BC Cancer Agency Centres

Lung Cancer – Diagnosis and Therapy update

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Abbotsford Cancer Centre

Disclosure

- Advisory board: Astra-Zeneca, Merck
- Honorarium: Merck, Janssen, Astra-Zeneca

Learning objectives

- By the end of this session, participants will be able to:

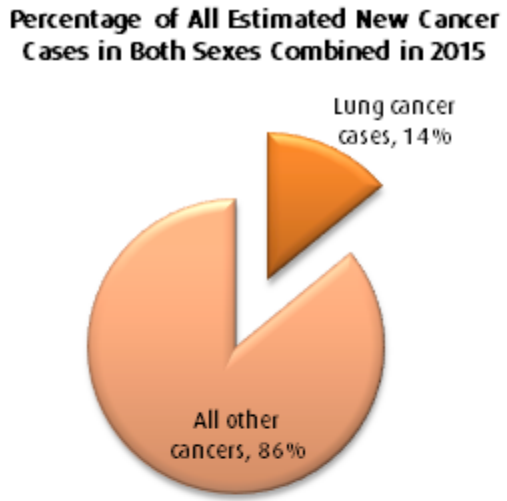
1) Describe the roles of various therapies for lung cancer;

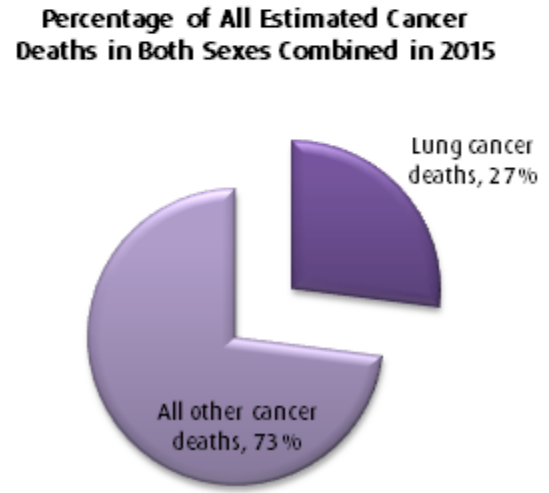
2) State the indications for surgical, radiation and immunotherapies; and

3) Discuss the management of side-effects from these therapies.

Still #1 killer

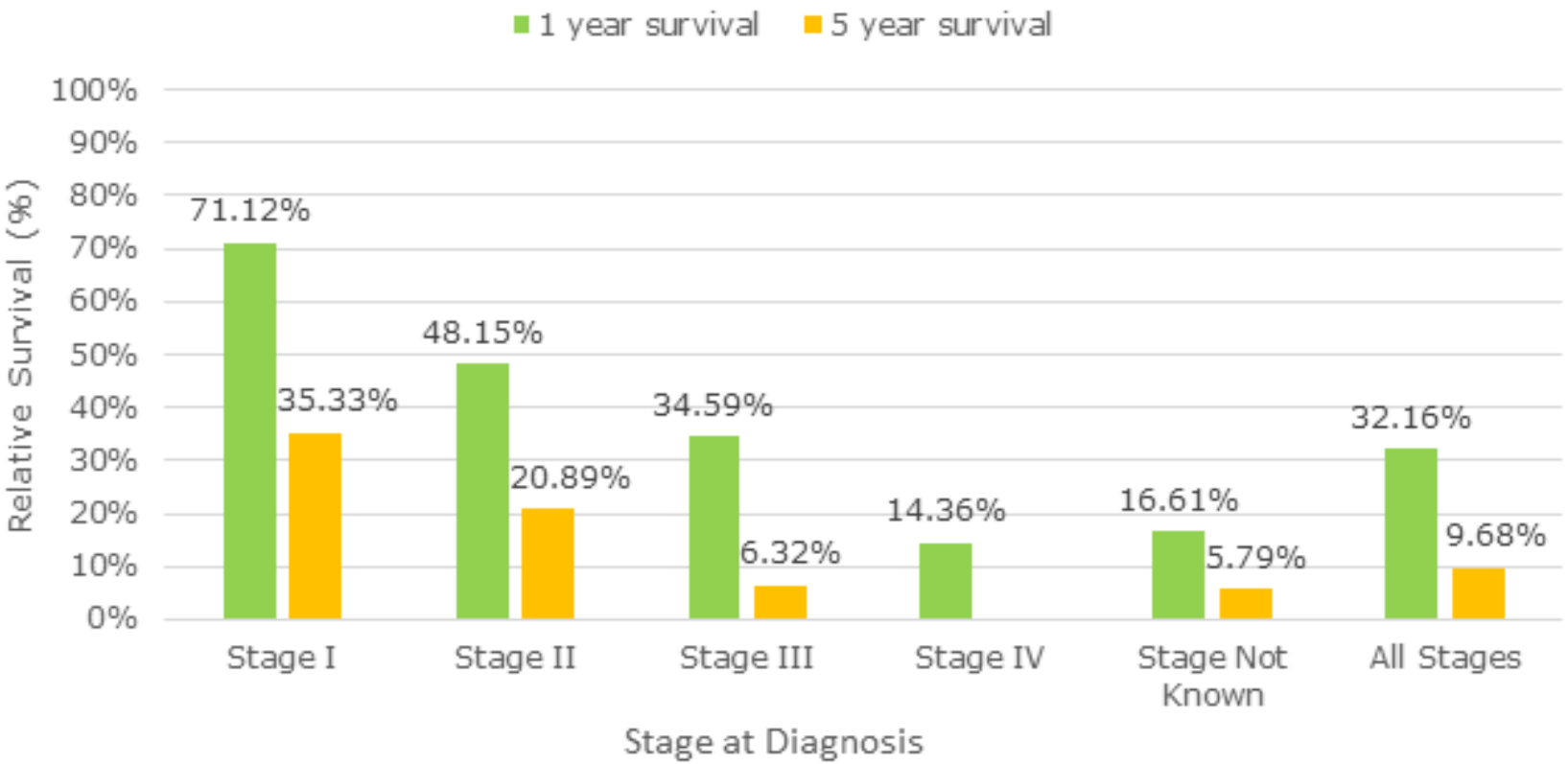
- Most common cause of cancer related mortality in men and women in Canada
- 26,000 new diagnoses/year
- 27% of all cancer deaths
- 10-15% non-smoker (?)



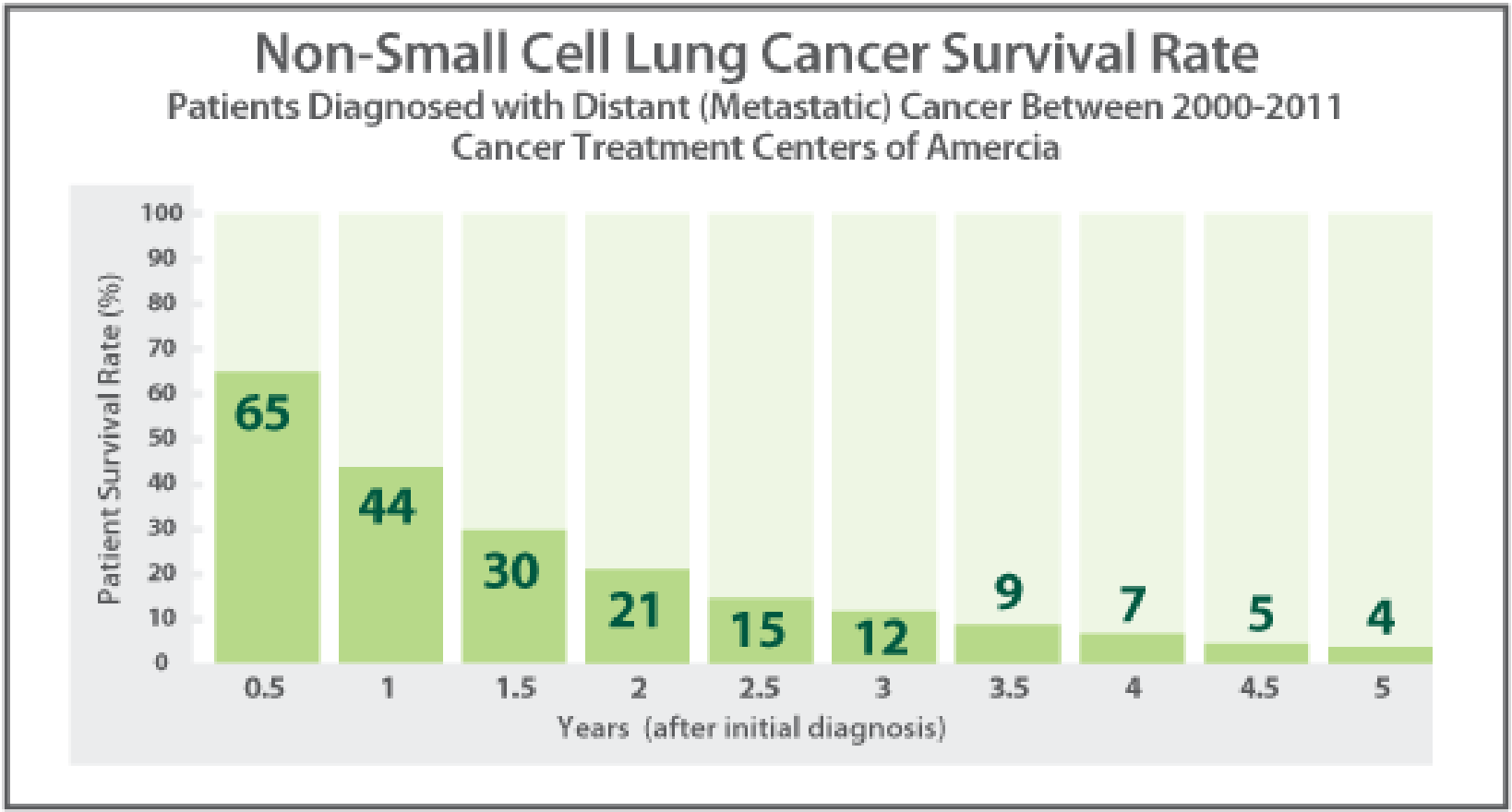


Canadian Cancer Society 2015

Survival


1 year survival
5 year survival
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Relative Survival (%)
71.12%
35.33%
48.15%
20.89%
34.59%
6.32%
14.36%
16.61%
5.79%
32.16%
9.68%
Stage I
Stage II
Stage III
Stage IV
Stage Not Known
All Stages
Stage at Diagnosis

Survival


Non-Small Cell Lung Cancer Survival Rate
Patients Diagnosed with Distant (Metastatic) Cancer Between 2000-2011
Cancer Treatment Centers of Amercia
Patient Survival Rate (%)
100
90
80
70
60
50
40
30
20
10
0
65
44
30
21
15
12
9
7
5
4
0.5
1
1.5
2
2.5
3
3.5
4
4.5
5
Years (after initial diagnosis)

What can we improve?

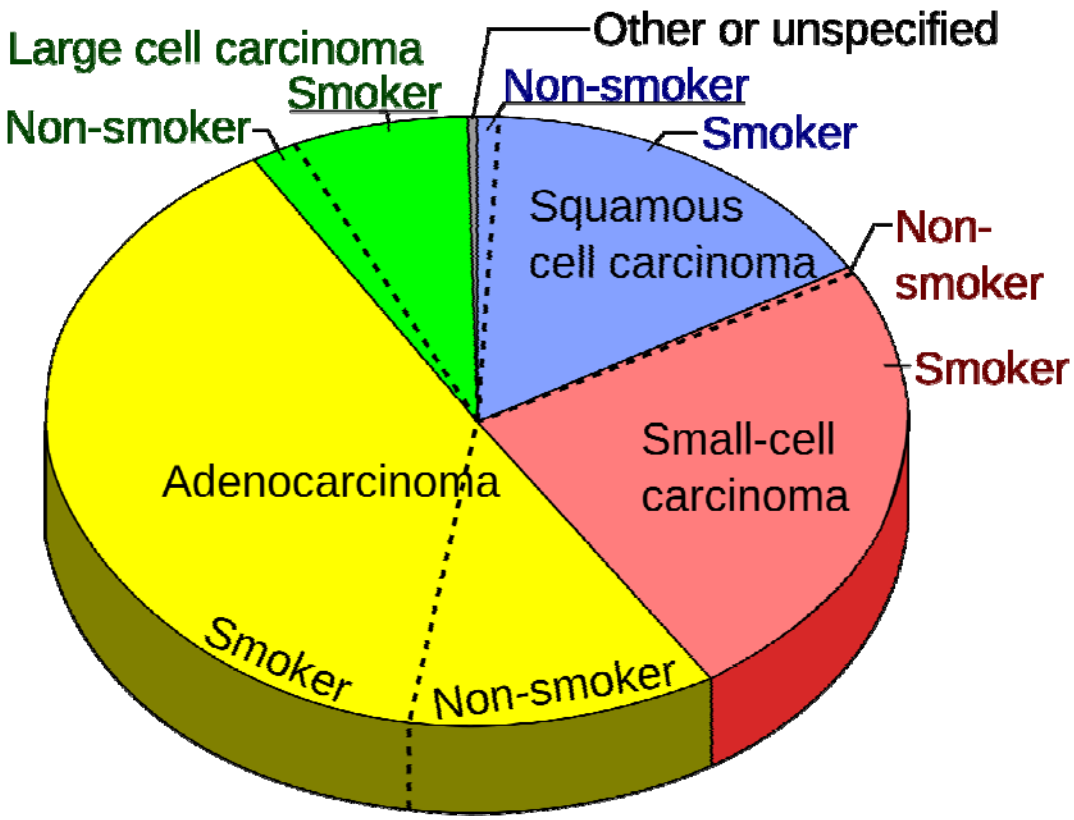
- Lung cancer screening
- Speedy diagnostic workup
- More effective treatment
- Better and earlier palliative care

Trivia

- What are the types of lung cancer?

- Answer: small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC)

Types of lung cancer



Trivia

- What are the stages of lung cancer?

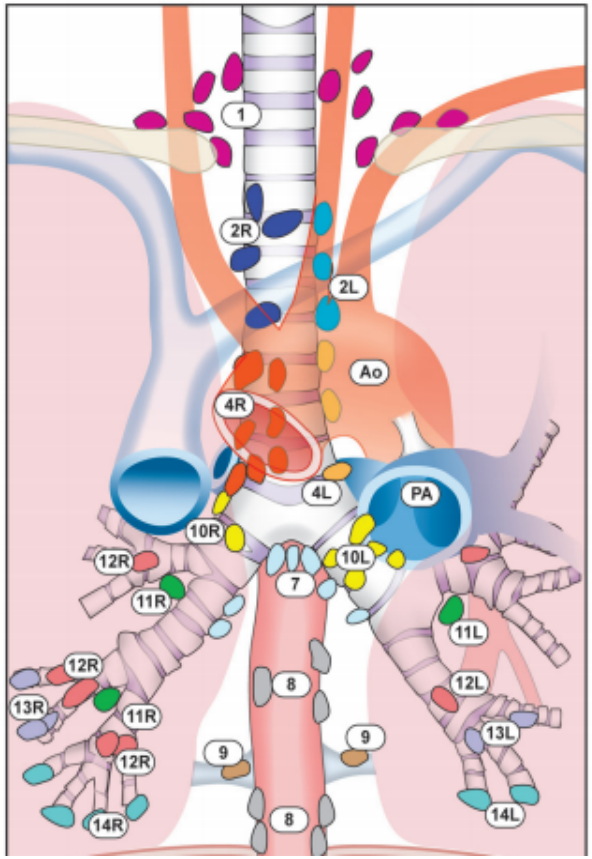
- Answer: I, II, III, IV

Trivia

- What are the TNM stages for stage III lung cancer?

- Answer
  - All N2 and N3 diseases
  - N>=1 + T3
  - All T4 diseases

Lymph nodes



Supraclavicular zone

- **1** Low cervical, supraclavicular, and sternal notch nodes

Superior Mediastinal Nodes

Upper zone

- **2R** Upper Paratracheal (right)
- **2L** Upper Paratracheal (left)
- **3a** Pre-vascular
- **3p** Retrotracheal
- **4R** Lower Paratracheal (right)
- **4L** Lower Paratracheal (left)

Aortic Nodes

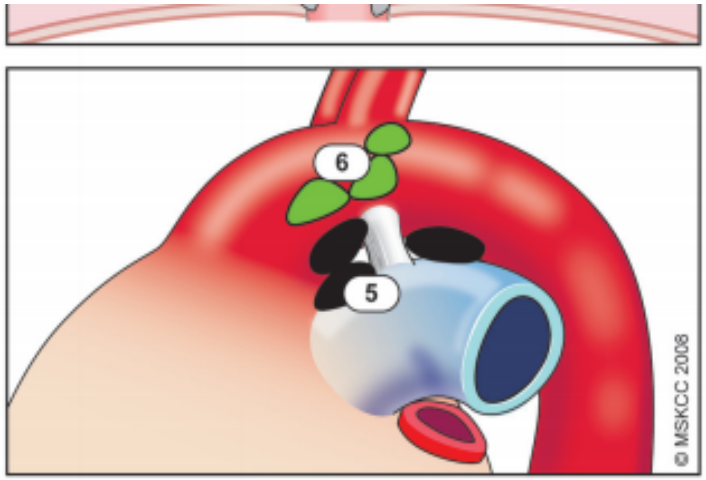
AP zone

- **5** Subaortic
- **6** Para-aortic (ascending aorta or phrenic)

Regional Lymph Nodes (N)

- **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)

Lymph nodes



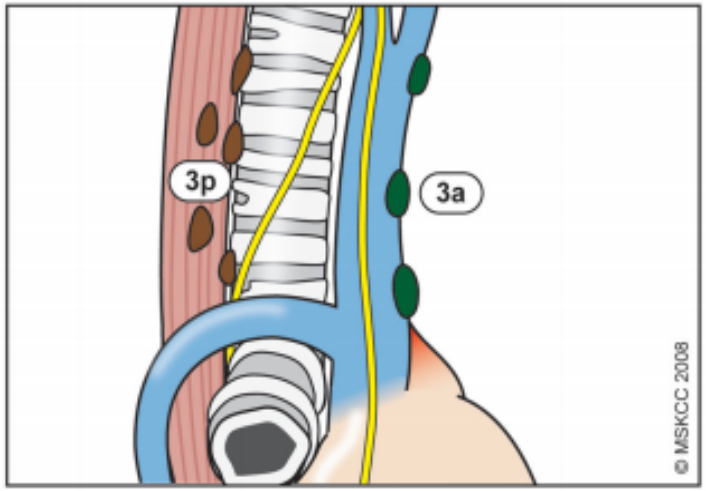
Inferior Mediastinal Nodes

Subcarinal zone

- **7** Subcarinal

Lower zone

- **8** Paraesophageal (below carina)
- **9** Pulmonary ligament



N_1 Nodes

Hilar/Interlobar zone

- **10** Hilar
- **11** Interlobar

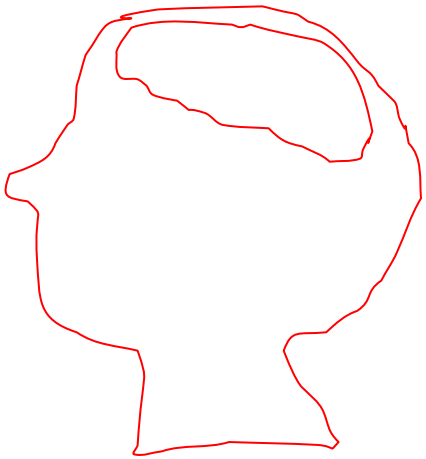
Peripheral zone

- **12** Lobar
- **13** Segmental
- **14** Subsegmental

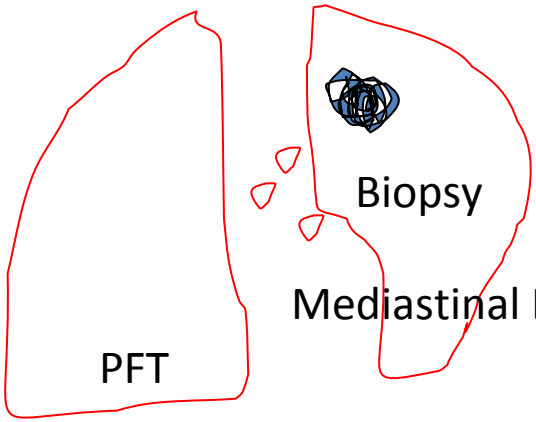
Staging

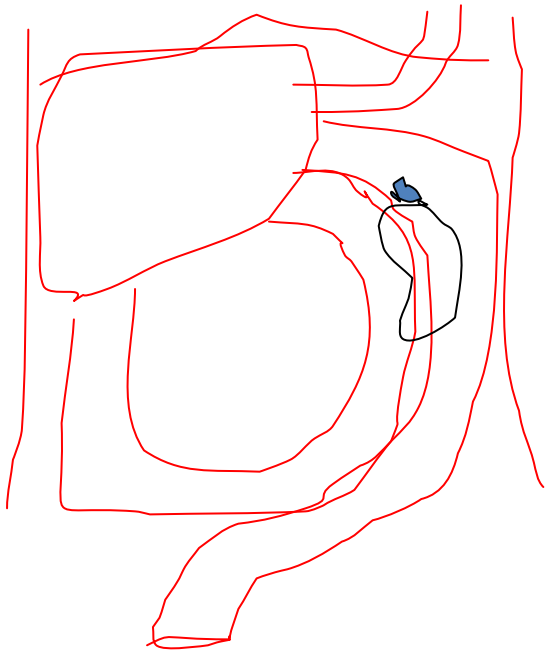
- Practical tips for consultation
  - Accurate assessment of functional status, comorbidities (esp cardiorespiratory) and geriatric evaluation
  - Patient situation (financial, work, health insurance, smoking status, support)
  - Plan investigations ahead of time
    - Always ensure CT contrast or MR of head, PFT, PET, BW including LFTs, proper lymph node staging have been done

Staging



CT contrast or MR head





PET + BW, LFTs

Small cell lung cancer

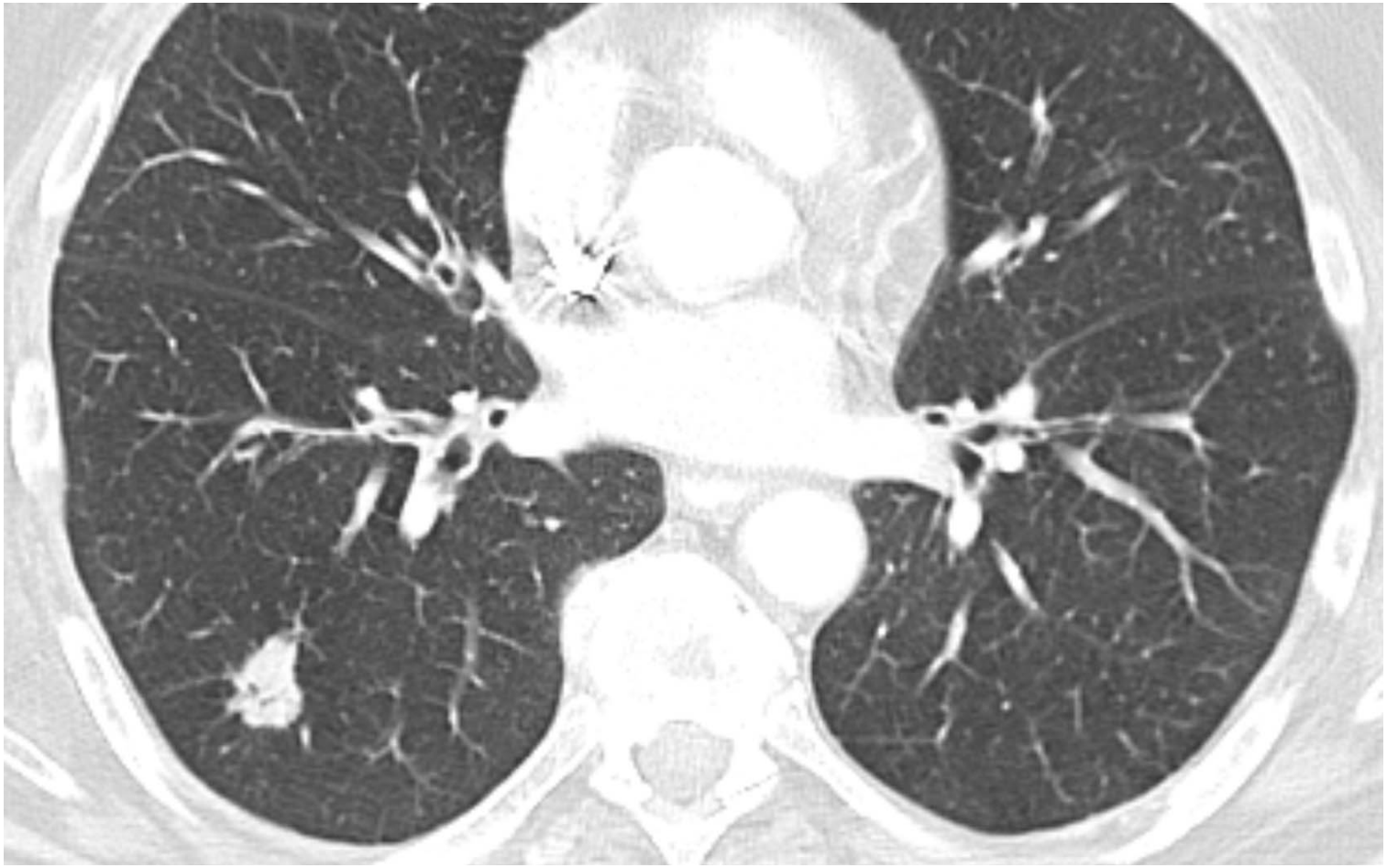
- Generally a systemic disease
- Very responsive to chemotherapy, but also very aggressive
- Platinum + etoposide x 4-6 cycles with concurrent radiation to chest followed by PCI if limited stage
- Platinum + etoposide x 4-6 cycles followed by PCI (+/- sequencial chest radiation) if extensive stage
- Generally treated very urgently

Non-small cell lung cancer

Case 1

- 80F, 50PY smoking history, quit 10y ago
- DM, CAD (stent 10 years ago), OA
- Uses walker
- Lives alone with support from daughter
- Due to cough, x-ray done then CT to follow-up
- FEV1 = 55% of predicted

Case 1



Case 1

- Independent predictors of major adverse outcomes after pneumonectomy
  - Age 65 years or older ($p < 0.001$)
  - Male sex ($p = 0.026$)
  - Congestive heart failure ($p = 0.04$)
  - Forced expiratory volume in 1 second less than 60% of predicted ($p = 0.01$)
  - Benign lung disease ($p = 0.006$)
  - Requiring extrapleural pneumonectomy ($p = 0.018$).
  - Those receiving neoadjuvant chemoradiotherapy were more at risk for major morbidity than patients without induction therapy ($p = 0.049$).

Grade ¾ events 30-35%, mortality 5-6%

Shapiro Ann Thorac Surg. 2010

Case 1

- Predictors of prolonged length of stay after lobectomy
  - Age per 10 years (odds ratio [OR], 1.30, $p < 0.001$)
  - Zubrod score (OR, 1.51; $p < 0.001$)
  - Male sex (OR, 1.45; $p = 0.002$)
  - American Society of Anesthesiology score (OR, 1.54; $p < 0.001$)
  - Insulin-dependent diabetes (OR. 1.71; $p = 0.037$)
  - Renal dysfunction (OR, 1.79; $p = 0.004$), induction therapy (OR, 1.65; $p = 0.001$)
  - Percentage predicted forced expiratory volume in 1 second in 10% increments (OR, 0.88; $p < 0.001$)
  - Smoking (OR, 1.33; $p = 0.095$)

Grade ¾ event 25%; Mortality 1-2%

Cao ACS 2012

Case 1

- PPO FEV1 = preoperative FEV1 x (1 – y/z) where y = number of functional or unobstructed lung segments to be removed, and z = total number of functional segments (typically 19)
- Similar formula for PPO DLCO
  - If both >60%, surgery is a go
  - If one of them <30%, additional exercise testing
  - If both <30%, no go

Case 1

- Wedge resection/segmentectomy
  - In 1 prospective study (Lung Cancer Study Group trial 801), increased rate of local recurrence (5.4 versus 1.9 percent) and trend toward worse survival for limited resection vs. lobectomy (stage IA)
  - In large retrospective studies, worse survival/outcome for wedge resection
  - Single institutional series/elderly patients: similar
  - 2014 meta-analysis: If lesion <2cm, probably similar
  - Ongoing clinical trials: Cancer and Leukemia Group B (CALGB) trial 140503 (NCT00499330) and the Japan Clinical Oncology Group (JCOG) 0802/WJOG 4607L 1000

Ginsberg Ann Thorac Surg 1995

Case 1

Table 1
Current common Canadian indications for lung, liver and spine stereotactic body radiotherapy and the total doses/number of fractions prescribed

Lung		Liver		Spine	
Medically inoperable T1/T2 N0M0 non-small cell lung cancer Lung metastases Tumours less than 5 cm	60 Gy/8 fractions 50 Gy/5 fractions 48 Gy/4 fractions 54–60 Gy/3 fractions 34 Gy/1 fraction	Hepatocellular cancer less than 8 cm Liver metastases less than 6 cm and/or five or fewer lesions	42–60 Gy/6 fractions 50 Gy/5 fractions 48 Gy/4 fractions 45 Gy/3 fractions	Previously irradiated spine metastases Spine metastases with no prior radiation Postoperative patients (± prior radiation exposure) Selected primary spinal tumours No more than three consecutive vertebrae	35 Gy/5 fractions 30 Gy/4 fractions 24–26 Gy/3 fractions 24–26 Gy/2 fractions 16–24 Gy/1 fraction

5Y local recurrence 7%
5Y locoregional recurrence 38%
5Y distant recurrence 15%

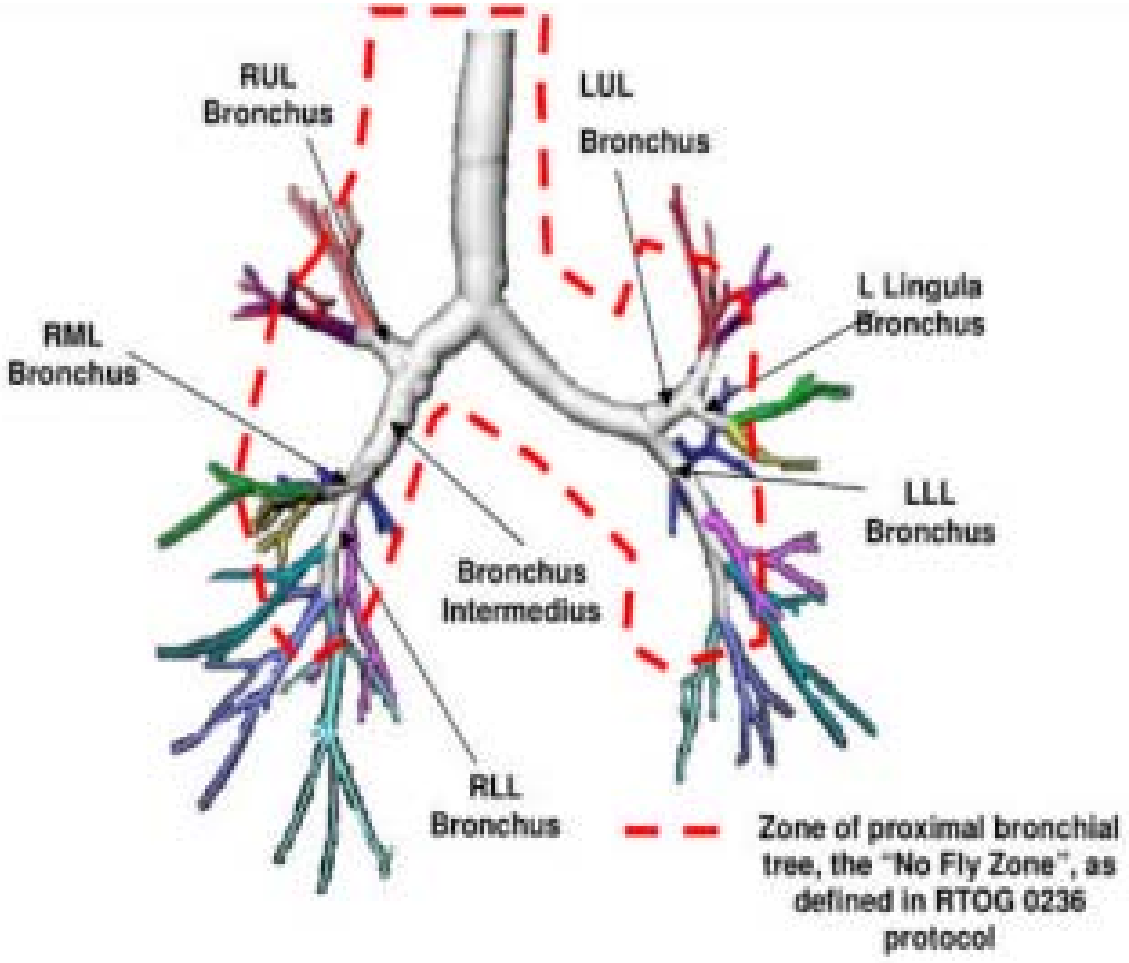
CARO 2012 Clinical Oncology

Case 1

- Exclusion for SBRT (per RTOG 0236)
  - Patients with T2 or T3 primary tumors > 5 cm or patients with T3 primary tumors involving the central chest and structures of the mediastinum
  - The primary tumor of any T-stage within or touching the zone of the proximal bronchial tree defined as a volume 2 cm in all directions around the proximal bronchial tree (carina, right and left main bronchi, right and left upper lobe bronchi, intermedius bronchus, right middle lobe bronchus, lingular bronchus, right and left lower lobe bronchi)

Timmerman JAMA 2010

Case 1


RUL
Bronchus
LUL
Bronchus
L Lingula
Bronchus
RML
Bronchus
LLL
Bronchus
Bronchus
Intermedius
RLL
Bronchus
Zone of proximal bronchial tree, the "No Fly Zone", as defined in RTOG 0236 protocol

Case 1

- Surgery vs. SBRT
  - ???????
  - STAR/ROSEL trials combined analysis
  - <4cm N0 lesions, n=58
  - 3YS 95% (95% CI 85–100) in the SABR group compared with 79% (64–97) in the surgery group (hazard ratio [HR] 0·14 [95% CI 0·017–1·190], log-rank p=0·037)
  - 3Y RFS 86% (95% CI 74–100) in the SABR group and 80% (65–97) in the surgery group (HR 0·69 [95% CI 0·21–2·29], log-rank p=0·54)
  - Ongoing clinical trials

Chang Lancet Oncol 2015

Case 1

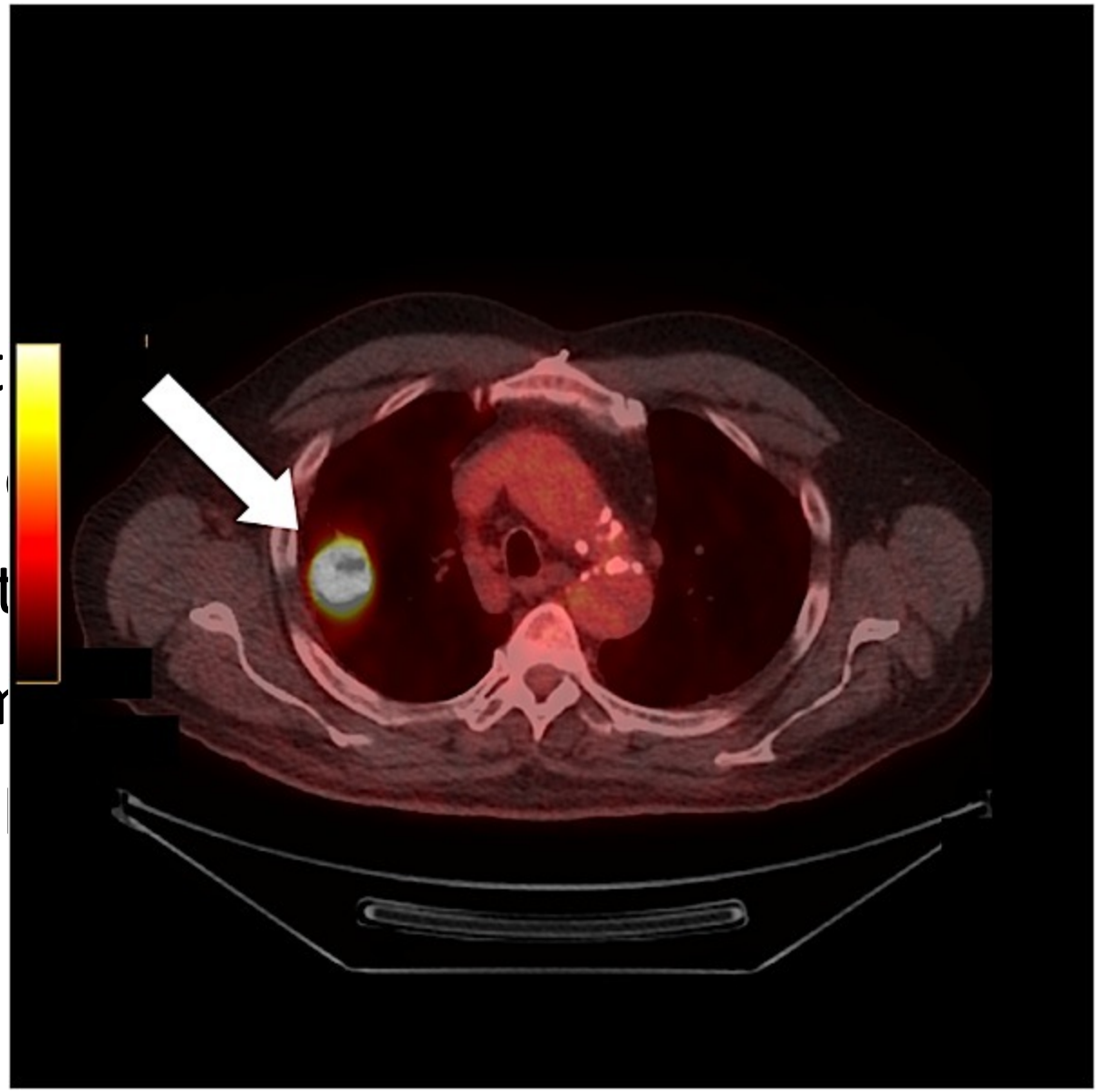
- Received SBRT over 2 weeks
- Tolerated very well with grade 1 fatigue only

Case 1

- Follow-up – unclear evidence for benefit
  - In retrospective studies, no difference
  - In 1 prospective study, CXR Q3m + bronch/CT Q6m --> of 136 with recurrence, 85 were diagnosed by a scheduled procedure, 36 of whom were asymptomatic. More than twice as many thoracic recurrences documented by a scheduled test were eligible for potentially curative resection (22 of 85 versus 6 of 51 [26 versus 12 %]).
  - Alberta: CXR/HP Q3m x 2 years then Q3m x 3 years + CT Q6m x 2 years then low dose CT Q1y x 3 years
  - BC guideline says “no evidence for routine scan” (?)

Walsh Ann Thorac Surg. 1995; Youne Chest. 1999 ; Westeel Ann Thorac Surg. 2000

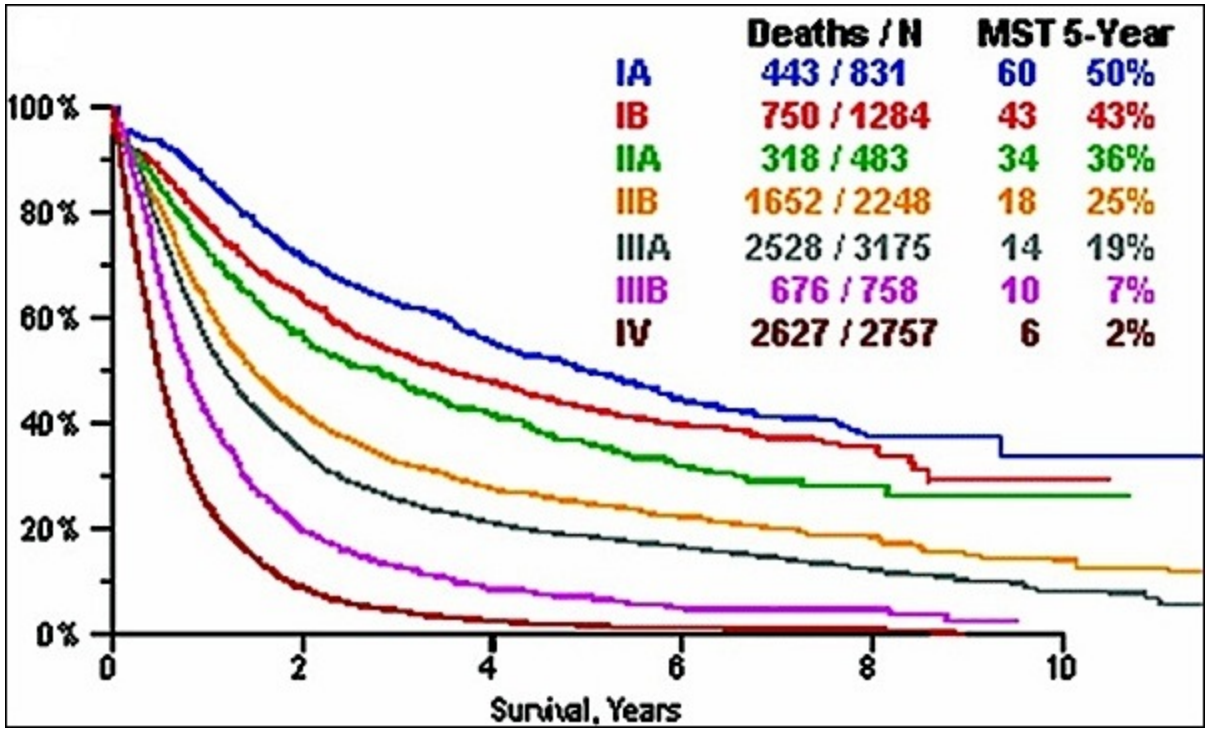
- 55M
- Light
- Incid
- Healt
- Norm
- On P



http://staginglungcancer.org/stages/IIA-T2aN1

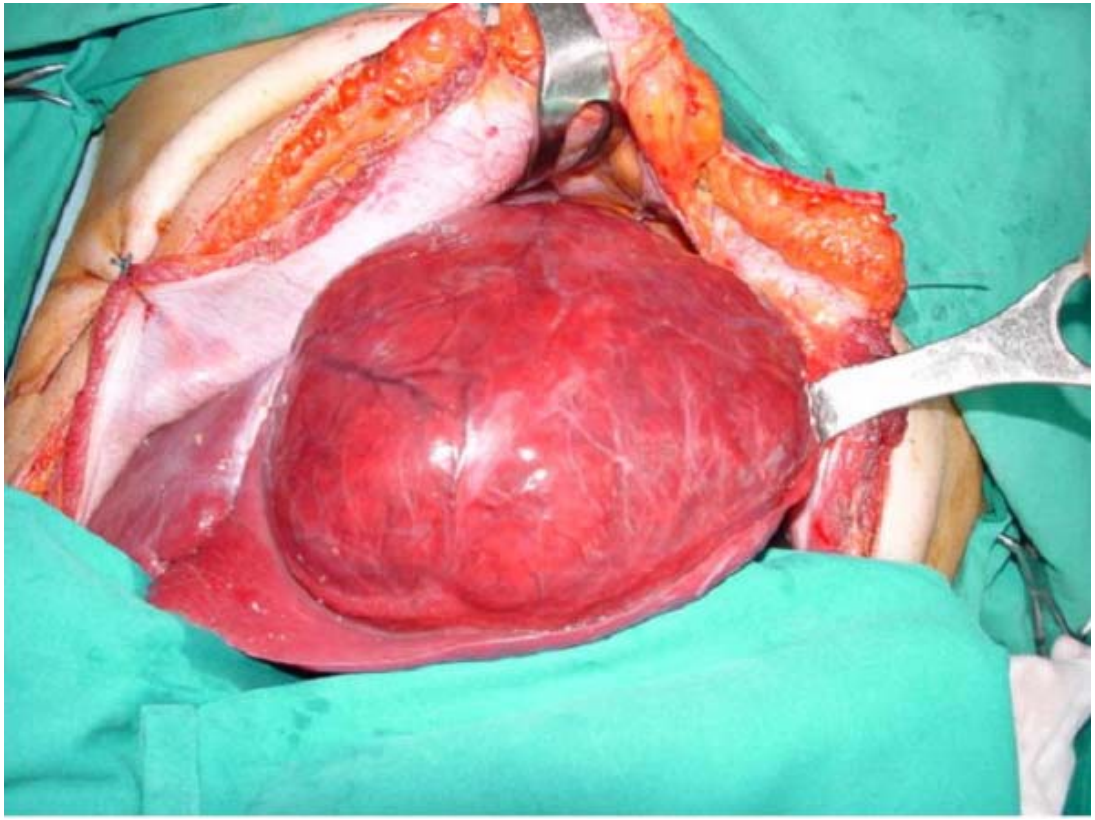
Case 2

- Surgery!
- T2aN1 = IIA



http://staginglungcancer.org/

Case 2



Case 2

- 4 weeks later…
  - Pre-op PET and CT head normal
  - Brief a.fib post-op but no significant morbidity
  - Recovered well otherwise
  - Normal lab other than slight anemia
  - Pathology report: pT2a (3.2cm) N1 (1/5 LN involved) moderately differentiated squamous cell carcinoma, 2 mediastinal LN resected

Case 2

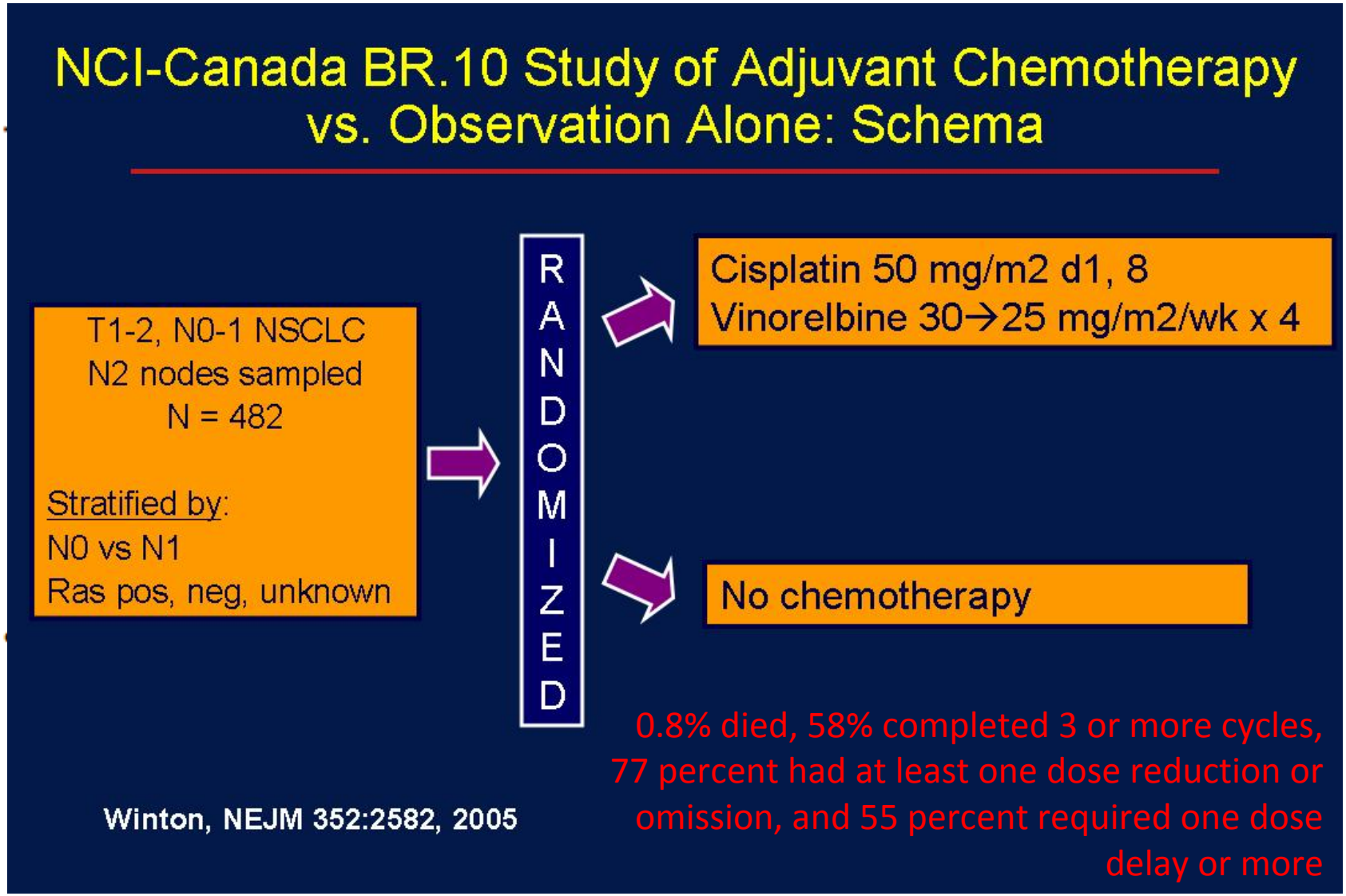
- Adjuvant chemotherapy?
  - Yes!
  - 5% survival benefit in 5 years
  - Need significant supportive care
  - Standard regimen vinorelbine/cisplatin
  - Carboplatin/paclitaxel – easier, but evidence of benefit less clear

Case 2

- How good should lymph node dissection be?
  - Meta-analysis: dissection of levels 4, 7, and 10 for right sided lesions, and levels 5 or 6 and 7 for left sided lesions, improved survival (HR 0.78)
  - Sampling vs dissection (Z0030): sampling of 2R, 4R, 7, and 10R for right-sided tumors and 5, 6, 7, and 10L for left-sided tumors; if all negative, dissection = no dissection in outcome (unexpected N2 + only 3.8%)

Manser Cochrane Database Syst Rev. 2005; Darling J Thorac Cardiovasc Surg. 2011

Case 2


NCI-Canada BR.10 Study of Adjuvant Chemotherapy vs. Observation Alone: Schema
T1-2, N0-1 NSCLC
N2 nodes sampled
N = 482
Stratified by:
N0 vs N1
Ras pos, neg, unknown
RANDOMIZED
Cisplatin 50 mg/m2 d1, 8
Vinorelbine 30→25 mg/m2/wk x 4
No chemotherapy
Winton, NEJM 352:2582, 2005
0.8% died, 58% completed 3 or more cycles, 77 percent had at least one dose reduction or omission, and 55 percent required one dose delay or more

Case 2

Table 1 Adjuvant chemotherapy of completely resected NSCLC

	N	Stage	Chemo	5-year survival (%)		HR (95% CI)	P
				Chemo	Control		
ALPI-EORTC	1,088	I-IIIA	MVP	49.0	48.0	0.96 (0.81-1.13)	NS
IALT	1,867	I-III	Cis/Vinca	44.5	40.4	0.86 (0.76-0.98)	<0.03
JBR.10	482	IB-II	Cis/Vino	69.0	54.0	0.69 (0.52-0.91)	0.04
ANITA	840	IB-IIIA	Cis/Vino	51.2	42.6	0.80 (0.66-0.96)	0.02
CALGB	344	IB	Carbo/Pacl	57.0	59.0	0.80 (0.60-1.07)	0.1
BLT	381	I-III	Cis-based	NR	NR	1.0	NS
LACE meta-analysis	4,584	I-IIIA	Cis-based	48.8	43.5	0.89 (0.82-0.96)	0.004

NR, not reported; NS, not significant; NSCLC, non-small cell lung cancer.

- Across the studies,
  - No predictive biomarker (e.g. ERCC1, KRAS etc)
  - Magnitude of benefit ~ 5-10%
  - Tumour has to be at least 4cm or larger if N0, or at least N1

Case 2

- PORT?
  - Generally no (?increases harm)
  - 2 cases in which PORT can be considered:
    - ➢ Positive margin
    - ➢ Resected N2 disease

PORT Meta-analysis Lancet. 1998; Lally J Clin Oncol. 2006; Wang J Clin Oncol. 2015

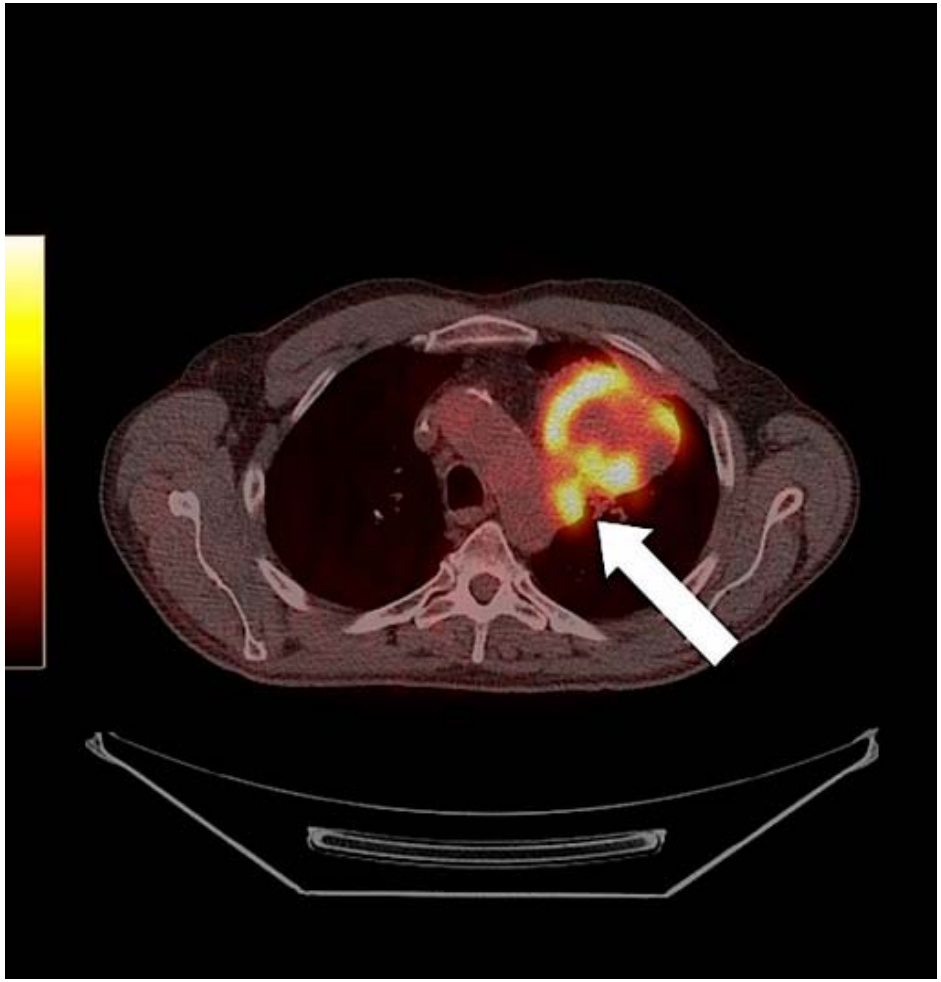
Case 2

- BR. 31
  - 2:1 randomization to durvalumab Q4w x 1 year vs. placebo Q4w x 1 year
  - Can be post adjuvant chemo or patients who refused chemo after surgery
  - Open at BCCA sites

Case 3

- 72M
- Current smoker
- FEV1 70%
- Frail looking, but well supported by wife
- No significant comorbidities, but has not gone to the doctor until recently
- CT head negative, lab reasonable

Case 3



Large left lung primary and periaortic ipsilateral LN
T2b N2 = IIIA

Case 3

- Biopsy revealed poorly differentiated adenocarcinoma from the main tumour.
- Mediastinal LN not accessed due to technical difficulties

Case 3

- RT/chemo vs RT trials
  - Shows approximately 5-10% 5Y survival benefit by adding chemotherapy in various trials (Furuse JCO 1999, CALGB8433, Intergroup ECOG 5488/RTOG 8808/CALGB 8433, Schaake-Koning NEJM 1992)
  - Meta-analysis
    - Pritchard 1999: HR 0.87 at 2 years, 0.83 at 3 years for adding chemo (concurrent or sequential) in 14 trials
    - Auperin 2006: absolute benefit of RT/chemo vs chemo 4% at 2 years in 6 trials
    - Le Chevalier 2007: absolute benefit of RT/chemo vs RT → chemo 2.2% at 5 years

Case 3

- Trimodality trials

Table 1. Selected Trials of Trimodality Therapy for Stage IIIB Non–Small-Cell Lung Cancer

Study/Reference	No. of Patients	Stage IIIB (%)	N3/T4 (%)	Chemotherapy	Radiotherapy	Complete Resection (%)*	Operative Mortality (%)	Median Survival		5-Year Survival (95% CI)	
								Months	95% CI (months)	%	95% CI (%)
Germany[6]	264	69	22/52	P, E	45 Gy† + C, Vin	37	9	16	13 to 18	3 yr: 28	22 to 33
Essen, Germany (retrospective series, operated patients)[7]	392	44	NR	P, E or C, T	45 Gy bid + P, E	NR	5	22	NR	IIIA: 5 yr: 36 IIIB: 5 yr: 26	
SWOG8805, United States (subgroup)[8]	51	100	53/47	P, E	45 Gy	63	10	17	NR	3 yr: 24	
IGR, France[9]	40	100	45/75	P, F, Vbl	42 Gy	58	7	14‡	NR	19	10 to 34
Rome, Italy[10]	39	100	13/87	P, F	50.4 Gy	56	0	18	NR	23	
Fukuoka, Japan[11]	27	100	19/81	P, U	40 Gy	81	4		NR	56	37 to 76
SAKK 16/01, Switzerland[5]	46	100	28/78	P, D	44 Gy†	59	5.7	29	16 to NA	40	24 to 55
Friedel, Germany[1]	120	73	29/53			48	12	18	14 to 22	25	
Subgroup stage IIIB	88	100		C, T	45 Gy bid + C, T			16	11 to 21	21	

Abbreviations: P, cisplatin; E, etoposide (VP-16); C, carboplatin; Vin, vindesine; NR, not reported; T, paclitaxel; bid, two times per day; SWOG, Southwest Oncology Group; IGR, Institut Gustave Roussy; F, fluorouracil; Vbl, vinblastine; U, UFT (tegafur); SAKK, Swiss Group for Clinical Cancer Research; D, docetaxel; NA, not available.

*Intention to treat, percentage of enrolled patients.

†Accelerated radiotherapy.

‡Estimated from survival curve.

Case 3

- Trimodality trials
  - Albain Lancet 2009 (Intergroup 0139/RTOG 9309)
    - n= 202 Patients w stage T1-3pN2M0 NSCLC
    - Concurrent induction chemo (2 cycles cisplatin 50mg/m2 d1,8,29,36 and Etoposide 50mg/m2 d1-5 and 29-33) plus RT (45Gy); if no progression, pts in group 1 underwent resection and group 2 continued RT uninterrupted up to 61Gy. 2 additional cycles of cisplatin/etoposide given in both groups.
    - Primary endpoint OS
    - PFS: 12.8 vs 10.5 mo, HR 0.77, p=0.017.
    - 5 year PFS 22 vs 11% (no p value)
    - OS 23.6 mo vs 22.2 mo (HR 0.87, p=0.24).
    - 5 yr OS 27% vs 20% (OR 0.63, p=0.10)
    - With N0 status at thoracomtomy, mOS 34.4 mo, 5 yr OS 41%.
    - Death rate 2 vs 1.8%
    - Exploratory analysis, OS improved for pts undergoing lobectomy, but not pneumonectomy, vs chemo+RT

Case 3

- Trimodality trials
  - Van Meerbeeck J Natl Cancer Inst 2007 (EORTC 08941)
    - Pts w stage IIIA-N2 NSCLC were given 3 cycles of platinum based induction chemo (3 cycles of cisplatin 80mg/m2 per cycles, or carboplatin, AUC at least 5 per cycle), combined with at least one other chemotherapy drug
    - Responding pts were subsequently randomly assigned to surgical resection or RT
    - 154 pts allocated to resection and 154 to RT
    - Primary endpoint OS
    - PFS 9 vs 11.3mo (p=0.6)
    - OS 16.4 (Surgery) vs 17.5 mo (RT) 5 year OS 15.7 vs 14% HR 1.06, (p=0.6)
    - Among irradiated pts, overall compliance to RT was 55% Operative mortality of pneumonectomy 7%
    - Only 50% patients randomized to surgical resection achieved a complete resection

Case 3

- My take on this:
  - Definitive N2 disease = safe to start from chemoradiation therapy
  - Stage III with N1 disease = consult with surgeon first
  - Always discuss each case with surgeon, send to him/her after PET
  - Avoid pneumonectomy, but in select cases lobectomy can help (?)
  - No good evidence for induction chemotherapy

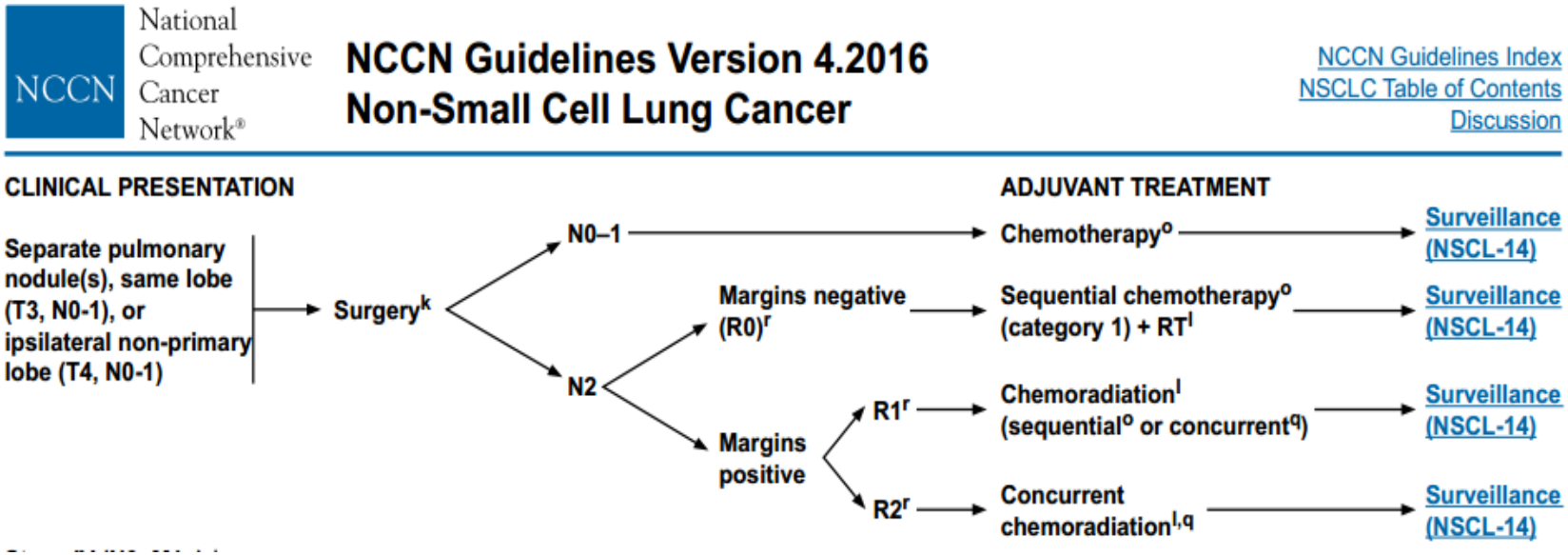
Case 3

- Choice of chemotherapy in chemoRT
  - No evidence for superiority
  - In BC: cisplatin/etoposide or carboplatin/paclitaxel used
  - Other regimens used in other regions (usually to lower toxicities such as esophagitis)
  - "Consolidative chemotherapy" in the PPO (controversial and not always appropriate?)
    - SWOG S9504, HOG LUN – docetaxel
    - SWOG 0023 – gefitinib
    - CALGB 30407 – pemetrexed
    - KCSG-LU05-04 (JCO 2015) – cisplatin/docetaxel
    - Yamamoto ASCO 2012 (meta-analysis) – 45 phase II/III studies, negative
    - (Does not this mean that there is level I evidence that fails to show evidence for consolidative chemotherapy? However, no phase III to study SAME chemo regimen used as consolidative chemotherapy so still discussed in some settings)

“In between” cases

- Fit patient with 2 ipsilateral 1cm lesions, different lobes, no lymph node involvement, after surgical resection
- Non-surgical candidate patient with 6cm lung lesion, no lymph node involvement
- Patient with multiple recurrent AIS (formerly known as BAC)
- Locoregional recurrence after surgery or SBRT
- Superior sulcus tumour
- Endobronchial or tracheal-wall limited disease

Fit patient with 2 ipsilateral 1cm lesions

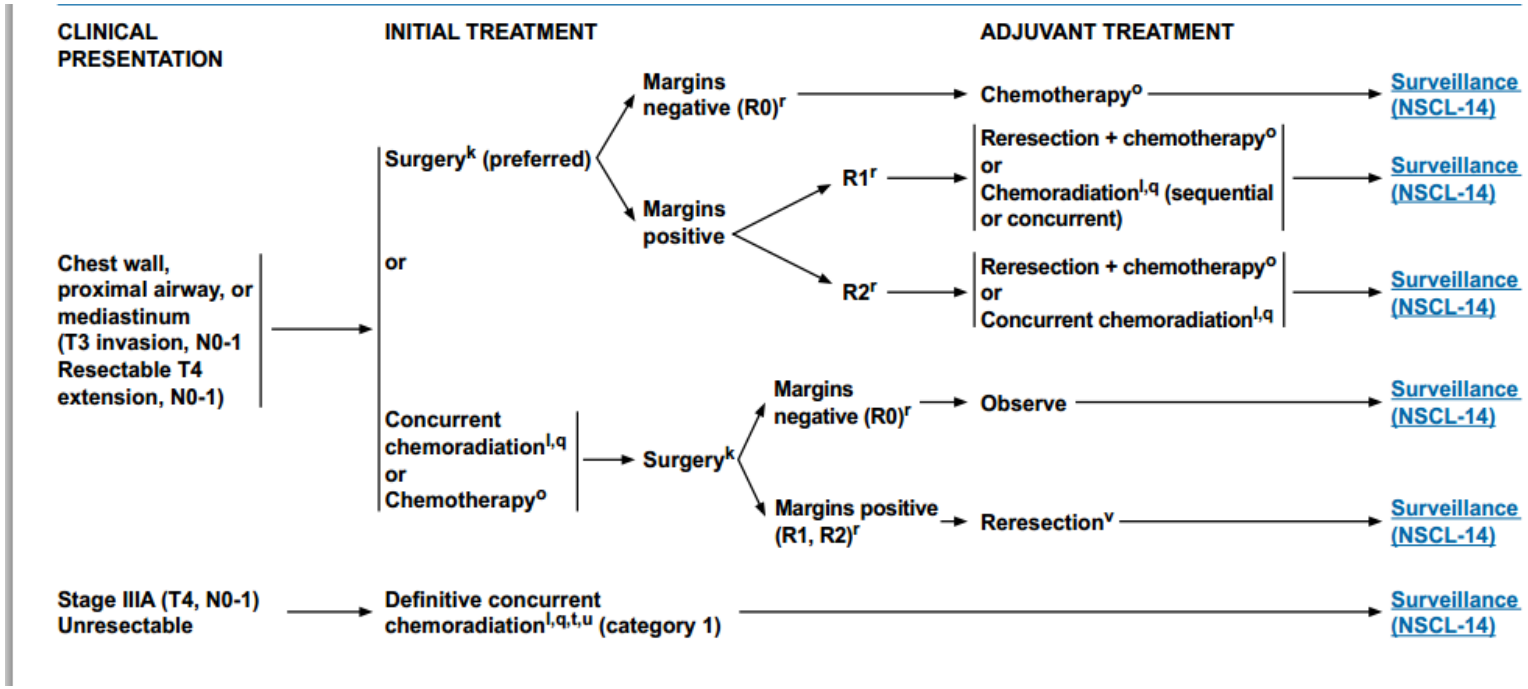


Included in ANITA

Not included in BR.10

Many experts recommend no adjuvant chemotherapy if both nodules <4cm and n0

Non-surgical candidate patient with 6cm lung lesion, no lymph node involvement



Many experts recommend no chemotherapy with radiation therapy in the case of N0 or 1

Patient with multiple recurrent AIS (formerly known as BAC)

- Multiple resection vs. observation
- ?RT (currently no role if pure AIS, but what if there is solid component?)
- Difficult to biopsy safely
- Very good prognosis as long as they do not transform into invasive adenocarcinoma

Locoregional recurrence after surgery or SBRT

- Most often, still attempt to treat with curative intent if possible

Endobronchial or tracheal-wall limited disease

- Multiple ablative techniques
  - Intra-tracheal/bronchial brachytherapy
  - External beam radiation
  - Endobronchial thermal, laser or cryotherapy

Stage IV NSCLC

- Why treat? Is it worth it?
- How do we diagnose?
- How do we treat?
- What about targeted therapy?
- What about immunotherapy?

Outcomes across a decade

TABLE 1. Baseline Characteristics of Patients Who Received Best Supportive Care (BSC) Versus Chemotherapy by Year of Diagnosis

	C1 1998		C2 2001		C3 2006		C4 2007			
	BSC (n = 464)	Chemo (n = 91)	BSC (n = 485)	Chemo (n = 146)	BSC (n = 453)	Chemo (n = 235)	BSC (n = 501)	Chemo (n = 249)	p across years BSC	p across years chemotherapy
Median age (range)	68 (38–93)	59 (36–84)	70 (39–96)	60 (35–83)	72 (37–95)	63 (33–86)	71 (43–101)	63 (34–86)	<0.005	<0.005
Gender (female/male)	199/265	41/50	198/287	81/65	200/253	125/110	213/288	123/126	0.78	0.38
Histology									0.48	0.22
Squamous	102 (22%)	13 (14%)	115 (24%)	20 (14%)	84 (19%)	41 (17%)	71 (14%)	22 (9%)		
Non-squamous	229 (49%)	58 (64%)	200 (41%)	91 (62%)	156 (34%)	108 (46%)	139 (28%)	94 (38%)		
Unknown	133 (29%)	20 (22%)	170 (35%)	35 (24%)	213 (47%)	86 (37%)	291 (58%)	133 (53%)		
Smoking status									0.006	0.25
Current	43 (10%)	9 (10%)	253 (53%)	64 (44%)	182 (40%)	90 (38%)	215 (43%)	88 (35%)		
Former	30 (6%)	15 (16%)	170 (35%)	61 (42%)	205 (45%)	107 (45%)	214 (43%)	109 (44%)		
Never	6 (1%)	7 (8%)	34 (7%)	17 (11%)	43 (9%)	35 (15%)	44 (9%)	50 (20%)		
Unknown	385 (83%)	60 (66%)	28 (6%)	4 (3%)	23 (6%)	3 (2%)	28 (5%)	2 (1%)		
Eastern Cooperative Group Performance Status									0.003	0.98
0–1	83 (18%)	34 (37%)	129 (27%)	88 (60%)	136 (30%)	139 (59%)	120 (24%)	148 (59%)		
≥2	144 (31%)	23 (25%)	355 (73%)	55 (38%)	315 (69%)	92 (39%)	381 (76%)	92 (37%)		
Unknown	237 (51%)	34 (38%)	1	3 (2%)	2 (1%)	4 (2%)	-	9 (4%)		
Ethnicity									0.053	<0.005
Asian	28 (6%)	7 (8%)	33 (7%)	7 (5%)	48 (11%)	29 (12%)	42 (8%)	44 (18%)		
Other	436 (94%)	84 (92%)	452 (93%)	139 (95%)	405 (89%)	206 (88%)	459 (92%)	205 (82%)		

Ho *J Thorac Oncol. 2014;9: 1180–1186*

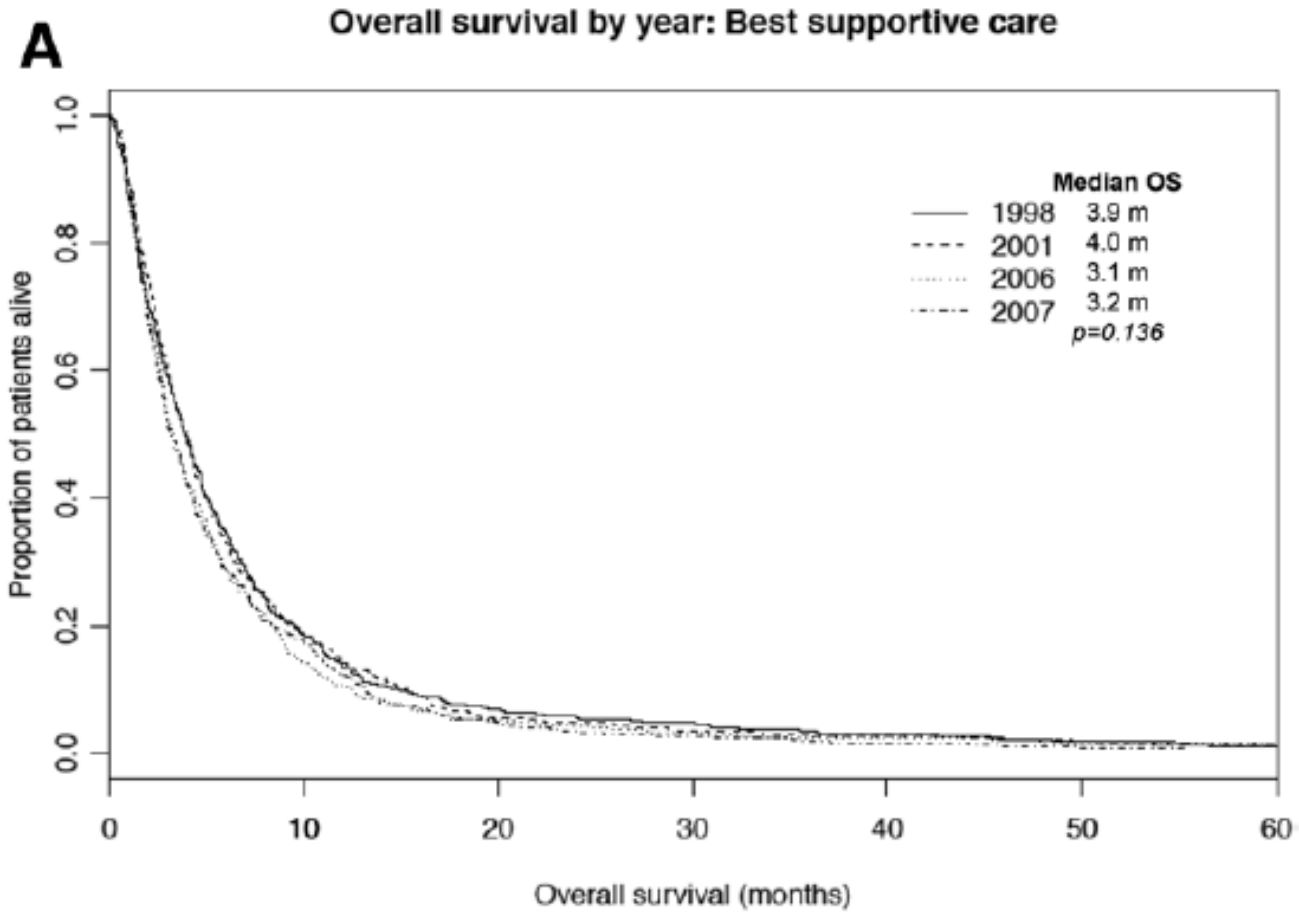
Outcomes across a decade

TABLE 2. Description of Types of Chemotherapy Administered in First, Second and Third Line by Year of Diagnosis (*p* Value Across Years)

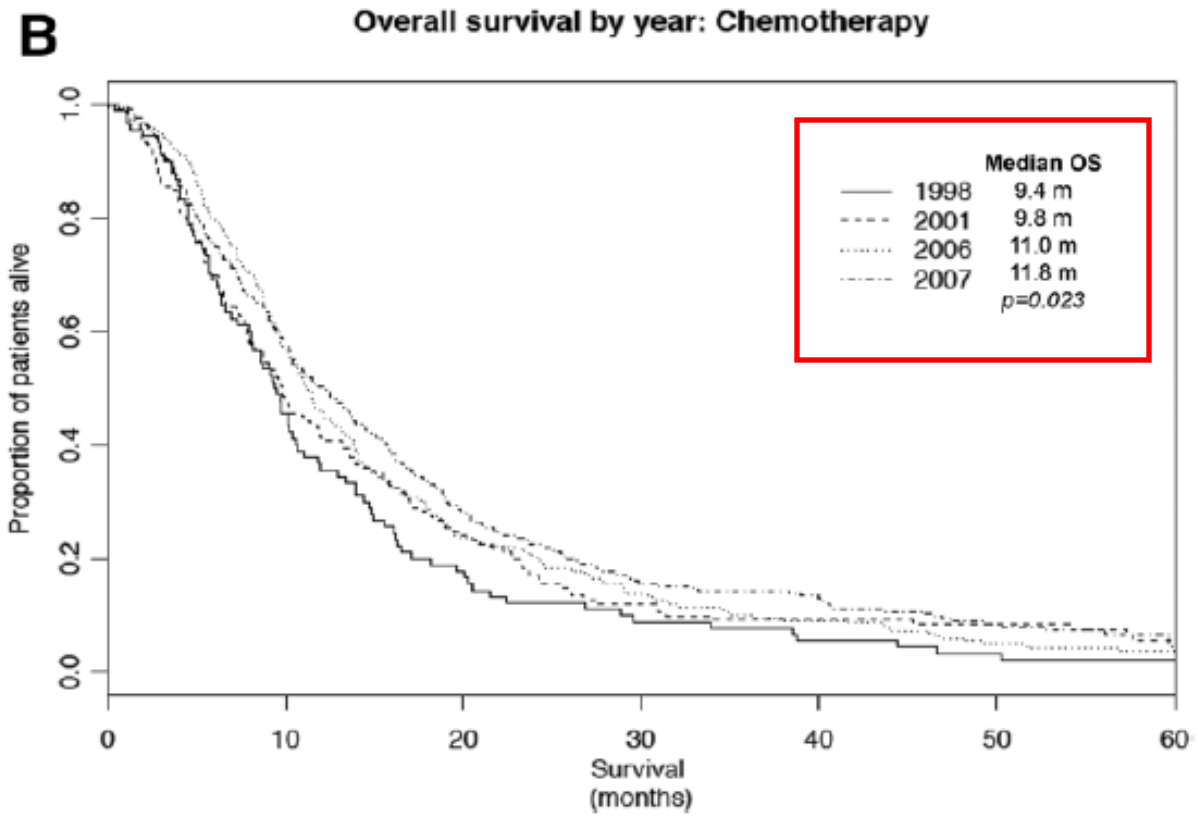
	C1 1998	C2 2001	C3 2006	C4 2007	
N	**565**	**631**	**688**	**750**	***p* value**
First line *n* (%)	91 (16%)	146 (23%)	235 (34%)	249 (33%)	<0.005
Median number of cycles	3	4	3	4	
Type					
Platinum/etoposide	10 (11%)	17 (12%)	24 (10%)	27 (11%)	
Platinum/taxane	5 (6%)	5 (3%)	31 (13%)	18 (7%)	
Platinum/vinorelbine	64 (70%)	104 (71%)	48 (21%)	31 (12%)	
Platinum/gemcitabine	—	—	78 (33%)	111 (45%)	
Epidermal growth factor receptor TKI	—	—	21 (9%)	21 (8%)	
Single agent/other	12 (13%)	20 (14%)	33 (14%)	41 (17%)	
Second line *n* (%)	19 (21%)	39 (27%)	88 (37%)	137 (55%)	<0.005
Median number of cycles	4	4	3	3	
Type					
Platinum doublet	5 (26%)	5 (13%)	21 (24%)	16 (12%)	
Docetaxel	9 (47%)	20 (51%)	15 (17%)	9 (7%)	
Epidermal growth factor receptor TKI	—	11 (28%)	33 (38%)	68 (50%)	
Pemetrexed	—	—	13 (15%)	36 (26%)	
Single agent/other	5	3 (8%)	6 (6%)	8 (5%)	
Third line *n* (%)	9 (47%)	15 (38%)	32 (36%)	62 (45%)	0.504
Median number of cycles	3	2	2	3	
Type					
Platinum doublet	1 (11%)	1 (7%)	3 (9%)	1 (2%)	
Docetaxel	6 (67%)	—	2 (6%)	4 (6%)	
Epidermal growth factor receptor TKI	—	11 (73%)	18 (57%)	34 (55%)	
Pemetrexed	—	—	6 (19%)	15 (24%)	
Single agent/other	2 (22%)	3 (20%)	3 (9%)	8 (13%)	

TKI, tyrosine kinase inhibitor.

Outcomes across a decade



Outcomes across a decade



Perception with stage IV lung cancer

- n=672 physicians

TABLE 1. Participating Physician Characteristics

	n	Physicians Answering Breast Cancer Questionnaire (*n* = 352)	Physicians Answering Lung Cancer Questionnaire (*n* = 320)	*p*
Years of practice	644	15.82	14.93	0.163
Number of patients per week	665	77.30	80.00	0.195
Number of breast cancer patients per year	653	7.61	7.12	0.802
Number of lung cancer patients per year	652	4.12	3.58	0.055
Gender	664			0.512
Female (%)		37	35	
Male (%)		63	65	
Age (yr)	634	46.30	46.14	0.702

Wassenaar J Thorac Oncol. 2007 Aug;2(8):722-8.

Perception with stage IV lung cancer

TABLE 2. Factors Contributing to the Primary Care Physicians' Decision to Refer their Patient to an Oncologist on the Basis of Disease Type and Patient Smoking Status

	n	Physicians Answering Breast Cancer Questionnaire (*n* = 352)	Physicians Answering Lung Cancer Questionnaire (*n* = 320)	*p*	*n*	Physicians Answering Nonsmoking Questionnaire (*n* = 352)	Physicians Answering Smoking Questionnaire (*n* = 320)	*p*
Type of cancer	655	2.47	2.59	0.185	655	2.51	2.55	0.785
Degree of symptoms	654	2.99	3.16	0.115	649	3.09	3.06	0.812
Patient's desire for referral	652	2.18	2.27	0.496	652	2.30	2.14	0.056
Patient's age	652	3.24	3.37	0.258	652	3.28	3.33	0.740
Patient's comorbid medical conditions	650	2.95	3.05	0.380	650	2.99	3.01	0.718
Distance patient has to travel for the referral	646	3.51	3.64	0.235	646	3.60	3.55	0.445

The following scale was used for quantification of the physicians' decision: 1 = extremely important in my decision making about referral; 2 = very important; 3 = somewhat important; 4 = not too important; 5 = not at all important in my decision making about referral.

Perception with stage IV lung cancer

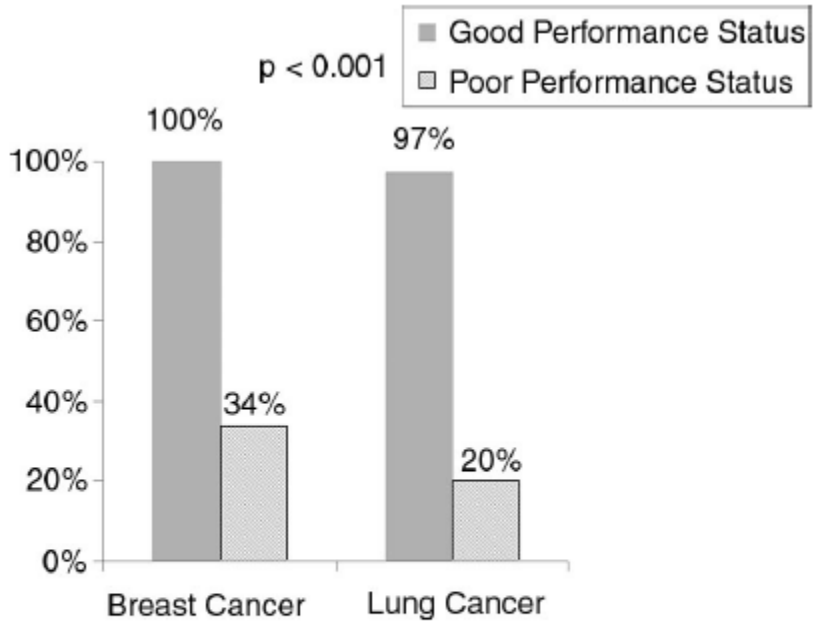


FIGURE 1. Number of patients with advanced-stage breast or lung cancer and with both good (<2) and poor (>2) performance status who would be referred to a medical oncologist.

Perception with stage IV lung cancer

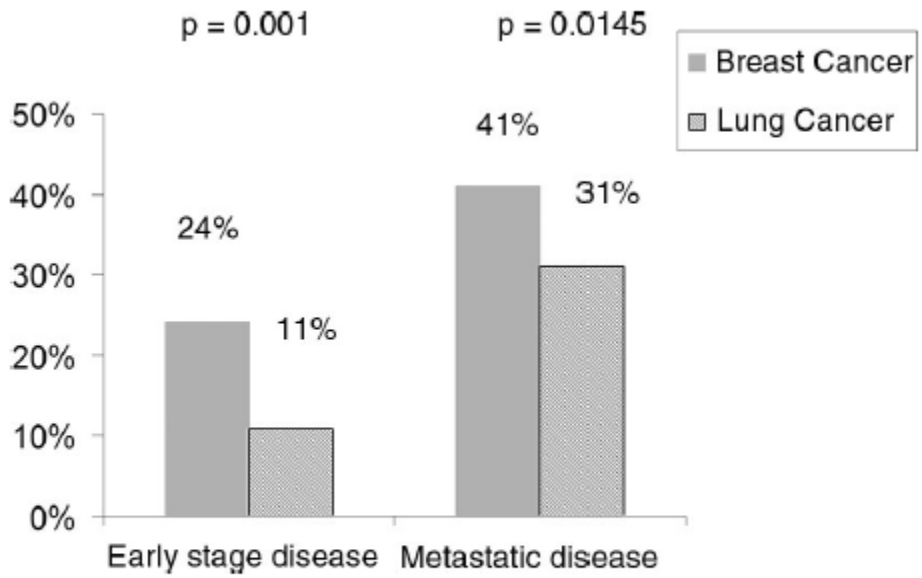


FIGURE 2. Percentage of physicians who felt that the patients with both early-stage and metastatic disease would have improved survival with chemotherapy.

More effective treatment

- Palliative care
- Palliative care
- Palliative care

- Chemotherapy
- Targeted therapy
  - Two genetic mutations currently in use to find targeted therapy: EGFR/ALK
- Immunotherapy
- Palliative RT

More effective treatment

- Chemotherapy
  - 4 cycles of platinum doublet +/- maintenance chemotherapy
  - Contemporary OS: 14 months

2013 JCO Paz-Ares LG

More effective treatment

- EGFR mutation
  - Generally non-smoker, younger, Asian female patients but still present in smoker, older, non-Asian male patients (~10-15%)
  - Need to test everyone
  - Asian patients – need to be very persistent in obtaining the testing (>20%, and in non-smoker females, up to 50%)

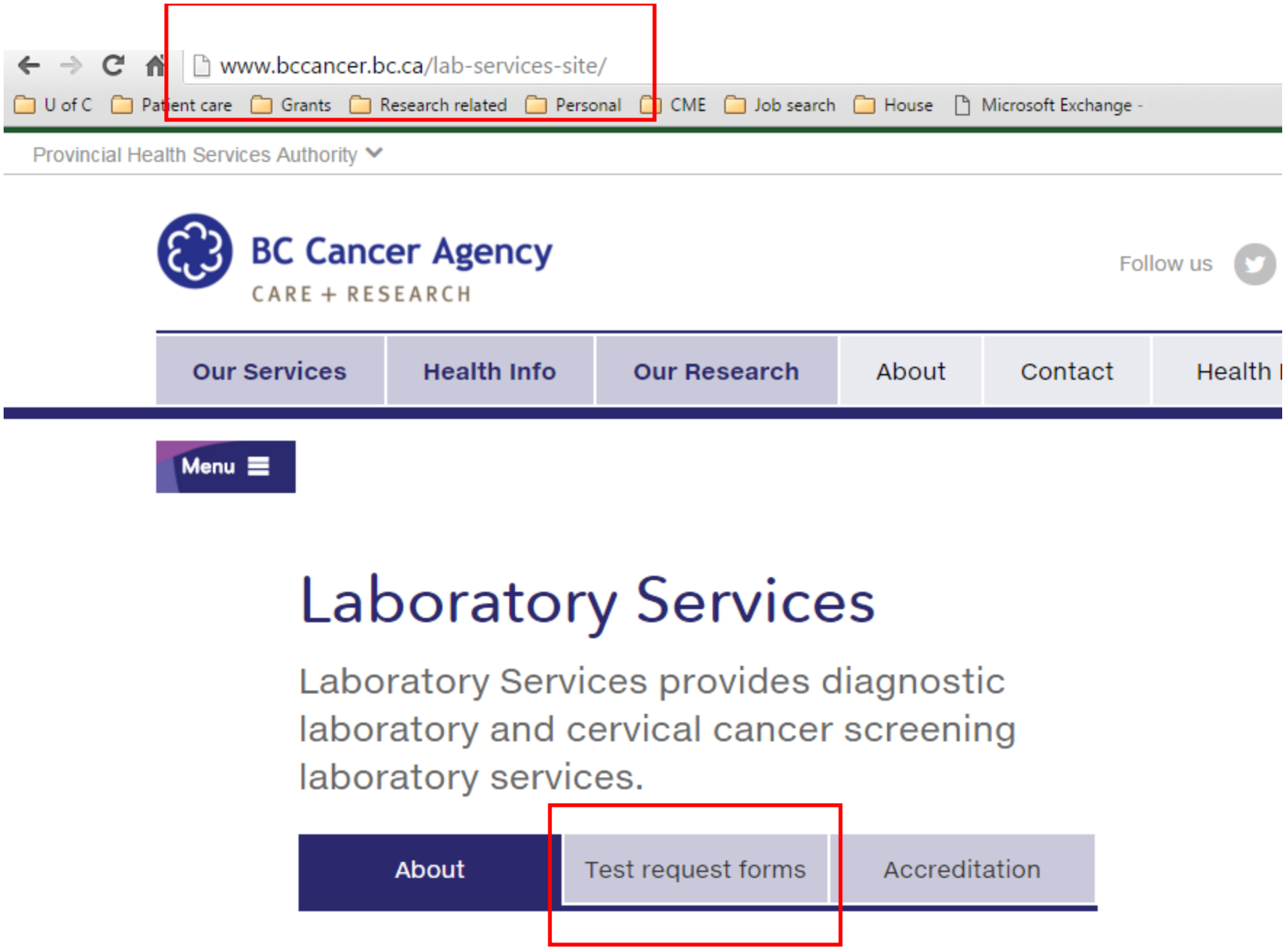
More effective treatment

- EGFR mutation
  - Contemporary OS 19 months, PFS 9 months
  - Potentially even longer with third-generation EGFR TKI (PFS 19m!)

2009 NEJM Mok TS; 2011 JCO Fukuoka M; 2012 Lancet Oncology Rosell R; 2014 Lancet Oncology Wu Y-L Lux –Lung 6; 2015 NEJM Janne

More effective treatment

- ALK mutation
  - 3%
  - However, if positive, ALK inhibitor very effective (similar numbers as EGFR TKIs)


www.bccancer.bc.ca/lab-services-site/
U of C
Patient care
Grants
Research related
Personal
CME
Job search
House
Microsoft Exchange -
Provincial Health Services Authority
BC Cancer Agency
CARE + RESEARCH
Follow us
Our Services
Health Info
Our Research
About
Contact
Health
Menu
Laboratory Services
Laboratory Services provides diagnostic laboratory and cervical cancer screening laboratory services.
About
Test request forms
Accreditation

These forms are updated regularly, they can also be found under the appropriate section heading. Please only use the current form and do not write in other tests that are not on the form.
All files are in pdf format.

Cancer genetics

Cancer Genetics Hematological Request Form

Cancer Genetics Solid Tumour Request Form

The following are now on the above form please do not use old forms:- ALK/EGFR; BRAF; GIST; KRAS

Cancer Genetics RET index testing requisition

CANCER GENETICS LABORATORY

BRITISH COLUMBIA CANCER AGENCY
DEPT. OF PATHOLOGY AND LABORATORY MEDICINE
ROOM 3305 - 600 WEST 10TH AVENUE
VANCOUVER BC V5Z-4E6

604-877-6000 EXT 67-2094
WWW.CANCERGENETICSLAB.CA
INFO@CANCERGENETICSLAB.CA
WWW.BCCANCER.BC.CA

BC Cancer Agency
CARE + RESEARCH

Provincial Health Services Authority
Province-wide solutions. Better health.

ADDRESSOGRAPH OR PATIENT LABEL

SOLID TUMOUR TESTING REQUISITION

See www.cancergeneticslab.ca for current Myeloid, Lymphoid, Solid Tumor and Hereditary test information and requisitions

Requesting Physician: Please complete and sign this requisition and then fax to the originating hospital lab holding the specimen
Lab: Please ship specimen with copies of this form and path report to: BCCA Pathology - Room 3225, 600 West 10th Avenue, Vancouver BC V5Z 4E6

PATIENT INFORMATION

Last Name	First and Middle Names		
Date of Birth dd/mmm/yyyy	Sex ☐ M ☐ F	PHN	BCCA ID#

REQUESTING PHYSICIAN

Name	MSC
Phone	Fax
Address	

SPECIMEN

Specimen Type	Originating Hospital	Collection Date dd/mmm/yyyy
☐ FFPE Block ☐ CGL Specimen ☐ Other_____	Referring lab/Hospital Sample ID	Tissue Type
	Tumour Content	Tumour Cellularity

COPY PHYSICIANS (ALL INFORMATION IS NECESSARY)

Name	MSC
Address	
Name	MSC
Address	
Name	MSC
Address	

REASON FOR TESTING/DIAGNOSIS/CLINICAL HISTORY (REQUIRED FOR TEST TO PROCEED)

MOLECULAR

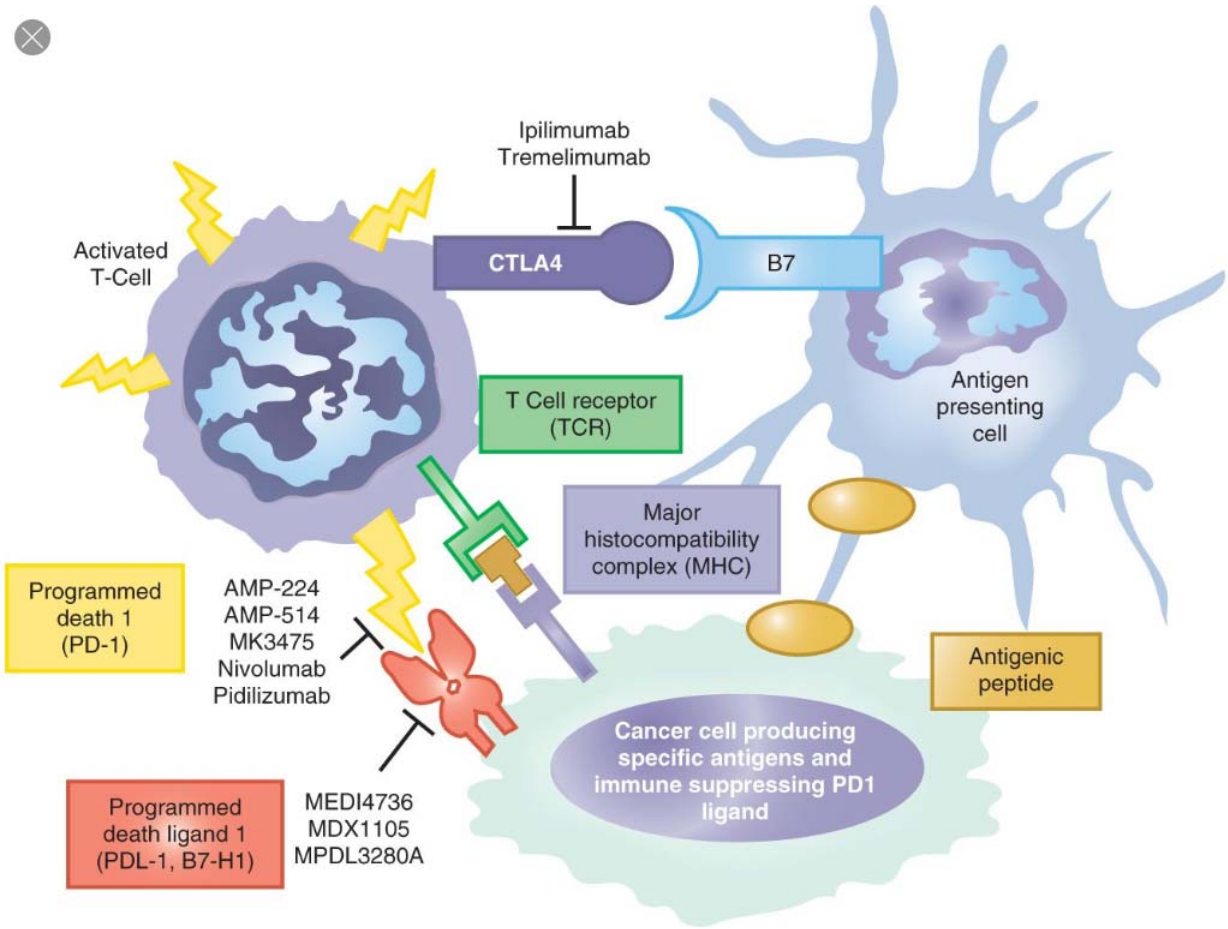
Select Oncopanel OR single-gene testing, both cannot be performed. Samples with limiting DNA may instead receive single-gene testing for the provided indication.
Tests requiring less than 14 day turnaround should select single-gene assay.

	Oncopanel (14-21 days)	Single-gene testing (<14 days)
Colorectal Cancer (Metastatic)	☐ Oncopanel	☐ *KRAS* (codons 12,13)
Gastrointestinal Stromal Tumour (GIST)	☐ Oncopanel	☐ *KIT* ☐ *PDGFRA*
Glioblastoma Multiforme		☐ *MGMT* promoter methylation
Low Grade Glioma	☐ Oncopanel	
Lung Cancer (Stage IIIB/IV Non-Squamous, Non-Neuroendocrine)	☐ Oncopanel, PDL1,*ALK* IHC/2p23 FISH	☐ *EGFR*, PDL1, *ALK* IHC/2p23 FISH
Melanoma (Non-Resectable/Metastatic)	☐ Oncopanel	☐ *BRAF* (V600 E,D,K)

CYTOGENETICS (FISH)

Alveolar Soft Part Sarcoma	Germ Cell Tumours	Oligodendroglioma (ODG)

Immunotherapy



Attempts (successes)

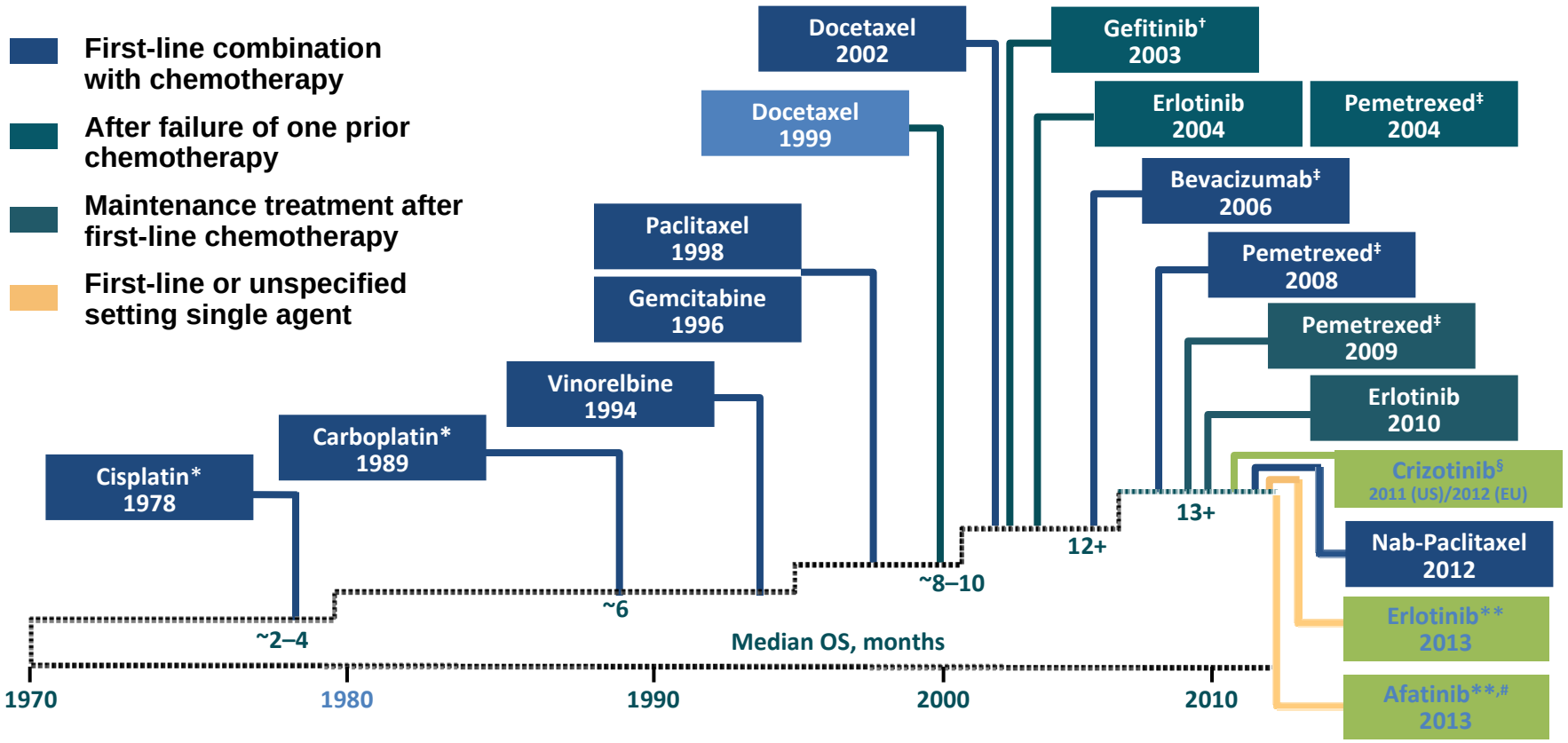
- Cancer vaccine (Sipuleucel T)
- Adaptive cell transfer (CAR cell therapy)
- Therapeutic antibodies (trastuzumab emtansine)
- Immune system modulator (IFN alpha, IL-2)

And now..

- Checkpoint inhibitors

- = stop the immune system breaks or regulatory/suppressor signals

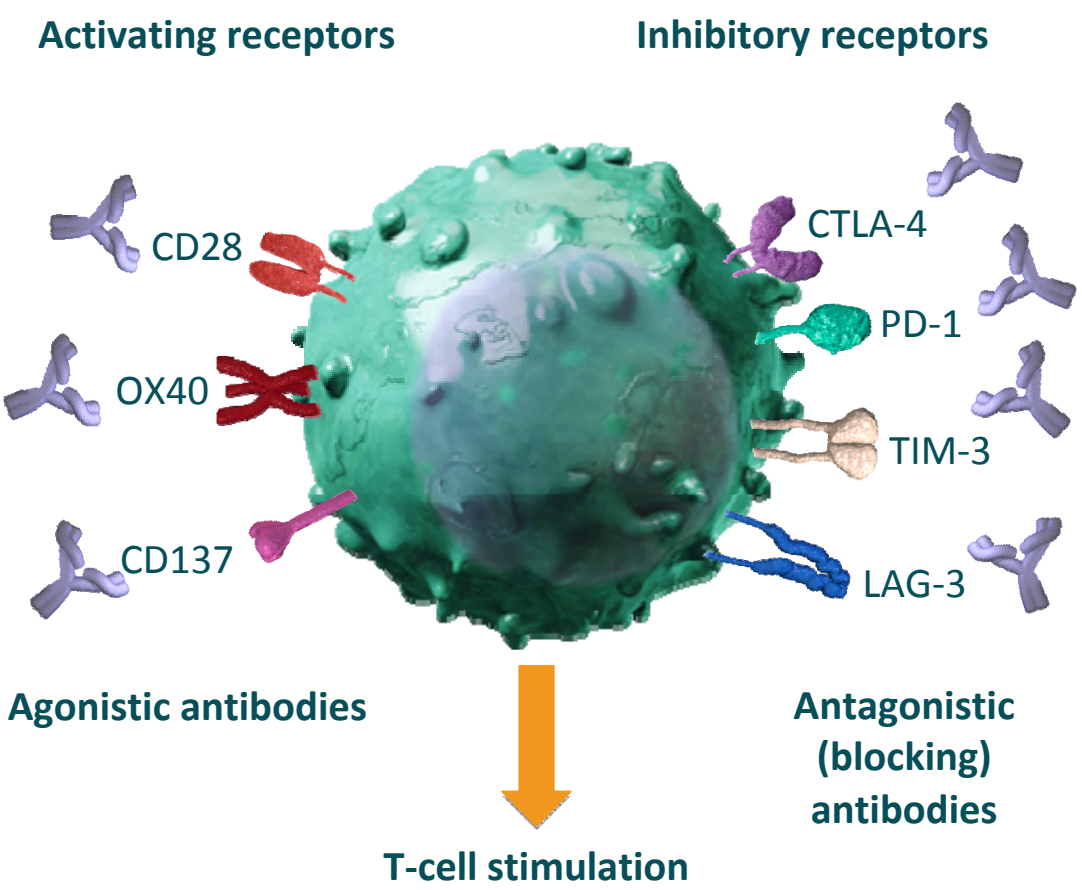
Despite Advances, Only Small Incremental OS Benefits in Overall Patient Population



*Not approved in NSCLC, but commonly used; †Restricted to patients participating in a clinical trial or continuing to benefit from treatment already initiated; ‡Non-squamous NSCLC only; § ALK-positive NSCLC only; **EGFR exon 19 deletions or exon 21 (L858R) substitution mutations only; #Afatinib is approved for the treatment of patients with activating EGFR mutations but only PFS data have been published (May 2014).

U.S. Food and Drug Administration. Available at www.fda.gov. Accessed September 2014; European Medicines Agency. Available at http://www.ema.europa.eu. Accessed September 2014; NCCN Guidelines. Non-small cell lung cancer. v3.2014.

T-cell Checkpoint Regulation



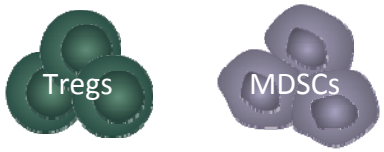
- T-cell responses are regulated though a complex balance of inhibitory ("checkpoint") and activating signals
- Tumours can dysregulate these pathways and consequently, the immune response
- Targeting these pathways is an evolving approach to cancer therapy

Adapted from Mellman I, *et al*. *Nature* 2011; 480(7378):480-9; Pardoll DM. *Nat Rev Cancer* 2012; 12(4):252-64.

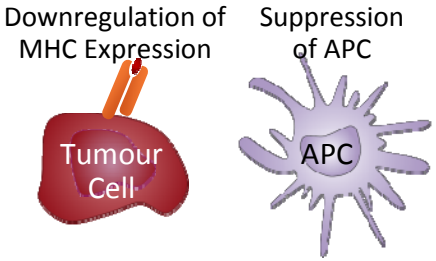
Immune Escape in Cancer

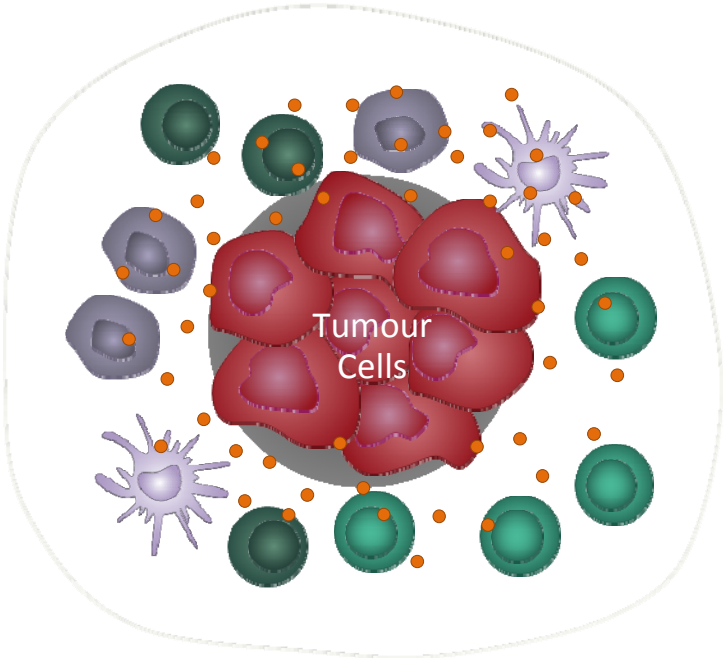
Many tumours escape the immune response by creating an immunosuppressive microenvironment that prevents an effective antitumour response[1,2]

Recruitment of immunosuppressive cells



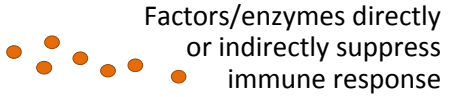
Ineffective presentation of tumour antigens to the immune system



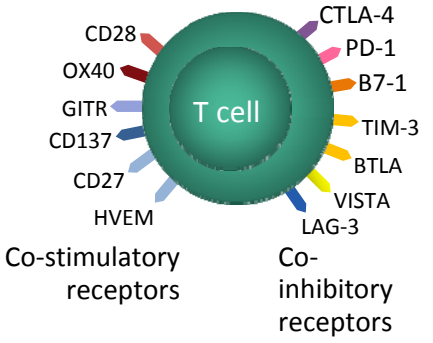


Tumour Microenvironment

Release of immunosuppressive factors



T-cell checkpoint dysregulation

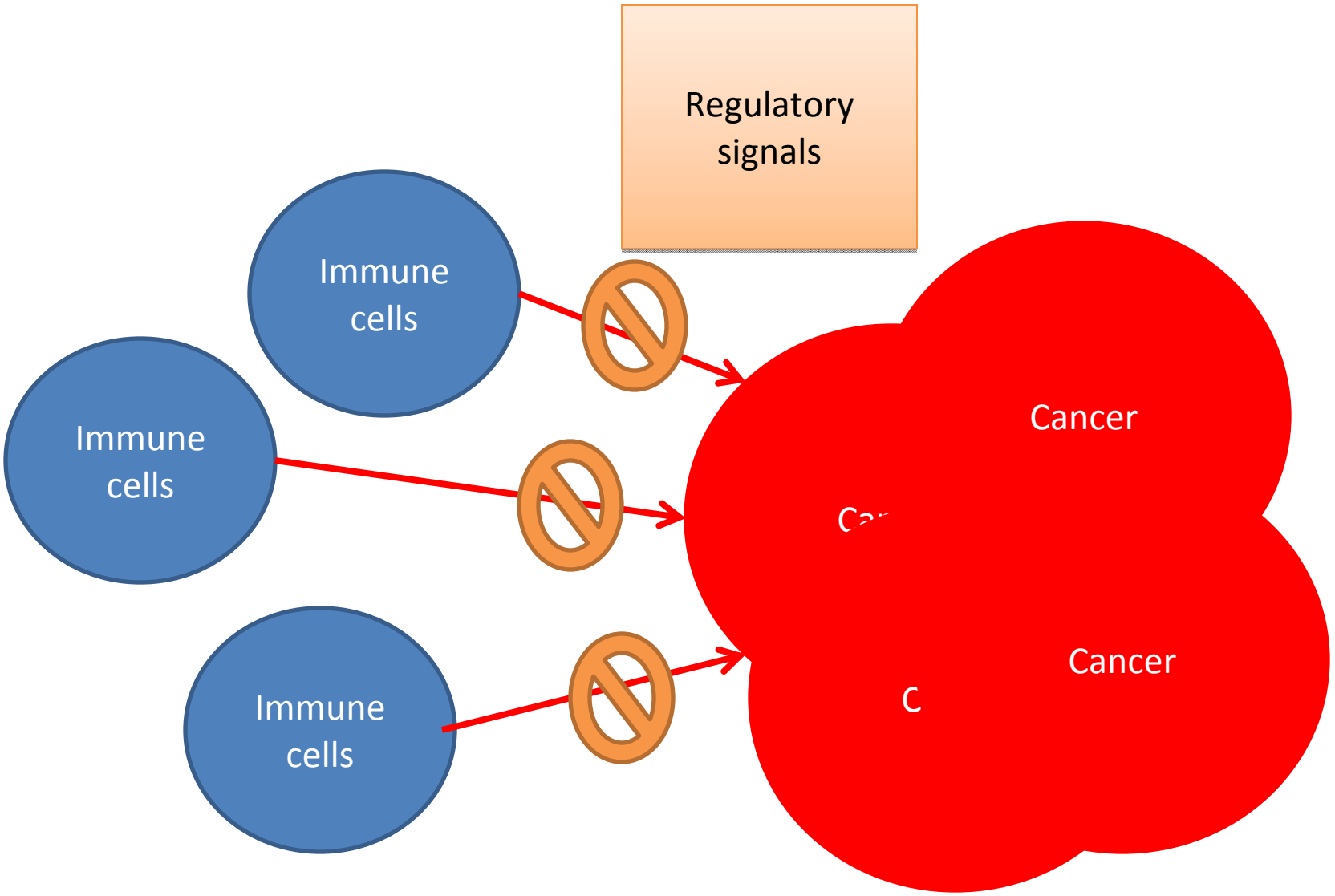


The mechanisms tumours use to escape the immune system provide a range of potential therapeutic targets for cancer

APC=antigen-presenting cell; MDSC=myeloid-derived suppressor cell; MHC=major histocompatibility complex; Treg=regulatory T cell.

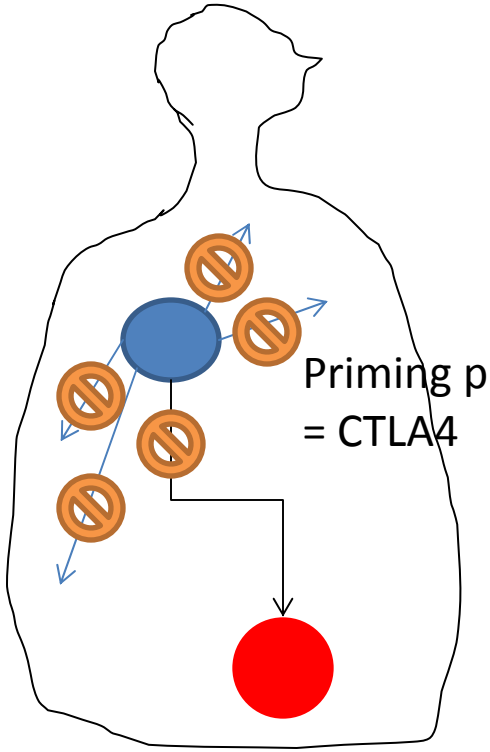
1. Bremnes RM *et al*. *J Thorac Oncol*. 2011;6:824-833. 2. Jadus MR *et al*. *Clin Dev Immunol*. 2012:160724.

Checkpoint inhibitors

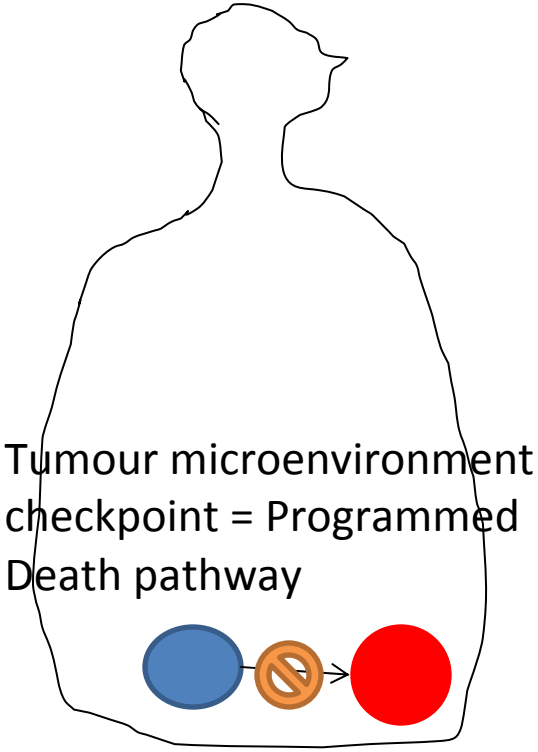


Checkpoint inhibitors

- T regulatory signals

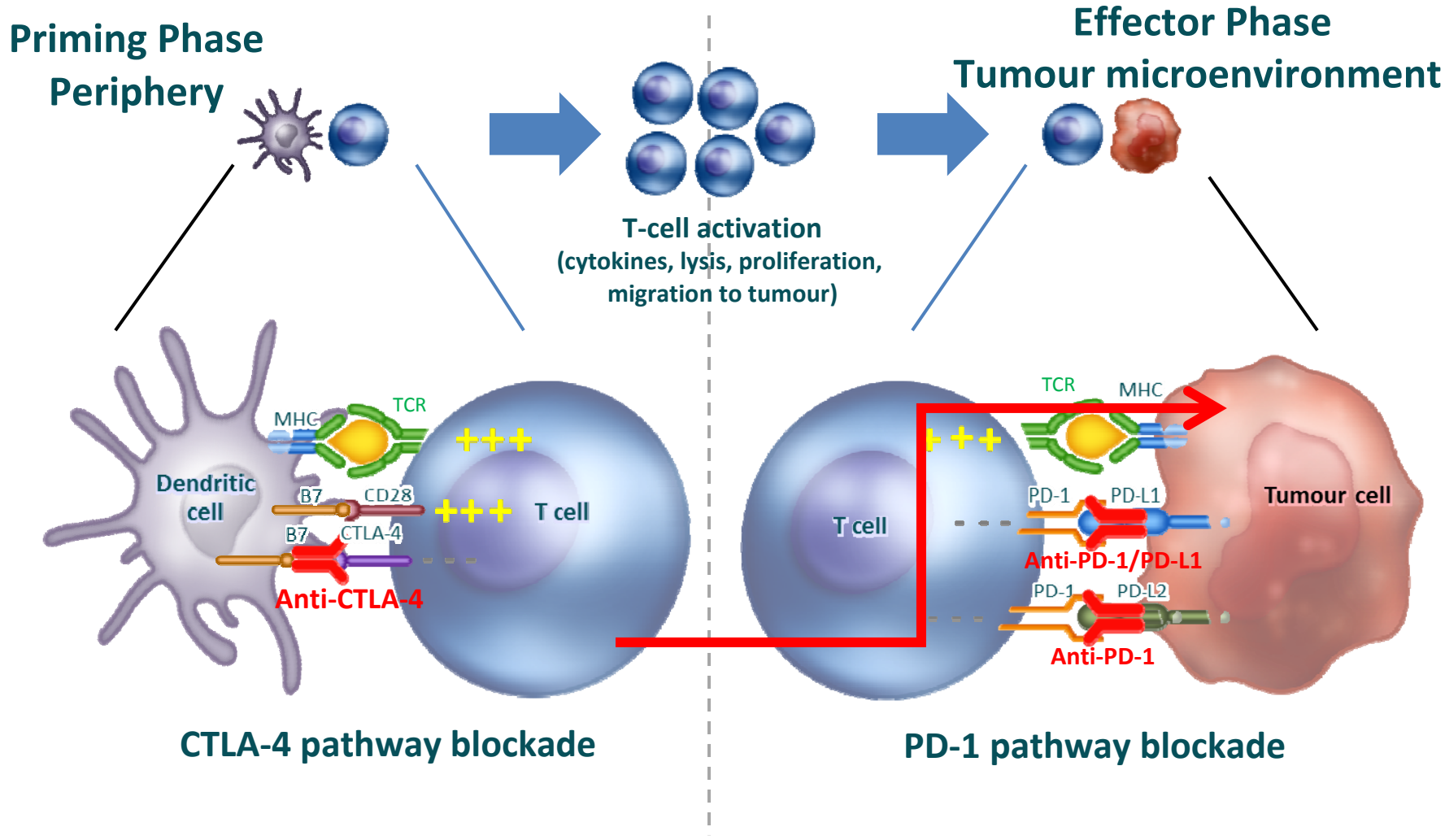


Priming phase
= CTLA4



Tumour microenvironment checkpoint = Programmed Death pathway

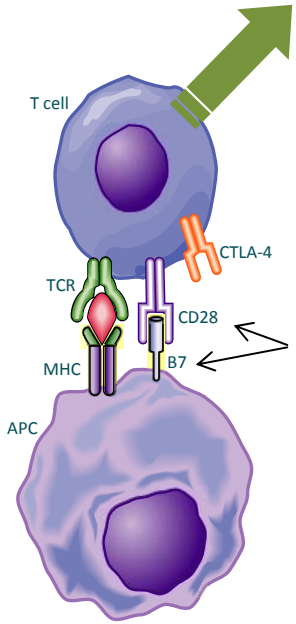
Immuno-oncology: Blocking CTLA-4 and PD-1 Pathways with Monoclonal Antibodies



CTLA-4=cytotoxic T-lymphocyte antigen-4; PD-1=programmed cell death 1; PD-L1/2=PD ligand 1/2; TCR=T cell receptor.
Adapted from Wolchock J, *et al*. Oral presentation at ASCO 2013 (Abstract 9012).

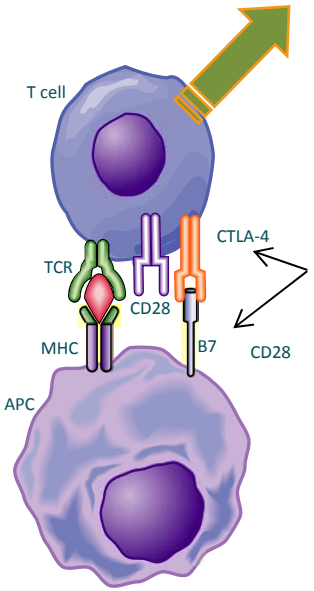
CTLA-4 inhibitor = ipilimumab etc

T-cell activation



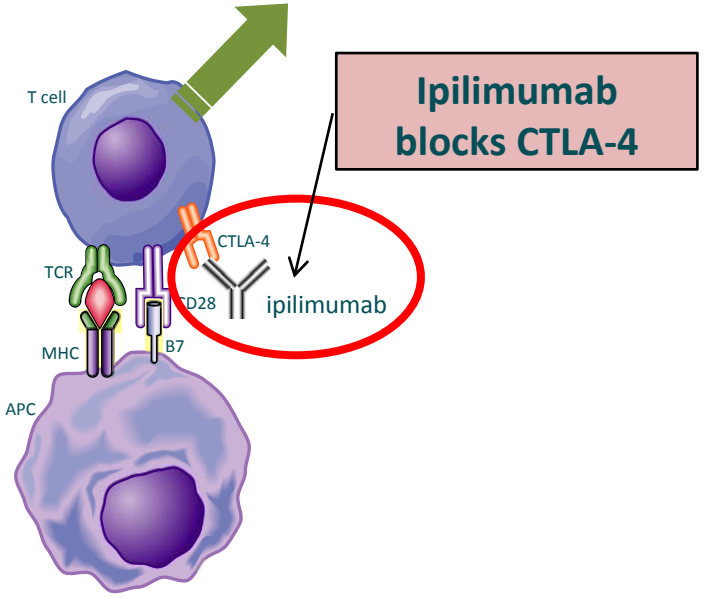
Antigen presentation and ligation of B7/CD28 co-activators results in T-cell activation

T-cell inhibition



In the activated T cell, CTLA-4 competes with CD28 and acts as the brakes on T-cell activation by binding to B7

T-cell activation and proliferation



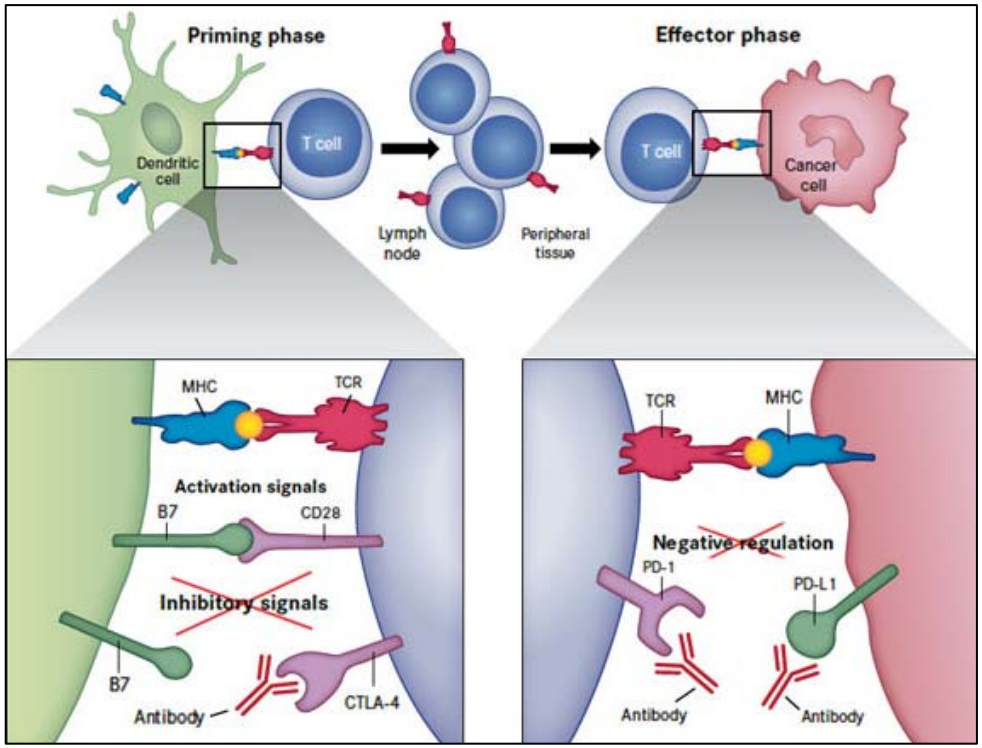
By inhibiting CTLA-4, ipilimumab releases the natural braking system and restores T-cell activation, allowing T-cell proliferation to continue

B7: B7.1 (CD80) or B7.2 (CD86)

APC=antigen-presenting cell; CTLA-4=cytotoxic T-lymphocyte-associated antigen-4; MHC=major histocompatibility complex; TCR=T-cell receptor.
Adapted from Lebbé C, *et al*. *Ann Oncol* 2008; 19(suppl 8):viii289-viii311.

PD-1 and PD-L1 Antibodies = nivolumab, pembrolizumab, atezolizumab etc

- PD-1 – inhibitory receptor found on activated lymphocytes and monocytes and is associated with tumour immune escape
- Binds with PD-L1 on tumour cells
- Interaction between PD-1 and PD-L1 suppresses the cytotoxic T-cell response



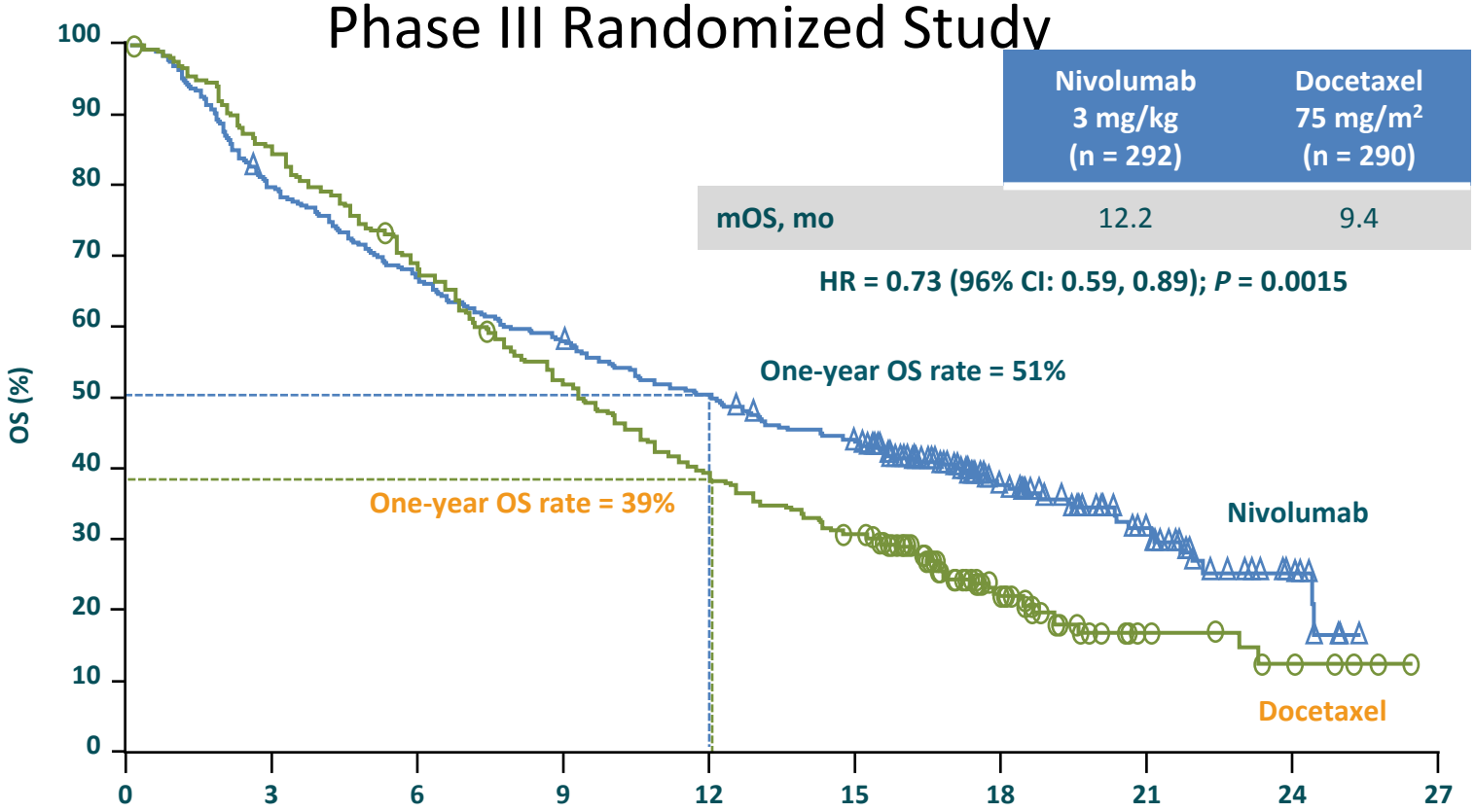
Adapted from *N Engl Med*. 2012;366(26):2517

CheckMate-057

Overall Survival with Nivolumab vs. Docetaxel for Pretreated Non-squamous NSCLC Patients: Phase III Randomized Study

	Nivolumab 3 mg/kg (n = 292)	Docetaxel 75 mg/m^2 (n = 290)
mOS, mo	12.2	9.4

HR = 0.73 (96% CI: 0.59, 0.89); *P* = 0.0015



Number of Patients at Risk

Nivolumab	292	232	194	169	146	123	62	32	9	0
Docetaxel	290	244	194	150	111	88	34	10	5	0

- **Nivolumab decreased risk of death by 27% in pretreated, non-squamous NSCLC vs. docetaxel.**
- **Nivolumab significantly improved overall survival of patients with non-squamous NSCLC by 2.8 months vs. docetaxel.**

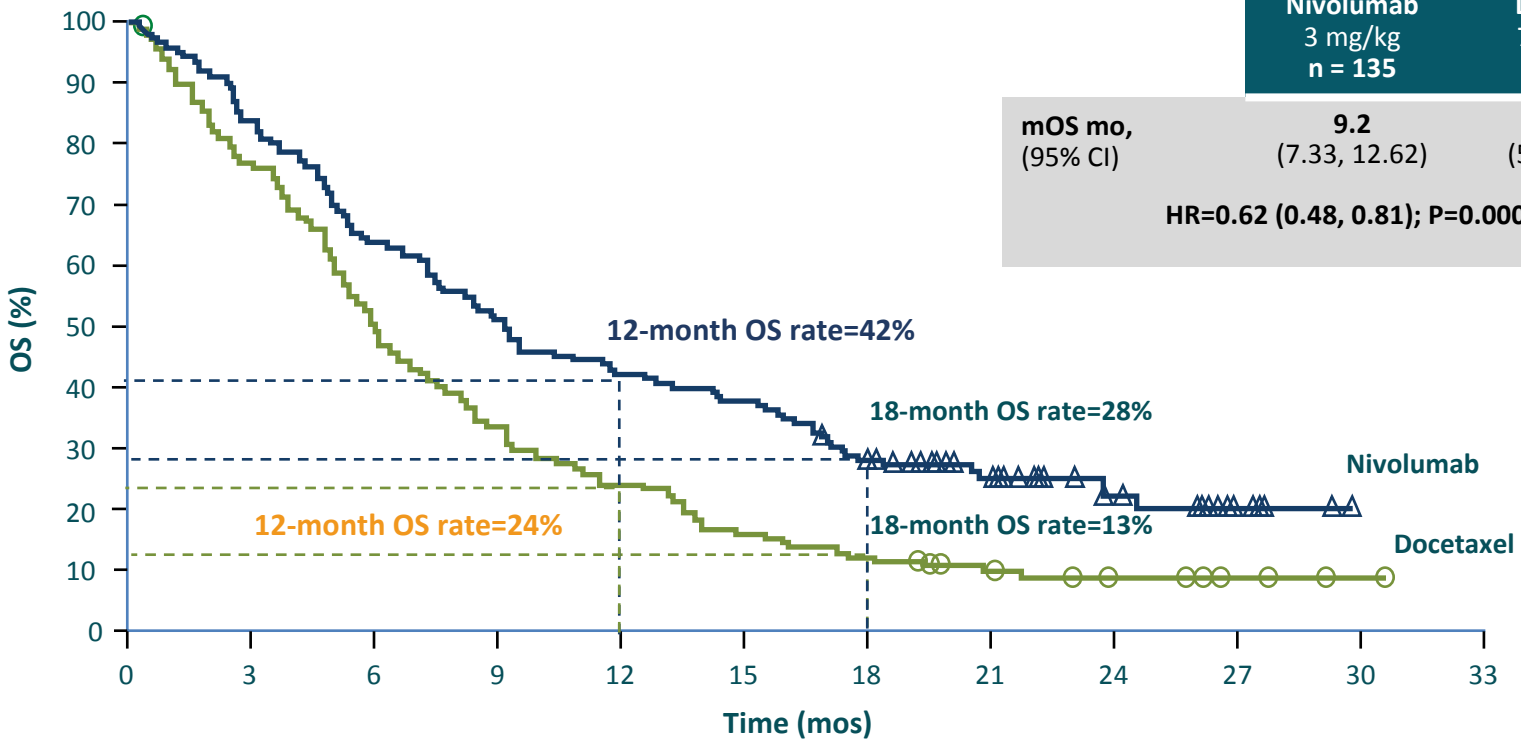
Symbols represent censored observations.

Paz-Arez L et al, Oral presentation. Presented at ASCO 2015.

CheckMate-017

Overall Survival with Nivolumab vs. Docetaxel for Pretreated Squamous NSCLC Patients: Phase III, Randomized Study

	Nivolumab 3 mg/kg n = 135	Docetaxel 75 mg/m² n = 137
mOS mo, (95% CI)	**9.2** (7.33, 12.62)	**6.0** (5.29, 7.39)
HR=0.62 (0.48, 0.81); P=0.0004		



Number of Patients at Risk

Nivolumab	135	113	86	69	57	51	37	25	14	6	0	0
Docetaxel	137	104	69	46	33	22	17	11	7	3	1	0

Minimum follow-up for survival: 18 months

- **Nivolumab decreased risk of death by 41% vs. docetaxel at 1 year and 38% at 18 months**
- **Nivolumab significantly improved median overall survival by 3.2 months vs. docetaxel.**

Reckamp K et al. Presented at World Lung Conference. 2015; Based on August 2015 DBL; symbols refer to censored observations.

Pembrolizumab vs. chemotherapy in first-line NSCLC PD-L1 >=50%

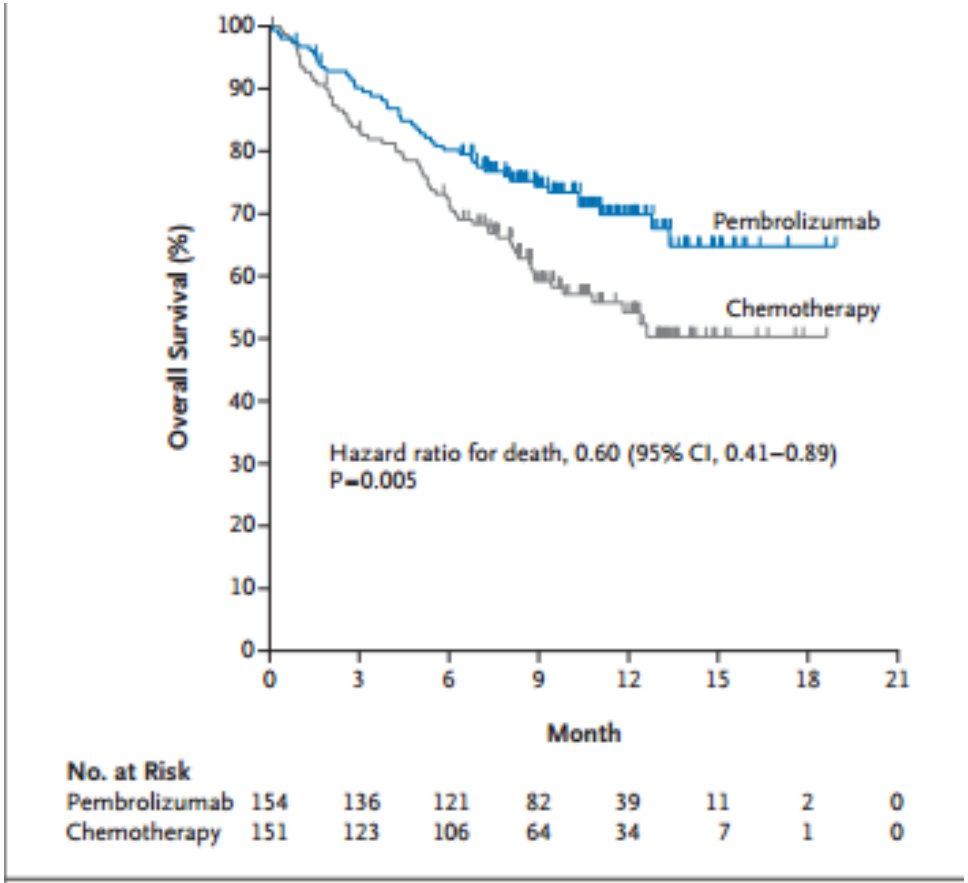


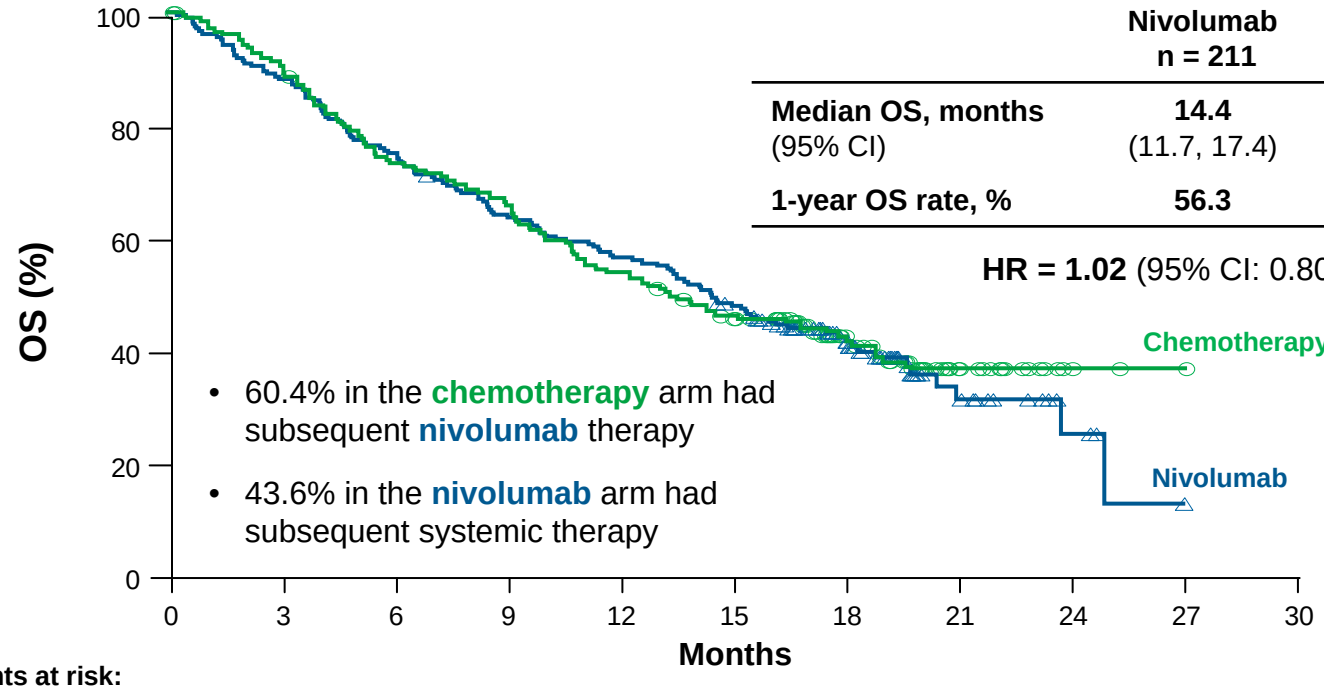
Figure 2. Overall Survival in the Intention-to-Treat Population.

Shown are Kaplan–Meier estimates of overall survival, according to treatment group. Tick marks represent data censored at the last time the patient was known to be alive. The intention-to-treat population included all patients who underwent randomization.

6m survival 80.2 vs 72.4%

Reck N Engl J Med 2016; 375:1823-1833

OS (≥5% PD-L1+)
CheckMate 026: Nivolumab vs Chemotherapy in First-line NSCLC



	Nivolumab n = 211	Chemotherapy n = 212
Median OS, months (95% CI)	**14.4** (11.7, 17.4)	**13.2** (10.7, 17.1)
1-year OS rate, %	**56.3**	**53.6**

HR = 1.02 (95% CI: 0.80, 1.30)

No. of patients at risk:											
Nivolumab	211	186	156	133	118	98	49	14	4	0	0
Chemotherapy	212	186	153	137	112	91	50	15	3	1	0

All randomized patients (≥1% PD-L1+): HR = 1.07 (95% CI: 0.86, 1.33)

Socinski ESMO 2016

Better and earlier palliative care

- We need more palliative care
- On ALL stage IV lung cancer consultations, we need to do the following upfront:
  - Address advance care planning
  - Connect them with palliative home care
  - Apply for palliative benefit
  - Patient needs ongoing and continual face to face support from their primary care physicians (unfortunately, due to time spent in cancer centre, disconnect happens often)
  - Pain and symptom management clinic at BCCA

Better and earlier palliative care

- Patient lives LONGER due to earlier palliative care
- Reduces distress and anxiety by patient and caregiver
- Reduces inappropriate ICU, CPR, critical care
- Patient better prepares for end of life care
- Increased patient satisfaction
- Better and faster response to patient symptom (it is NOT good enough to be able to see cancer patients with significant symptoms in 2-3 weeks)
- Total suffering, spiritual and psychological care

2010 Temel NEJM, 2014 Zimmerman Lancet Oncol

Better and earlier palliative care

The 'surprise' question in advanced cancer patients: A prospective study among general practitioners

Matteo Moroni[1,2]
Donato Zocchi[3]
Deborah Bolognesi[4]
Amy Abernethy[5]
Roberto Rondelli[6]
Giandomenico Savorani[3]
Marcello Salera[3]
Filippo G Dall'Olio[7]
Giulia Galli[7]
Guido Biasco[2,7]
on behalf of the SUQ-P group[3]

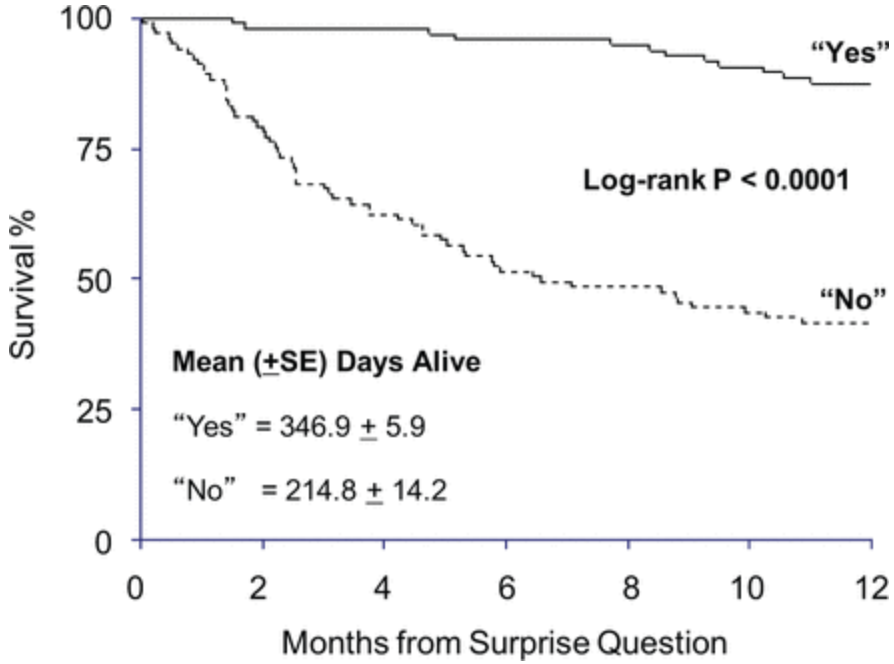
Moroni Palliat Med July 2014 vol. 28 no. 7 959-964

Better and earlier palliative care

Table 2. Sensitivity, specificity, predictive value of the 'surprise' question (231 evaluable cases).

Group	Living	Deceased	Predictive value
'Yes'	88	17	Positive 83.8% CI: 75.3–90.3
'No'	39	87	Negative 69.0% CI: 60.2–77.0

CI: confidence interval.
Sensitivity = 69.3% (CI: 60.5–77.2); specificity = 83.6% (CI: 75.1–90.2); Matthews correlation coefficient (MCC) = 0.53.



Better and earlier palliative care

Table 4. Multivariate Cox regression to predict status at 1 year.

Variable	Hazard ratio	95% CI	*p* value
Site of cancer (pancreas)	2.228	0.772–6.432	0.139
Surprise question (reference = yes)	6.978	2.418–20.134	0.000

CI: confidence interval.

Summary

- Vigilance for potential high risk patients in cancer screening and early diagnosis
- Streamlined FAST diagnostic workup
- Effective treatments on the horizon… but only 1/3 get to them
- EARLY and effective primary and palliative care is critical.

Thank you!