Clinical practice: approaching the reality of individual patients

centro hospitalar do Porto

U.PORTO

INSTITUTO DE CIÊNCIAS BIOMÉDICAS ABEL SALAZAR
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Disclosure slide

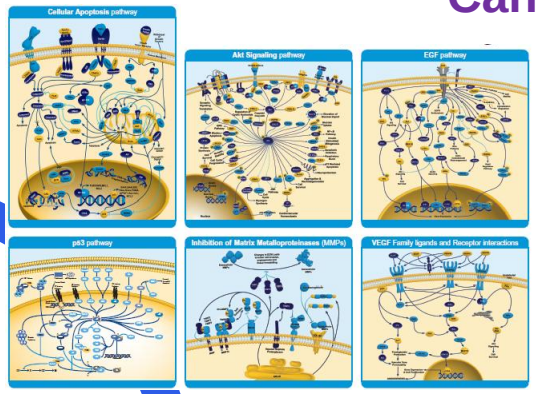
I provided consultations or attended advisory boards for Astra-Zeneca, Eli Lilly Oncology, F. Hoffman-La Roche Ltd, Merck, Astellas and Pfizer, for which I received appropriate honoraria.

All different, yet all equal

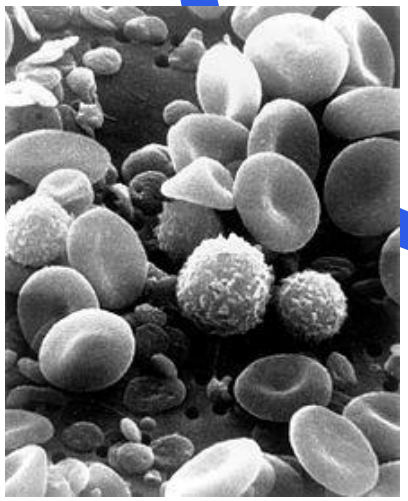
Lung cancer – all different

Patient

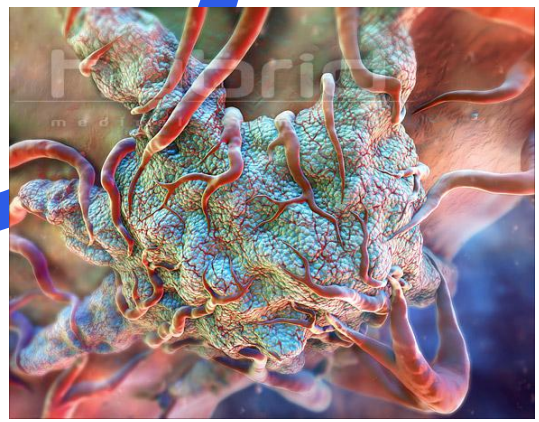
Cancer



Immunity



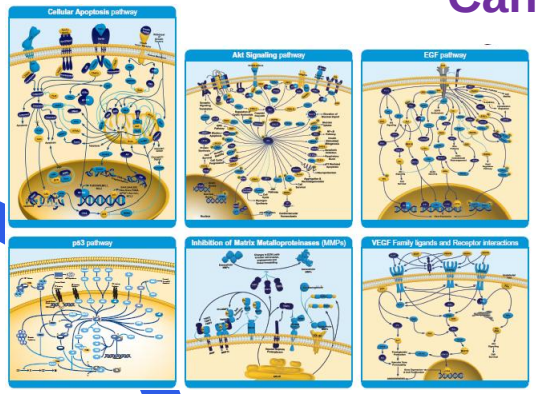
Microenvironment



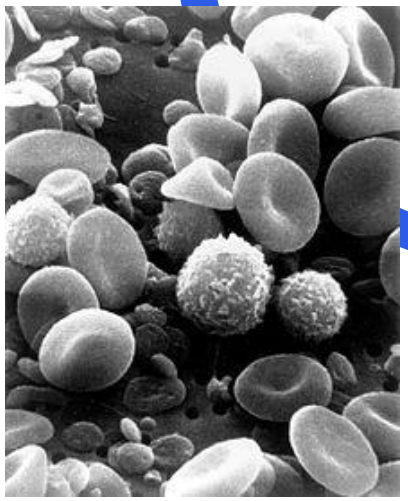
Lung cancer – all different

Patient

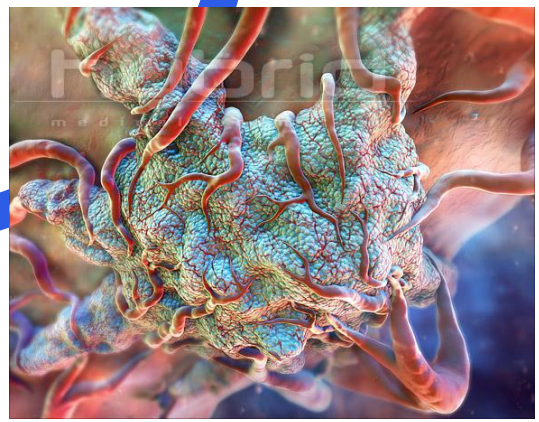
Cancer



Immunity



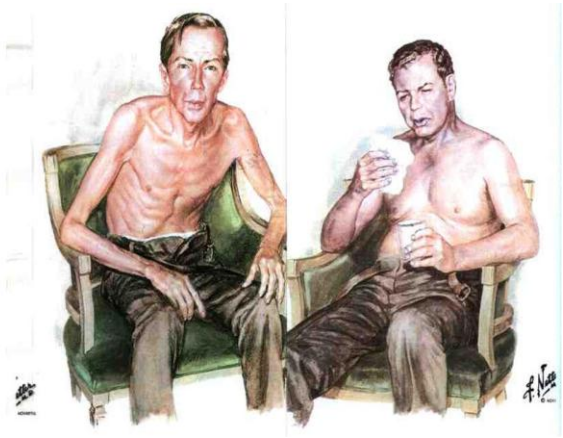
Microenvironment



Cancer patient - all equal, yet all different

Age

Comorbidities and PS (driven by cancer or by comorbidities)



Patient preferences

Lung cancer – all different (stage)

Stage 1A **Stage 1A**

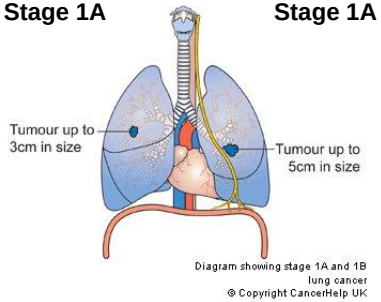


Diagram showing stage 1A and 1B lung cancer

Stage 2A

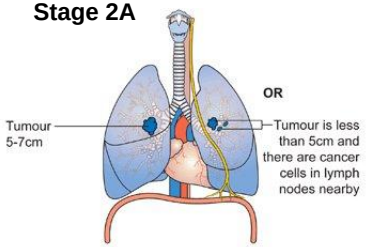


Diagram showing stage 2A lung cancer

Stage 2B

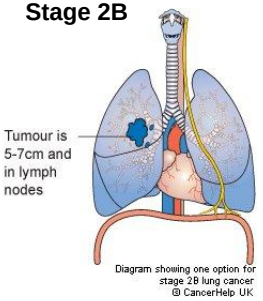


Diagram showing one option for stage 2B lung cancer

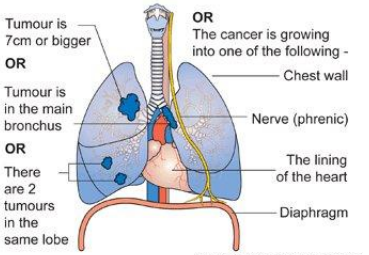


Diagram showing one option for stage 2B lung cancer

Stage 3A

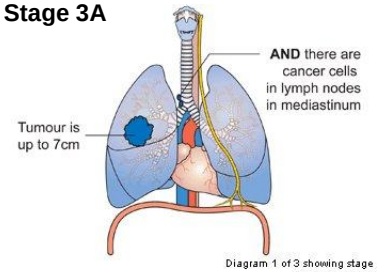


Diagram 1 of 3 showing stage 3A lung cancer

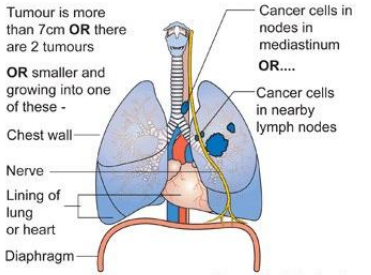


Diagram 2 of 3 showing stage 3A lung cancer

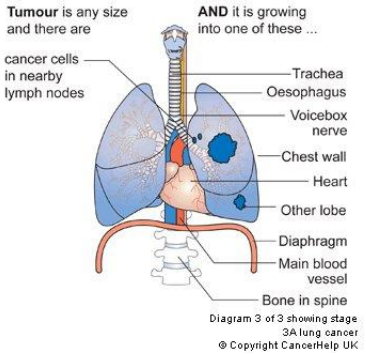


Diagram 3 of 3 showing stage 3A lung cancer

Stage 3B

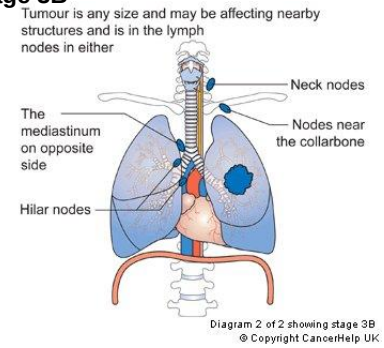


Diagram 2 of 2 showing stage 3B

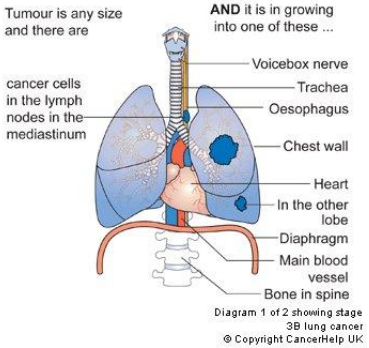


Diagram 1 of 2 showing stage 3B lung cancer

Stage 4

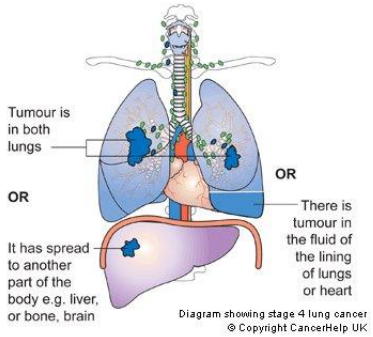
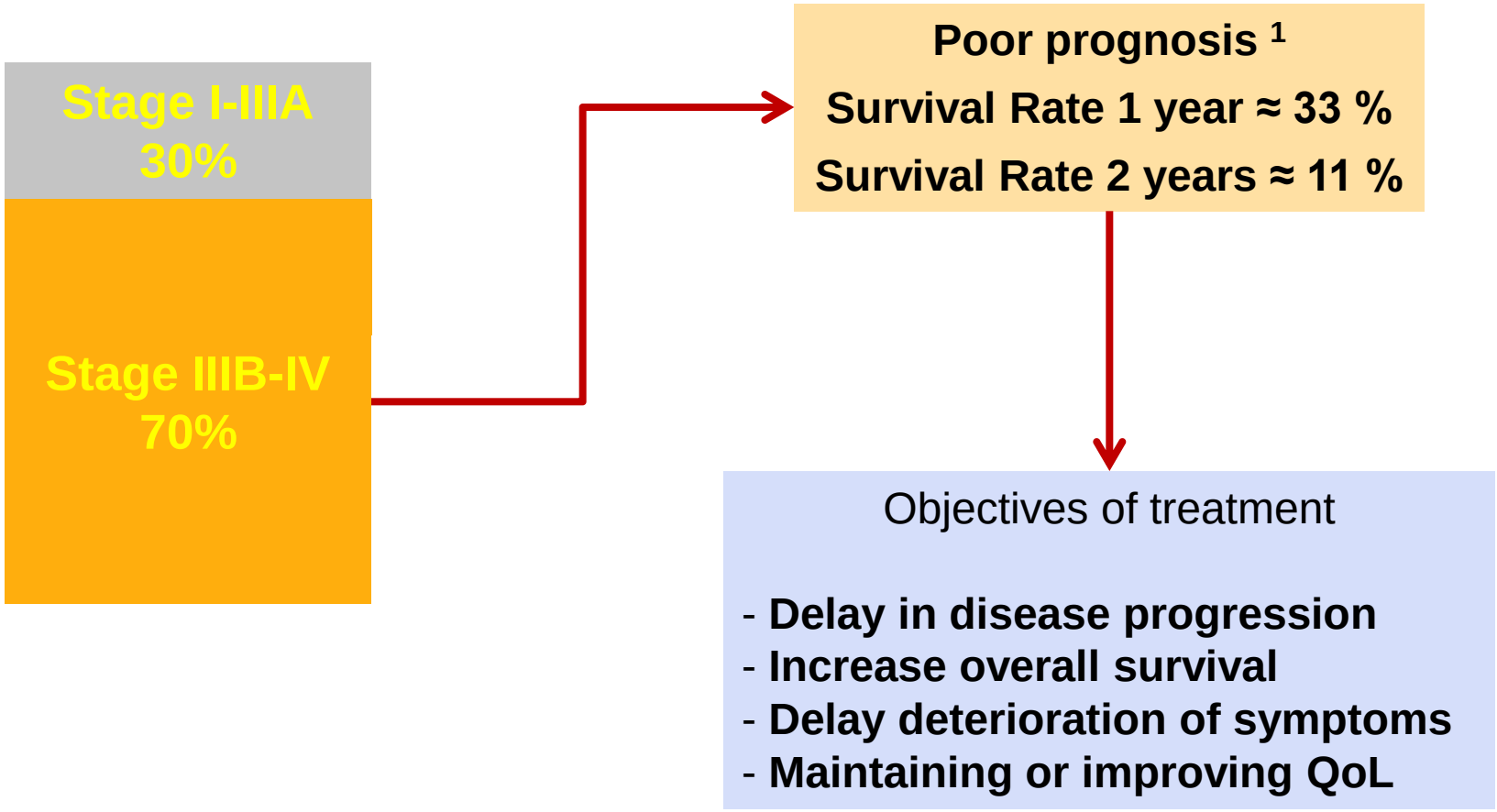


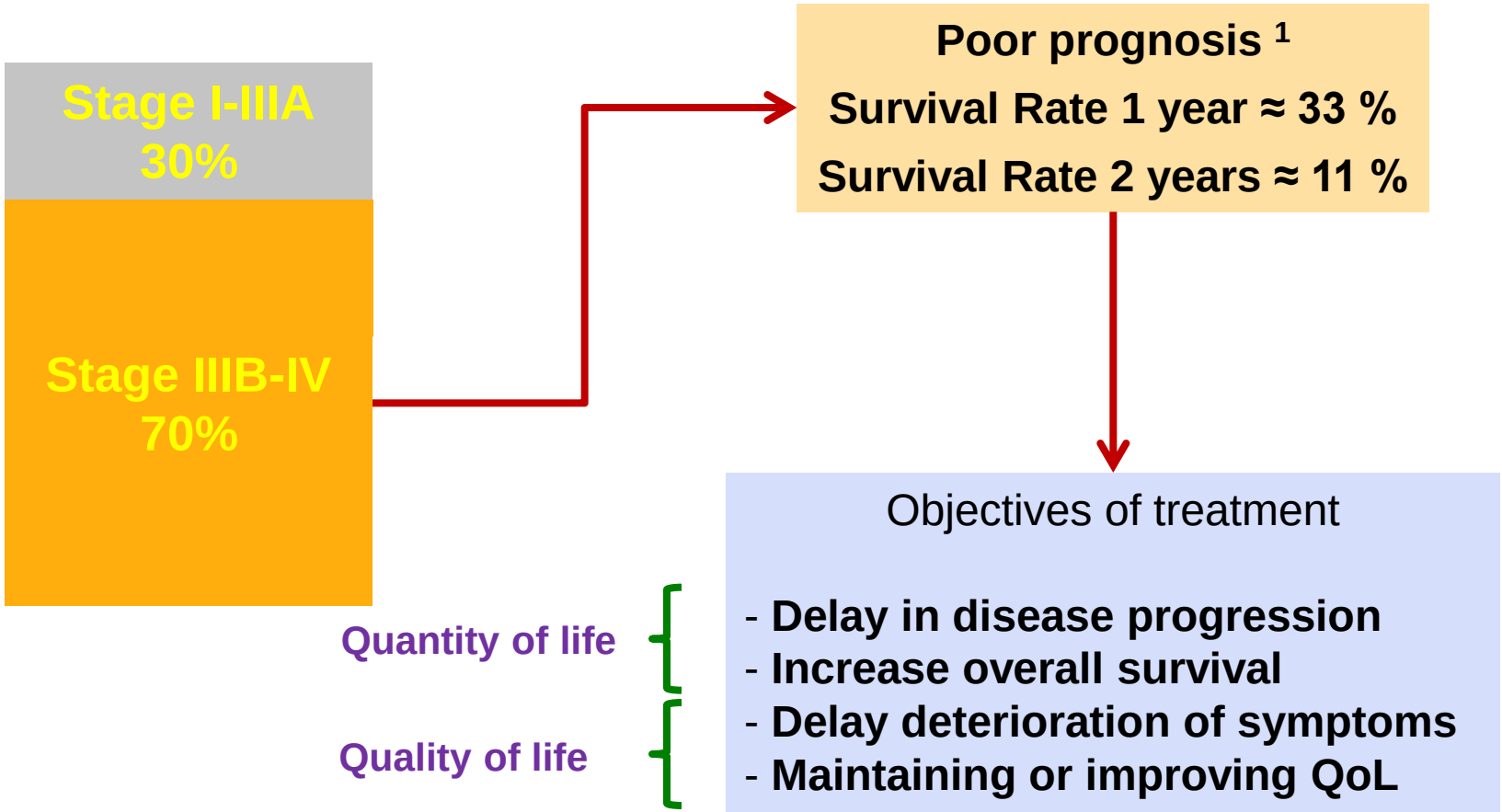
Diagram showing stage 4 lung cancer

NSCLC is a rapidly progressive disease



1. Schiller J et al, N Eng J Med 346:92-98, 2002

NSCLC is a rapidly progressive disease

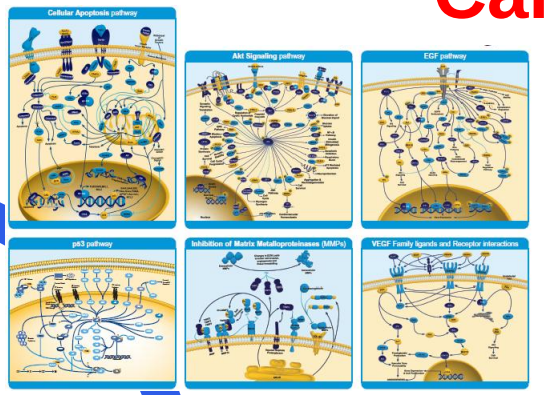


1. Schiller J et al, N Eng J Med 346:92-98, 2002

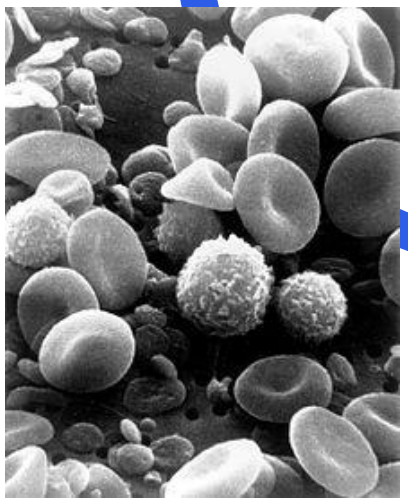
Lung cancer – all different

Patient

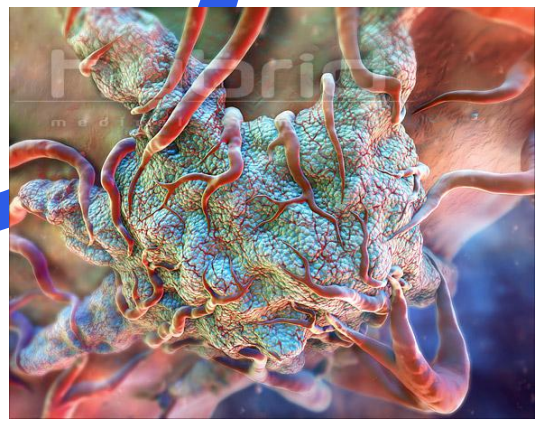
Cancer



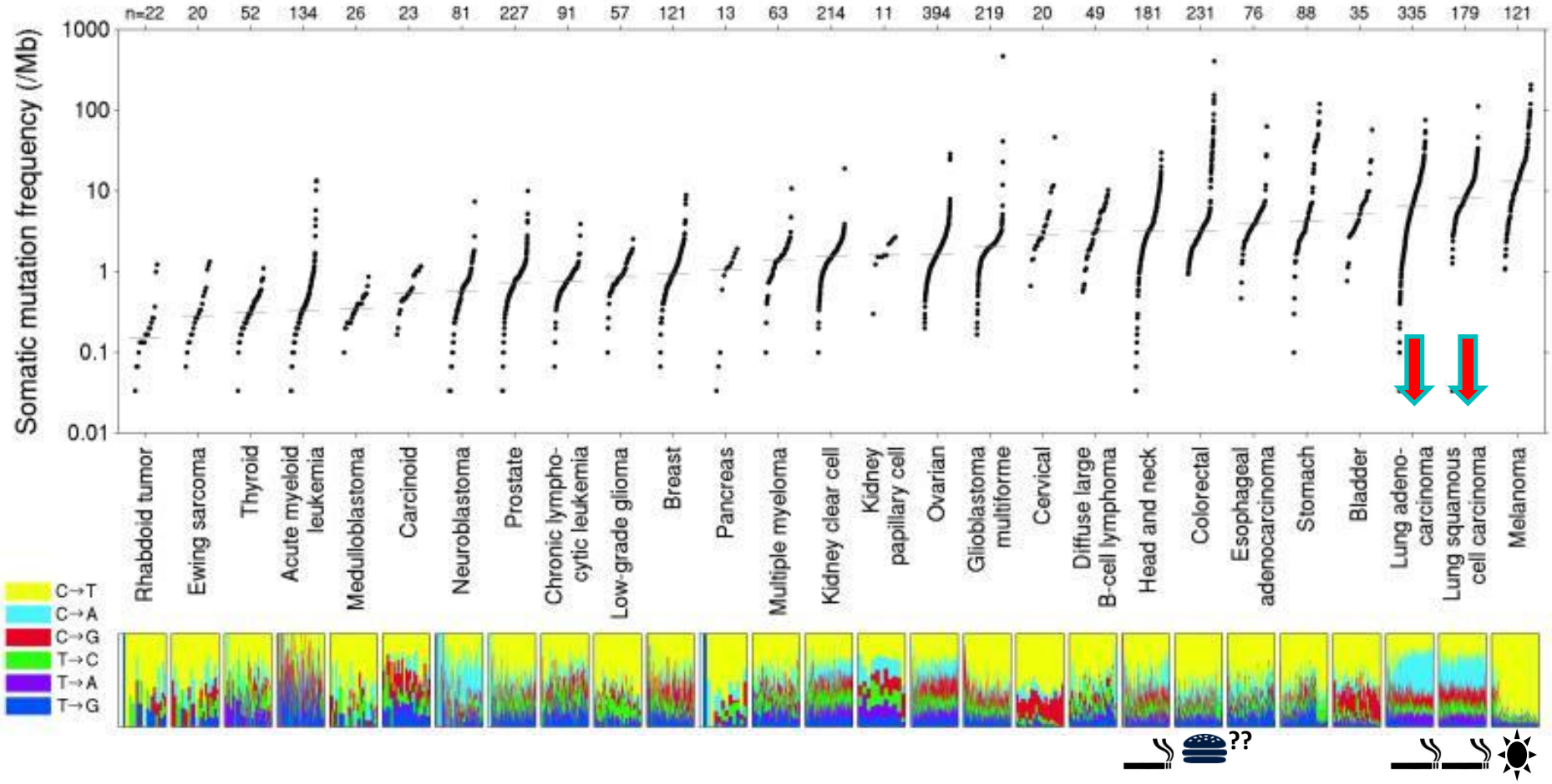
Immunity



Microenvironment

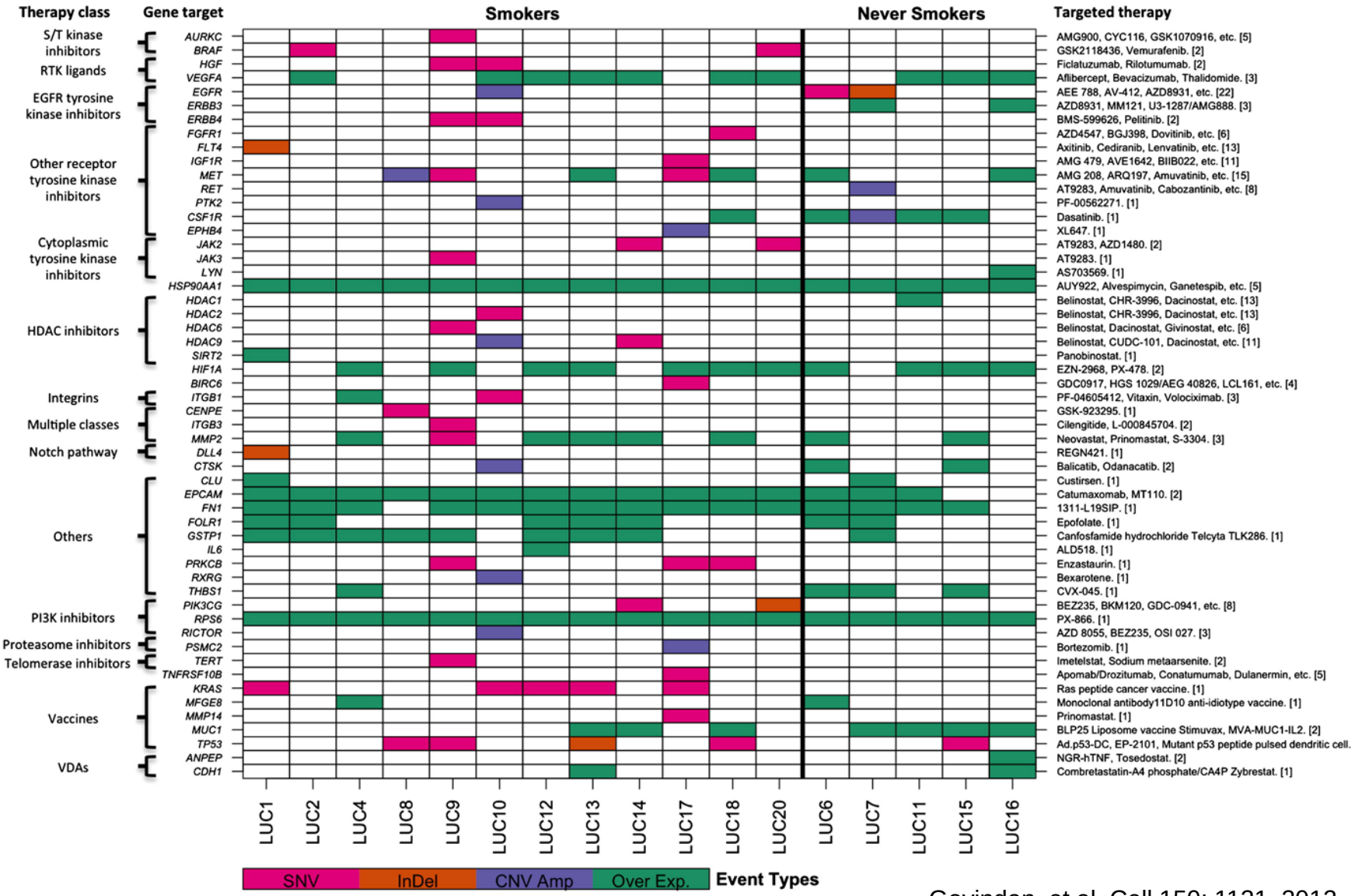


Magnitude of genomic derangement



Lawrence MS, et al. Nature 499: 214-218, 2013

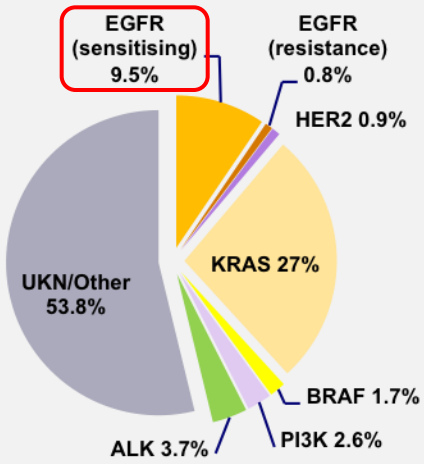
Drugable targets in smokers and never smokers



Govindan ,et al. Cell 150: 1121, 2012

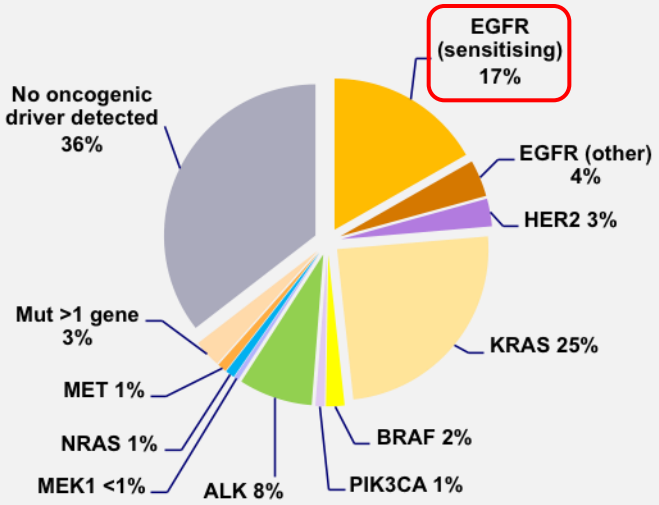
Molecular alterations in lung cancer – racial differences

Europe
All histology



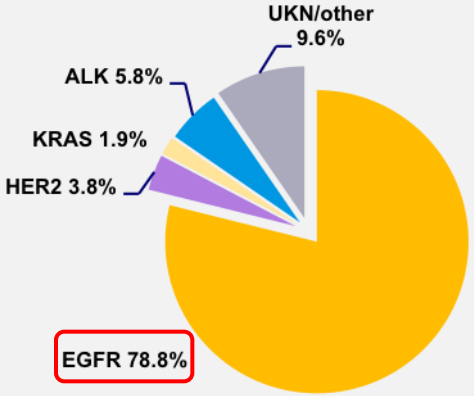
(n=9,911)

US
Adenocarcinoma



(n=733)

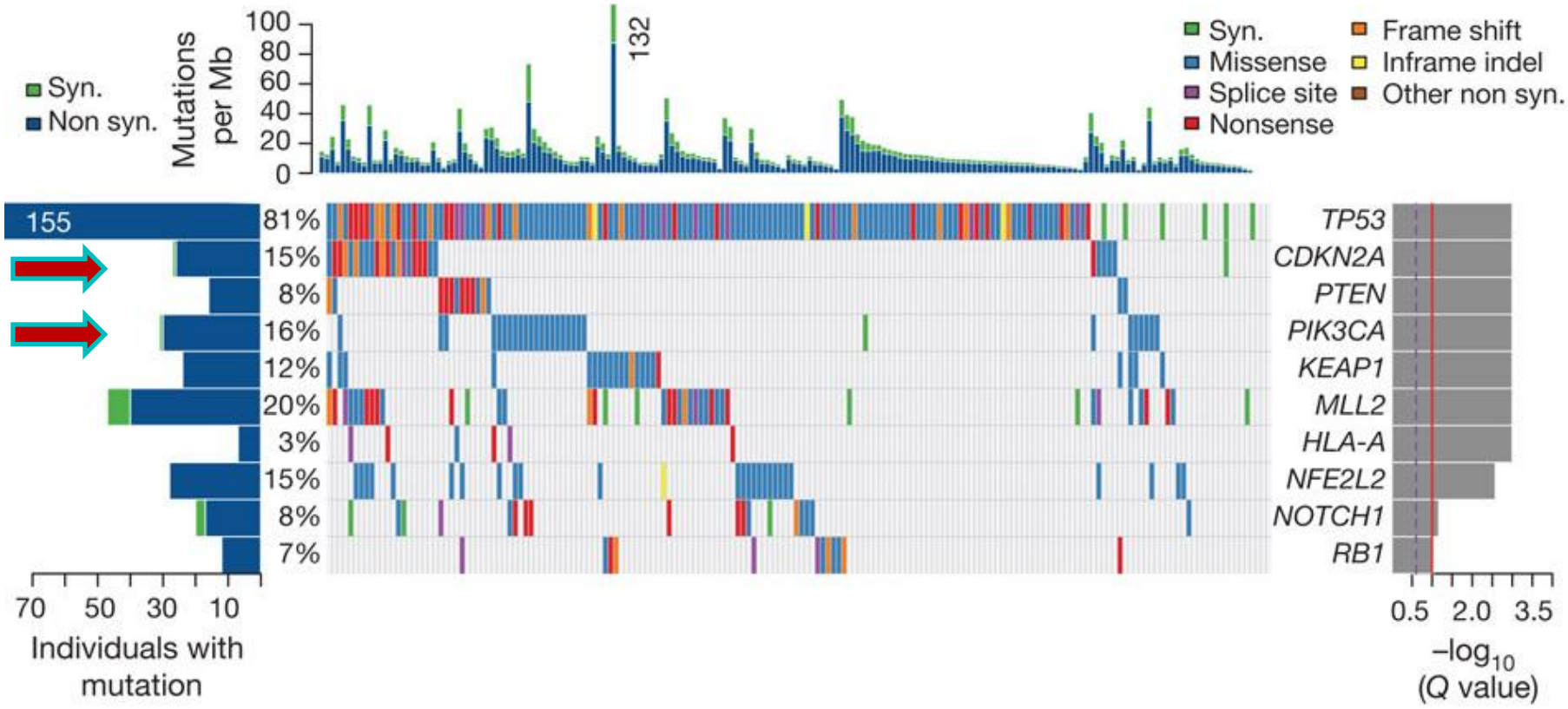
East Asia
Adenocarcinoma, never smokers



(n=52)

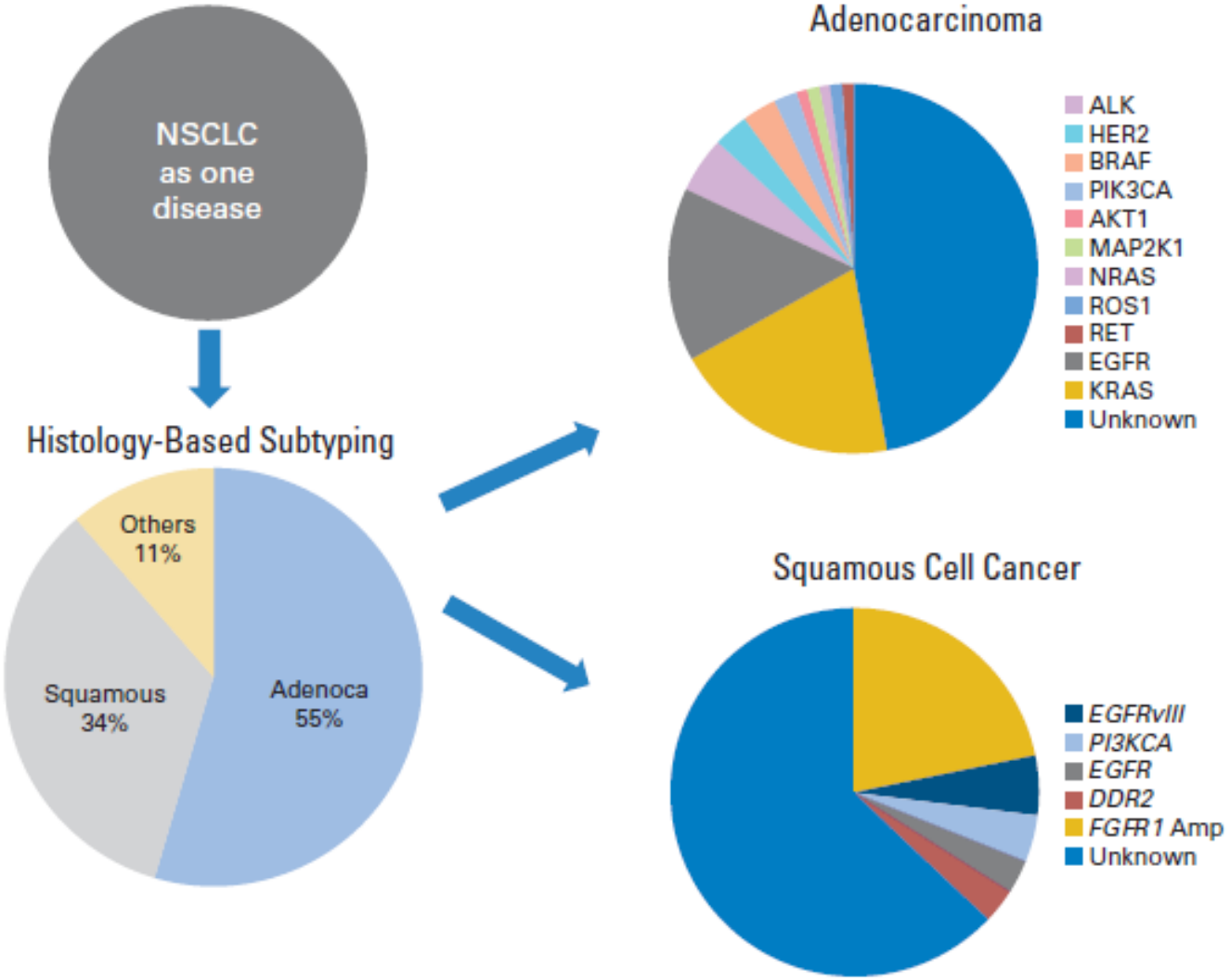
Johnson, et al. ASCO 2013
Sun, et al. J Clin Oncol 2010; Barlesi, et al. ASCO 2013

Significantly mutated genes in squamous NSCLC



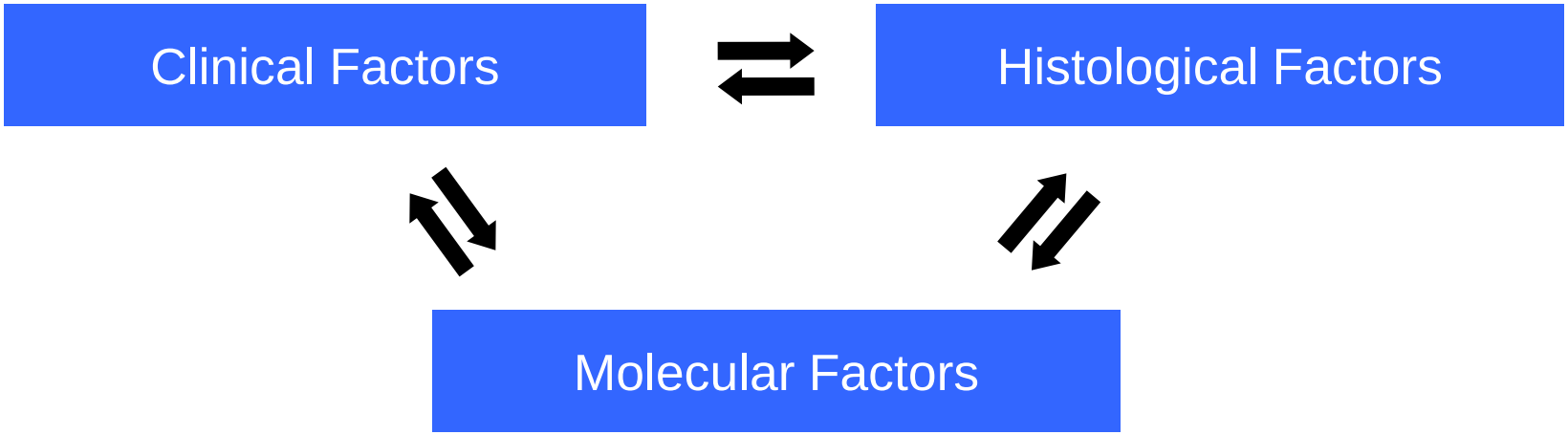
Nature 489:519-525, 2012

Evolution of NSCLC,
from histology to molecular characteristics



Li T, et al. JCO, 2013

Individualized therapy of lung cancer

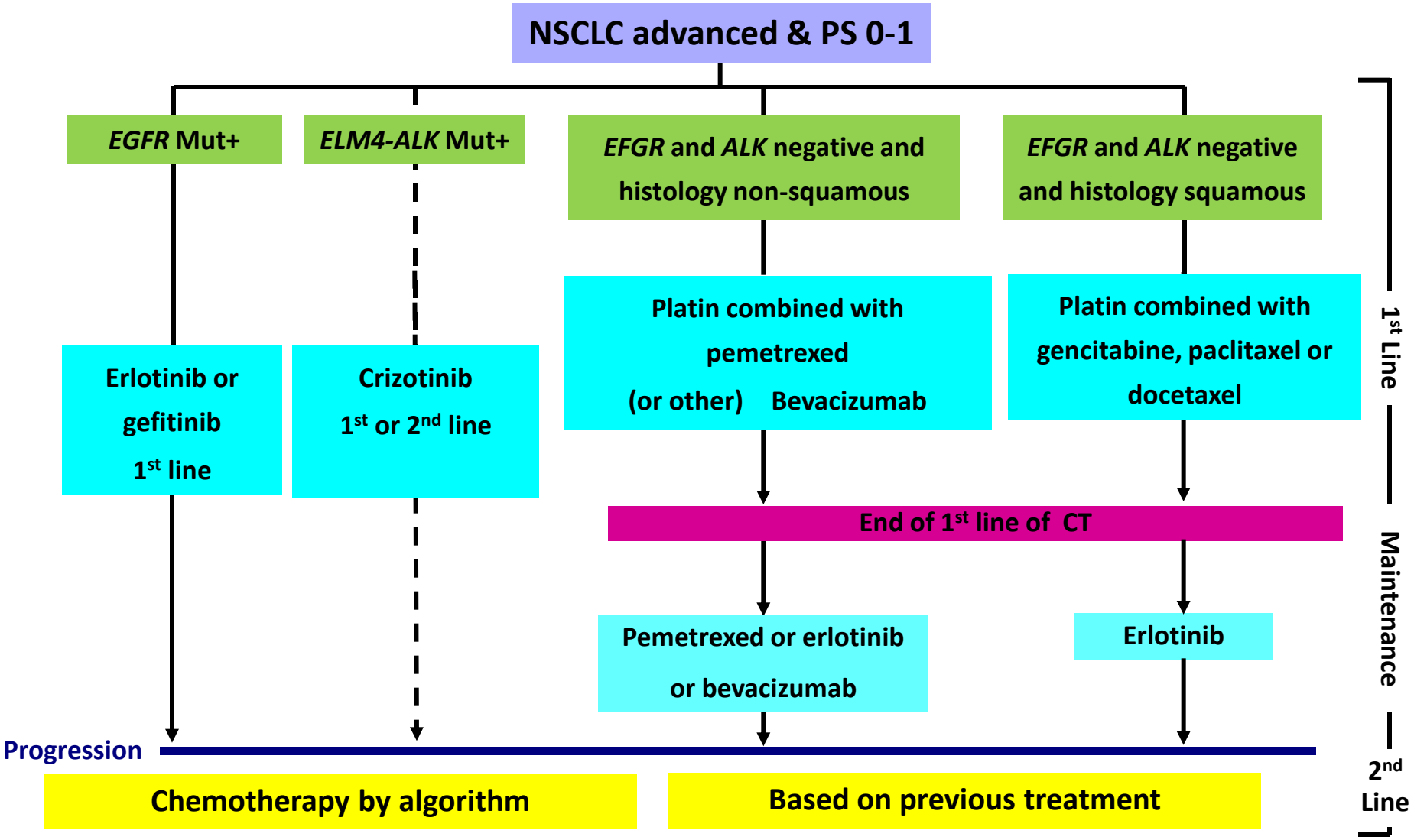


Factors are interrelated and are not independent

From therapy “one size fits all” to “tailored”

Updated from Gandara DR, et al. Clin Lung Cancer 10:392-394, 2009

Algorithm for the treatment of advanced NSCLC in 2014



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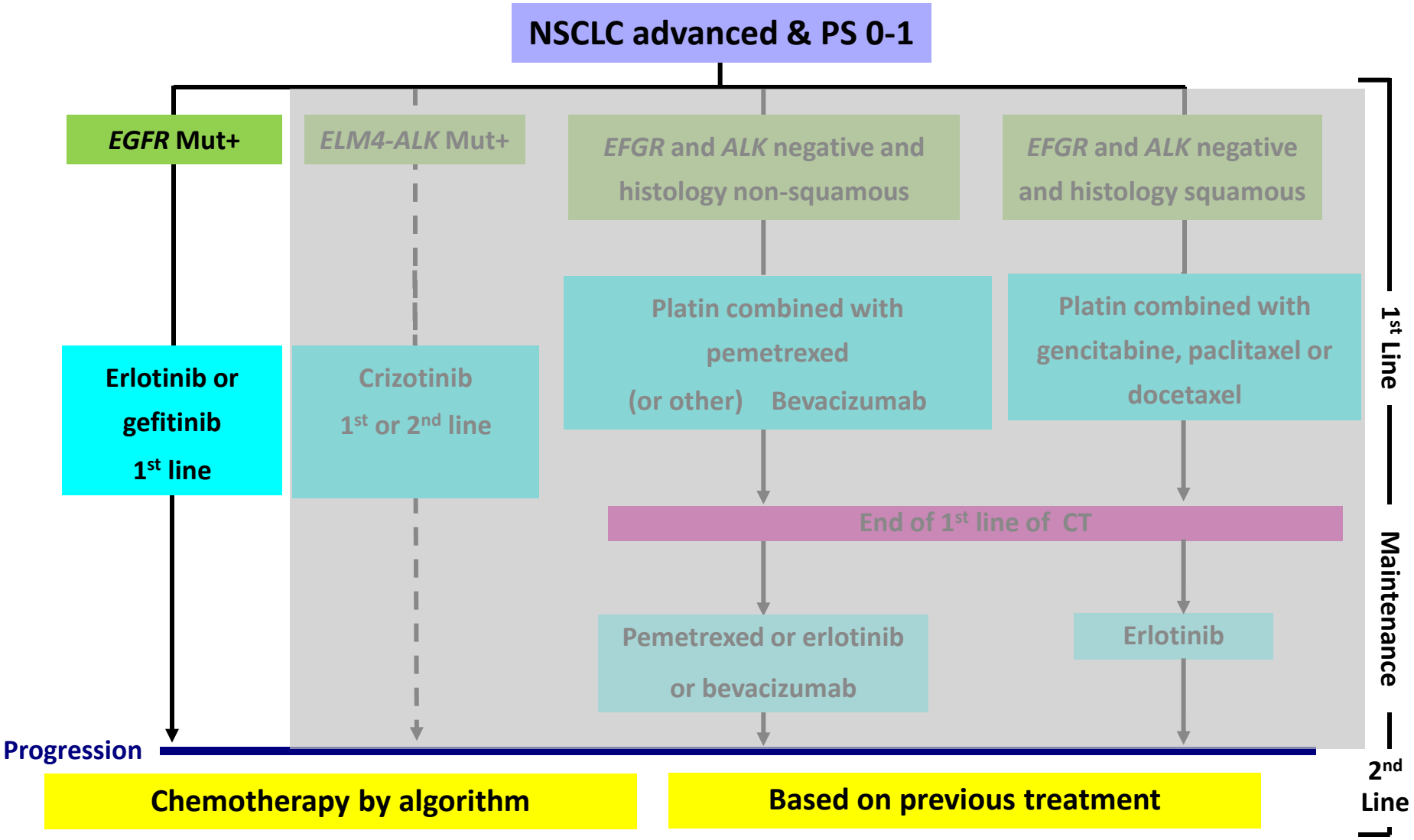
Algorithm for the treatment of advanced NSCLC in 2014



Updated from Gandara DR, et al. Clin Lung Cancer 10:392-394, 2009

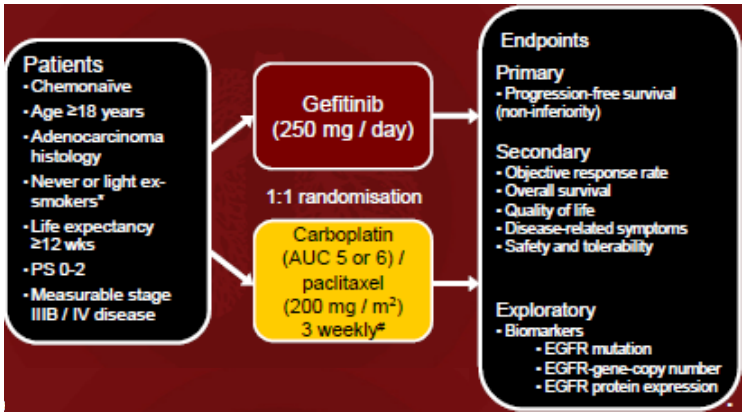
Use of TKI's of EGFR

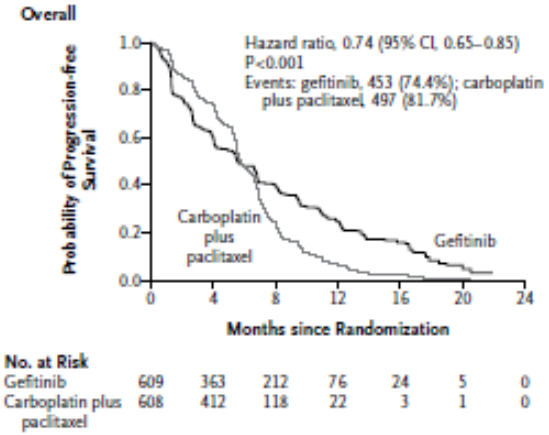
Study	Ref.	TKI	CTx	N #	PFS mos	HR 95% CI	OS mos
IPASS	**Mok** [1]	**Gefitinib**	Cb/Pac	261	**9.5** vs 6.3	**0.48** 0.36-0.64	21.6 vs 21.9
First-SIGNAL	**Han** [2]	**Gefitinib**	Cis/Gem	42	**8.0** vs 6.3	**0.54** 0.26-1.10	27.2 vs 25.6
NEJ002	**Maemondo** [3]	**Gefitinib**	Carb/Pac	230	**10.8** vs 5.4	**0.35** 0.22-0.41	30.5 vs 23.6
WJTOG 3405	**Mitsudomi** [4, 5]	**Gefitinib**	Cis/Doc	172	**9.2** vs 6.3	**0.49** 0.33-0.71	36 vs 39
OPTIMAL	**Zhou** [6] **, Zhang** [7]	**Erlotinib**	Carb/Gem	165	**13.1** vs 4.6	**0.16** 0.10-0.26	22.7 vs 28.9
EURTAC	**Rosell** [8]	**Erlotinib**	P/Doc or Gem	174	**9.7** vs 5.2	**0.34** 0.23-0.49	19.3 vs 19.5
LUX-Lung 3	**Sequist** [9]	**Afatinib**	Cis/Pem	345	**11.1** vs 6.9	**0.47** 0.34-0.65	Not reported

[1] Mok TS, et al. NEJM 2009; [2] Han JY, et al. JCO 2012; [3] Maemondo M, et al. NEJM 2010; [4,] Mitsudomi T, et al. Lancet Oncol, 2010 ; [5] Mitsudomi T, et al. ASCO, 2012; [6] Zhou C, et al. Lancet Oncol, 2011; [7] Zhang C, et al. ASCO, 2012; [8] Rosell R, et al. Lancet Oncol 2012; [9] Sequist LV, et al. JCO, 2013

Gefitinib in 1st line of NSCLC

IPASS - PFS

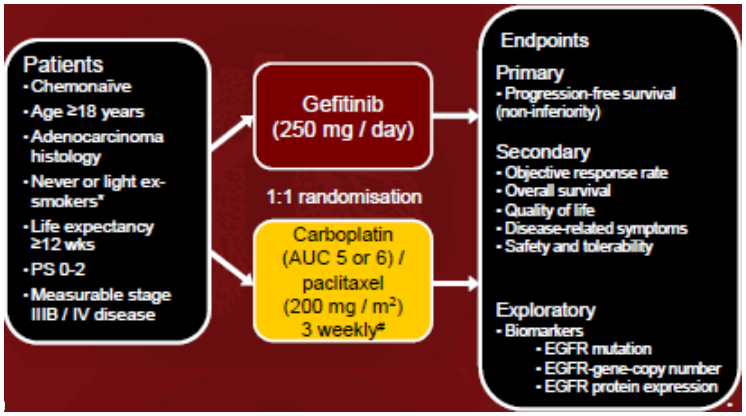


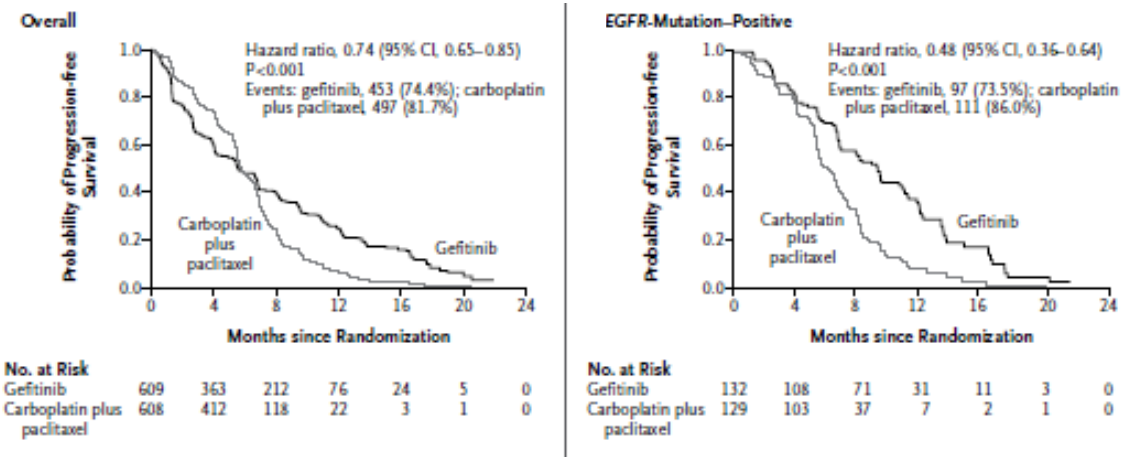


Mok T, et al. N Engl J Med 361:947-957, 2009
Fukuoka M, et al. JCO 29:2866-2874, 2011

Gefitinib in 1st line of NSCLC

IPASS - PFS





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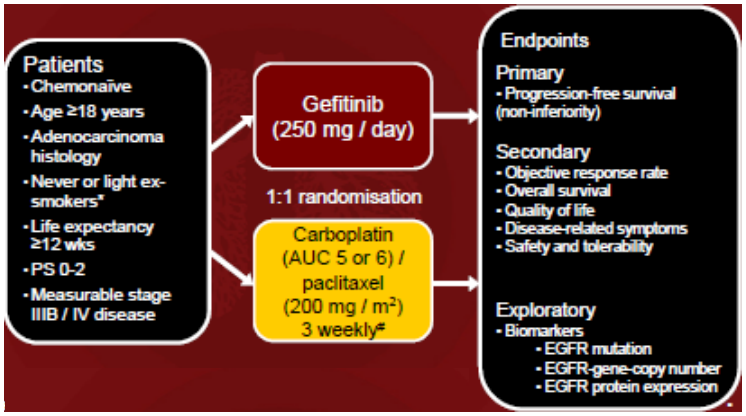
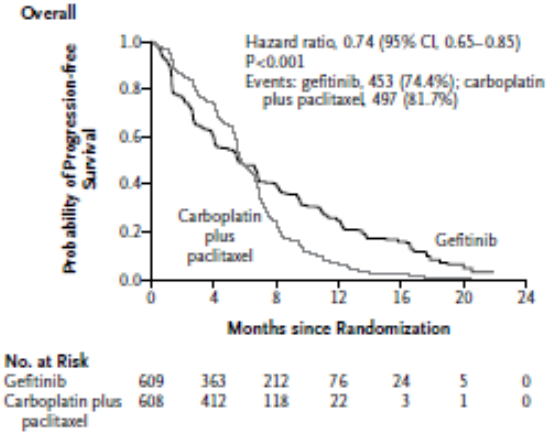
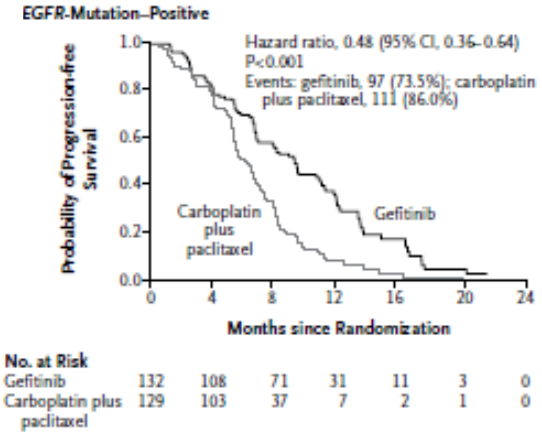
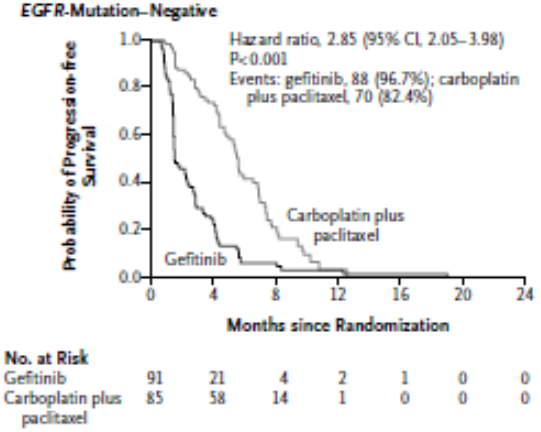
Gefitinib in 1st line of NSCLC

IPASS - PFS





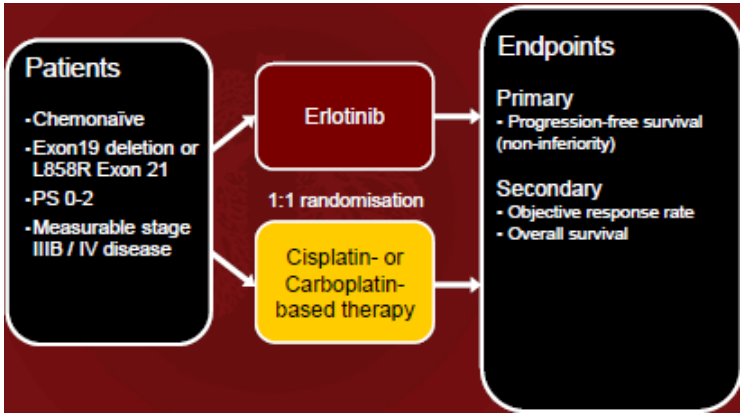


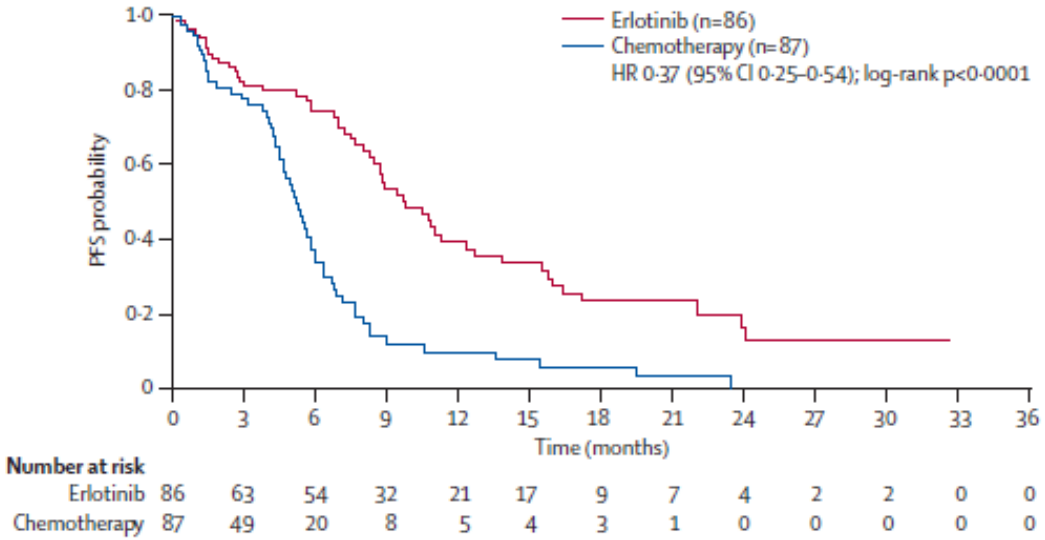


Mok T, et al. N Engl J Med 361:947-957, 2009
Fukuoka M, et al. JCO 29:2866-2874, 2011

Erlotinib in 1st line of NSCLC

EURTAC - PFS





Rosell R, et al. Lancet Oncol 13:239-246, 2012

Gefitinib & Erlotinib in 1st line of NSCLC

Adverse Events

IPASS

Adverse Event	Gefitinib (N=607)		Carboplatin–Paclitaxel (N=589)	
	All Adverse Events	CTC Grade 3, 4, or 5	All Adverse Events	CTC Grade 3, 4, or 5
	number (percent)			
Rash or acne†	402 (66.2)	19 (3.1)	132 (22.4)	5 (0.8)
Diarrhea	283 (46.6)	23 (3.8)	128 (21.7)	8 (1.4)
Dry skin	145 (23.9)	0	17 (2.9)	0
Anorexia†	133 (21.9)	9 (1.5)	251 (42.6)	16 (2.7)
Pruritus†	118 (19.4)	4 (0.7)	74 (12.6)	1 (0.2)
Stomatitis†	103 (17.0)	1 (0.2)	51 (8.7)	1 (0.2)
Asthenic conditions†	102 (16.8)	2 (0.3)	259 (44.0)	11 (1.9)
Nausea	101 (16.6)	2 (0.3)	261 (44.3)	9 (1.5)
Paronychia	82 (13.5)	2 (0.3)	0	0
Vomiting	78 (12.9)	1 (0.2)	196 (33.3)	16 (2.7)
Constipation	73 (12.0)	0	173 (29.4)	1 (0.2)
Alopecia	67 (11.0)	0	344 (58.4)	0
Neurotoxic effects†	66 (10.9)	2 (0.3)	412 (69.9)	29 (4.9)
Myalgia	47 (7.7)	3 (0.5)	186 (31.6)	10 (1.7)
Arthralgia	39 (6.4)	1 (0.2)	113 (19.2)	6 (1.0)
Neutropenia‡				
Any	NA	22 (3.7)	NA	387 (67.1)
Febrile	1 (0.2)	1 (0.2)	17 (2.9)	17 (2.9)
Anemia‡	NA	13 (2.2)	NA	61 (10.6)
Leukopenia‡	NA	9 (1.5)	NA	202 (35.0)

EURTAC

	Erlotinib (n=84)			Standard chemotherapy (n=82)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Fatigue	43 (51%)	5 (6%)	0	43 (52%)	16 (20%)	0
Rash	56 (67%)	11 (13%)	0	4 (5%)	0	0
Diarrhoea	44 (52%)	4 (5%)	0	15 (18%)	0	0
Appetite loss	26 (31%)	0	0	26 (32%)	2 (2%)	0
Anaemia	9 (11%)	0	1 (1%)	37 (45%)	3 (4%)	0
Neutropenia	0	0	0	15 (18%)	12 (15%)	6 (7%)
Alopecia	12 (14%)	0	0	13 (16%)	2 (2%)	0
Neuropathy	7 (8%)	0	1 (1%)	11 (13%)	1 (1%)	0
Arthralgia	8 (10%)	1 (1%)	0	4 (5%)	1 (1%)	0
Thrombocytopenia	1 (1%)	0	0	1 (1%)	6 (7%)	6 (7%)
Aminotransferase rise	3 (4%)	2 (2%)	0	5 (6%)	0	0
Febrile neutropenia	0	0	0	1 (1%)	1 (1%)	2 (2%)
Pneumonitis	0	1 (1%)	0	0	1 (1%)	0

Mok T, et al. N Engl J Med 361:947-957, 2009; Fukuoka M, et al. JCO 29:2866-2874, 2011;
Rosell R, et al. Lancet Oncol 13:239-246, 2012

Use of TKI's of EGFR

GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

Annals of Oncology 23 (Supplement 7): vii56–vii64, 2012
doi:10.1093/annonc/mds226

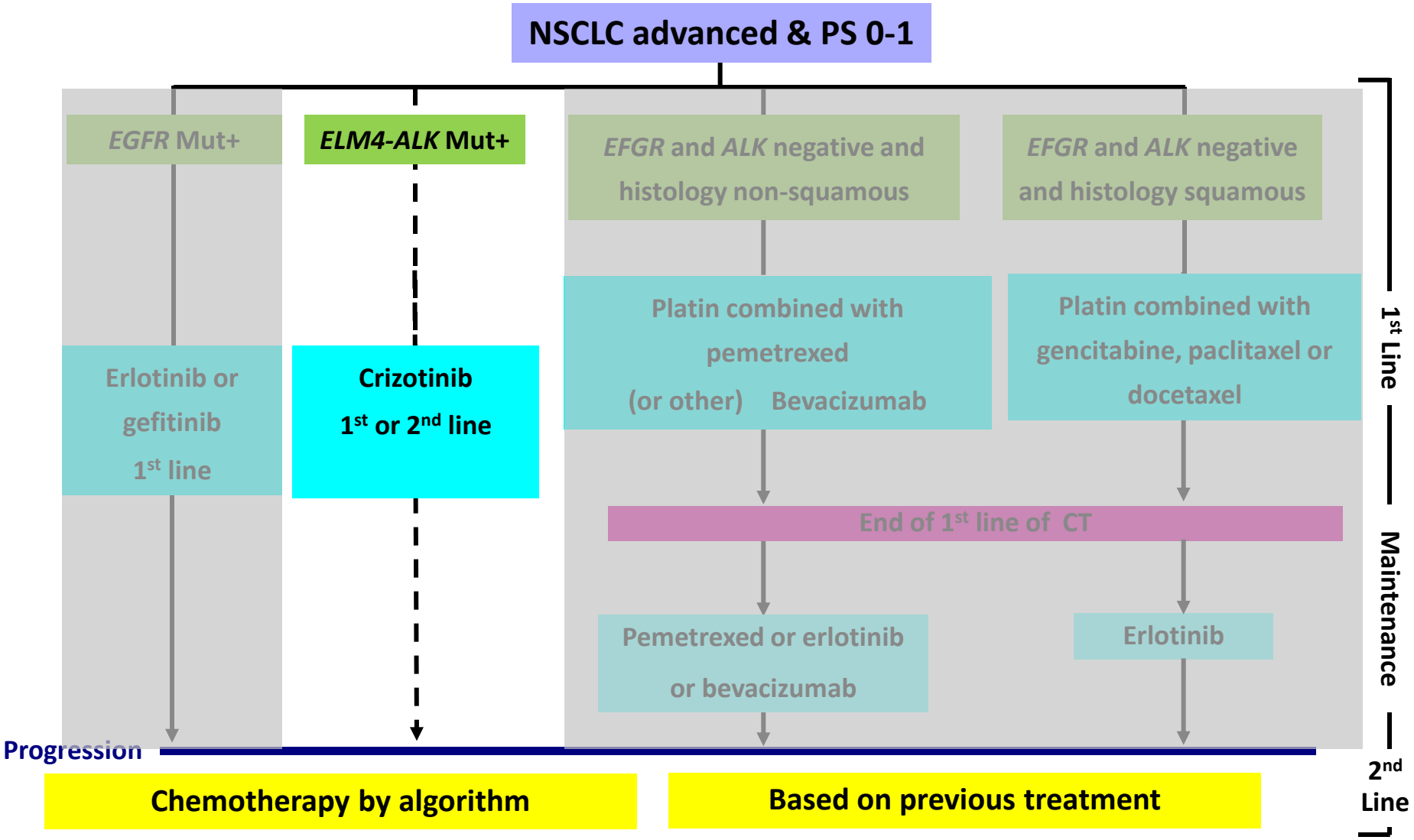
clinical practice guidelines

Metastatic non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

First-line treatment with a TKI (erlotinib or gefitinib) should be prescribed to patients with tumors bearing an activating (sensitizing) EGFR mutation because of significantly higher RR, longer PFS, and better QoL when compared with first-line chemotherapy [32, 33] [I, A].

Level of evidence: I **Strenght of recommendation: A**

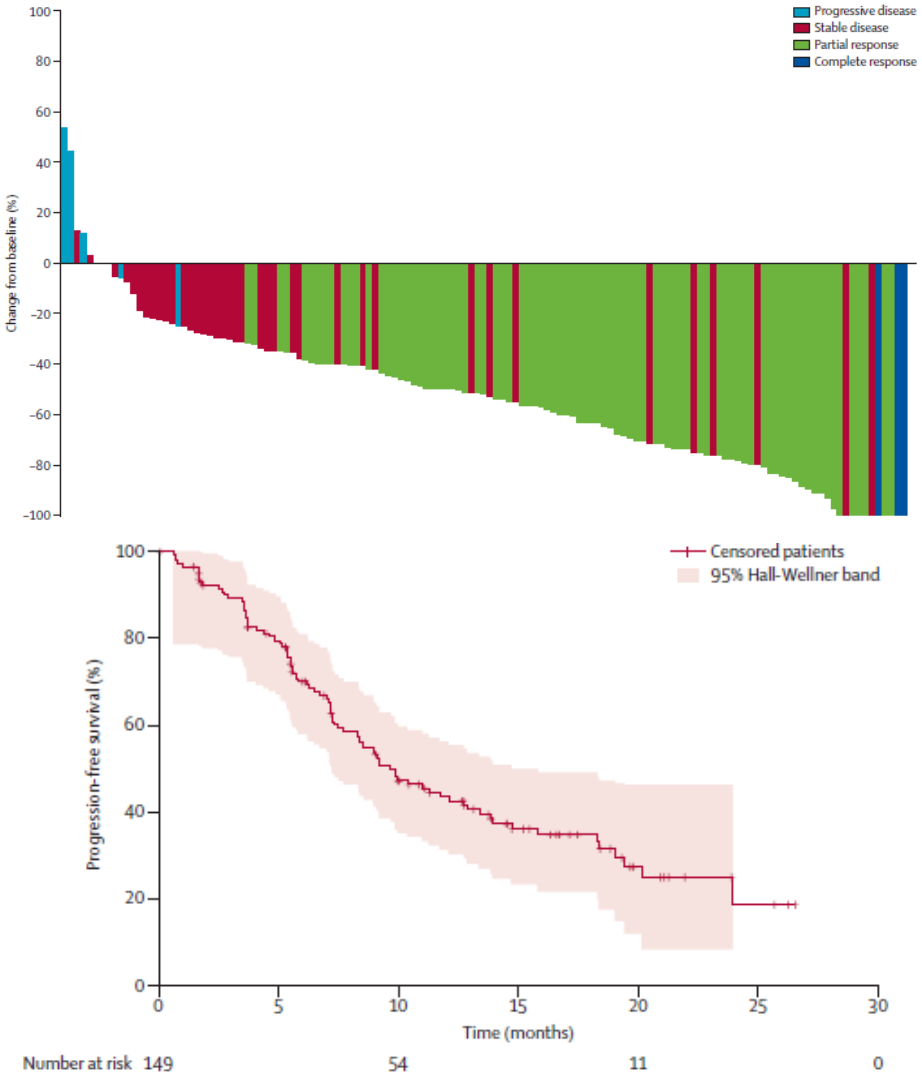
Algorithm for the treatment of advanced NSCLC in 2014



Updated from Gandara DR, et al. Clin Lung Cancer 10:392-394, 2009

Crizotinib and NSCLC – phase 1 study

PROFILE 1005



	All grades	Grade 3 or 4
Any adverse event	144 (97%)	36 (24%)
Visual effects*	96 (64%)	0 (0%)
Nausea	84 (56%)	1 (<1%)
Diarrhoea	74 (50%)	0 (0%)
Vomiting	58 (39%)	1 (<1%)
Peripheral oedema	44 (30%)	0 (0%)
Constipation	41 (28%)	1 (<1%)
Dizziness	31 (21%)	0 (0%)
Decreased appetite	24 (16%)	0 (0%)
Fatigue	24 (16%)	2 (1%)
Increased alanine aminotransferase	18 (12%)	6 (4%)
Rash	17 (11%)	0 (0%)
Dysgeusia	16 (11%)	0 (0%)
Increased aspartate aminotransferase	15 (10%)	5 (3%)

Camidge DR, et al. Lancet Oncol 13:1011-1019, 2012

Crizotinib in 2nd line of NSCLC

PROFILE 1007

Key entry criteria

- *ALK*+ by central FISH testing[a]
- Stage IIIB/IV NSCLC
- 1 prior chemotherapy (platinum-based)
- ECOG PS 0–2
- Measurable disease
- Treated brain metastases allowed

RANDOMIZE

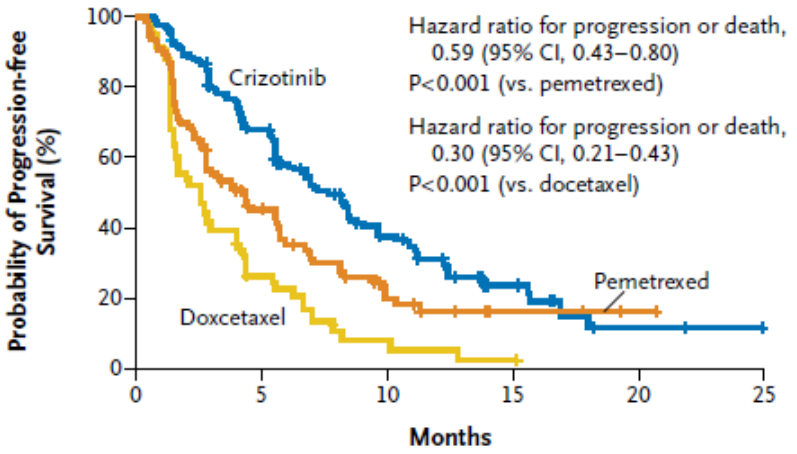
N=318

Crizotinib 250 mg BID
PO, 21-day cycle
(n=159)

Pemetrexed 500 mg/m²
or
Docetaxel 75 mg/m²
IV, day 1, 21-day cycle
(n=159)

CROSSOVER TO CRIZOTINIB ON PROFILE 1005

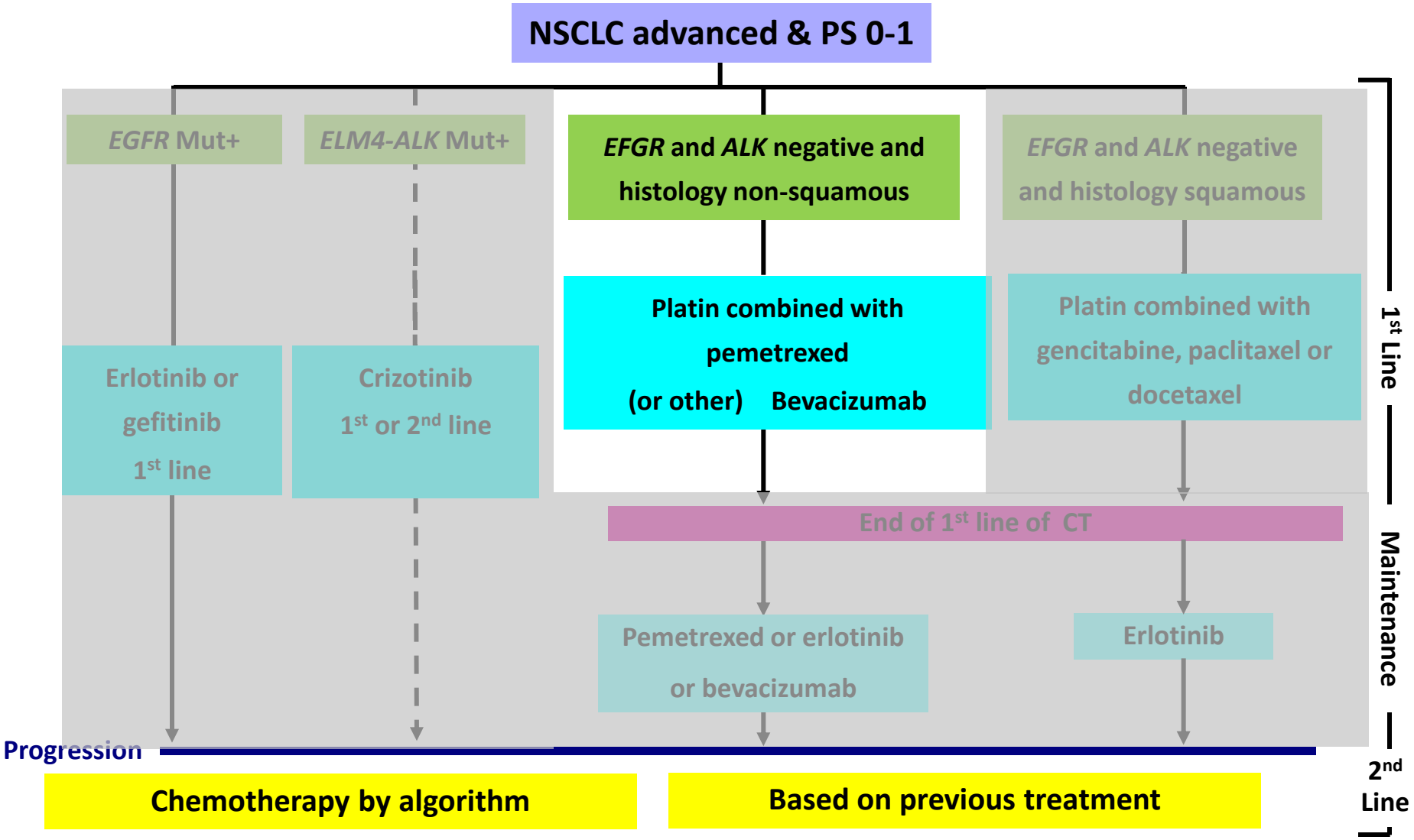
Progression-free Survival with Crizotinib vs. Pemetrexed or Docetaxel



Adverse Event	Crizotinib (N=172)		Chemotherapy (N=171)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	no. of patients (%)			
Vision disorder†‡	103 (60)	0	16 (9)	0
Diarrhea	103 (60)	0	33 (19)	1 (1)
Nausea§	94 (55)	2 (1)	64 (37)	1 (1)
Vomiting§	80 (47)	2 (1)	30 (18)	0
Constipation	73 (42)	4 (2)	39 (23)	0
Elevated aminotransferase levels†	66 (38)	27 (16)¶	25 (15)	4 (2)
Edema†	54 (31)	0	27 (16)	0
Fatigue	46 (27)	4 (2)	57 (33)	7 (4)
Upper respiratory infection†	44 (26)	0	22 (13)	1 (<1)
Dysgeusia	44 (26)	0	16 (9)	0
Dizziness†	37 (22)	1 (1)	14 (8)	0
Dyspnea†‖	23 (13)	7 (4)	32 (19)	5 (3)
Rash	15 (9)	0	29 (17)	0
Alopecia	14 (8)	0	35 (20)	0

Shaw AT, et al. N Engl J Med 368:2385-2394, 2013

Algorithm for the treatment of advanced NSCLC in 2014



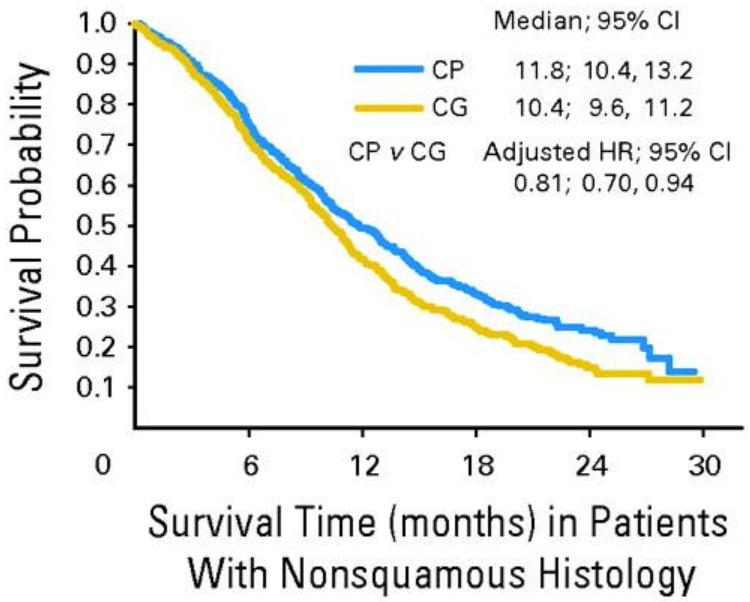
Updated from Gandara DR, et al. Clin Lung Cancer 10:392-394, 2009

Efficacy of Pemetrexed – Histology

1st Line of CT

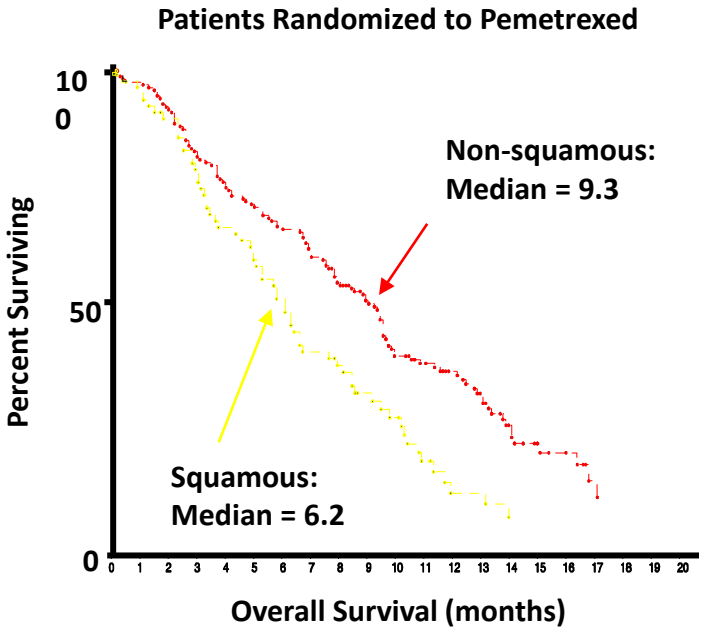
Advanced-stage, previously untreated NSCLC patients (N = 1725)

- Cisplatin 75 mg/m² on Day 1 + Gemcitabine 1250 mg/m² on Days 1 and 8 Six 3-wk cycles
- Cisplatin 75 mg/m² on Day 1 + Pemetrexed 500 mg/m² on Day 1 Six 3-wk cycles



Peterson et al WCLC 2007 Abst P2 328
Scagliotti et al. J Thorac Oncol 6:64-70, 2011

2nd Line of CT



Hanna N et al, J Clin Oncol 22:1589-1597, 2004
Scagliotti GV et al, J Clin Oncol 26:3543-3551, 2008

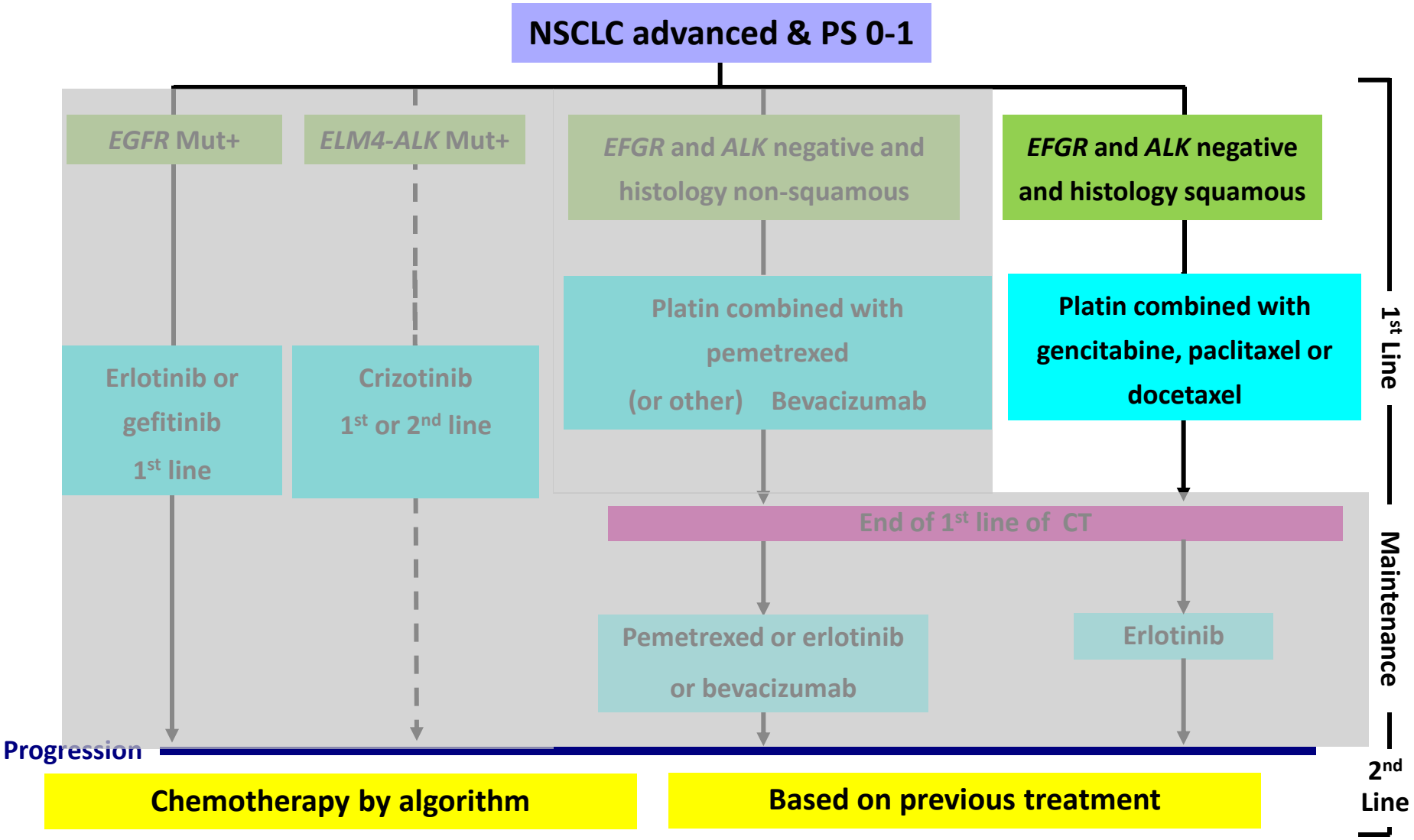
Toxicity profile of Pemetrexed

Grade 3 and 4 hematologic toxicities

Toxicities	Cis/Pem N=839	Cis/Gem N=830	*P*	Pem N=265	Doc N=276	*P*
Anemia	5.6%	9.9%	0.001	4.2%	4.3%	0.99
Neutropenia	15.1%	26.7%	< 0.001	5.3%	40.2%	< 0.001
Thrombocytopenia	4.1%	12.7%	< 0.001	1.9%	0.4%	0.116
Febrile Neutropenia	1.3%	3.7%	0.002	1.9%	12.7%	< 0.001

Scagliotti GV et al, J Clin Oncol 26:3543-3551, 2008
Hanna N et al, J Clin Oncol 22:1589-1597, 2004

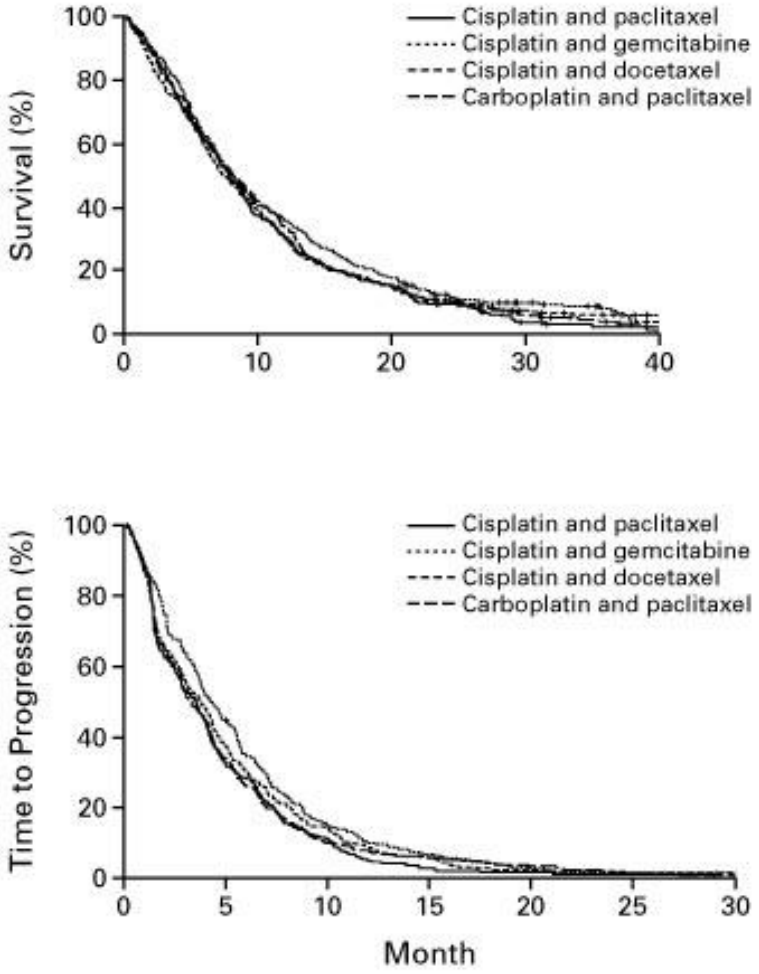
Algorithm for the treatment of advanced NSCLC in 2014



Updated from Gandara DR, et al. Clin Lung Cancer 10:392-394, 2009

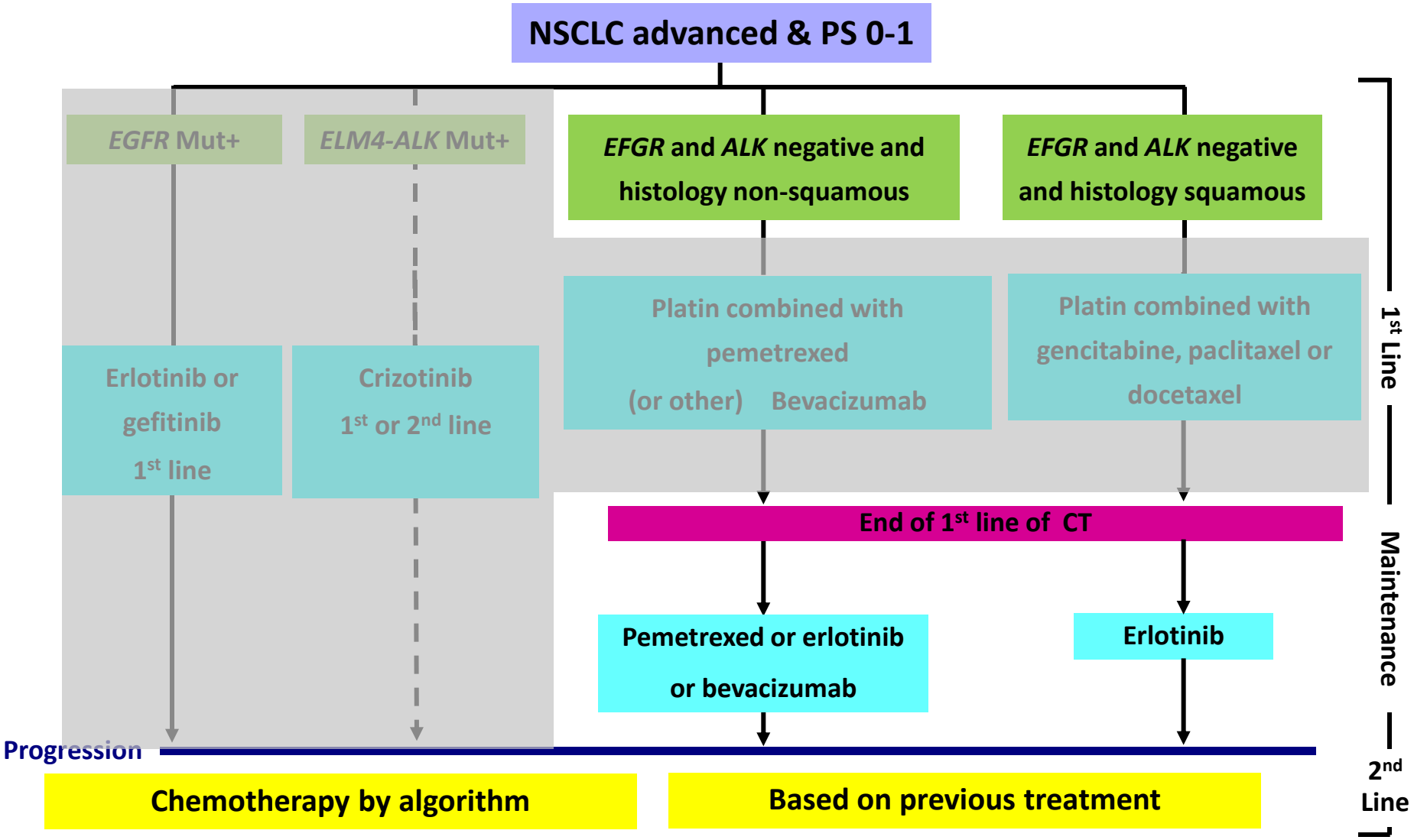
Squamous NSCLC

ECOG 1594



Schiller JH, et al. N Engl J Med 346:92-98, 2002

Algorithm for the treatment of advanced NSCLC in 2014



Updated from Gandara DR, et al. Clin Lung Cancer 10:392-394, 2009

Switch maintenance for NSCLC

Study	n	Induction	Intervention	Primary endpoint	Median PFS		Median OS	
					Months	*P*	Months	*P*
Fidias et al [1]	309	CarbG x 4 cycles	Immediate vs delayed docetaxel	OS	5.7 / 2.7	< 0.001	12.3 / 9.7	0.0853
Ciuleanu et al [2]	663	Platinum-based doublet x 4 cycles	Pemetrexed vs placebo	PFS	4.0 / 2.0	< 0.0001	13.4 / 10.6	0.012
Capuzzo et al [3]	889	Platinum-based doublet x 4 cycles	Erlotinib vs placebo	PFS	2.83 / 2.55	< 0.001	12.0 / 11.0	0.0088
Pérol et al [4]	464	CisG x 4 cycles	Erlotinib vs gencitabine vs observation	PFS	2.9 / 3.8 / 1.9	< 0.001 0.003	11.4 / 15.2 / 10.8	0.3043 0.3867
Miller et al [5]	768	Platinum-based doublet + bevacizumab x 4 cycles	Erlotinib + Bevacizumab vs Placebo + Bevacizumab	PFS	4.76 / 3.75	0.0012	15.9 / 13.9	0.2686

[1] Fidias PM et al. JCO 27:591-598, 2009; [2] Ciuleanu T et al. Lancet 374:1432-1440, 2009; [3] Cappuzo F et al. JCO 11:521-529, 2010; [4] Pérol M et al. JCO 30:3516-3524, 2012; [5] Miller VA et al. JCO 27(Suppl);Abstract LBA8002, 2009.

Switch maintenance for NSCLC

Non-squamous population

CR, PR or SD after 4 cycles

of one of the following induction therapies:

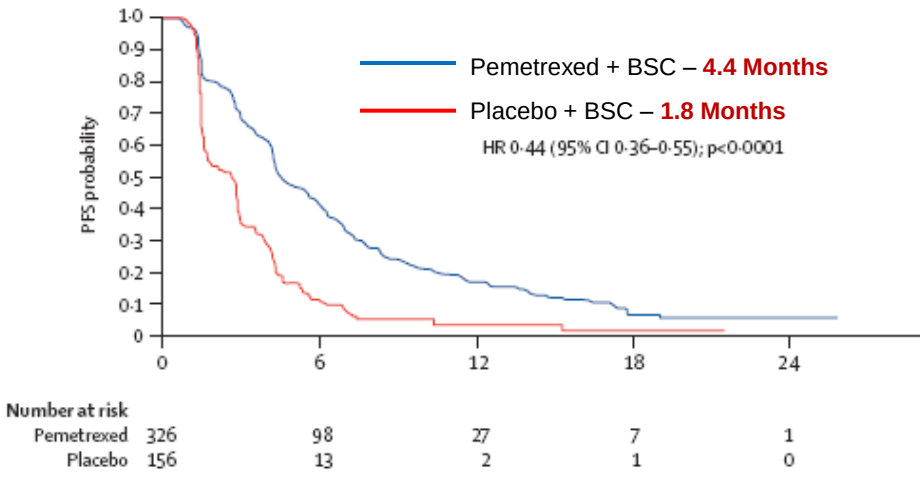
- Gemcitabine + Platin
- Paclitaxel + Platin
- Docetaxel + Platin

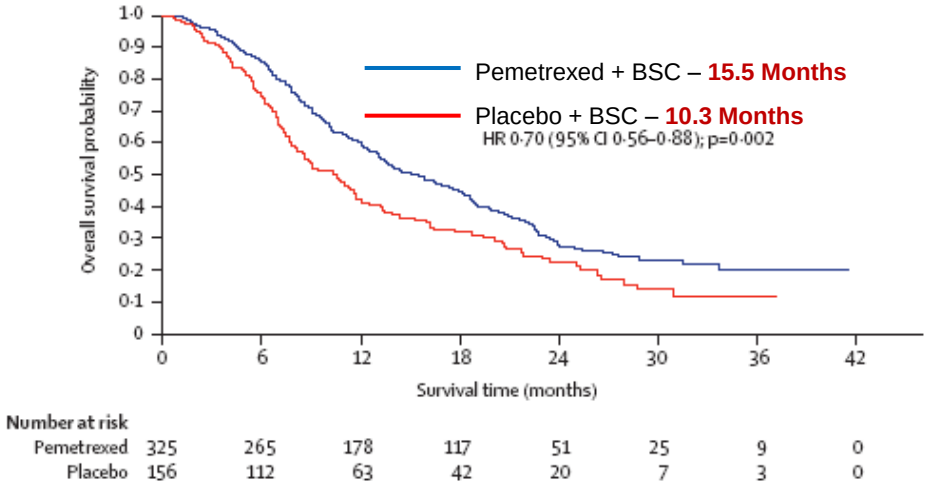
→ **R A N D O M I Z E** (2:1)

→ **Pemetrexed 500** mg/m² EV, d1 + **BSC** Until disease progression — **n=441**

Both arms received folic acid, vit. B12 and dexametasone

→ **Placebo** EV, d1 + **BSC** Until disease progression — **n=222**

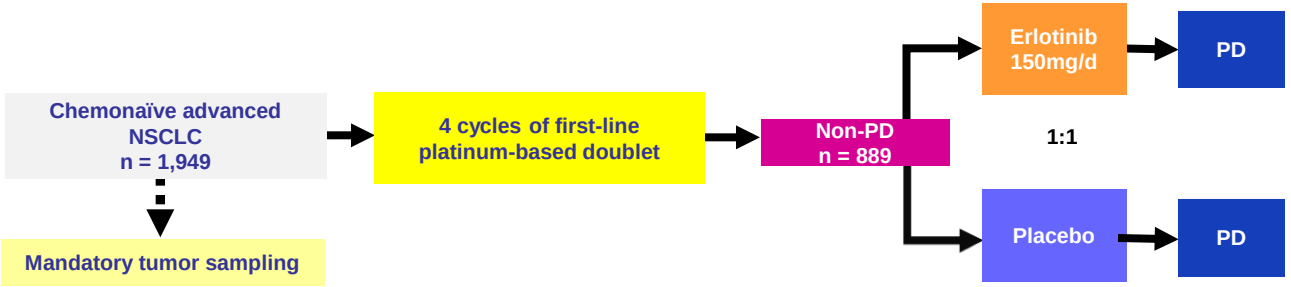




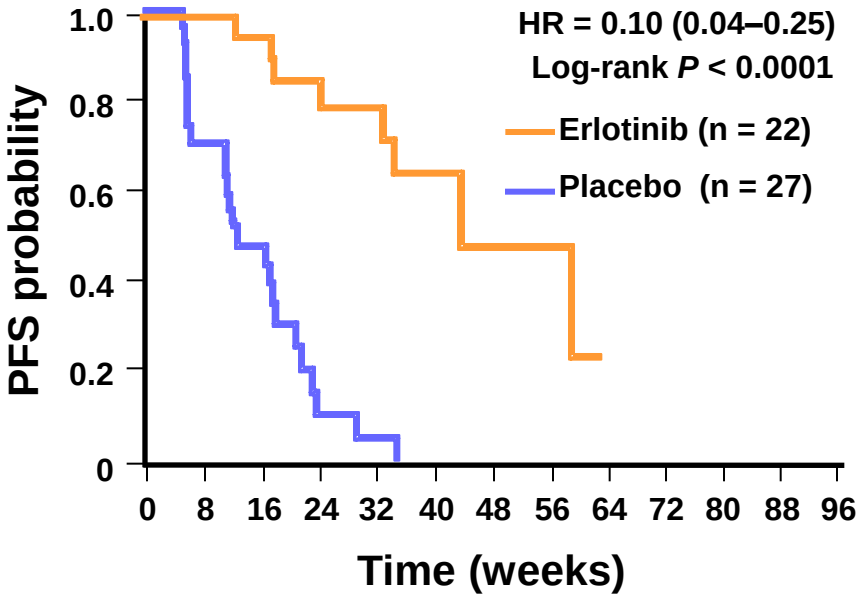
Ciuleanu T et al, Lancet 374:1432-1440, 2009

Switch maintenance for NSCLC

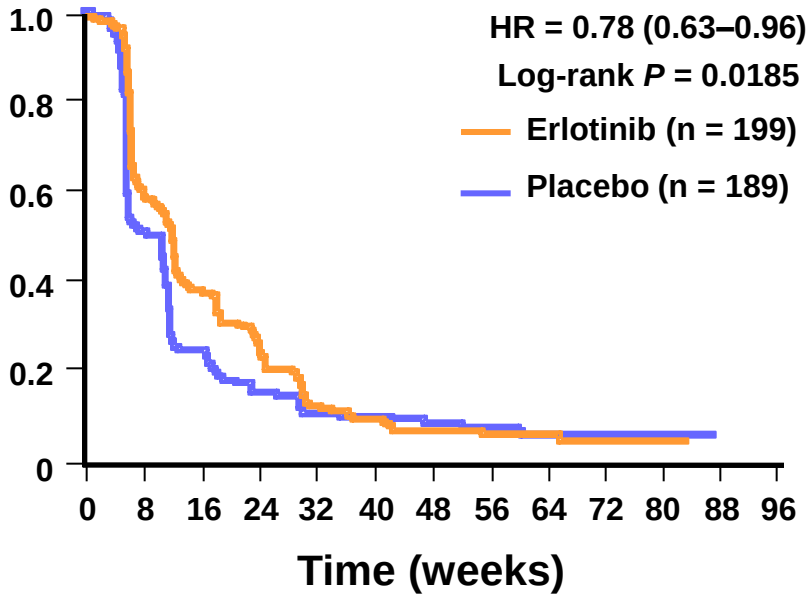
SATURN: PFS according *EGFR* mutation status



EGFR Mutation +



EGFR Wild-type



Cappuzzo F et al, Lancet Oncol 11:521-529, 2010

Continuation maintenance for NSCLC

Study	Induction	Nº Cycles	Randomize	Intervention	Comparator	Objective ↑ OS	Objective ↑ PFS
Smith et al 2001[1]	Mitomicin +Vinblastine +Cisplatin	3	Induction	3 more cycles mais (n=153)	Observation (n=155)	No	No
Socinski et al 2002[2]	Carboplatin +Paclitaxel	4	Induction	Continuous treatmento (n=116)	Observation (n=114)	No	No
Belani et al 2003[3]	Carboplatin +Paclitaxel	2-4	Induction	Paclitaxel (n=65)	Observation (n=65)	No	No
Westeel et al 2005[4]	Mitomicin +Ifosfamide +Cisplatin	2-4	Pos-Induction	Vinorelbina (n=91)	Observation (n=90)	No	No
Brodowicz et al 2006[5]	Gemcitabine +Cisplatin	4	Pos-Induction	Gemcitabine (n=138)	BSC (n=68)	No	TTP: Yes
Park et al 2007[6]	Paclitaxel, docetaxel or gemcitabine +Cisplatin	2	Pos-Induction	4 more cycles (n=158)	2 more cycles (n=156)	No	TTP: Yes

1. Smith IE, et al. *J Clin Oncol* 2001;19:1336-1343; 2. Socinski MA, et al. *J Clin Oncol* 2002;20:1335-1343;
3. Belani CP, et al. *J Clin Oncol* 2003;21:2933-2939; 4. Westeel V, et al. *J Natl Cancer Inst* 2005;97:499-506;
5. Brodowicz T, et al. *Lung Cancer* 2006;52:155-163; 6. Park JO, et al. *J Clin Oncol* 2007;25:5233-5239.

Continuation maintenance for NSCLC

Study	n	Induction	Intervention	Primary endpoint	Median PFS		Median OS	
					Months	*P*	Months	*P*
Sandler et al [1]	878	Carboplatin + Paclitaxel +/- Bevacizumab x 6 cycles	Bevacizumab vs observation	OS	6.2 / 4.5	< 0.001	12.3 / 10.3	0.003
Pirker et al [2]	1125	Cisplatinum + Vinorelbin +/- Cetuximab X 6 cycles	Cetuximab vs observation	OS	4.8 / 4.0	0.39	11.3 / 10.1	0.044
Paz-Ares et al [3]	539	Cisplatinum + Pemetrexed x 4 cycles	Pemetrexed vs placebo	PFS	6.9 / 5.6	< 0.0001	16.9 / 14.0	0.0191

[1] Sandler A et al. N Engl J Med 355:2542-2550, 2006; [2] Pirker R et al. Lancet 373:1525-1531, 2009;
[3] Paz-Ares L et al. Lancet Oncol 13:247-255, 2012.

Continuation maintenance for NSCLC

Study	n	Induction	Intervention	Primary endpoint	Median PFS		Median OS	
					Months	*P*	Months	*P*
Sandler et al [1]	878	Carboplatin + Paclitaxel +/- Bevacizumab x 6 cycles	Bevacizumab vs observation	OS	6.2 / 4.5	< 0.001	12.3 / 10.3	0.003
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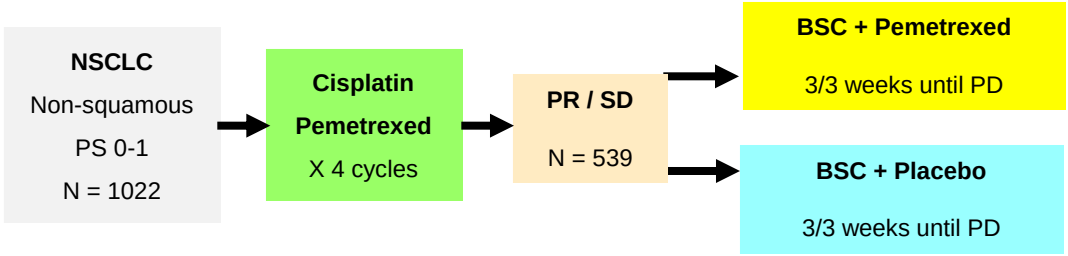
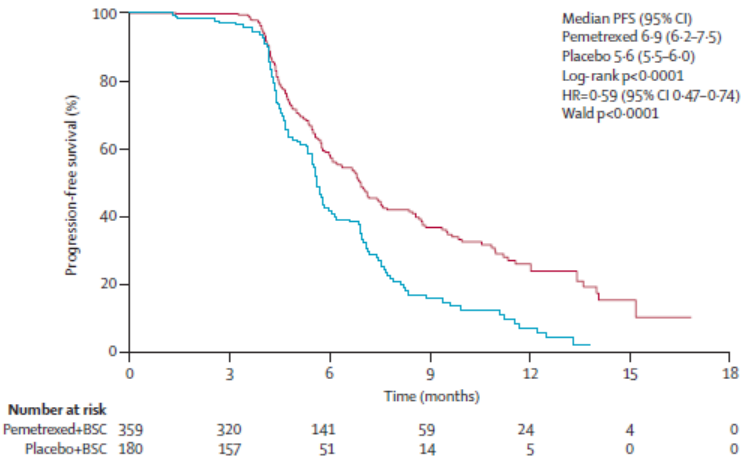
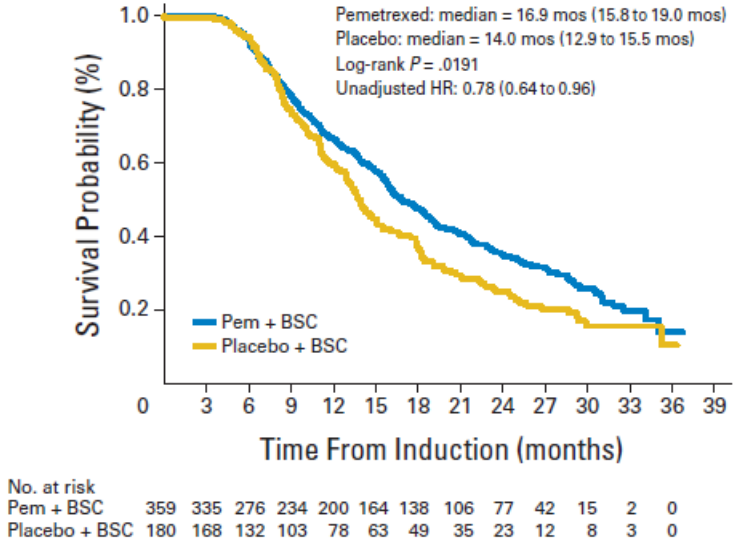
[1] Sandler A et al. N Engl J Med 355:2542-2550, 2006; [2] Pirker R et al. Lancet 373:1525-1531, 2009;
[3] Paz-Ares L et al. Lancet Oncol 13:247-255, 2012.

Continuation maintenance for NSCLC

Paramount trial







Paz-Ares L et al. Lancet Oncol 13:247-255, 2012
Paz-Ares L et al. J Clin Oncol 31:2895-2902, 2013

Continuation maintenance for NSCLC

Paramount trial

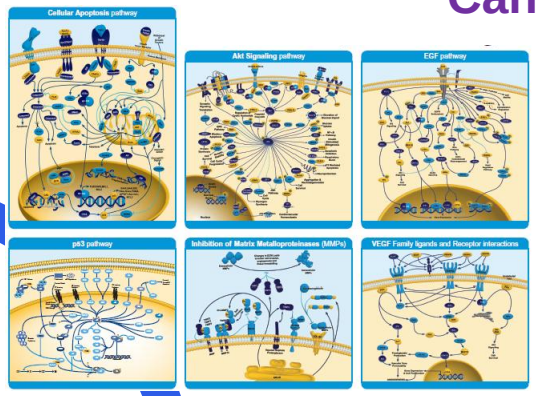
	Grade 1–2, *n* (%)		Grade 3–4,[b] *n* (%)	
Toxicity[a]	Pemetrexed (N = 359)	Placebo (N = 180)	Pemetrexed (N = 359)	Placebo (N = 180)
Laboratory				
Anemia	34 (10)[c]	7 (4)[c]	16 (4)[c]	1 (0.6)[c]
Neutropenia	17 (5)[c]	1 (0.6)[c]	13 (4)[c]	0 (0)[c]
Nonlaboratory				
Fatigue (asthenia, lethargy, malaise)	44 (12)	18 (10)	15 (4)[c]	1 (0.6)[c]
Anorexia	13 (4)	2 (1)	1 (0.3)	0 (0)
Constipation	8 (2)	5 (3)	0 (0)	0 (0)
Diarrhea	10 (3)	3 (2)	0 (0)	0 (0)
Mucositis/stomatitis	17 (5)	4 (2)	1 (0.3)	0 (0)
Nausea	38 (11)[c]	4 (2)[c]	1 (0.3)	0 (0)
Vomiting	21 (6)[c]	3 (2)[c]	0 (0)	0 (0)
Edema	17 (5)	6 (3)	0 (0)	0 (0)
Neuropathy: sensory	9 (3)	9 (5)	1 (0.3)	1 (0.6)
Watery eye (epiphora, tearing)	9 (3)	1 (0.6)	0 (0)	0 (0)
Pain	11 (3)	3 (2)	3 (0.8)	0 (0)

Gridelli C et al, J Thorac Oncol 7:1713-1721, 2012

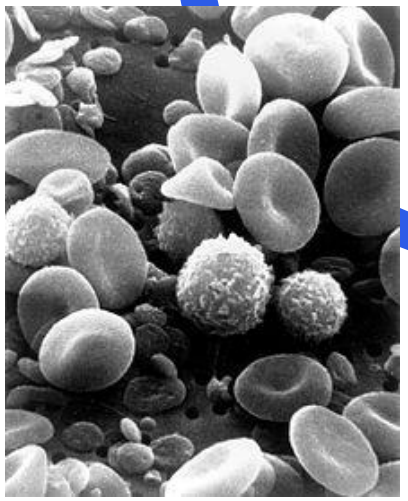
Lung cancer – all different

Patient

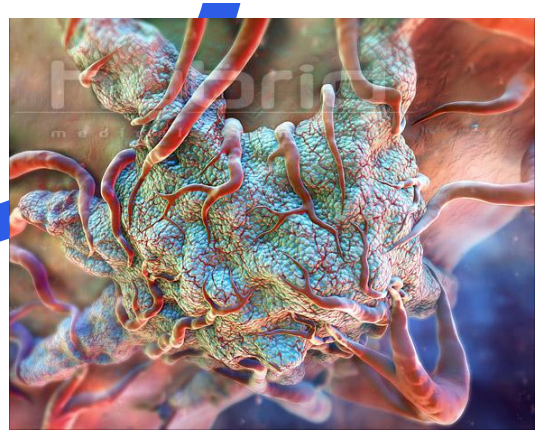
Cancer



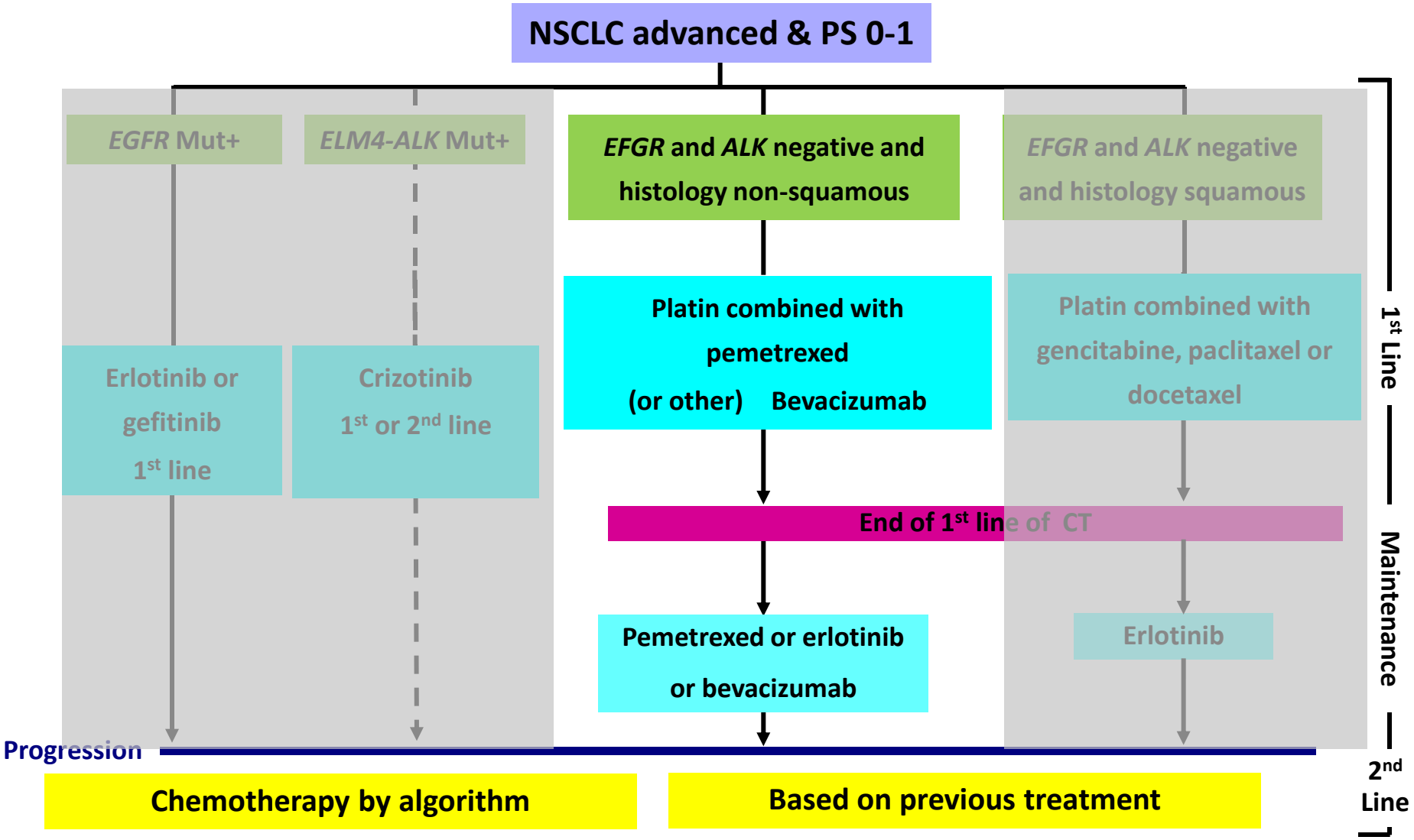
Immunity



Microenvironment



Algorithm for the treatment of advanced NSCLC in 2014

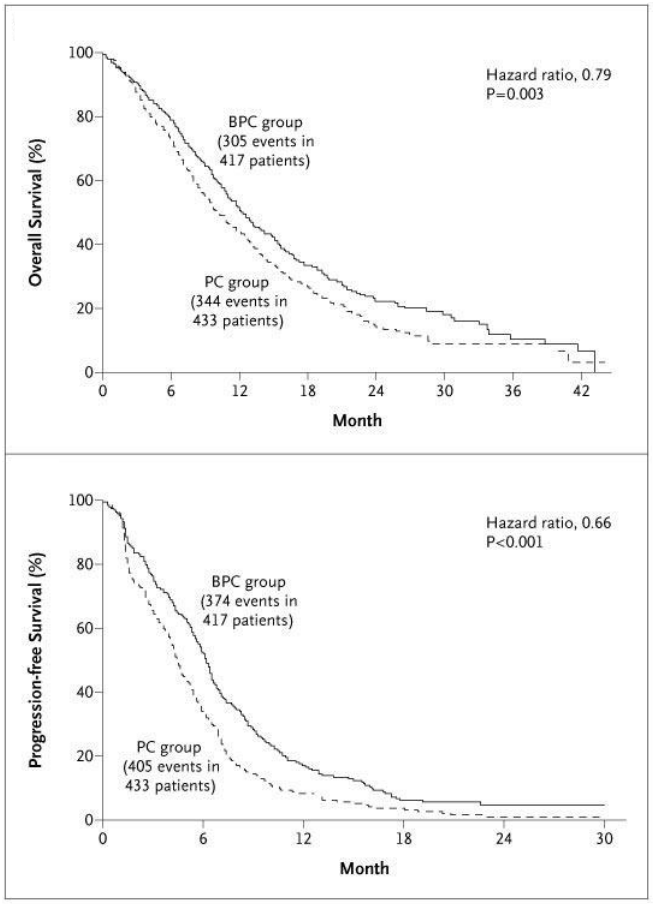


Updated from Gandara DR, et al. Clin Lung Cancer 10:392-394, 2009

Bevacizumab plus CT for NSCLC

ECOG 4599

RR: 15% for Paclitaxel/Carboplatin vs 35% for Paclitaxel/Carboplatin + Bevacizumab



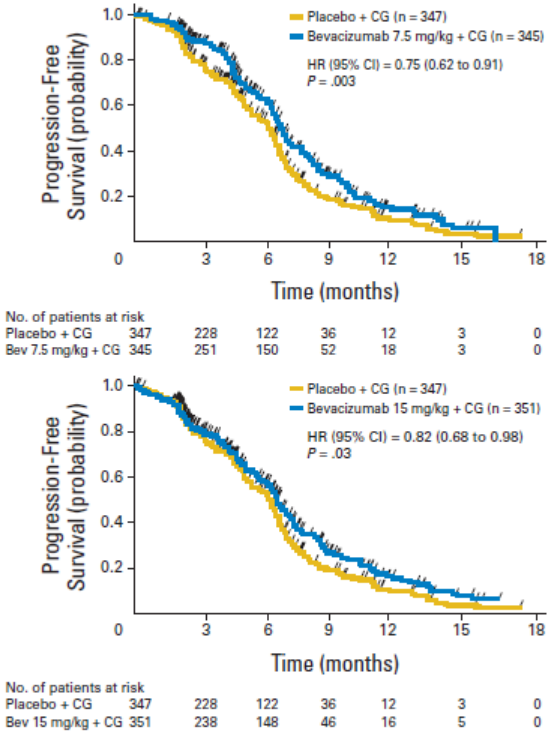
Adverse Event	Paclitaxel–Carboplatin Group (N=440)			Paclitaxel–Carboplatin–Bevacizumab Group (N=427)			P Value
	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5†	
	number of patients (percent)						
Neutropenia		74 (16.8)			109 (25.5)		0.002
Thrombocytopenia		1 (0.2)			7 (1.6)		0.04
Anemia		4 (0.9)			0		NS
Febrile neutropenia	8 (1.8)		1 (0.2)	17 (4.0)		5 (1.2)	0.02
Hyponatremia	4 (0.9)	1 (0.2)		11 (2.6)	4 (0.9)		0.02
Hypertension	2 (0.5)	1 (0.2)		29 (6.8)	1 (0.2)		<0.001
Proteinuria				11 (2.6)	2 (0.5)		<0.001
Headache	2 (0.5)			13 (3.0)			0.003
Rash or desquamation	2 (0.5)			10 (2.3)			0.02
Bleeding events (all)	3 (0.7)			19 (4.4)			<0.001
Central nervous system hemorrhage					3 (0.7)		
Epistaxis	1 (0.2)			3 (0.7)			
Hematemesis						2 (0.5)	
Hemoptysis	1 (0.2)			2 (0.5)	1 (0.2)	5 (1.2)	
Melena or gastrointestinal bleeding	1 (0.2)		1 (0.2)	3 (0.7)	1 (0.2)		
Other hemorrhage				1 (0.2)	1 (0.2)		

Sandler A et al, N Eng J Med 355:2542-2550, 2006

Bevacizumab plus CT for NSCLC

AVAIL

Endpoint	CG + Placebo	CG + Bevacizumab (7.5 mg/kg)	CG + Bevacizumab (15 mg/kg)
PFS, HR (95% CI; *P* value)	NA	0.75 (0.62-0.91; .0026)	0.82 (0.68-0.98; .0301)
RR, % (*P* value)	20	34 (< .0001)	30 (< .017)
Median survival, mos HR (*P* value)	13.1 (-)	13.6 0.92 (.3664)	13.4 1.02 (.8420)



AE	Bevacizumab 7.5 mg/kg + CG (n = 330)		Bevacizumab 15 mg/kg + CG (n = 329)	
	No. of Patients	%	No. of Patients	%
Patients with ≥ 1 severe (grade ≥ 3) AE	252	76	265	81
Neutropenia*	132	40	117	36
Thrombocytopenia	89	27	77	23
Anemia	34	10	34	10
Asthenia	17	5	15	5
Vomiting	24	7	31	9
Hypertension	21	6	28	9
Severe AEs of interest				
Bleeding	14	4	14	4
Proteinuria	1	< 1	4	1
GI perforation	—	—	1	< 1
Ischemic events†	8	2	10	3
Venous thromboembolic events	24	7	23	7
Hemoptysis (all grades)	23	7.0	32	9.7
Pulmonary hemorrhage (grade ≥ 3)	5	1.5	3	0.9
Fatal pulmonary hemorrhage	4	1.2	3	0.9

Reck M et al, J Clin Oncol 27:1227-1234, 2009

Bevacizumab plus CT for NSCLC

PointBreak

- Patients with advanced nonsquamous NSCLC
- No prior systemic treatment for lung cancer
- ECOG PS = 0/1
- N = 939

R

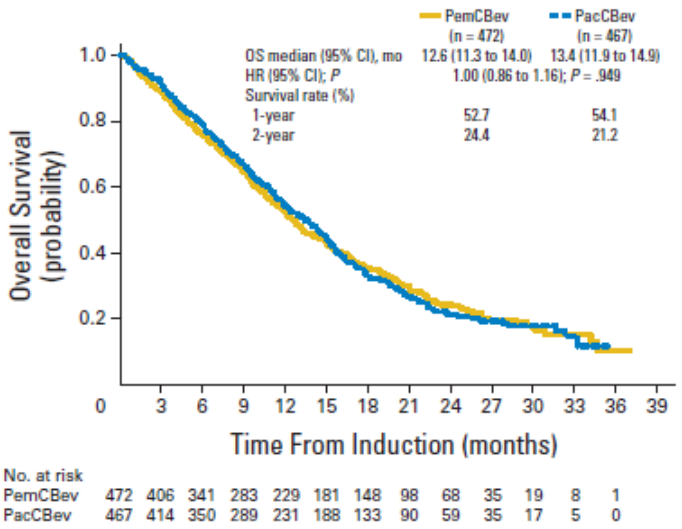
1:1

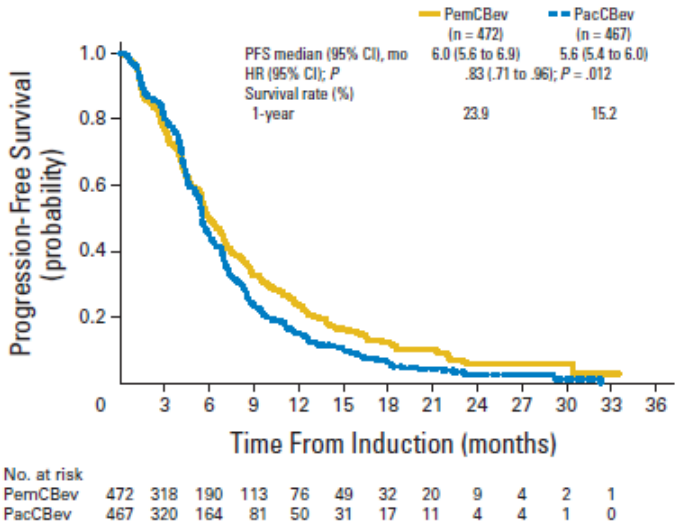
Pemetrexed/carboplatin/bevacizumab every 3 wk up to 4 cycles*; N = 472

Paclitaxel/carboplatin/bevacizumab every 3 wk up to 4 cycles†; N = 467

Primary End Point:

- OS (superiority study)



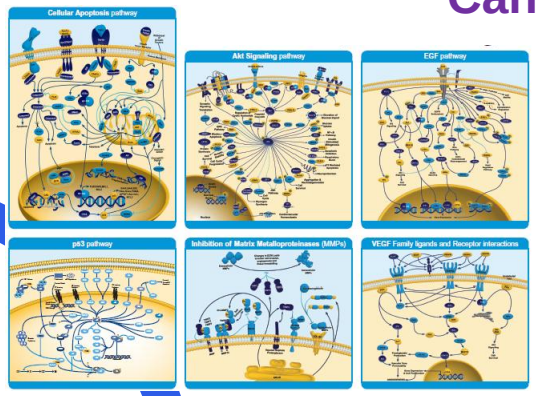


Patel J et al, J Clin Oncol 31:4349-4357, 2013

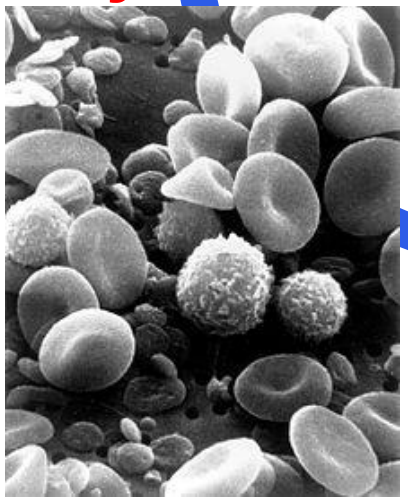
Lung cancer – all different

Patient

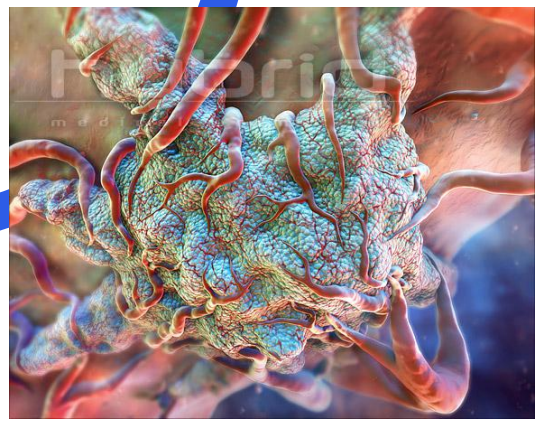
Cancer



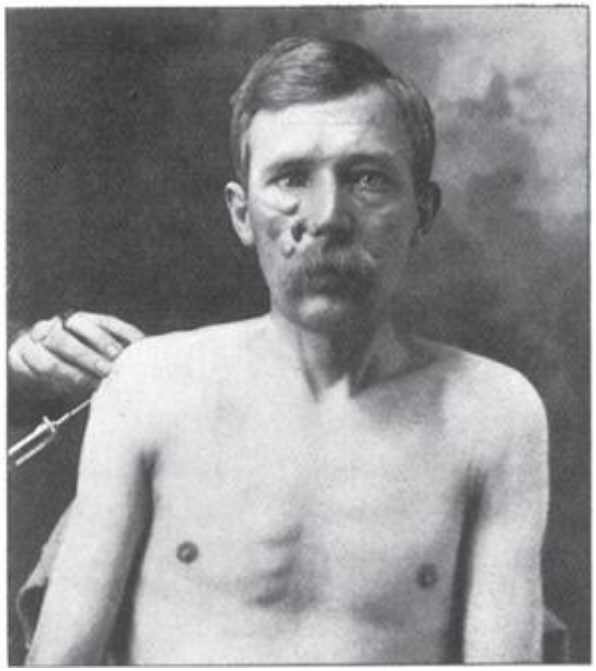
Immunity



Microenvironment

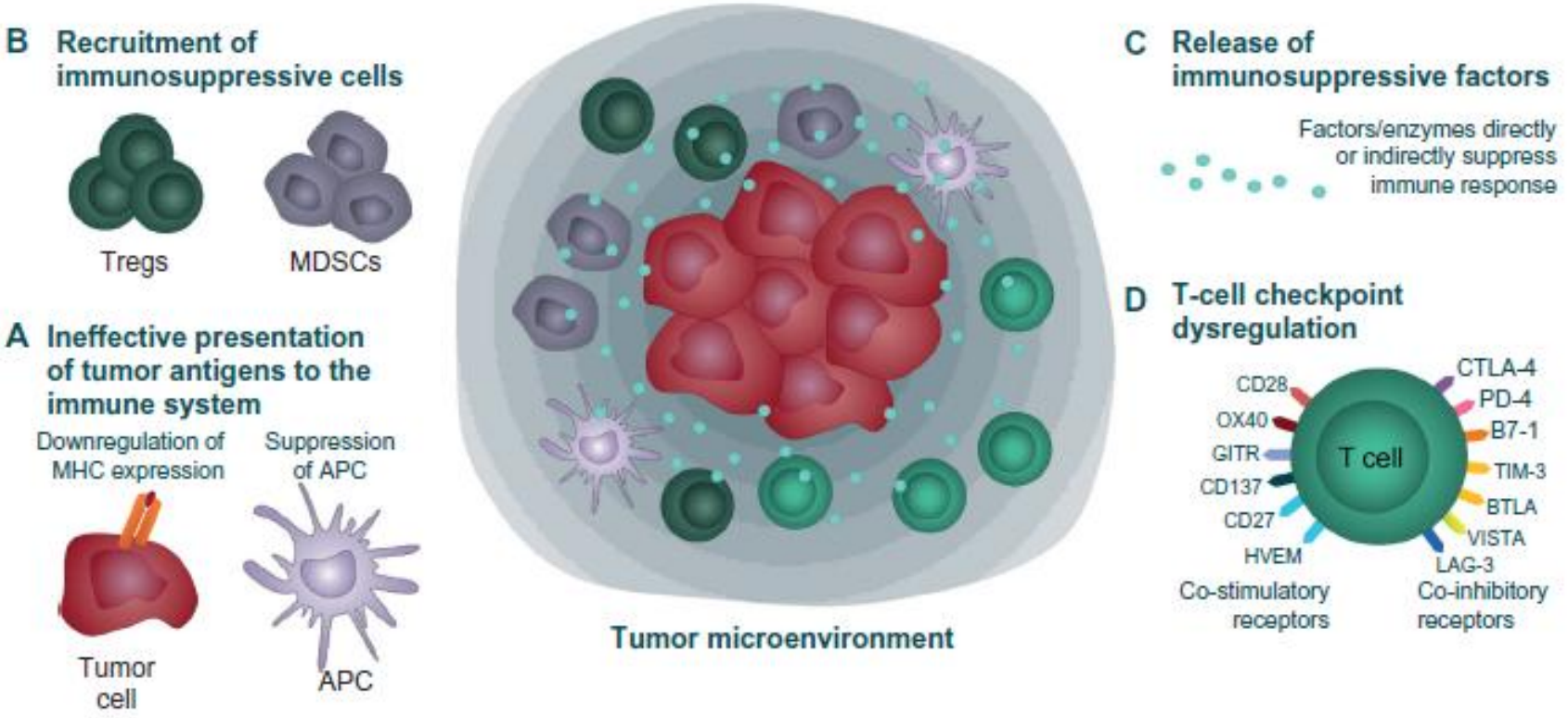


Willam Coley (1862 – 1936)



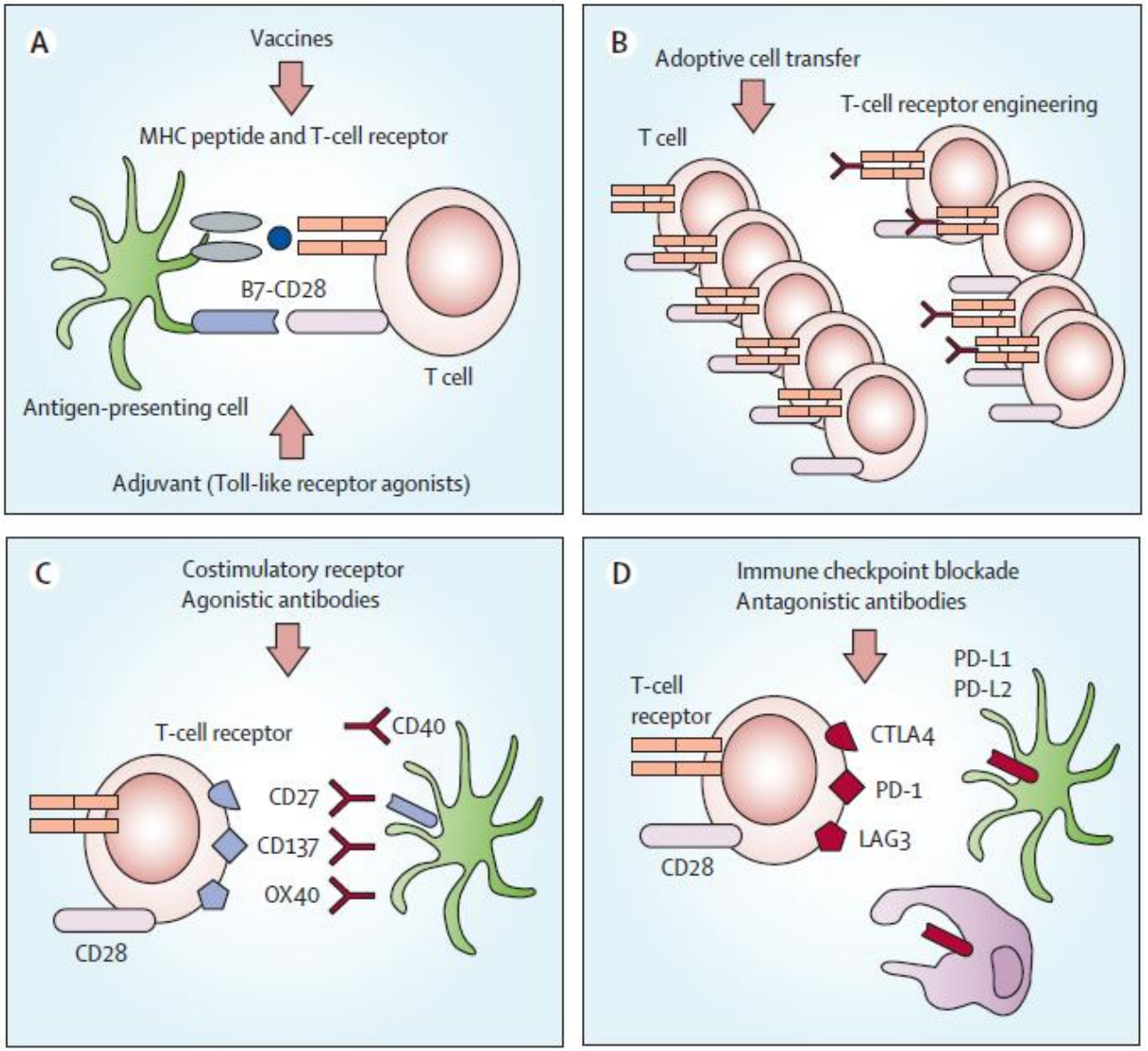
Tumours use various mechanisms to escape the immune system

Immune escape mechanisms are complex and frequently overlapping



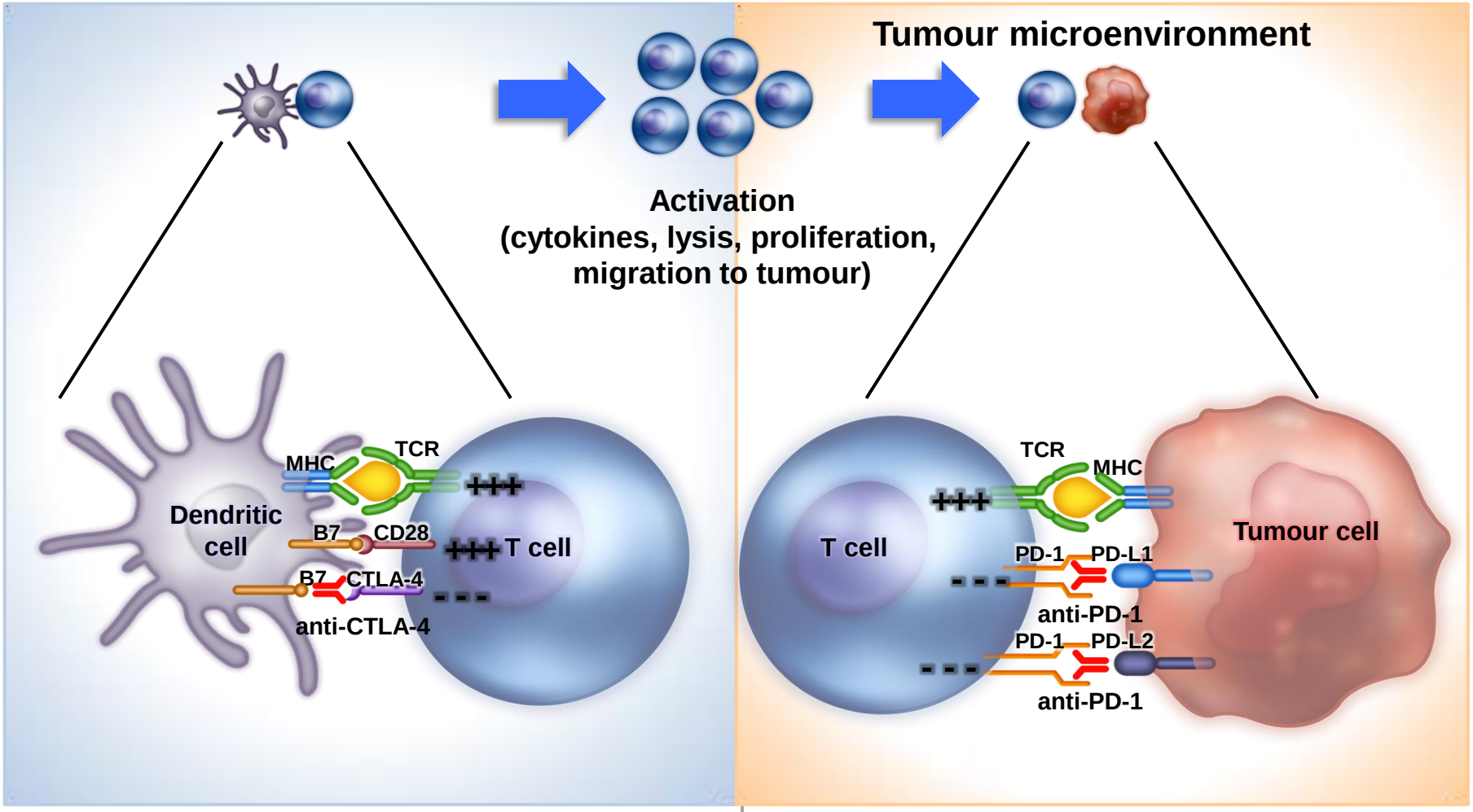
Davies M, et al. Cancer Management and Research 6:63-75, 2014

T-cell based immunomodulation



Tartour E, et al. Lancet Respir Med 1:551-563, 2013

Differences in CTLA-4 and PD-1 blockade



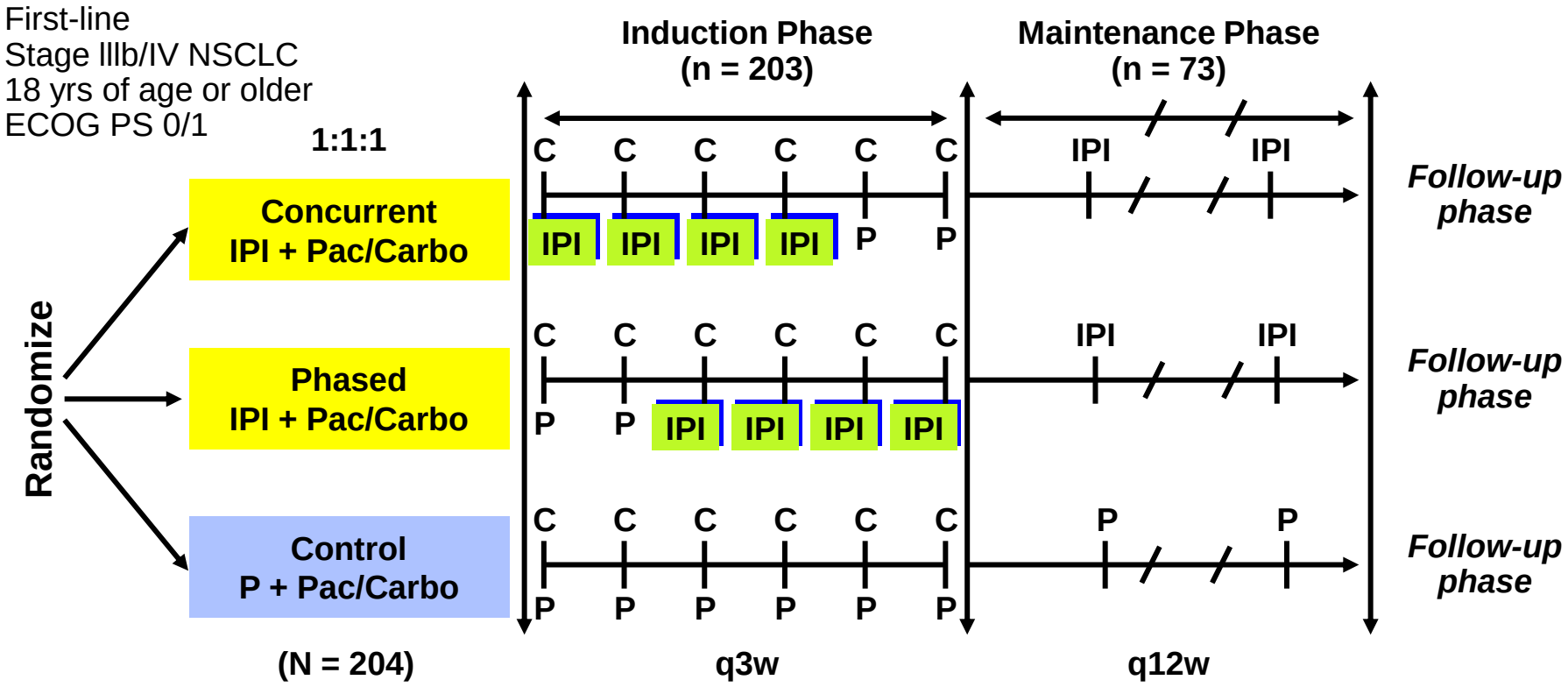
Ribas A, et al. N Engl J Med 366:2517–2519, 2012

Somme immune checkpoint inhibitors in NSCLC

Compound	Company	Target	Development Stage in NSCLC
Ipilimumab	Bristol-Myers Squibb	CTLA4	Phase III
Tremelimumab	MedImmune	CTLA4	Phase I
Nivolumab (BMS-936558)	Bristol-Myers Squibb	PD-1	Phase III
Lambrolizumab (MK-3475)	Merck	PD-1	Phase III
BMS-936559	Bristol-Myers Squibb	PD-L1	Phase I
Medi-4736	MedImmune	PD-L1	Phase I
MPDL-3280A	Genentech	PD-L1	Phase III

Champiat S, et al. J Thorac Oncol 9:144-153, 2014

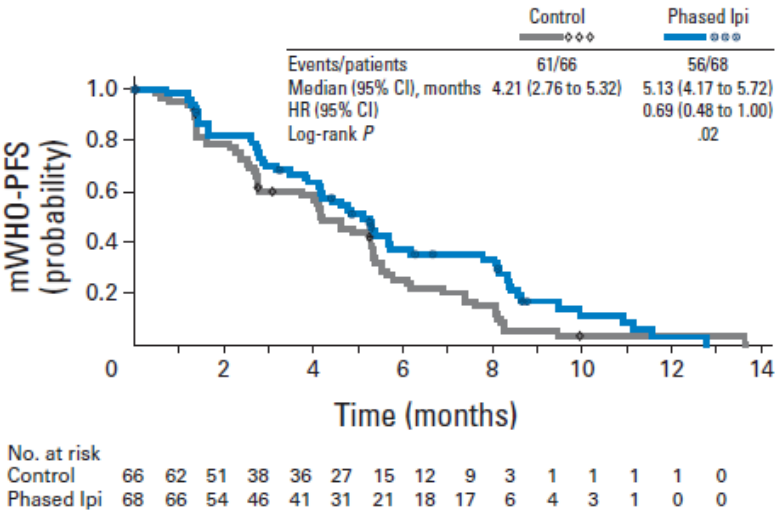
Randomized phase II study of Ipilimumab and CT in advanced NSCLC

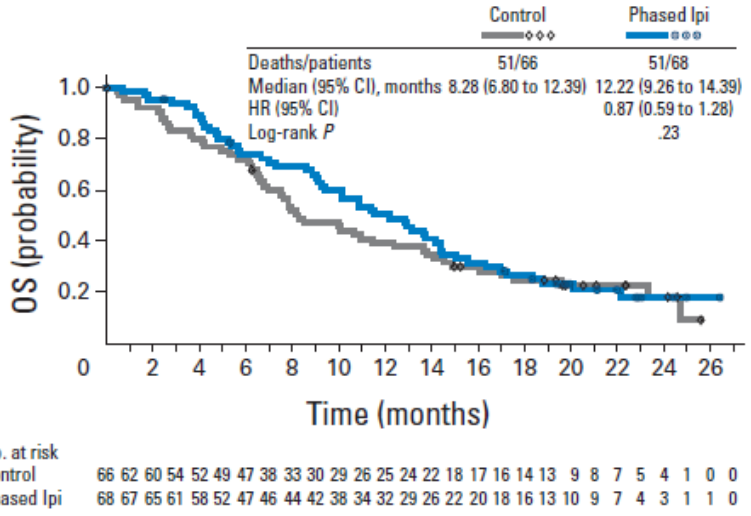


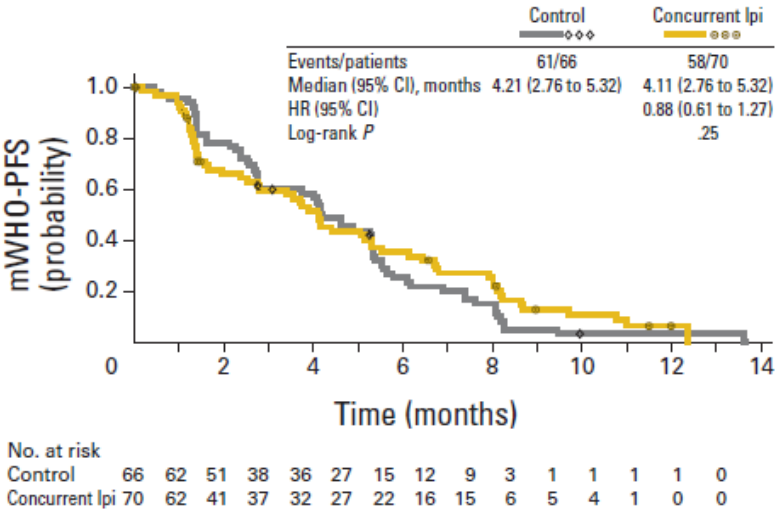
- Primary endpoint: irPFS
- Cx regimen: Pac 175 mg/m^2/carbo AUC 6 prior to start of ipilimumab (10 mg/kg)

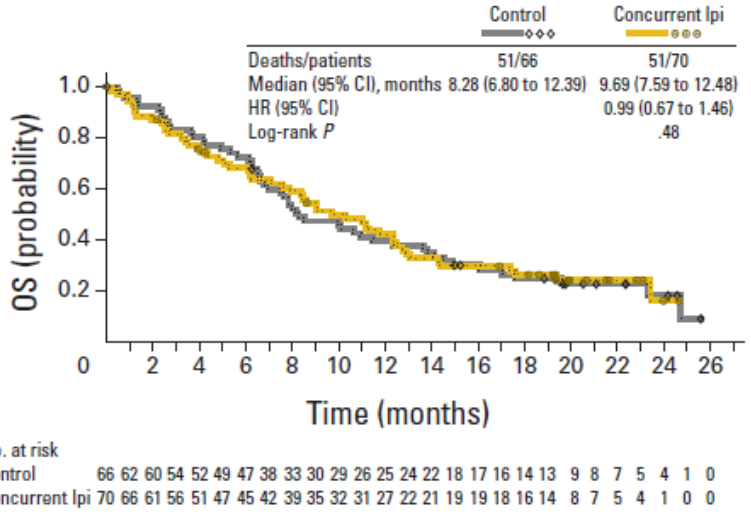
Lynch TJ ,et al. J Clin Oncol 30:2046-2054, 2012

Randomized phase II study of Ipilimumab and CT in advanced NSCLC









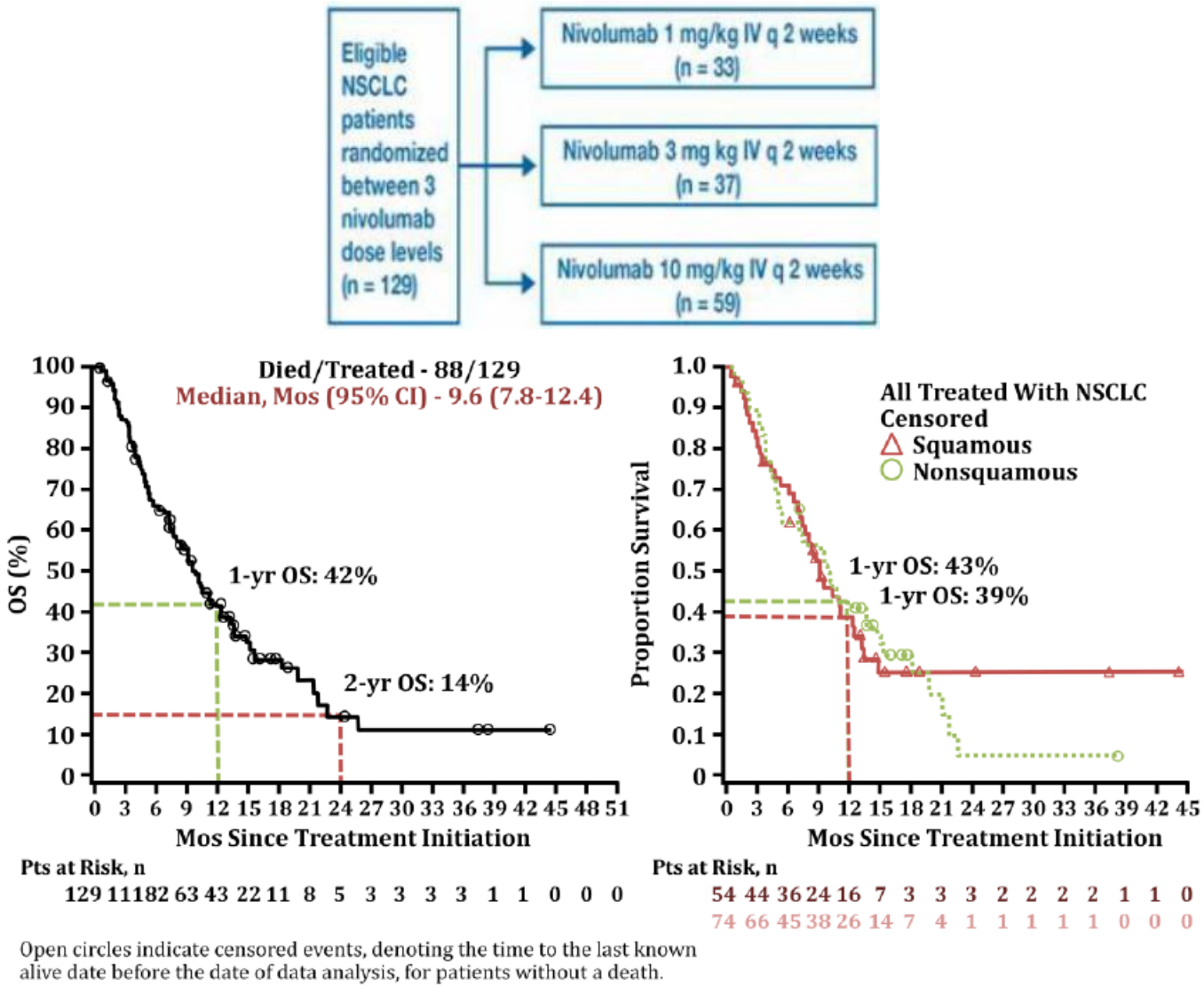
Lynch TJ, et al. J Clin Oncol 30:2046-2054, 2012

Randomized phase II study of Ipilimumab and CT in advanced NSCLC

Event	Control (n = 65)			Concurrent Ipilimumab (n = 71)			Phased Ipilimumab (n = 67)		
	Grades 1 and 2	Grade 3	Grade 4	Grades 1 and 2	Grade 3	Grade 4	Grades 1 and 2	Grade 3	Grade 4
Any adverse event, %	31	29	11	16	30	27	19	42	12
Any treatment-related adverse event, %	43	29	8	35	24	17	43	31	8
Treatment-related non-hematologic adverse events, %									
Fatigue	22	5	0	20	7	1	19	5	0
Alopecia	46	NA	NA	34	NA	NA	45	NA	NA
Rash	8	2	0	25	3	0	10	3	0
Pruritus	5	2	0	17	0	0	8	0	0
Arthralgia	11	0	0	16	0	0	12	2	0
Asthenia	3	2	0	4	3	0	16	2	0
Diarrhea	14	3	0	23	7	0	18	5	0
Nausea	31	2	0	25	1	0	31	2	0
Vomiting	15	2	0	17	1	0	16	2	0
Peripheral neuropathy*	23	2	0	13	1	0	10	0	0
Peripheral sensory neuropathy*	11	2	0	8	0	0	16	3	0
Hematologic abnormalities, %†									
Thrombocytopenia	35	8	2	39	2	0	40	3	0
Neutropenia	32	8	2	26	5	3	34	2	0
Anemia	89	6	0	80	8	3	92	6	0
Liver-function enzymes, %†									
ALT	35	2	0	40	2	0	29	2	0
AST	32	2	0	25	2	0	31	2	0

Lynch TJ, et al. J Clin Oncol 30:2046-2054, 2012

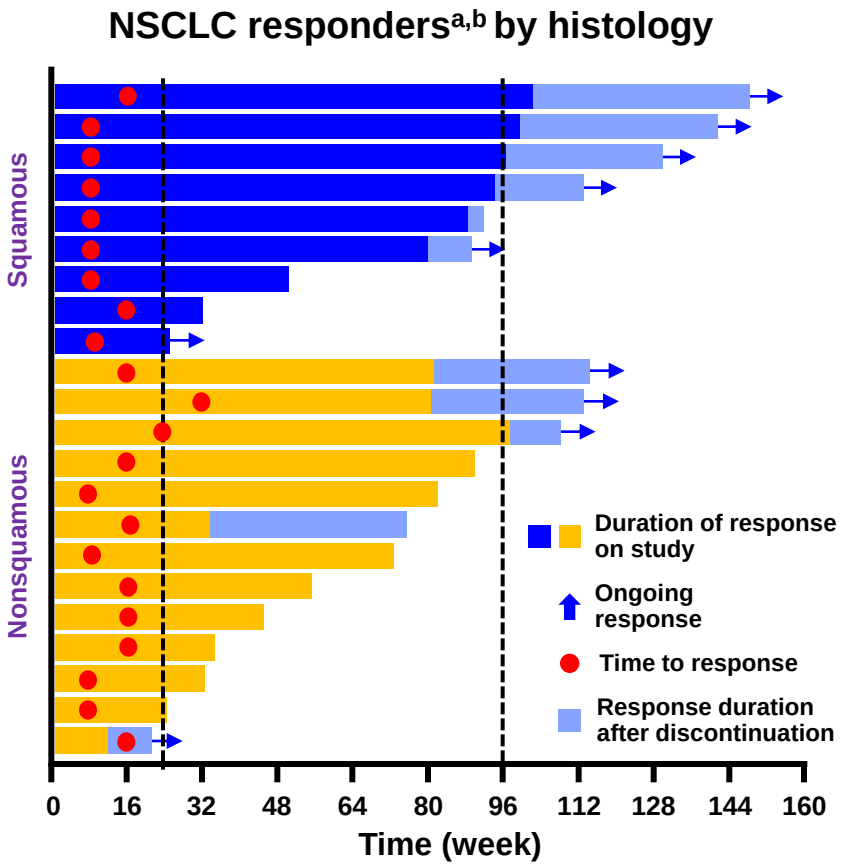
Nivolumab phase I trial in squamous/nonsquamous NSCLC

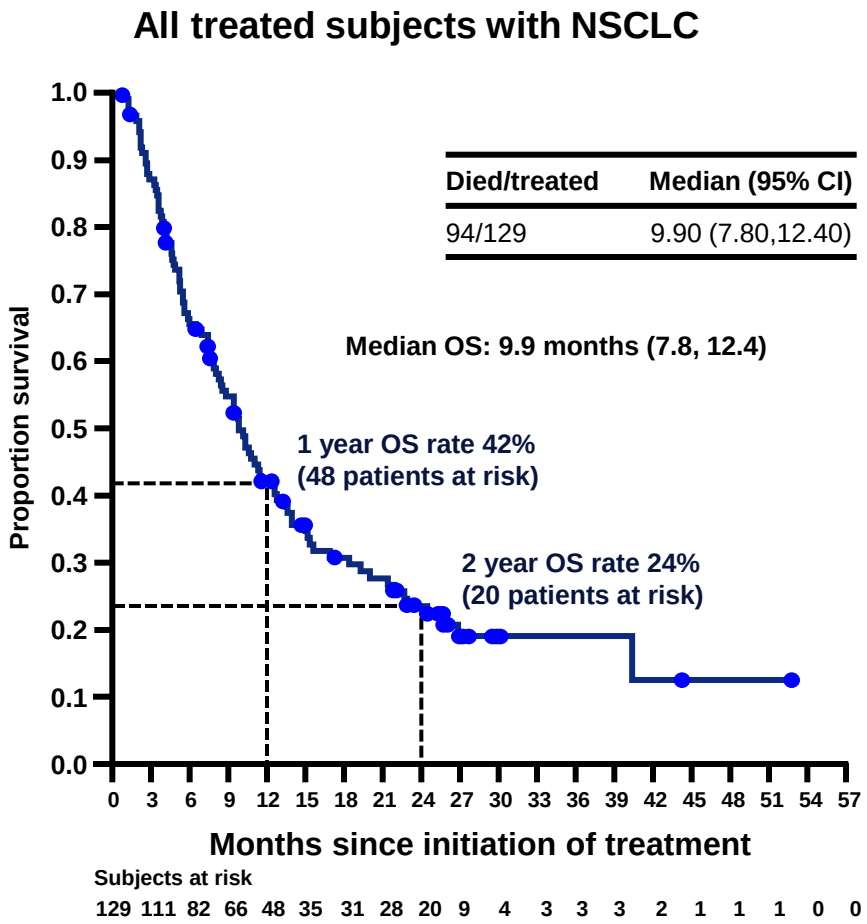


Open circles indicate censored events, denoting the time to the last known alive date before the date of data analysis, for patients without a death.

Brahmer JR, et al. ASCO 2013. Abstract 8030

Duration of response and overall survival with nivolumab monotherapy in NSCLC





Vertical line at 96 weeks = maximum duration of continuous nivolumab therapy

[a]Responses were assessed by modified RECIST v1.0

[b]All efficacy analyses based on data collected as of September 2013

Adapted from Brahmer JR, et al. Mini-Oral presentation at WCLC 2013. *J Thorac Oncol.* 2013;8(suppl 2):abstract: MO18.03

Nivolumab: activity across NSCLC histology

NSCLC histology	Dose (mg/kg)	ORR % (n/N)	Stable disease rate ≥24 week, % (n/N)
Squamous	All doses	16.7 (9/54)	14.8 (8/54)
	1	0 (0/18)	26.7 (4/15)
	3	22.2 (4/18)	5.6 (1/18)
	10	23.8 (5/21)	14.3 (3/21)
Nonsquamous	All doses	17.6 (13/74)	6.8 (5/74)
	1	5.6 (1/18)	5.6 (1/18)
	3	26.3 (5/19)	10.5 (2/19)
	10	18.9 (7/37)	5.4 (2/37)

Brahmer JR, et al. ASCO 2013. Abstract 8030

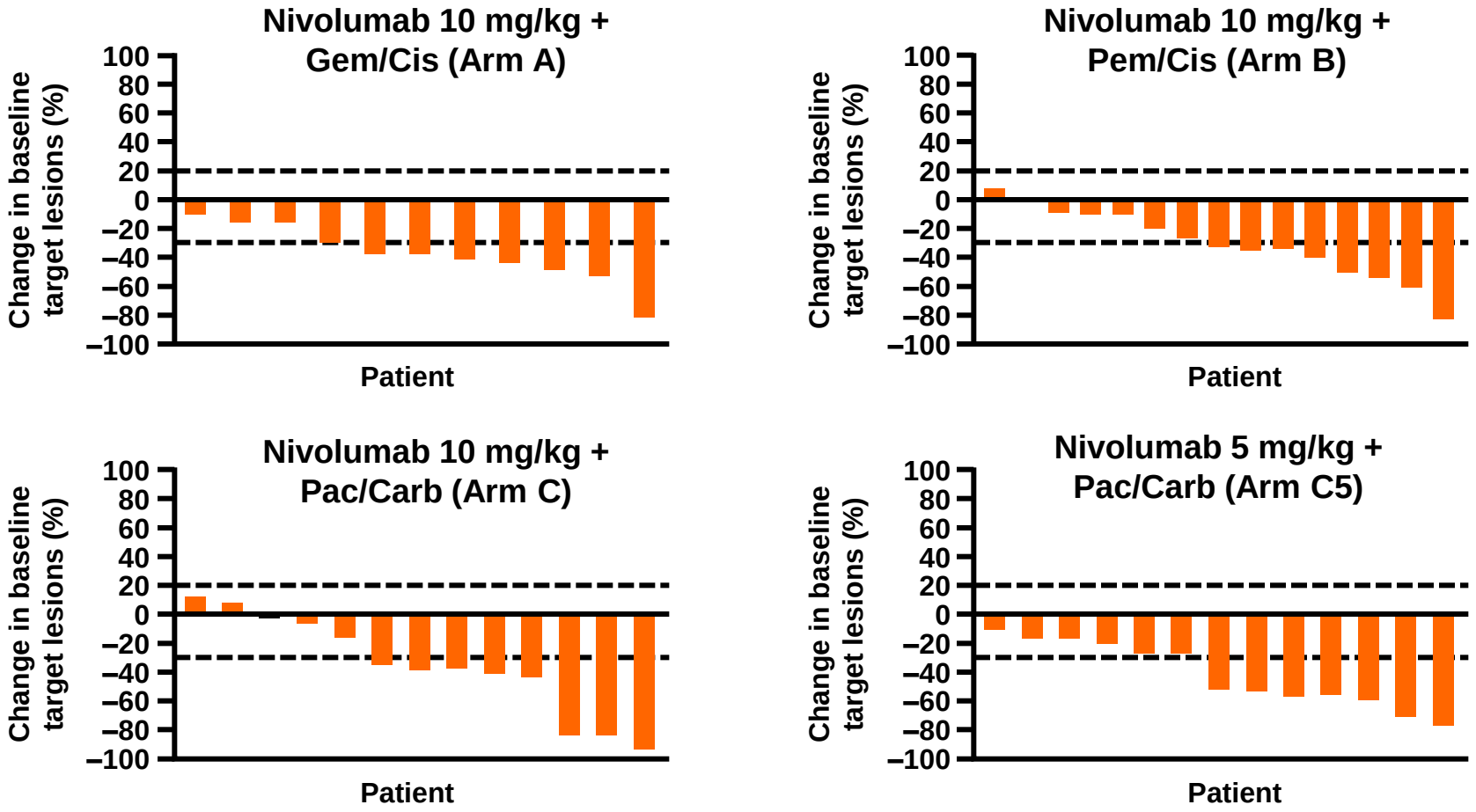
Selected adverse events (≥1%) in patients with NSCLC treated with nivolumab

- Select adverse event defined as an event with potential immunological aetiologies that require more frequent monitoring and/or unique intervention
- All patients have ≥1 year of follow-up
- Drug-related pneumonitis (any grade) occurred in 8 NSCLC patients (6%); 3 patients (2%) had grade 3-4 pneumonitis of which 2 cases were fatal

	Patients, n (%) N=129	
	Any grade	Grade 3/4
Any treatment-related select adverse event	**41 (53)**	**5 (6)**
Skin	**16 (20)**	**0**
Gastrointestinal	**12 (15)**	**1 (1)**
Pulmonary	**7 (9)**	**2 (3)**
Endocrinopathies	**6 (8)**	**0**
Hepatic	**5 (6)**	**1 (1)**
Infusion reaction	**4 (5)**	**1 (1)**
Renal	**3 (4)**	**0**

Adapted from Brahmer JR, et al. Mini-Oral presentation at WCLC 2013. *J Thorac Oncol.* 2013;8(suppl 2):abstract: MO18.03

Nivolumab plus CT: change in tumour burden

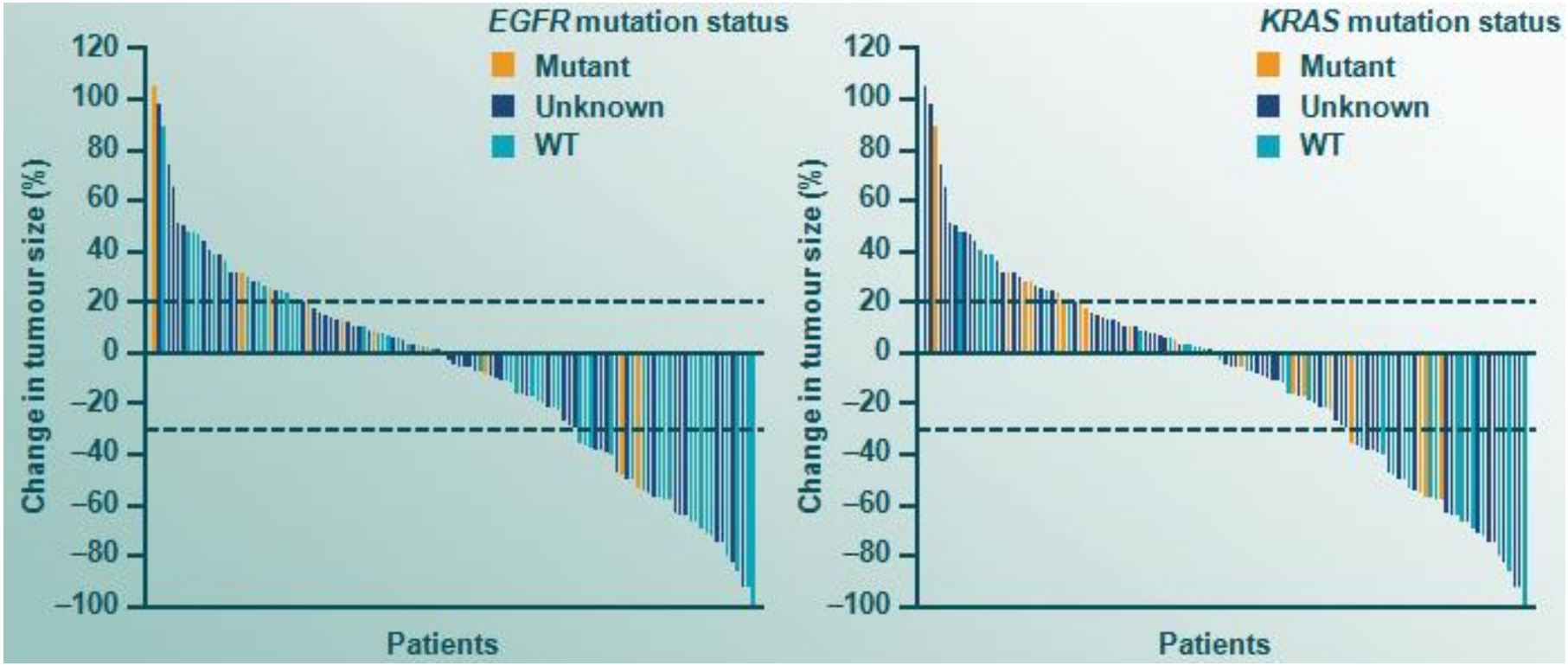


Baseline tumour measurements are standardised to zero; tumour burden is measured as the sum of the longest diameters of target lesions

Horizontal lines denote 30% decrease for PR and 20% increase for PD per RECIST 1.1 Only patients with both baseline and on-study target lesion measurements are included

Rizvi NA, et al. ASCO 2013. Abstract 8072

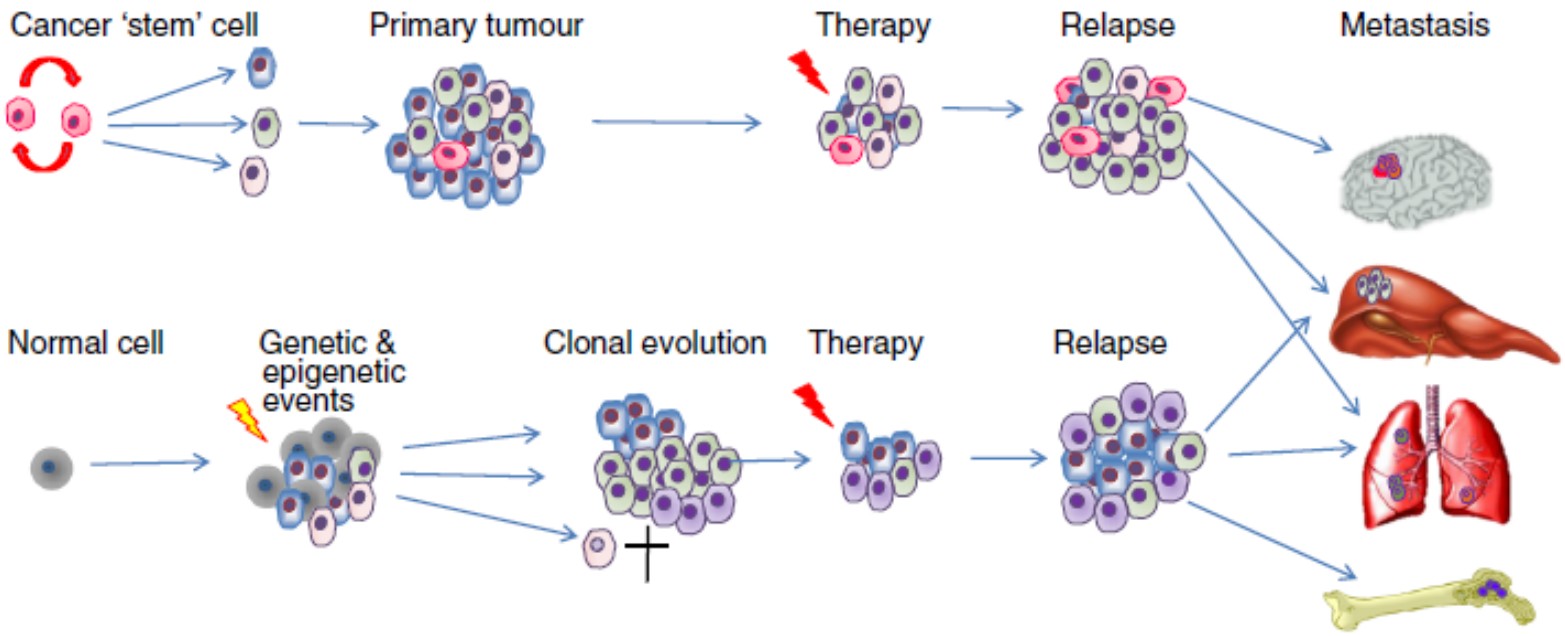
Nivolumab: change in tumour burden according to *EGFR* and *KRAS* mutation status



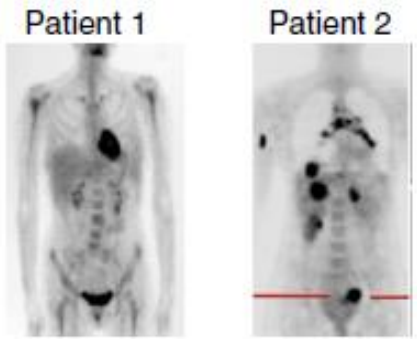
Dashed horizontal lines denote 30% decrease for PR (in the absence of new lesions) and 20% increase for PD per RECIST v1.0

Adapted from Gettinger S, et al. Poster presentation at WCLC 2013. *J Thorac Oncol.* 2013;8(suppl 2):abstract: P2.11-038

Tumor heterogeneity



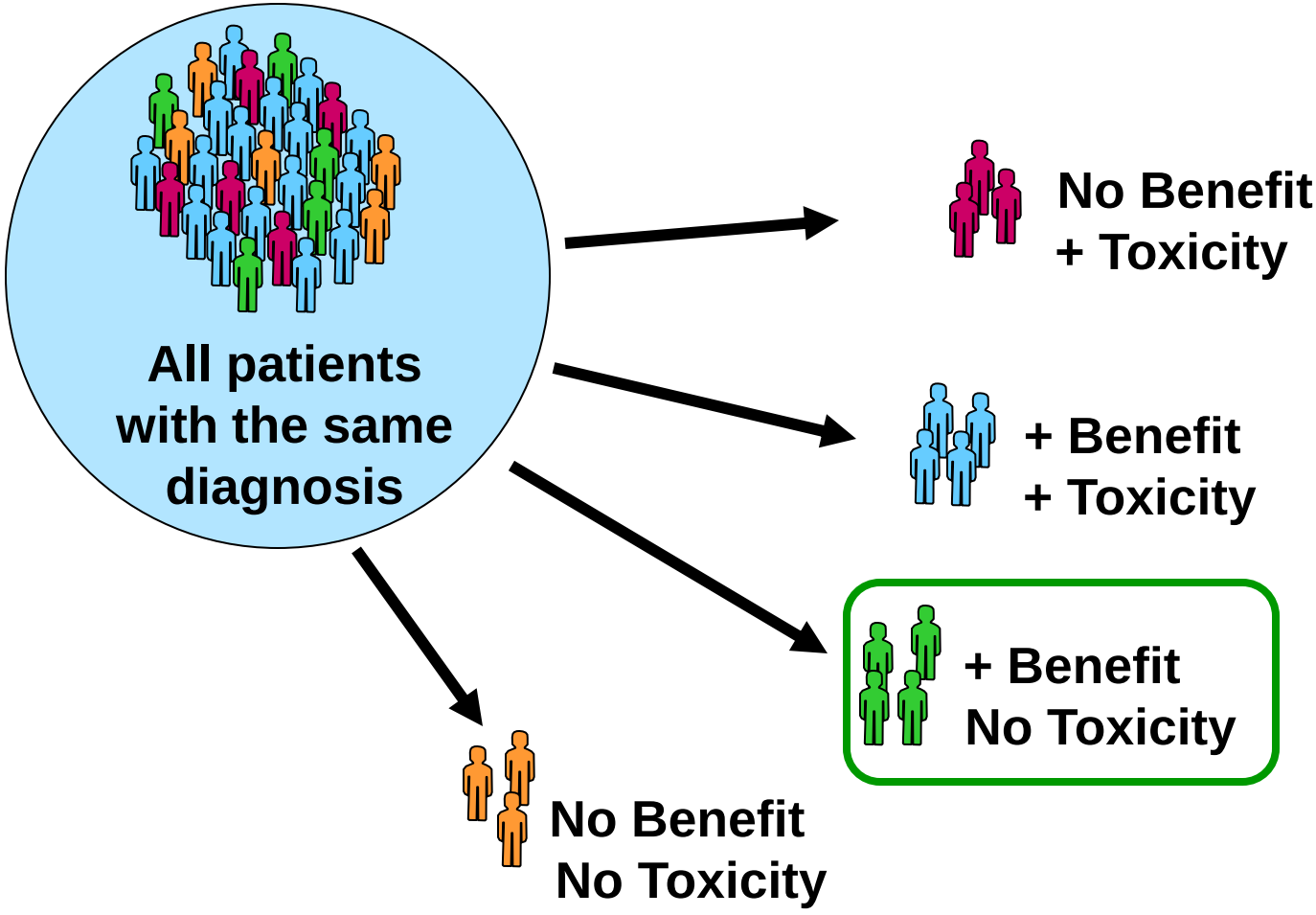
Tumors with identical histological type and biochemical parameters



Eccles S, et al. Breast Cancer Res 15:R92, 2013

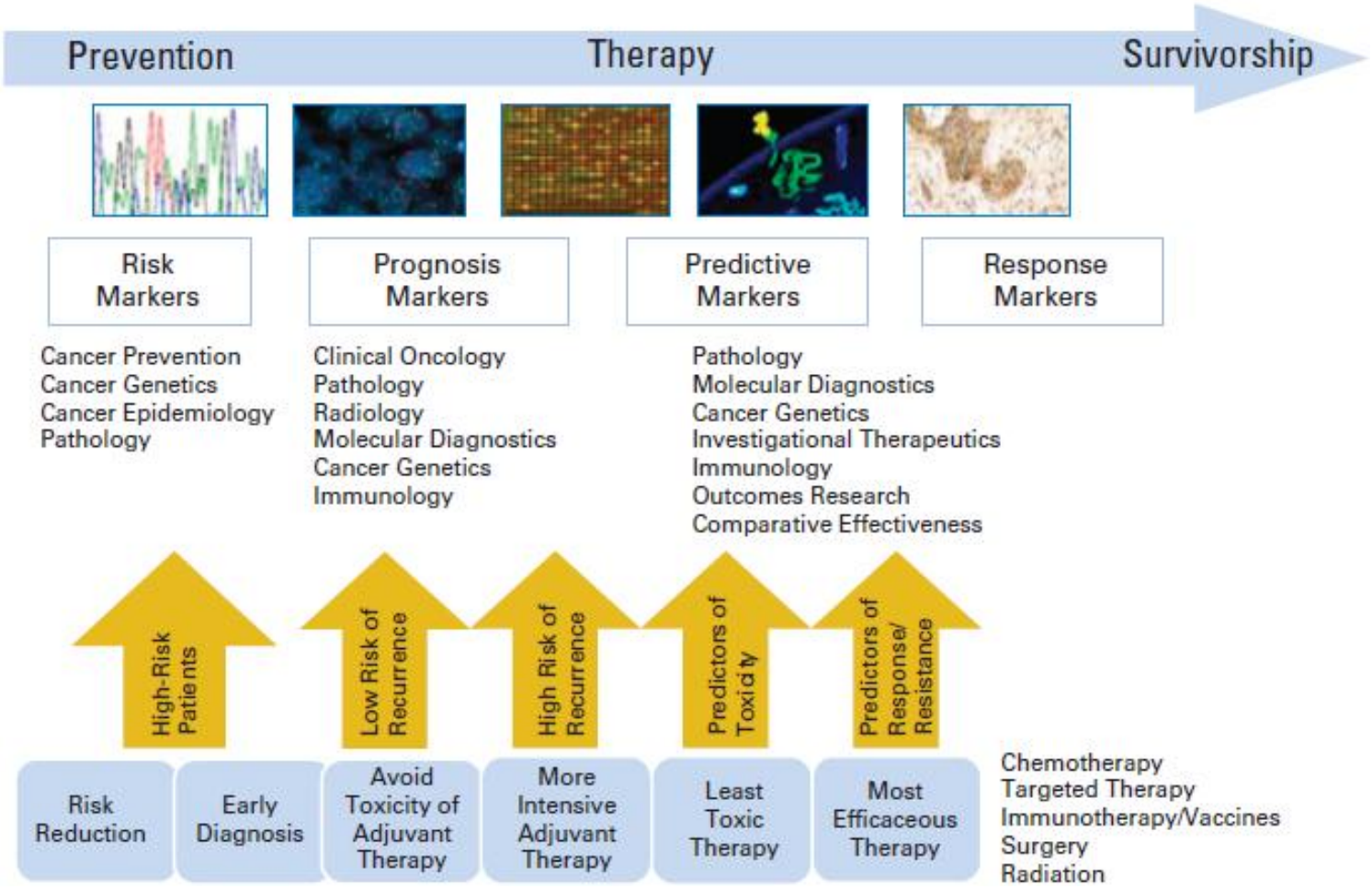
Non small cell lung Cancer

The promise of pharmacogenomic testing



Walgren RA et al. J Clin Oncol 23:7342-7349, 2005

The personalized cancer care continuum



Meric-Bernstam F et al. J Clin Oncol 31:1849-1857, 2013

Conclusions

- ✓ Advanced NSCLC: A prevalent and deadly cancer
- ✓ First-line therapy: Several CT and targeted agents approved in recent years; choices driven specially by histology and/or mutational status (ie, EGFR and ALK and …)
- ✓ Second-line therapy: Choices depend on ECOG PS, prior treatment, current organ function, tumor histology, and molecular variables
- ✓ Special considerations: Important to consider patient age, initiating early palliative care, management of treatment-related adverse effects (eg, CINV, rash/cutaneous, cardiac)
- ✓ Future directions/ongoing needs: Many patients do not respond to or relapse on existing therapies; many promising agents under investigation

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