94	-1.65	15.12
JLCSSG	59/111	52/98	0.98	27.38
Subtotal	298/706	316/688	-21.58	151.83
Total	1484/2422	1138/2035	24.57	630.01



BMJ 311:899, 1995

Prospective Validation of the Meta-analysis Subset

IALT (International Lung Adjuvant Trial) Study

Allowed:

- Various stages (I, II, III)
- Cisplatin-based regimen
- Various partner drugs (Etoposide or a Vinca)
- Various cycles (3-4)
- Some received sequential chest radiation

Adjuvant Chemotherapy Trials

- **IALT (International Lung Adjuvant Trial):** NEJM Jan 22, 2004; 350:351-60.
  Stage I – III (1867 patients: Chemo N=932 vs Control N=935): Cisplatin-based adjuvant chemotherapy after curative surgery.
  Chemo: Cisplatin + Vindesine / Vinblastine / Vinorelbine / Etoposide. x4
  Adjuvant XRT: planned for 30.6% patients (1.9% in pN0, 33.7% in pN1, and 64.3% in pN2 disease)
  5 year-survival increased by **4.1%**.
- **NCIC – JBR.10 Study:** Cisplatin + Vinorelbine for resected stage IB/II patients
  Overall Survival improved by **15%**.
- **ANITA Trial (Adjuvant Navelbine International Trialist Association):**
  Cisplatin + Vinorelbine (x4) for resected stage IB+II+IIIA patients
  Overall survival benefit **9%** (5-yrs) and **8%** (7-yrs).
- **CALGB 9633:** Stage **IB** – specific phase 3 RCT; uses Carboplatin-backbone chemotherapy (PC)x4
  Initial results, reported in 2004, showed a significant survival advantage (12% at 4-yrs);
  ……. But the 2006 updated results are no longer statistically significant.

- Role of adjuvant chemotherapy for Stage IB remains controversial (negative).
- No convincing evidence from RCT that adjuvant chemotherapy is effective in Stage IA.

Lung Adjuvant Cisplatin Evaluation: Pooled Analysis by the LACS Collaborative Group

Table 1. Trial Description

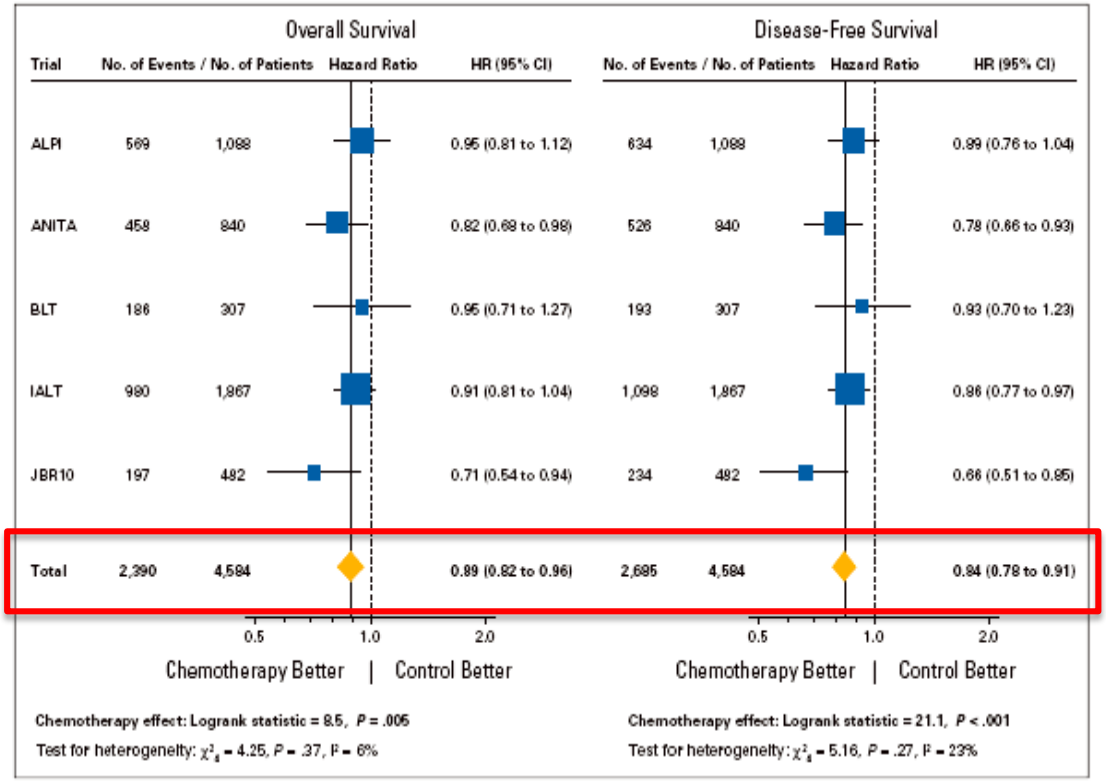
Trial Name	Inclusion Criteria	Chemotherapy (No. of cycles, dose of cisplatin by cycle, daily dose × No. of doses for other drugs)	Radiotherapy	Inclusion Period	No. of Patients Included
JBR10	pT2pN0* or pT1-2pN1	4 cycles, cisplatin (50 × 2) mg/m^2 Vinorelbine 25 mg/m^2 × 16	No radiotherapy	1994-2001	482
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.

N=4,584

JCO 26: 3552-3559, 2008

Lung Adjuvant Cisplatin Evaluation: Pooled Analysis by the LACS Collaborative Group



JCO 26: 3552-3559, 2008

Lung Adjuvant Cisplatin Evaluation: Pooled Analysis by the LACS Collaborative Group

Median F/U time: 5.2 years.

Overall Hazard Ratio of Death: 0.89 (95% CI, 0.82 – 0.96, *P*=0.005).

5-year Absolute Benefit of **5.4%** from chemotherapy.

No heterogeneity of chemotherapy effect among trials.

The Benefit varied with **Stage** (test for trend *P*=0.04): **Hazard Ratio (<1 favors chemo)**

Stage IA:	1.40	95% CI 0.95 – 2.06;
IB:	0.93	0.78 – 1.10;
Stage II:	**0.83**	0.73 – 0.95;
Stage III:	**0.83**	0.72 – 0.94

No interaction between chemotherapy effect and :
Gender, Age, Histology, Type of Surgery,
Planned Radiotherapy, or Planned Total Dose of Cisplatin.

JCO 26: 3552-3559, 2008

Adjuvant chemotherapy, with or without postoperative radiotherapy, in operable non-small-cell lung cancer: two meta-analyses of individual patient data

Lancet 2010; 375: 1267–77

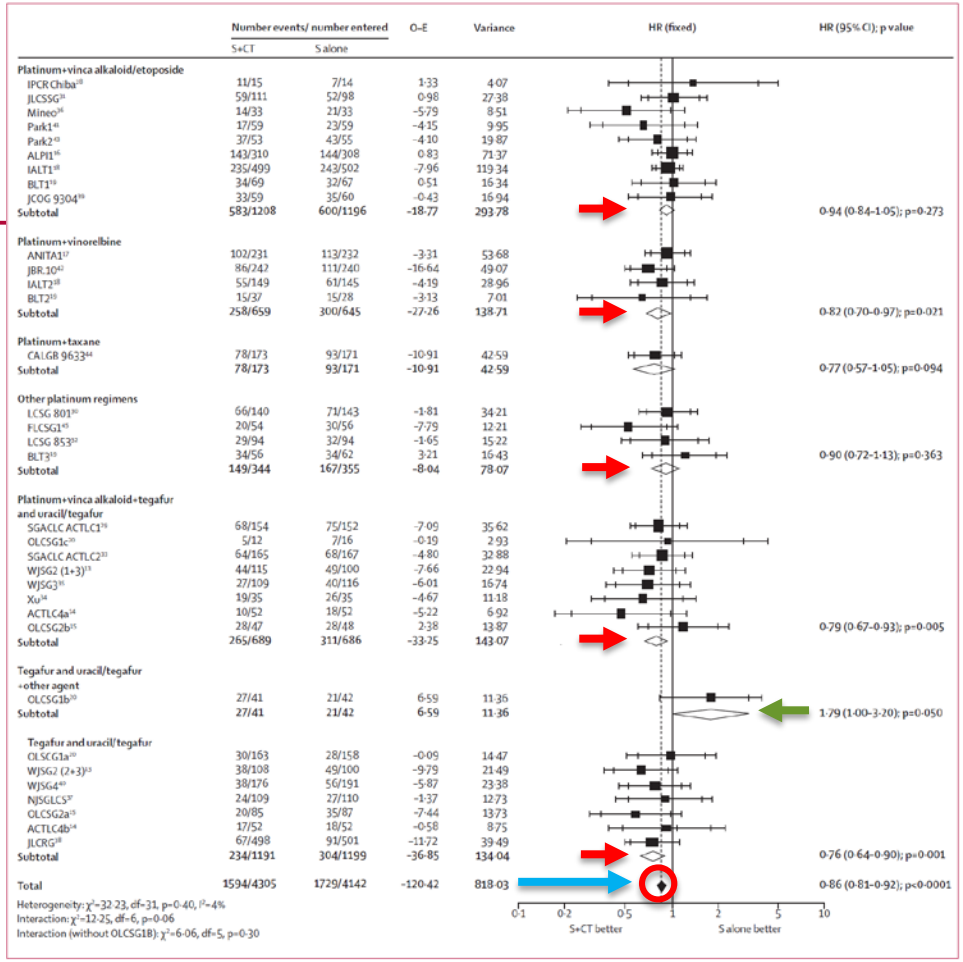


Figure 1: Effect of surgery (S) and chemotherapy (CT) versus surgery on survival, by type of chemotherapy

Adjuvant Chemotherapy in Stage IB Resected Lung Cancer?

Studies	IA	IB	II	III
ALPI	NO	NO	NO	NO
IALT	NO	NO	NO	YES
BLT	NO	NO	NO	NO
JBR.10		NO	YES	
ANITA		NO	YES	YES
CALGB9633		NO		
LACE (meta)	NO	NO	YES	YES

Adjuvant Chemotherapy in Resected Lung Cancer – IB: Does Size matter?

Stage IB survival by tumor size

Tumor Size	Hazard Ratio (HR)
≥ 4 cm	HR=0.78, *p=0.087*
> 7 cm	**HR=0.52**, *p=0.048*

Strauss G. et al., ASCO 2011 (abst 7015)

Adjuvant Chemotherapy in Resected Lung Cancer – How about the Elderly

BMJ 2011;343:d4013 doi: 10.1136/bmj.d4013

RESEARCH

Survival and risk of adverse events in older patients receiving postoperative adjuvant chemotherapy for resected stages II-IIIA lung cancer: observational cohort study

Juan P Wisnivesky *associate professor of medicine*[1 2], Cardinale B Smith *assistant professor of medicine*[3 4], Stuart Packer *assistant professor of medicine*[3], Gary M Strauss *professor of medicine*[5], Linda Lurslurchachai *project manager*[1], Alex Federman *associate professor of medicine*[1], Ethan A Halm *professor of medicine*[6]

Results Overall, 21% (n=684) of patients received platinum based chemotherapy. Analyses adjusted, stratified, or matched by propensity scores showed that chemotherapy was associated with improved survival (hazard ratio range 0.78-0.81). The beneficial effect of chemotherapy was also observed among patients treated with radiation therapy (0.75-0.77) or without radiation therapy (0.74-0.77); however, chemotherapy was not beneficial for patients aged 80 or more (1.32-1.46). Adjuvant chemotherapy was associated with an increased odds of serious adverse events (odds ratio 2.0, 95% confidence interval 1.5 to 2.6).

Conclusions Platinum based adjuvant chemotherapy is associated with reduced mortality and increased risk of serious adverse events in older patients with stages II-IIIA lung cancer. The magnitude of the benefit is similar to that observed in randomised controlled trials carried out among selected patients.

Adjuvant Chemotherapy Regimens

- Nausea, vomiting
- Hair loss (alopecia)
- Infusion reactions
- Kidney insufficiency (Cisplatin/Carboplatin, Pemetrexed)
- Peripheral neuropathy (Taxanes)
- Skin rashes
- Time and Emotional burden (anxiety) – 4 cycles, usually Q3 weeks x4 (but Gemcitabine: weekly)

Challenges for Patients – Adjuvant Chemotherapy: Adverse Effects

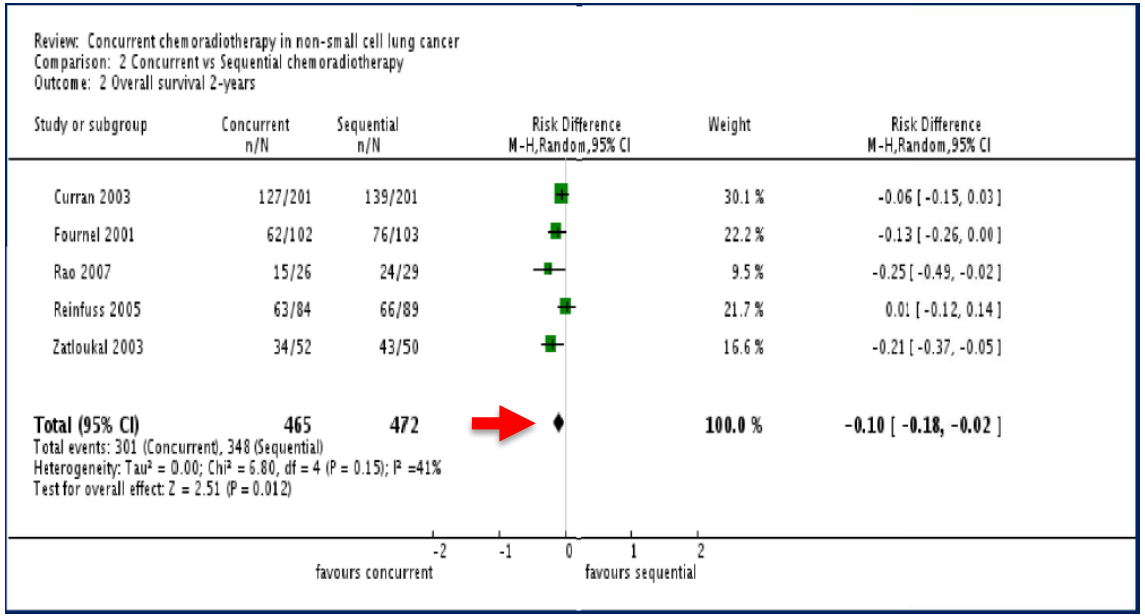
- Nausea, vomiting
- Hair loss (alopecia)
- Infusion reactions
- Kidney insufficiency (Cisplatin/Carboplatin, Pemetrexed)
- Peripheral neuropathy (Taxanes)
- Skin rashes
- Time and Emotional burden (anxiety) – 4 cycles, usually Q3 weeks x4 (but Gemcitabine: weekly)

Challenges for Medical Oncologist – Adjuvant Chemotherapy

- Seeing patients AFTER the curative surgery
- High expectation of Cure
- Navigation of risks and benefits before and during the chemotherapy
- Surveillance follow-up (surgeons and medical oncologists and radiation oncologists)
- Recurrence during or soon after chemotherapy (it does happen : (

Management of Unresectable Stage IIIA/B

- **Chemo-radiation** is the SOC
  - Weigh risks/benefits of Concurrent vs. Sequential

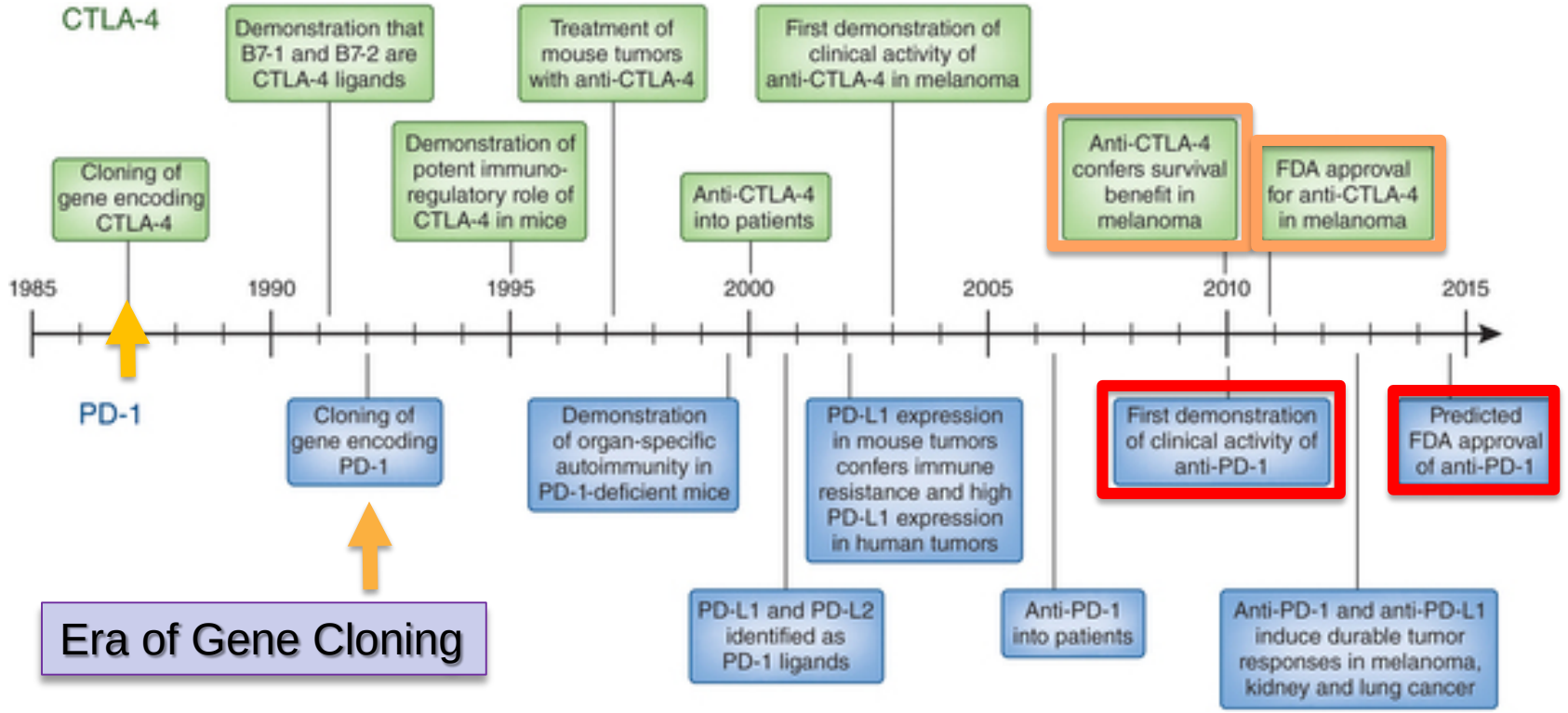


Management of Unresectable Stage IIIA/B

- **Chemo-radiation** is the SOC
  - Weigh risks/benefits of Concurrent vs. Sequential
  - EP-XRT or Carboplatin/Paclitaxel-XRT are reasonable options
  - Cisplatin/Pemetrexed-XRT is reasonable in Adenocarcinoma
  - Radiation (XRT) beyond 60 Gy is unproven
  - No survival benefit in poor PS patients or those with significant weight loss

- ***Consolidation chemotherapy*** in NOT SOC
  - and evidence-based medicine weighs against Routine Use, BUT ….. Still PERMISSIBLE in various guidelines.

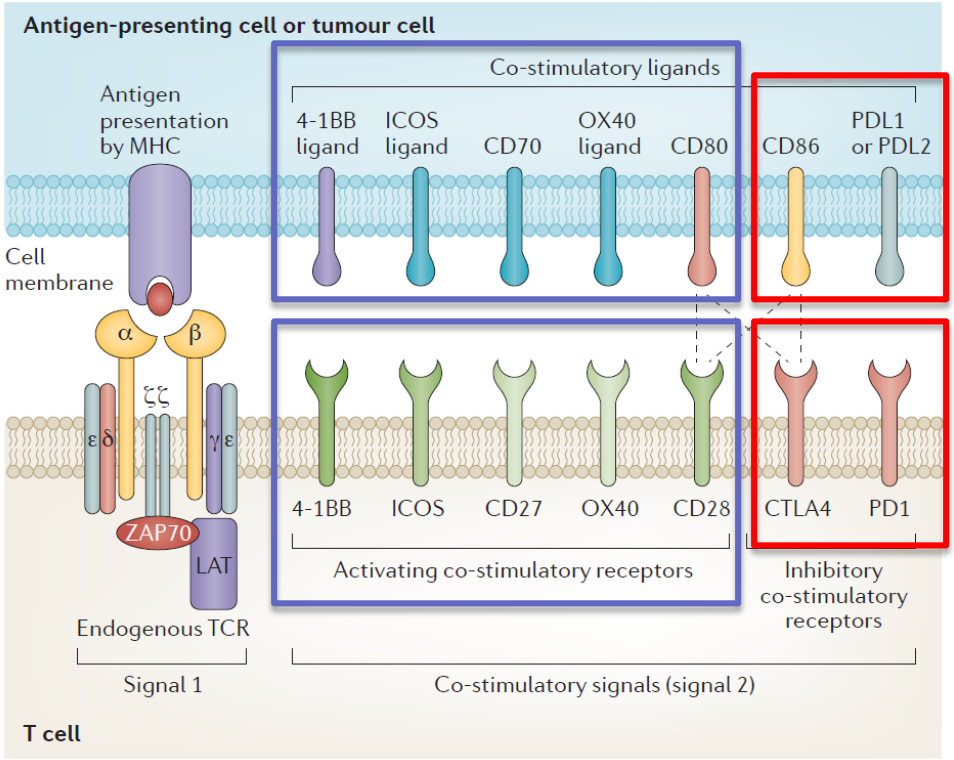
30 Years Progress of Immuno-Oncology



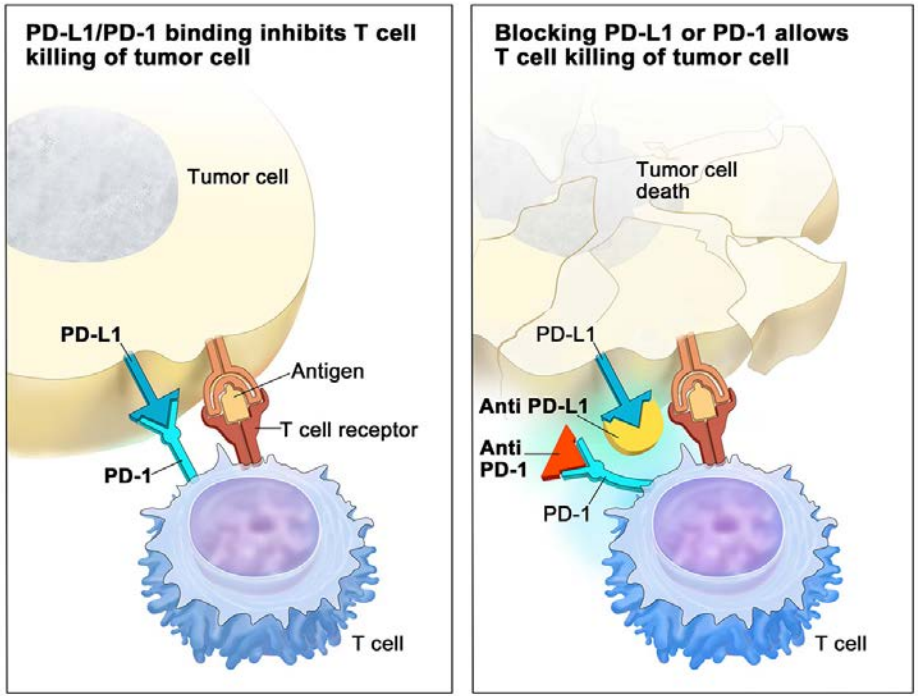
T-Cell Receptor and Co-stimulatory Activation or Inhibition of T cells

Antigen-presenting cell or Tumor cell

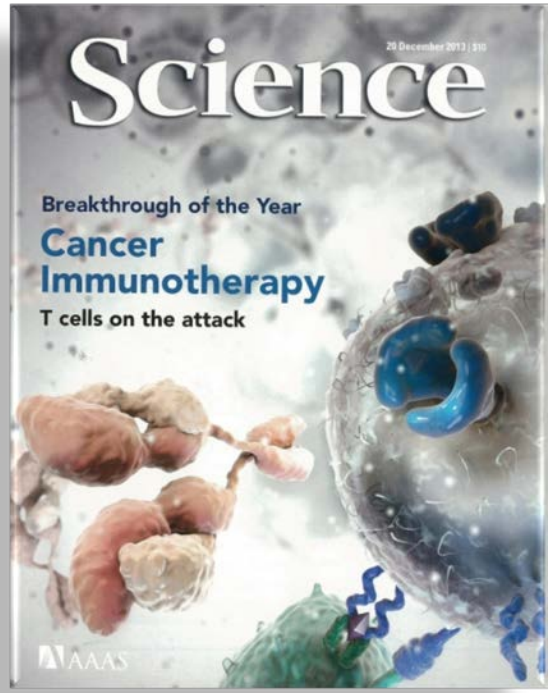
T cell



Targeting Immune PD-L1/PD-1 Checkpoint Pathway: Systemic Therapy



FDA - Immune PD-L1/PD-1 Checkpoint Pathway



LUNG CANCER:

Nivolumab – 2nd Line: **3/4/2015** (Squamous)
10/9/2015 (Non-Squamous)

Pembrolizumab – 2nd Line: **10/2/2015** (NSCLC, PD-L1+)
1st Line: **10/24/2016**: PD-L1 Tumor Proportion Score (TPS) ≥50%
5/10/2017: 1st Line Rx for Non-Sq NSCLC combined w/ chemo (Cabroplatin-Pemetrexed)

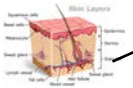
Atezolimumab – 10/18/2016 (NSCLC, 2nd Line Rx)

FDA Approval of Immunotherapy Drugs

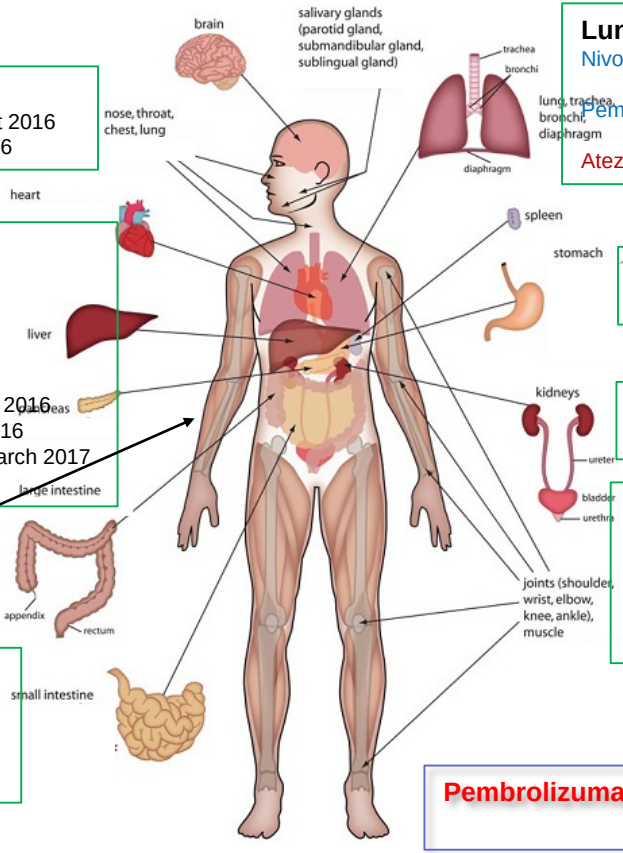
(Jan 2015 – May 2017)

Head and Neck:
Pembrolizumab (PD-1 mAb): Recurrent/mets SCCHN, Oct 2016
Nivolumab (PD-1 mAb): Recurrent/mets SCCHN, Nov 2016

Heme Malignancy:
Ofatumumab (CD20-mAb): Relapsed CLL, Aug 2016
Blinatumomab (CD19-directed CD3-T cell engager Ab):
Ph(-) pre-B ALL, Jan 2015
Daratumumab (CD38-Ab): Myeloma, Nov 2016/2016
Elotuzumab (SLAM F7-mAb): Myeloma, Nov 2015
Obinutuzumab (mAb): Relapsed/refractory Follicular NHL, Feb 2016
Nivolumab (PD-1 mAb): Classic Hodgkin's Lymphoma, May 2016
Pembrolizumab (PD-1 mAb): Classic Hodgkin's Lymphoma, March 2017
Lenalidomide (Immunomodulatory): Myeloma, Feb 2015, 2017



Skin:
Ipilimumab (CTLA-4 mAb): Melanoma, 2011, Oct 2015 (+Nivo)
Talimogene laherparapvec (Viral Rx): Melanoma, Oct 2015
Nivolumab (PD-1 mAb): Oc 2015, Jan 2016
Pembrolizumab (PD-1 mAb): Melanoma, Dec 2015



Lung:
Nivolumab (PD-1 mAb): 2L Sq NSCLC, March 2015;
NSCLC, Oct 2015
Pembrolizumab (PD-1 mAb): 2L NSCLC, Oct 2015;
1L NSCLC, Oct 2016; May 2017 (chemo/Pembro)
Atezolizumab (PD-L1 mAb): 2L NSCLC, Oct 2016

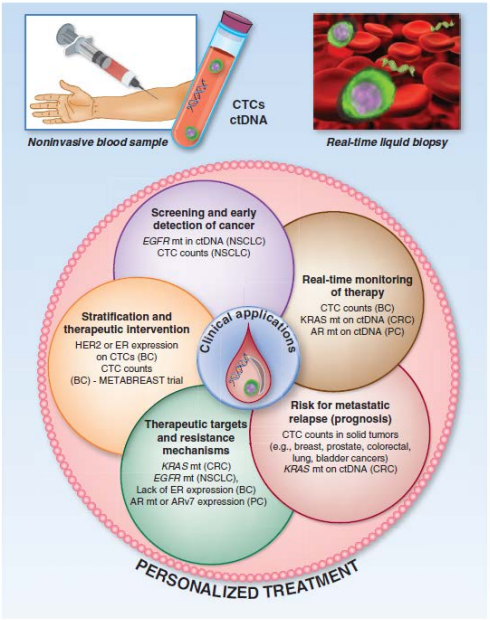
Stomach:
Pembrolizumab (PD-1 mAb): Gastric Ca, Oct 12, 2017

Renal:
Nivolumab (PD-1 mAb): Renal Cell Ca, Nov 2015

Bladder:
Atezolizumab (PD-L1 mAb): Bladder Ca, May 2016, April 2017
Nivolumab (PD-1 mAb): Bladder Ca, Feb 2017
Avelumab (PD-L1-mAb): Merkel cell; Bladder Ca; March/May 2017
Pembrolizumab (PD-1 mAb): Bladder Ca, May 2017
Durvalumab (PD-L1 mAb): Bladder Ca, May 2017

Pembrolizumab (PD-1 mAb): Biomarker indication solid tumors, MSI-H / MMR-def, May 2017

Future Technology on the Horizon – Paradigm Shift



MEDICAL RESEARCH

Personalized test tracks cancer relapse

Genomic analysis of lung-tumour evolution has been used to create personalized blood tests that enable successful clinical monitoring for early signs of cancer relapse — a promising step on the road to precision medicine. SEE ARTICLE P.446

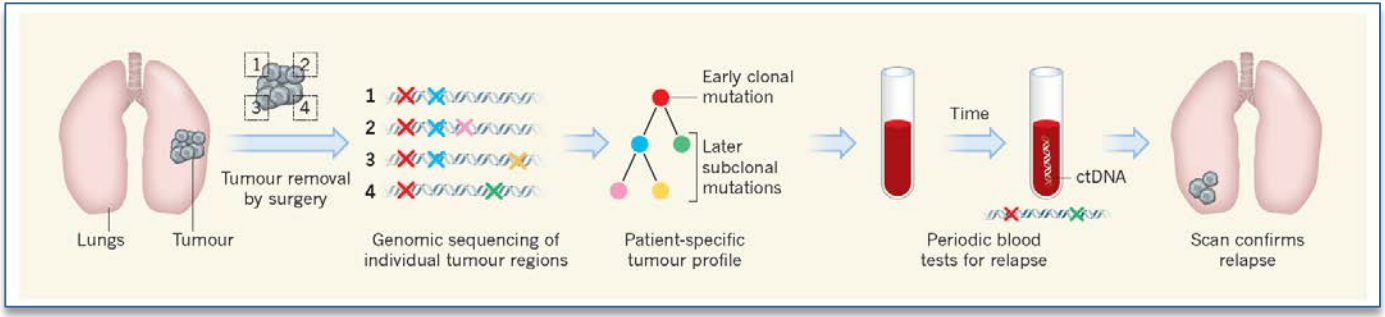


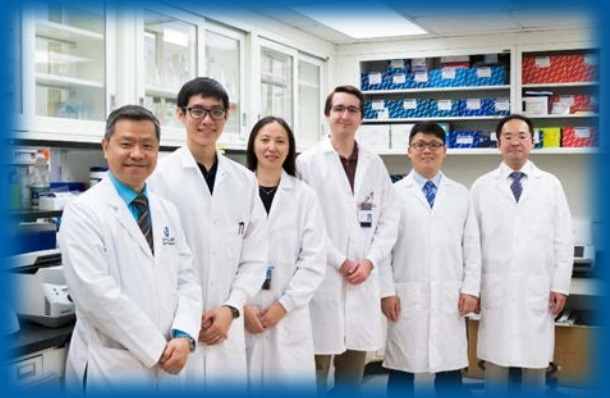
Figure 1 | Monitoring lung-cancer evolution to detect early relapse after surgery. In the TRACERx clinical study[1,2], non-small-cell lung tumours were surgically removed from individuals, and samples were isolated from various regions of the tumour (indicated by the numbers 1–4). Using these samples, Jamal-Hanjani *et al.*[2] sequenced protein-coding genomic regions, and identified DNA changes (shown as X symbols) that arose in these areas of the tumour. By analysing the patterns of DNA changes, the authors could determine the relationship between mutations. For example, early mutations are likely to be present in all tumour cells (clonal alterations), whereas later mutations occur in only some cells (subclonal alterations). The authors created a phylogenetic tree showing how an individual's tumour evolved. Abbosh *et al.*[1] used the genetic profiles obtained by Jamal-Hanjani *et al.* to design a liquid-biopsy blood test for circulating tumour DNA (ctDNA) that could be used to spot the specific genetic hallmarks of cancer relapse appearing in an individual. This personalized testing approach identified signs of tumour recurrence a median of 70 days before relapse was identified through imaging scans. Such recurrence is often seen at different locations from the primary site of tumour formation.

Elucidating Molecular Mechanisms of Tumor Reprogramming and Drug Resistance

WVU011117 - Serial ProspECtive bIopsy for Appalachian Lung Cancer Molecular Profiling **(SPECIAL)** Study

- Serial tumor “biopsies-rebiopsies” and “blood” collection on treatments
- Genomics next-gen sequencing and profiling
- Proteomics-Metabolomics profiling
- Predictive biomarkers discovery for treatment response-resistance
- Novel diagnostics development
- Novel evolutionary treatment strategies and drug discovery

Acknowledgement



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Lung Cancer Patients & Families