



Diagnóstico e Tratamento do Cancro do Pulmão: Estado da Arte



U. PORTO



INSTITUTO DE CIÊNCIAS BIOMÉDICAS ABEL SALAZAR
UNIVERSIDADE DO PORTO

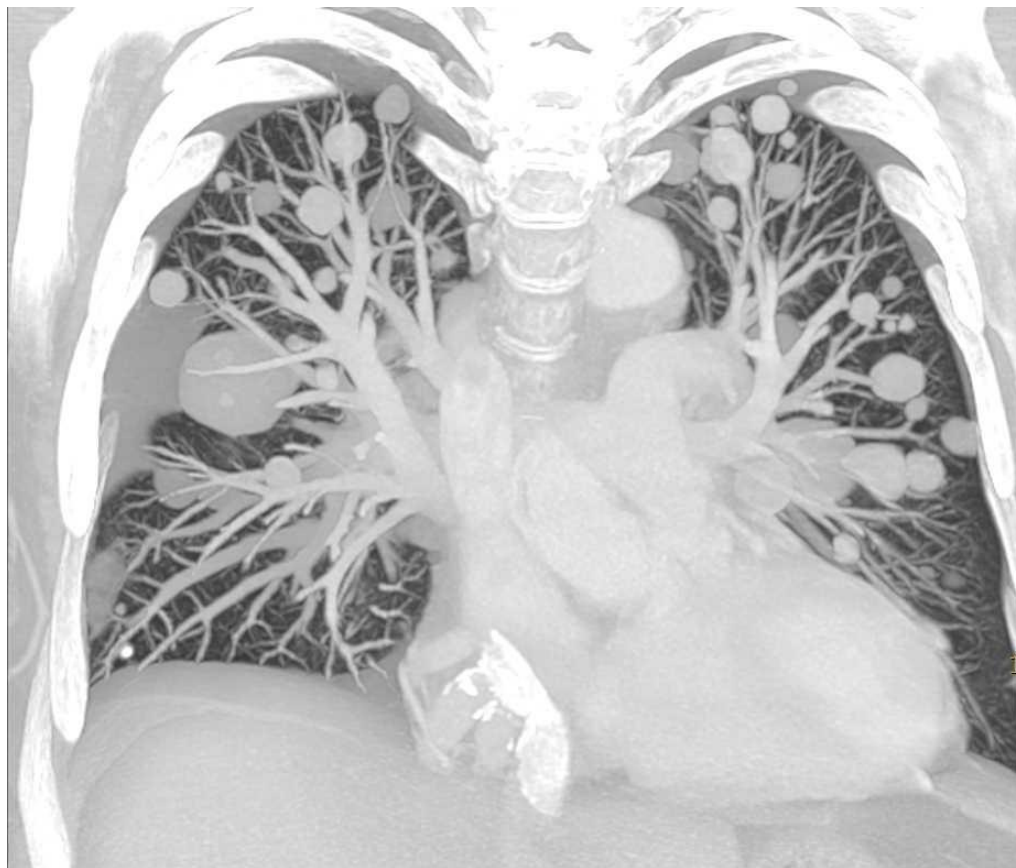
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Cancro do Pulmão



Incidência

Mundo

População - 2000

6,109,000,000

3,080,000,000

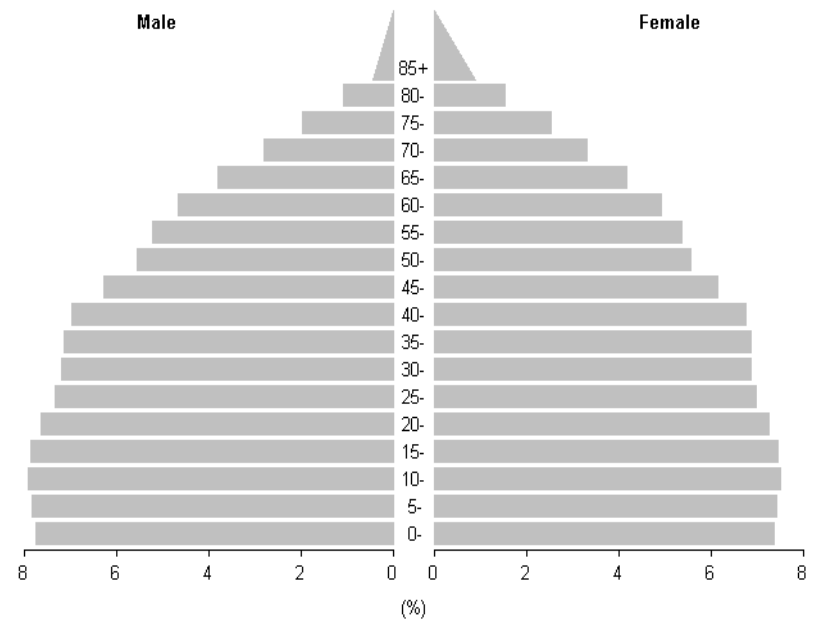
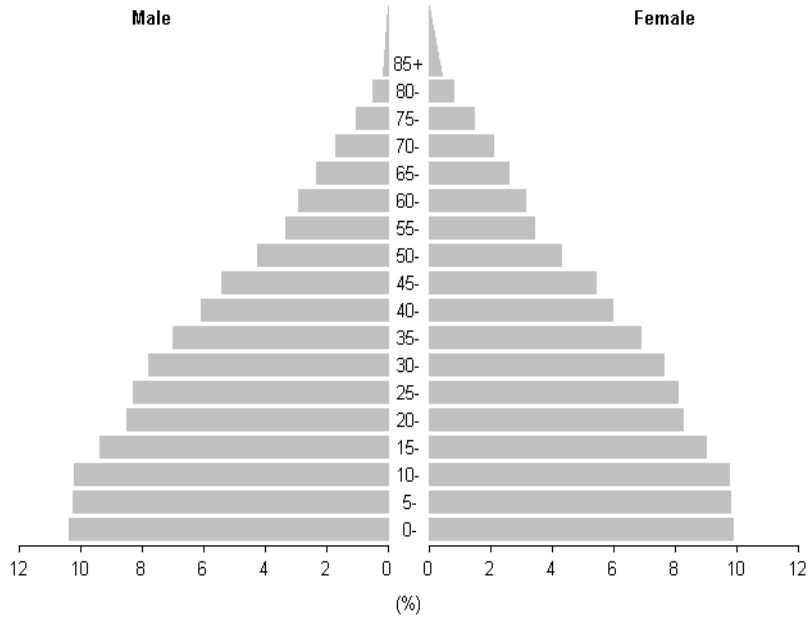
3,029,000,000

População - 2030

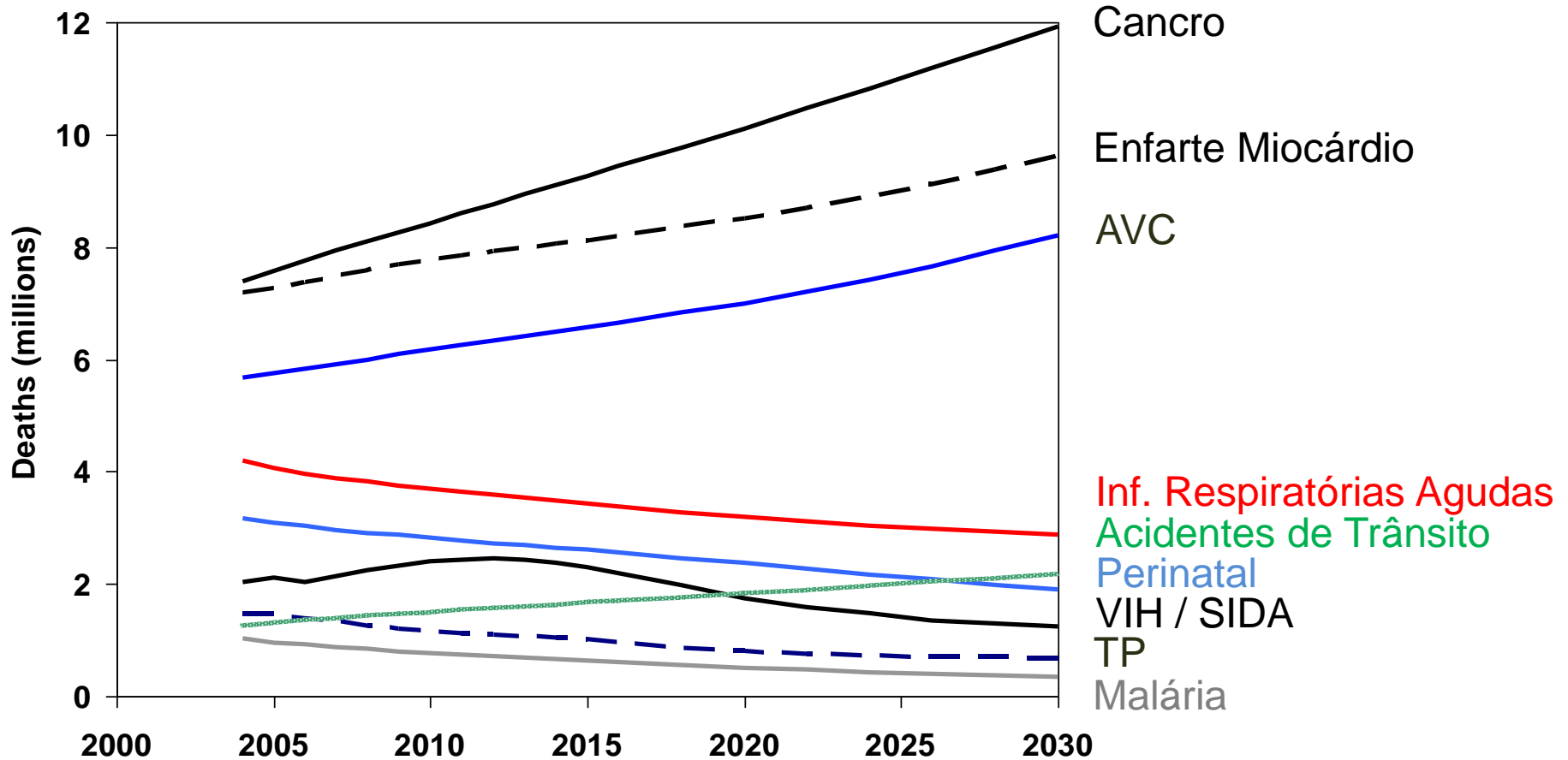
8,293,000,000

4,165,000,000

4,128,000,000

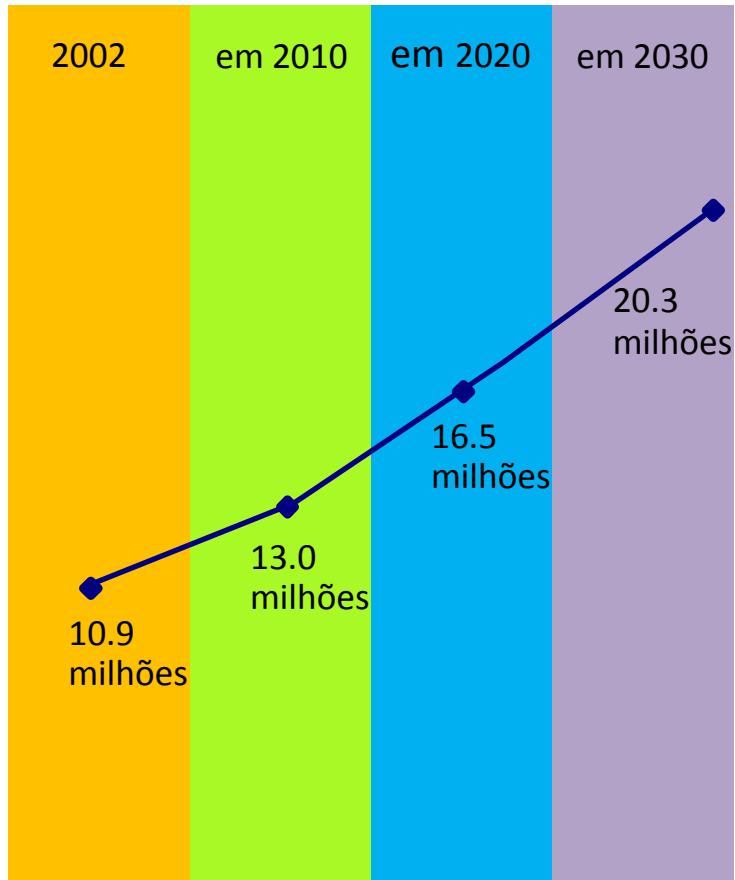


Projeções globais, 2004 to 2030



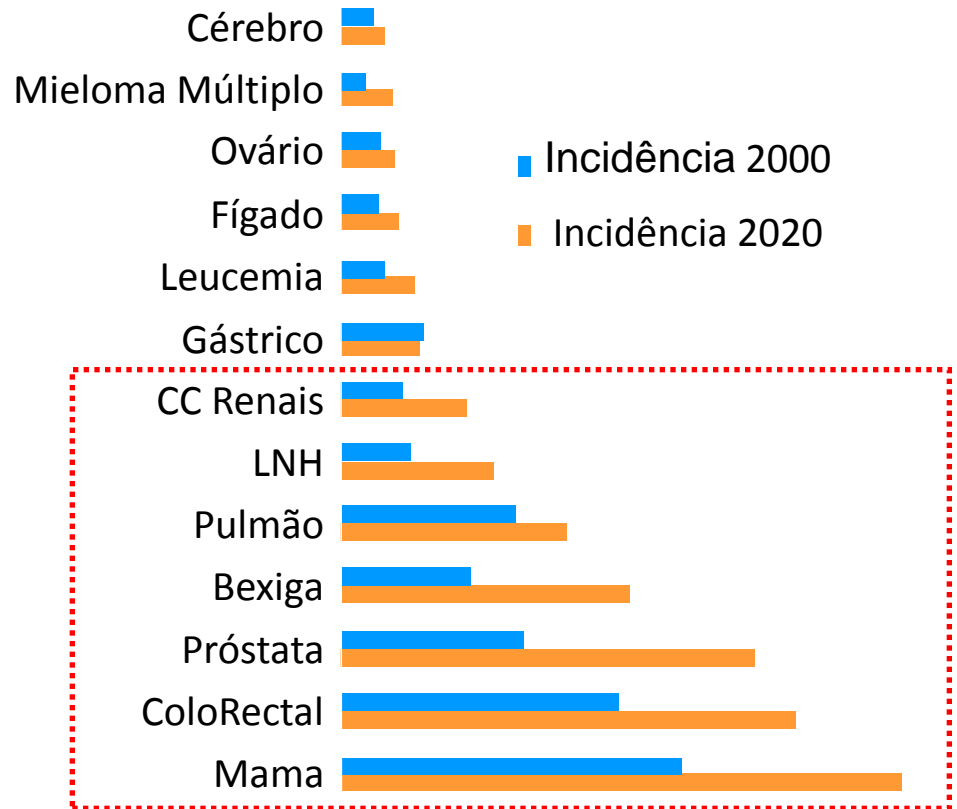
Taxas de incidência de todos os tumores

Novos casos de cancro no mundo



Nº Anual

Fonte: The Cancer Atlas 2006



Incidência para 5 maiores países EU
Fonte : Globocan 2002 & internal figures

WORLD HEALTH ORGANIZATION



International Agency for Research on Cancer

WORLD CANCER REPORT



Editors

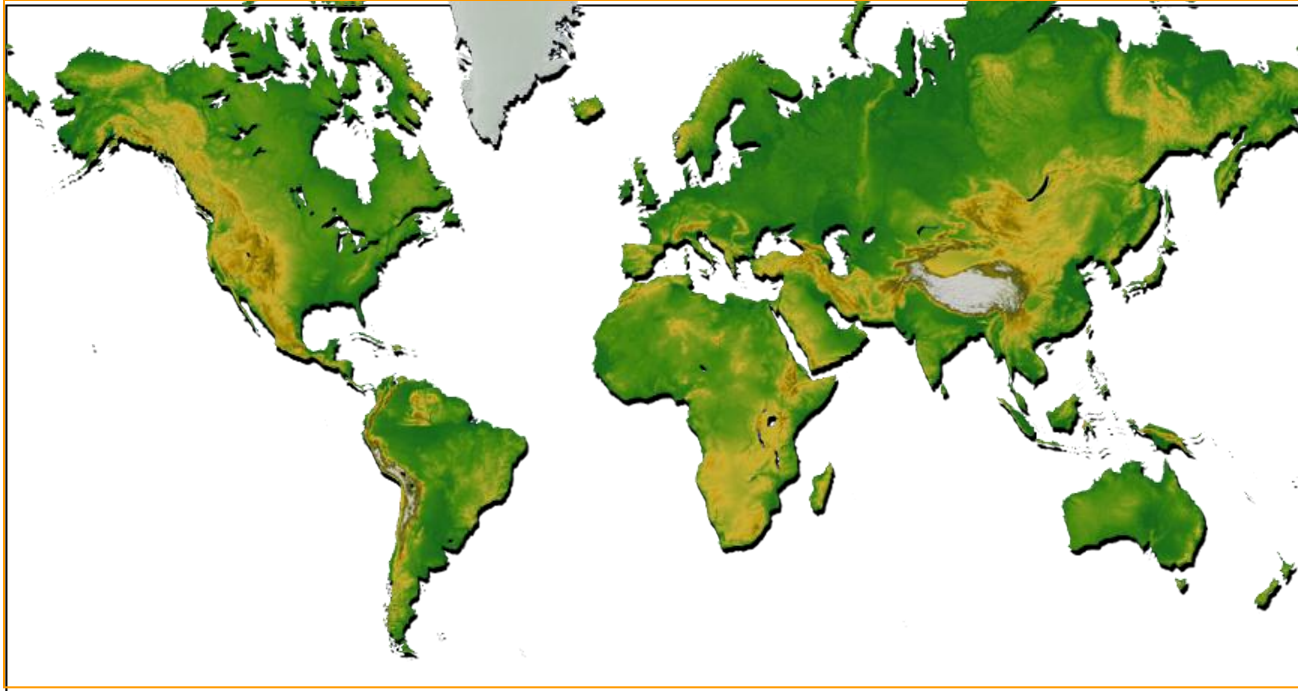
Peter Boyle, Bernard Levin, Miklòs Kasler, Murat Tuncer and Twalib Ngoma

Collaborating Editors

Philippe Autier, Paolo Boffetta, Eric Duell, Silvia Franceschi, Pierre Hainaut, Hiroko Ohgaki and Sean Tavtigian

2008

Peso mundial do cancro, 2008 - 2030



12.5 milhões de novos casos

7.6 milhões de mortes

28 milhões vivem com cancro

26.4 milhões de novos casos

17.1 milhões de mortes

80 milhões vivem com cancro

Tx incidência estimada
Europa / 100.000, 2006

Country	Stomach (C16)		Colon and rectum (C18-21)		Lung (C33-34)		Breast (C50)	Uterus (C53-55)	Prostate (C61)	All cancers (C00-97/C44)	
	M	F	M	F	M	F				M	F
		14.3	8.8	57.6	30.9	54.0	22.3	91.5	29.1	134.6	444.6
	10.3	3.8	53.3	34.3	93.0	22.9	137.8	32.7	160.8	543.3	343.1
	16.2	8.7	41.2	29.0	66.1	9.5	88.4	23.3	74.6	373.3	269.6
Czech Republic	17.0	8.2	94.4	46.0	78.9	22.9	84.8	44.8	76.1	484.0	346.0
Denmark	9.1	4.5	61.0	48.0	65.0	48.7	122.6	28.7	80.3	442.0	413.6
Estonia	33.4	17.5	50.0	33.9	80.3	13.2	71.1	40.5	65.3	411.1	298.5
Finland	11.8	6.8	39.2	29.4	45.8	14.7	119.8	25.4	149.7	406.0	314.0
France	12.0	4.5	59.8	36.8	75.5	15.0	127.4	22.2	133.5	527.5	329.0
Germany	17.6	8.5	70.2	45.1	61.2	20.8	121.2	26.4	113.0	451.4	333.7
Greece	18.9	8.9	31.0	21.3	88.7	12.7	81.8	21.3	81.0	423.9	259.5
Hungary	26.6	10.9	106.0	50.6	119.3	42.4	118.0	51.6	85.6	598.8	408.7
Ireland	14.7	7.6	65.2	36.9	60.2	34.1	131.4	28.8	182.0	513.6	382.2
Italy	22.1	11.1	52.0	30.3	84.7	15.6	105.3	25.1	108.4	499.7	323.6
Latvia	28.6	14.6	47.0	28.7	82.5	10.2	64.8	39.7	85.7	419.4	265.2
Lithuania	36.8	17.9	53.1	32.5	91.9	9.9	68.7	63.4	109.7	500.1	320.5
Luxembourg	14.8	5.4	61.9	36.1	69.8	16.3	116.9	20.0	93.6	440.0	312.5
Malta	13.7	7.7	51.5	36.2	43.9	6.5	94.5	25.7	68.8	322.8	279.5
The Netherlands	13.4	6.3	61.2	43.9	63.4	32.5	128.0	22.1	98.4	435.0	355.4
Poland	34.8	8.8	43.1	27.7	100.0	28.0	74.1	37.9	51.0	443.2	311.9
Portugal	28.9	15.4	58.9	30.9	44.5	11.7	103.5	33.1	101.2	427.8	289.4
Slovakia	25.2	10.3	87.1	42.6	71.7	11.6	69.7	40.0	51.2	434.1	288.4
Slovenia	27.5	11.0	69.0	36.3	75.6	22.9	87.5	42.8	70.2	438.5	319.0
Spain	15.9	8.4	54.4	25.4	68.3	13.8	93.6	24.5	77.2	416.9	263.4
Sweden	9.2	4.9	49.2	37.4	28.6	23.8	125.8	31.7	157.2	418.2	361.3
United Kingdom	14.3	5.7	54.9	34.8	57.1	34.6	122.2	25.2	107.3	410.5	348.9
European Union (EU25)	18.2	8.1	59.0	35.6	71.8	21.7	110.3	28.3	106.2	463.0	325.5
Iceland	14.1	6.4	50.2	36.8	40.6	45.6	121.6	27.3	140.5	429.2	383.6
Norway	11.2	5.4	66.4	51.2	53.8	33.7	109.1	34.1	133.2	458.7	381.5
Switzerland	16.4	3.9	79.1	55.6	52.7	26.2	126.5	29.2	137.0	493.6	369.0
EEA and Switzerland	18.1	8.0	59.4	36.1	71.3	21.9	110.5	28.3	106.9	463.4	326.7
Bulgaria	25.5	13.6	49.6	31.3	67.3	11.5	74.0	53.0	36.0	336.6	269.0
Romania	30.6	13.0	40.7	25.1	81.0	15.4	61.2	64.1	32.2	371.8	279.1
Albania	59.4	21.5	13.6	21.4	95.0	26.2	82.4	22.2	62.1	444.7	312.1
Belarus	45.1	20.4	42.8	29.0	86.5	6.7	55.5	39.3	38.0	380.7	251.4
Bosnia Herzegovina	37.8	14.4	34.6	27.3	76.0	17.5	79.0	43.8	42.0	369.4	287.0
Croatia	27.5	8.6	57.0	36.9	69.3	13.9	79.4	25.9	67.8	421.3	244.4
Macedonia	37.3	16.0	49.4	30.0	71.8	8.9	85.4	49.1	31.9	363.0	280.2
Republic of Moldova	28.3	14.4	38.7	26.7	63.7	12.5	51.6	45.0	18.7	331.2	238.3
Russian Federation	47.8	21.1	46.5	33.9	92.7	11.2	67.3	39.2	30.1	389.0	261.9
Serbia and Montenegro	16.9	5.9	41.0	30.4	61.5	17.3	69.2	60.0	32.3	300.1	268.5
Ukraine	37.1	15.1	41.7	27.0	74.6	9.5	53.3	40.0	26.7	333.6	227.4
Europe	24.8	11.6	55.4	34.6	75.3	18.3	94.3	33.5	86.7	439.7	303.0

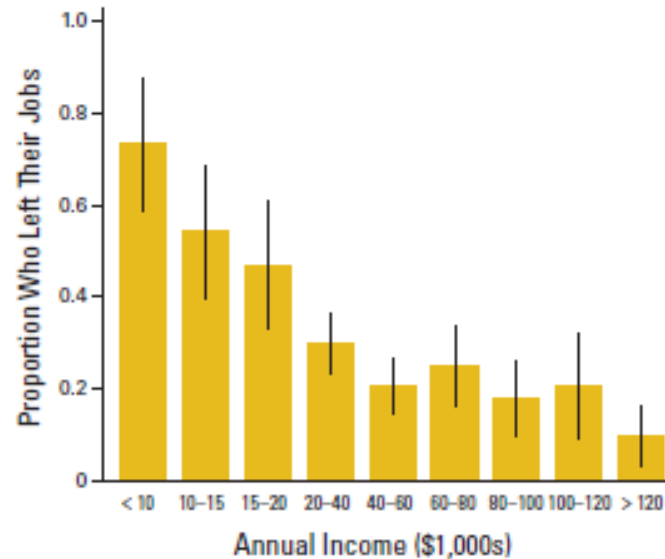
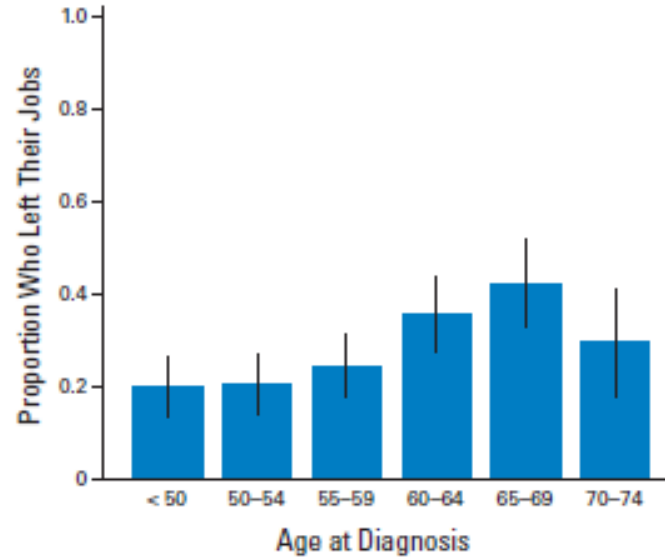
Taxa incidência estimada na Europa / 100.000, 2006

	Male	Female	Total*	Lung cancer share of cancer incidence	Rank in incidence among cancers
Sweden	28.6	23.8	26.2	6.7%	4
Portugal	44.5	11.7	28.1	7.8%	4
Finland	45.8	14.7	30.3	8.4%	4
Austria	54.0	22.3	38.2	10.3%	4
Switzerland	52.7	26.2	39.5	9.1%	4
Germany	61.2	20.8	41.0	10.4%	4
Spain	68.3	13.8	41.1	12.1%	2
Norway	53.8	33.7	43.8	10.4%	4
France	75.5	15.0	45.3	10.6%	4
United Kingdom	57.1	34.6	45.9	12.1%	3
Ireland	60.2	34.1	47.2	10.5%	4
The Netherlands	63.4	32.5	48.0	12.1%	4
Italy	84.7	15.6	50.2	12.2%	3
Greece	88.7	12.7	50.7	14.8%	1
Czech Republic	78.9	22.9	50.9	12.3%	2
Russian Federation	92.7	11.2	52.0	16.0%	1
Denmark	65.0	48.7	56.9	13.3%	2
Belgium	93.0	22.9	58.0	13.1%	3
Poland	103.0	28.6	65.8	17.4%	1
Hungary	119.3	42.4	80.9	16.0%	1
Europe	75.3	18.3	46.8	12.6%	2

2ª país com menor incidência

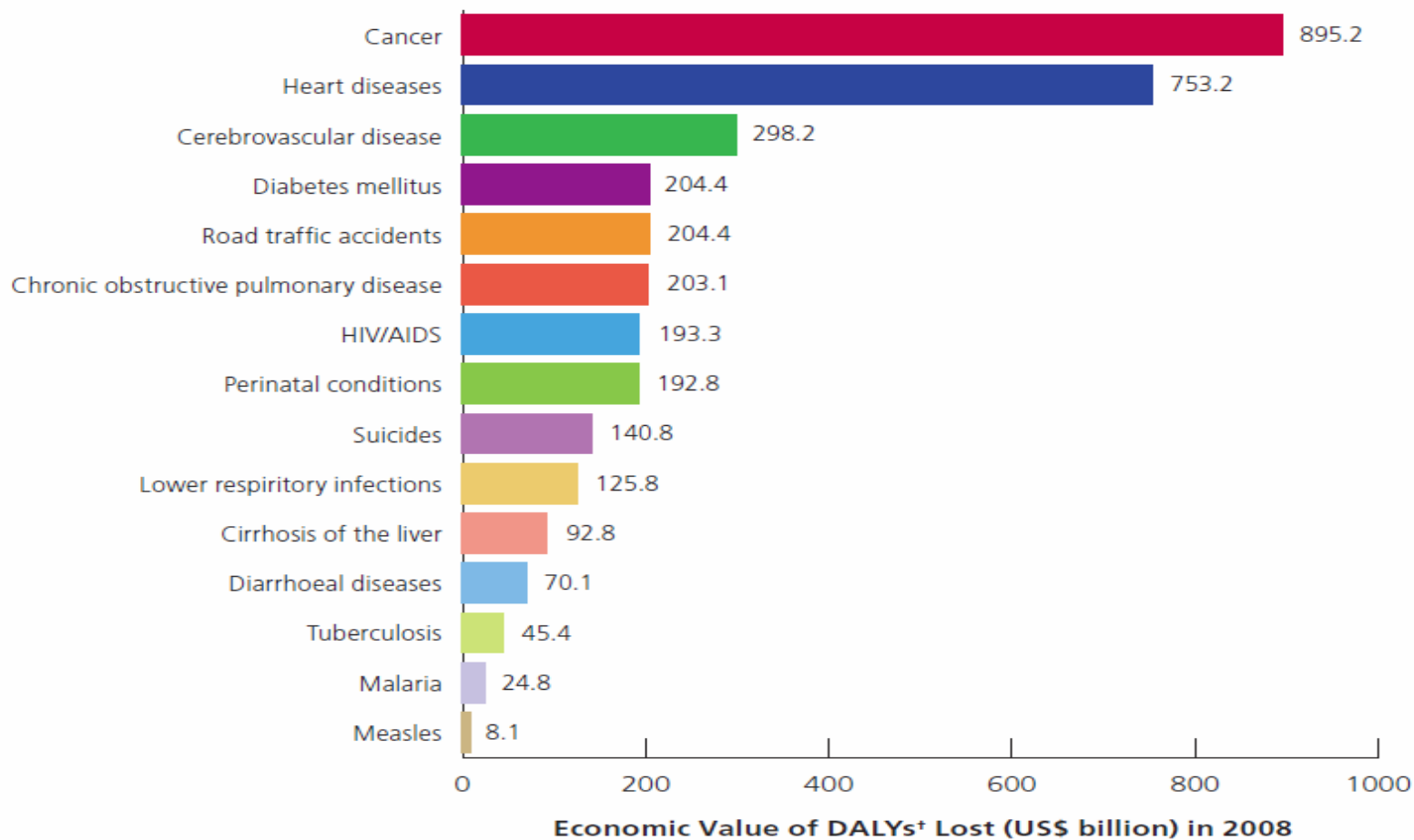
4ª neoplasia mais frequente

Impacto social do cancro do pulmão



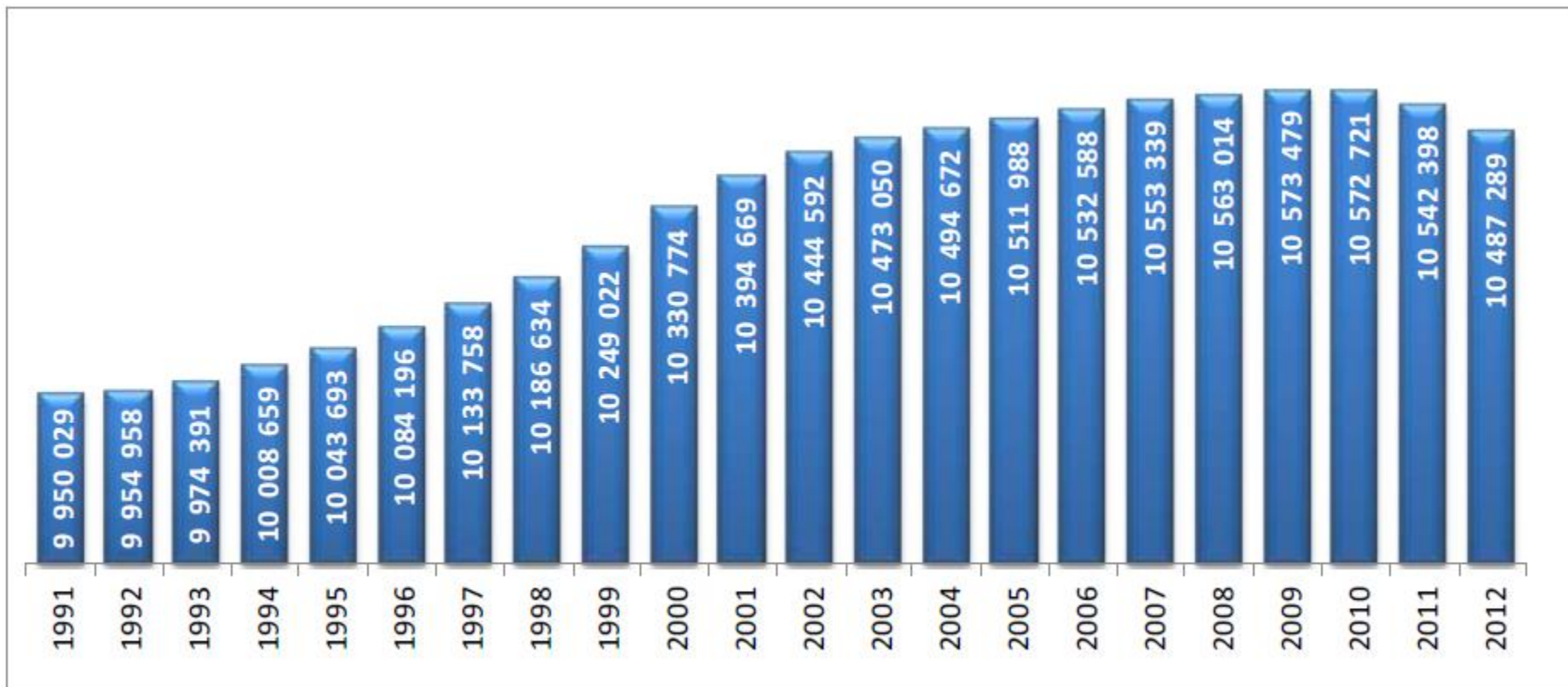
Impacto social do cancro do pulmão

Economic Loss From the Top 15 Global Causes of Death



†Disability-adjusted Life Year

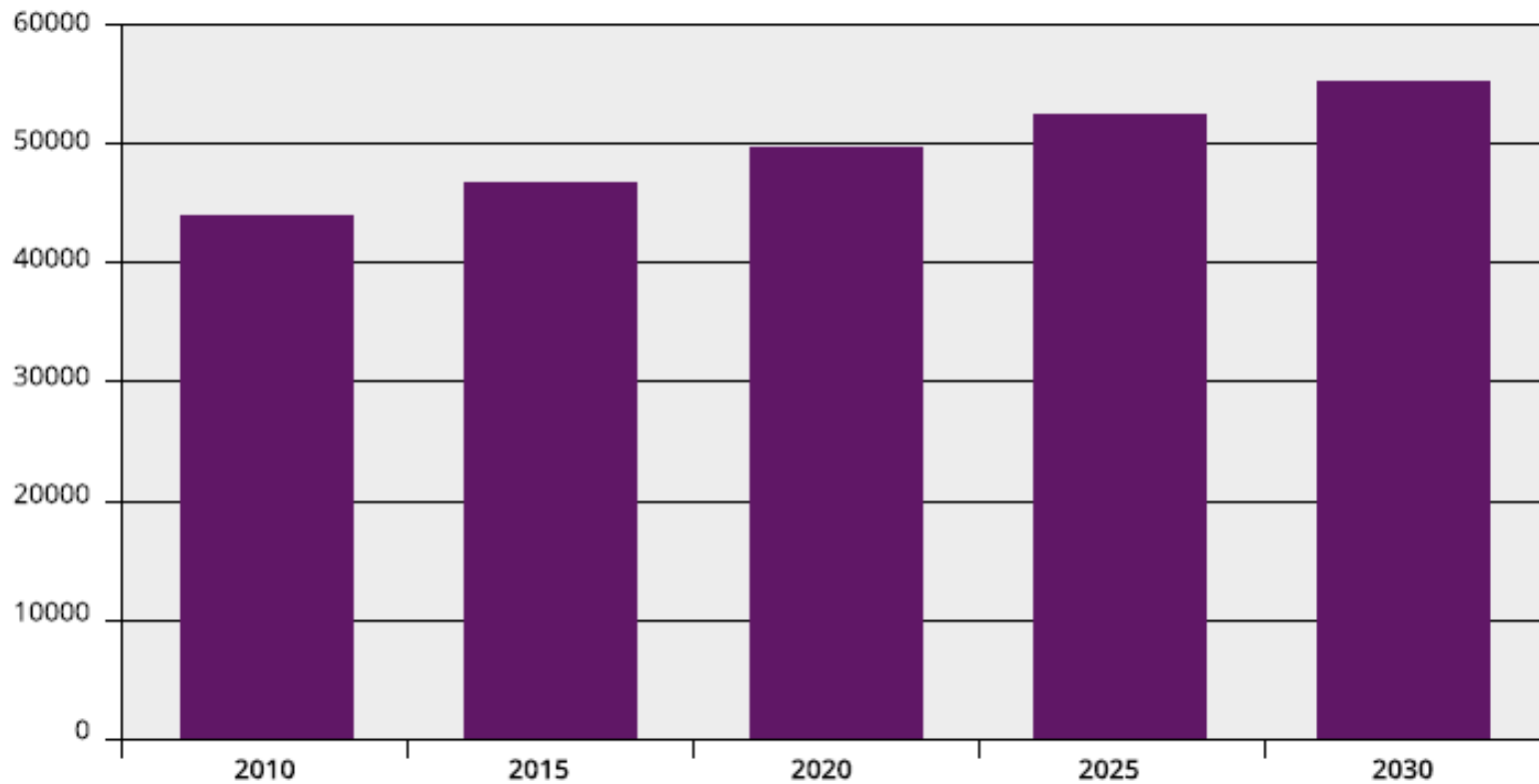
População residente (Nº), Portugal, 1991 - 2012



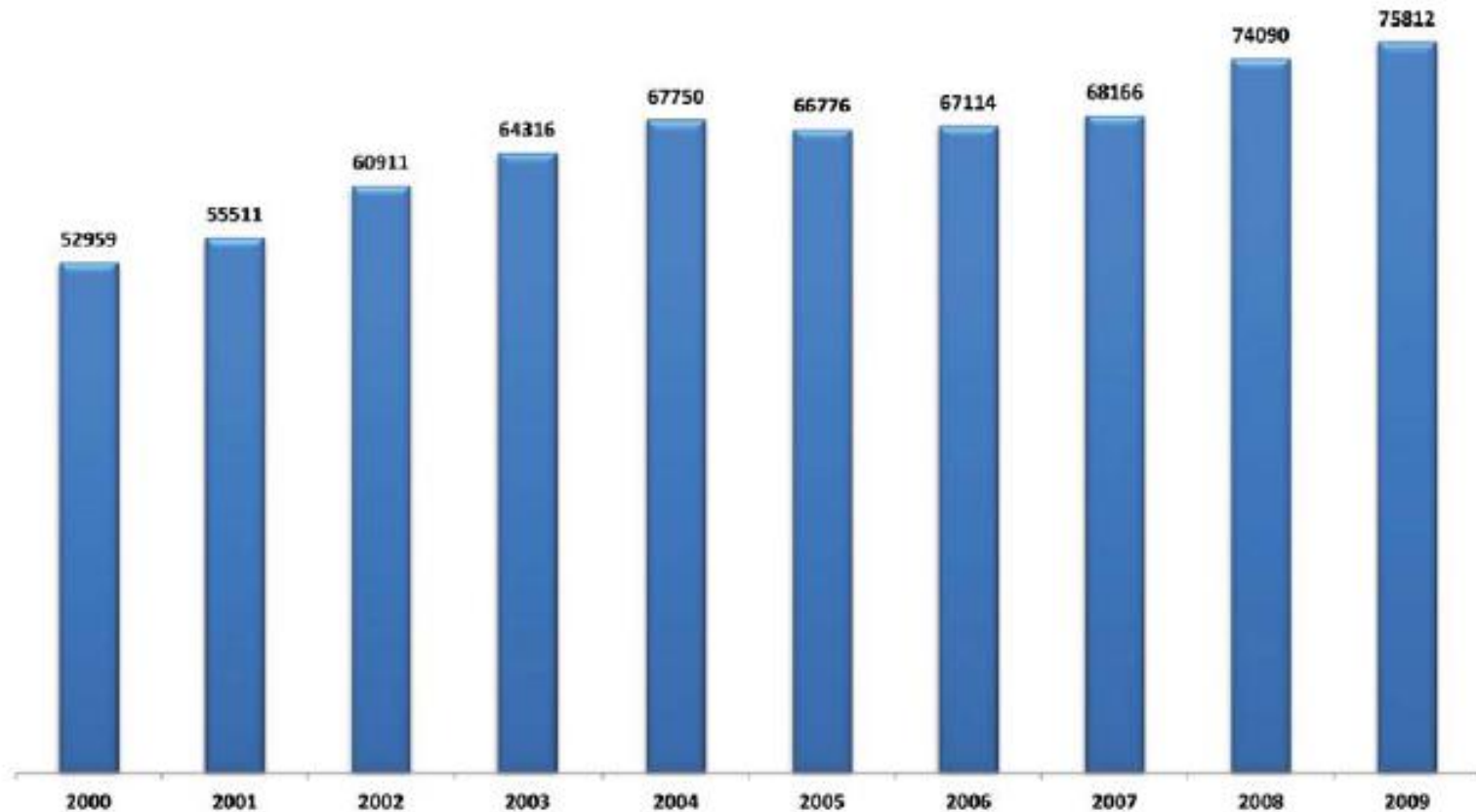
Pirâmides etárias, Portugal, 1991 e 2012



Previsão da evolução da incidência de cancro em Portugal, 2010 a 2030



Altas por cancro nos hospitais públicos, Portugal, 2000 - 2009



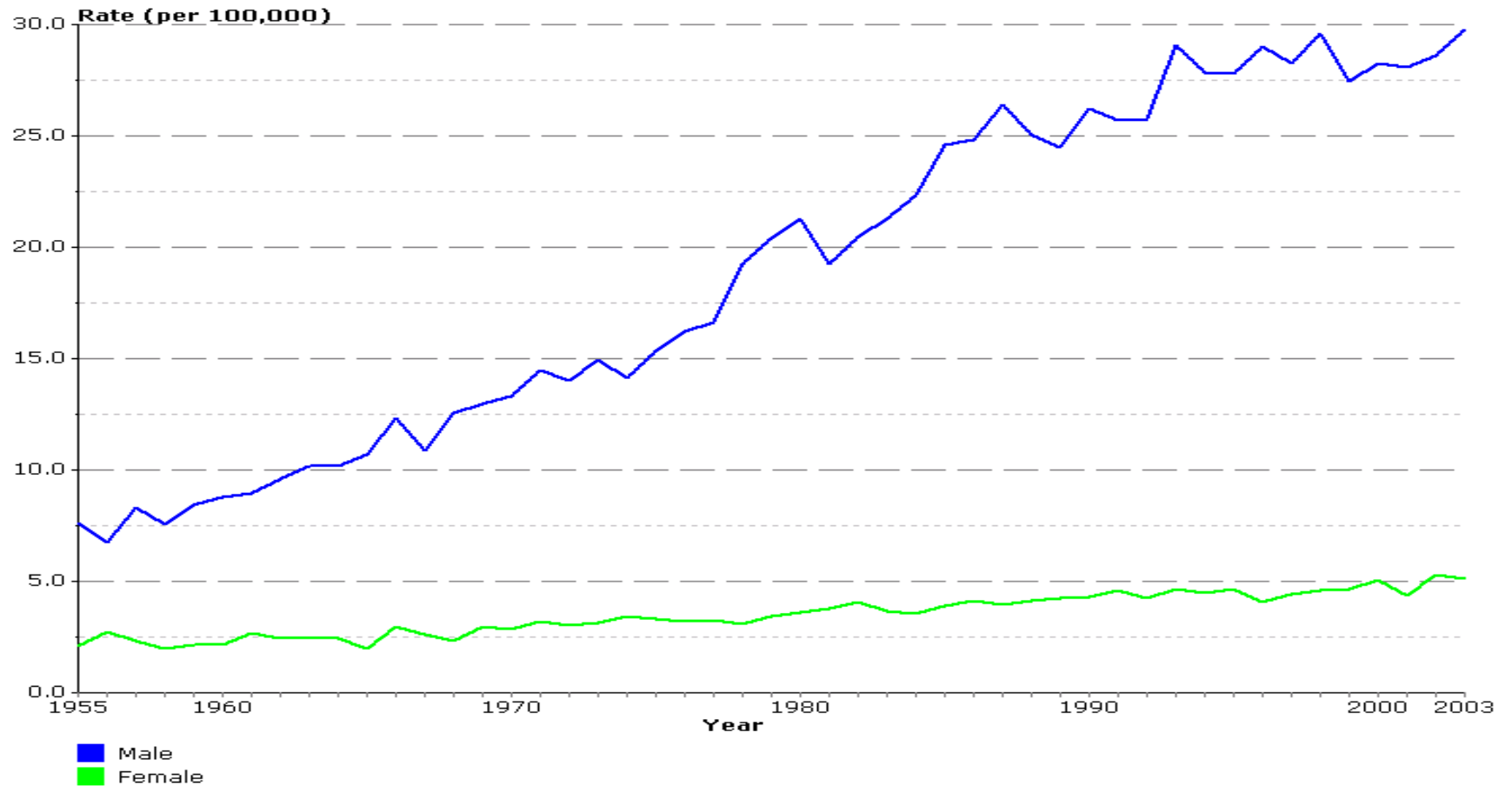
Growing rate – 43,2 %

Taxas de mortalidade, Portugal

	Infantil	Neonatal	Doenças do aparelho circulatorio	Tumores malignos
%				
Portugal				
2000	5,5	3,4	4,0	2,1
2001	5,0	2,9	4,0	2,1
2002	5,0	3,4	4,0	2,1
2003	4,1	2,7	3,9	2,2
2004	3,8	2,6	3,5	2,1
2005	3,5	2,2	3,5	2,2
2006	3,3	2,1	3,1	2,1
2007	3,4	2,1	3,2	2,2
2008	3,3	2,1	3,2	2,3
2009	3,6	2,5	3,1	2,3
2010	2,5	1,7	3,2	2,3
2011	3,1	2,4	3,0	2,4
	Infant	Neonatal	Circulatory system diseases	Malignant neoplasms

Cancro do pulmão

Evolução da mortalidade, Portugal, 1955 - 2003



Taxa de incidência de tumores malignos por patologia, Portugal, 2007

Taxa de Incidência de Tumores Malignos por Patologia (por 100000)			
	Incidência Bruta	Incidência Padronizada	
Estômago	27,20	19,60	
Cólon	42,80	30,30	3º
Reto	24,00	17,50	
Mama Feminina	101,80	82,40	2º
Traqueia, Brônquios e Pulmão	30,60	23,60	4º
Próstata	114,00	89,70	1º
Corpo do Útero	15,60	11,40	
Colo do Útero	12,80	11,10	
Bexiga	17,80	12,30	
Linfomas não Hodgkins	15,70	11,40	

Tumores malignos mais frequentes por sexo, Portugal, 2007

% Homens

(10) Cérebro e SNC	1.8
(8) Laringe	2.2
(3) Pulmão/Brônquios	10.6
(4) Estômago	7.3
(9) Rim	2.0
(2) Cólon	10.8
(6) Bexiga	6.3
(5) Recto	6.6
(1) Próstata	24.3



% Mulheres

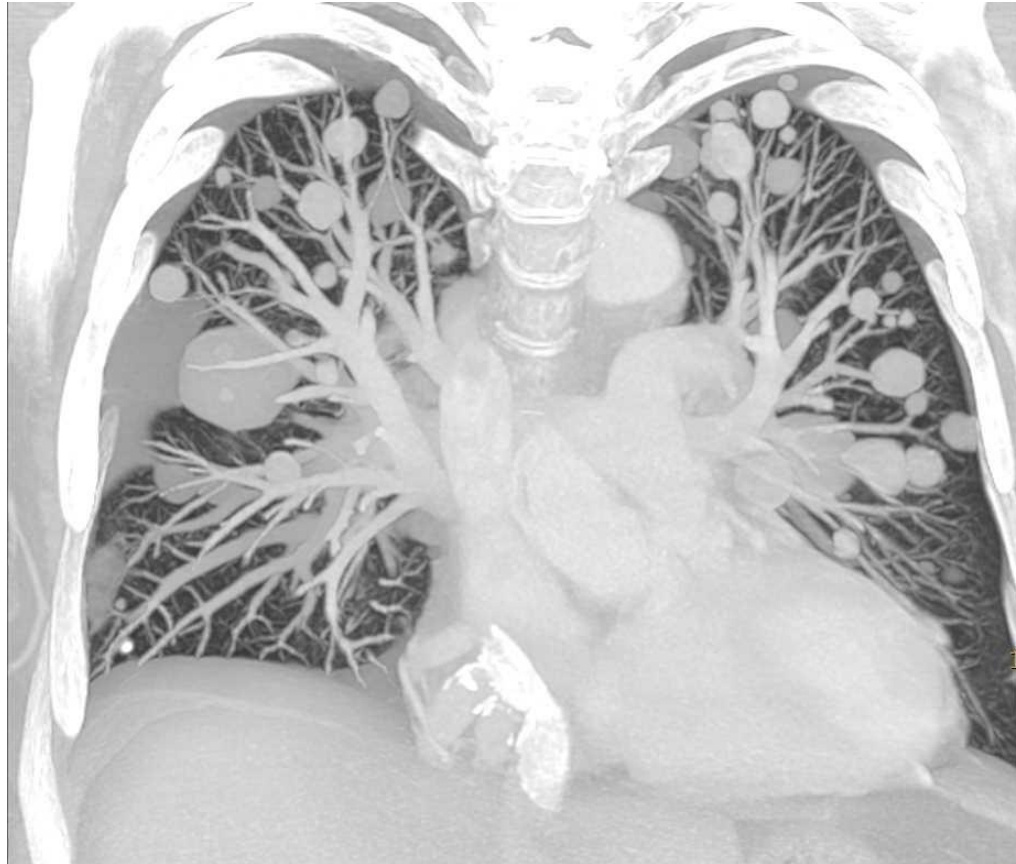
Tiróide (4)	5.3
Pulmão/Brônquios (8)	3.8
Mama (1)	29.9
Estômago (3)	6.0
Cólon (2)	10.4
Corpo Uterino (6)	4.6
Recto (5)	5.1
Colo Uterino (9)	3.8
Linfoma não Hodgkin (7)	4.0
Melanoma da Pele (10)	2.4



(7) Linfoma não Hodgkin 3.8

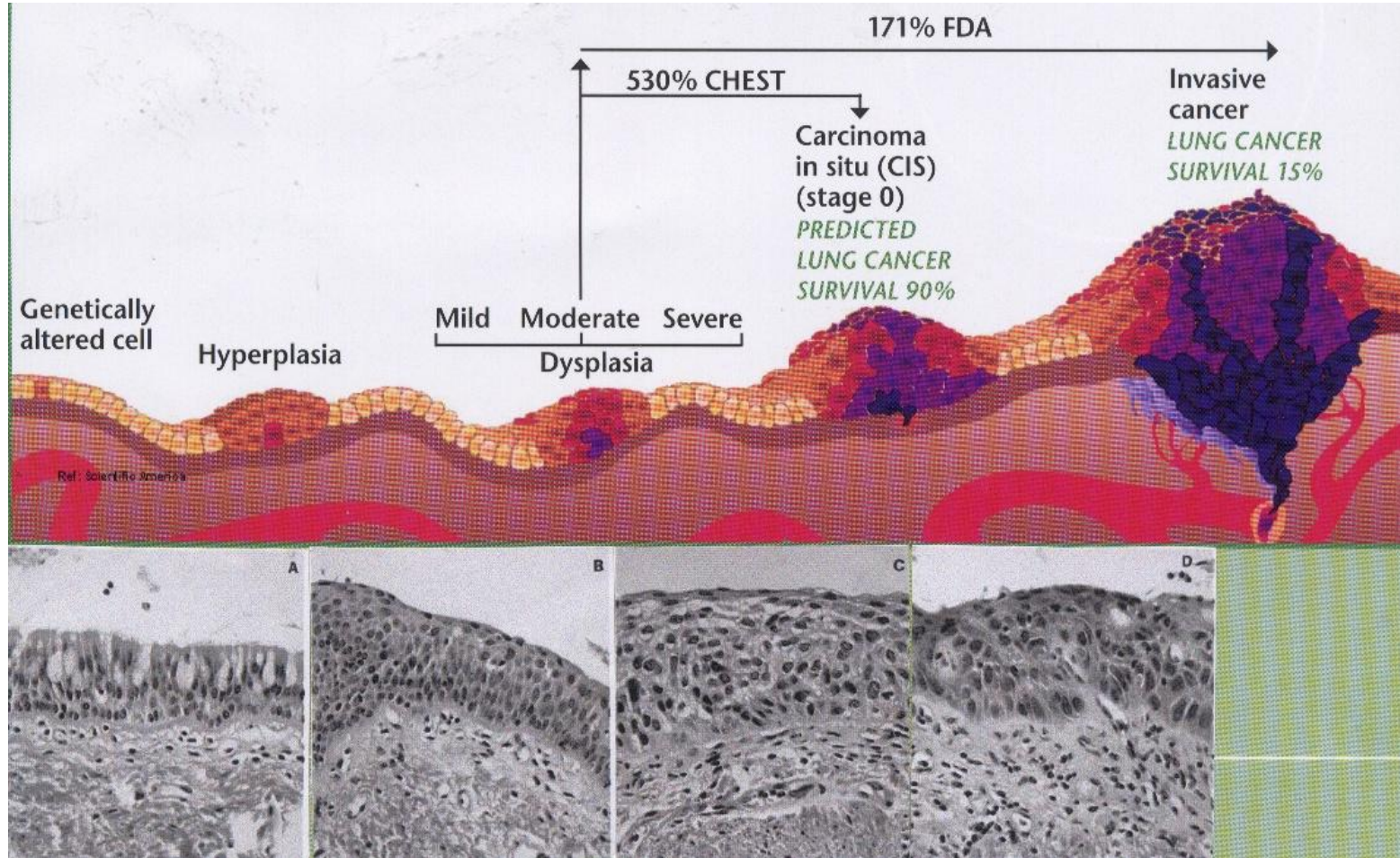
4.0
2.4


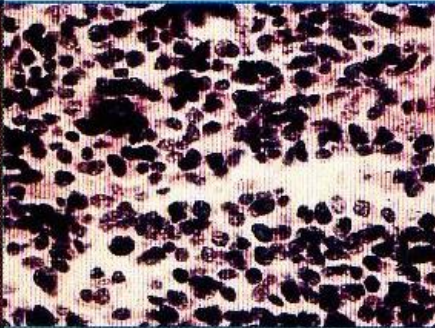
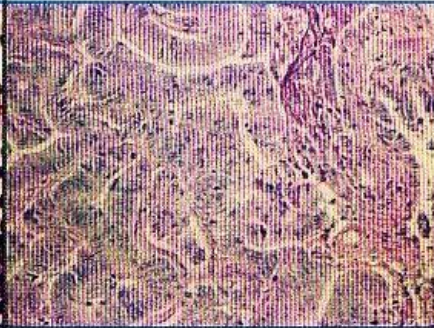
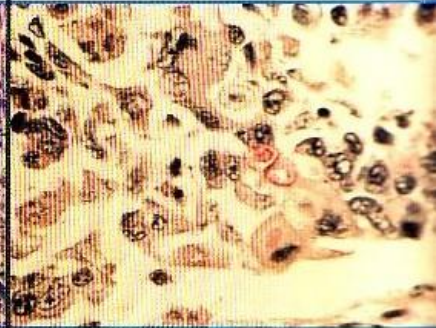
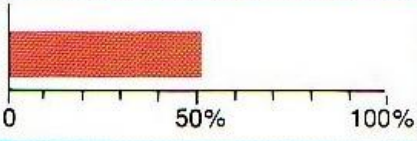
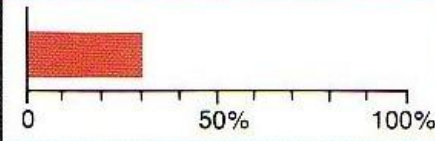
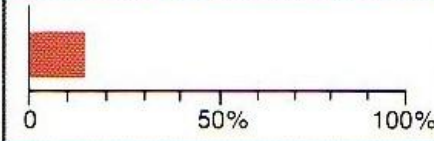
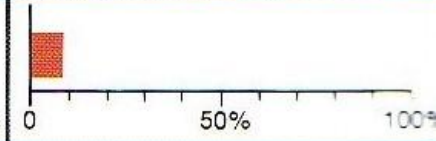

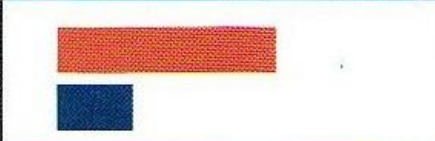
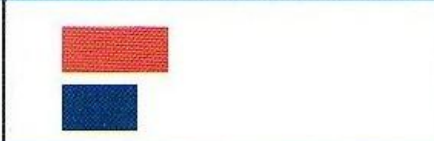

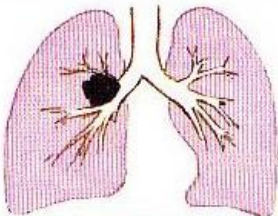
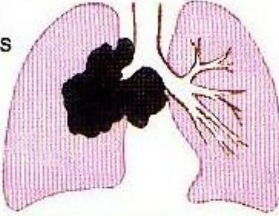
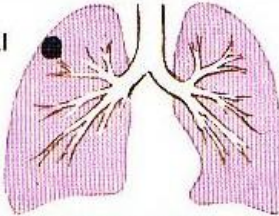
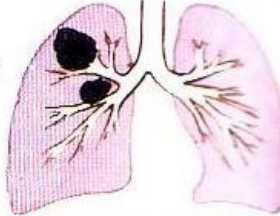
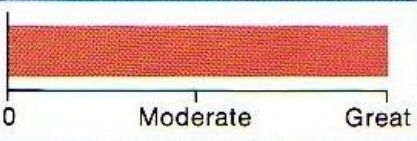
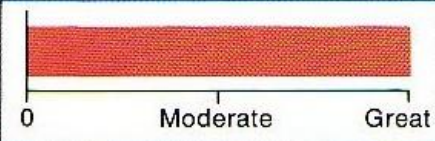
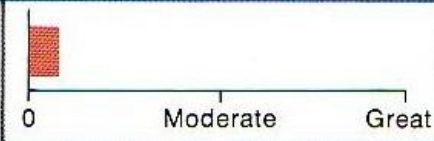

Cancro do Pulmão



Diagnóstico

Cancro do pulmão



Type	Epidermoid (squamous cell)	Small cell anaplastic (oat cell)	Adenocarcinoma	Large cell anaplastic
Histology				
Incidence (% of all lung carcinoma)				
Males vs females				
Location tendency (variable)	Hilar 	Hilar; but metastases often present when first discovered 	Peripheral (usually < 4 cm) 	Variable; peripheral or central 
Smoking relation				
Growth rate	Relatively slow	Very rapid	Intermediate	Rapid
Metastatic tendency	Late; then primarily to hilar nodes	Very early; to mediastinum or distally	Intermediate	Early
Resectability	Fair	0	Poor	Poor

Diagnóstico do cancro do pulmão

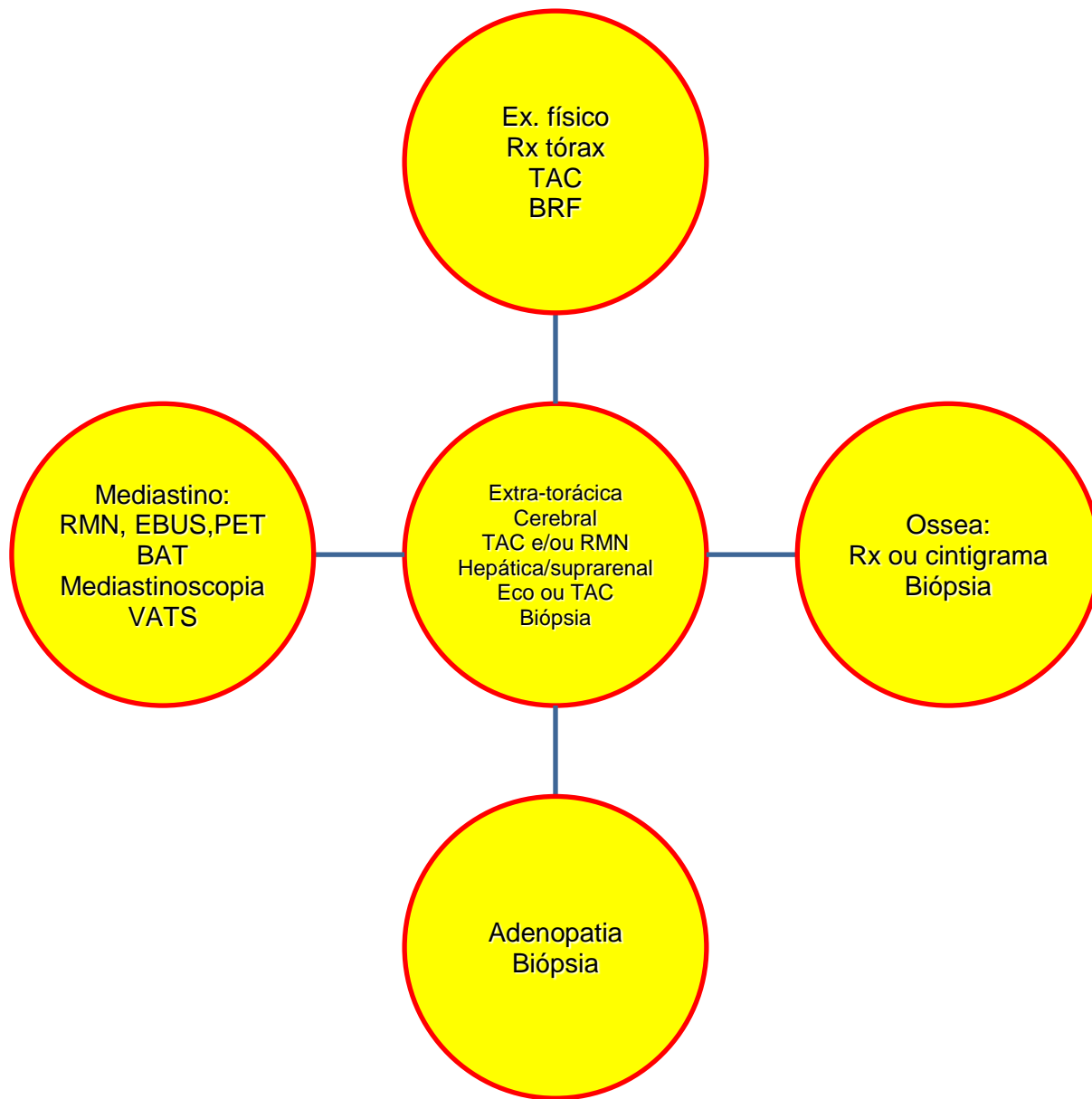
Rx Tórax PA e perfil
TAC torácica

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graph TD; A[Rx Tórax PA e perfil TAC torácica] --> B[Tumor periférico: BAT (biopsia aspirativa transtorácica), BRF (broncofibroscopia), VATS, Toracotomia]; A --> C[Tumor central: Citologia, BRF, BAT, VATS];
```

Tumor periférico:
BAT
(biopsia aspirativa
transtorácica),
BRF (broncofibroscopia),
VATS, Toracotomia

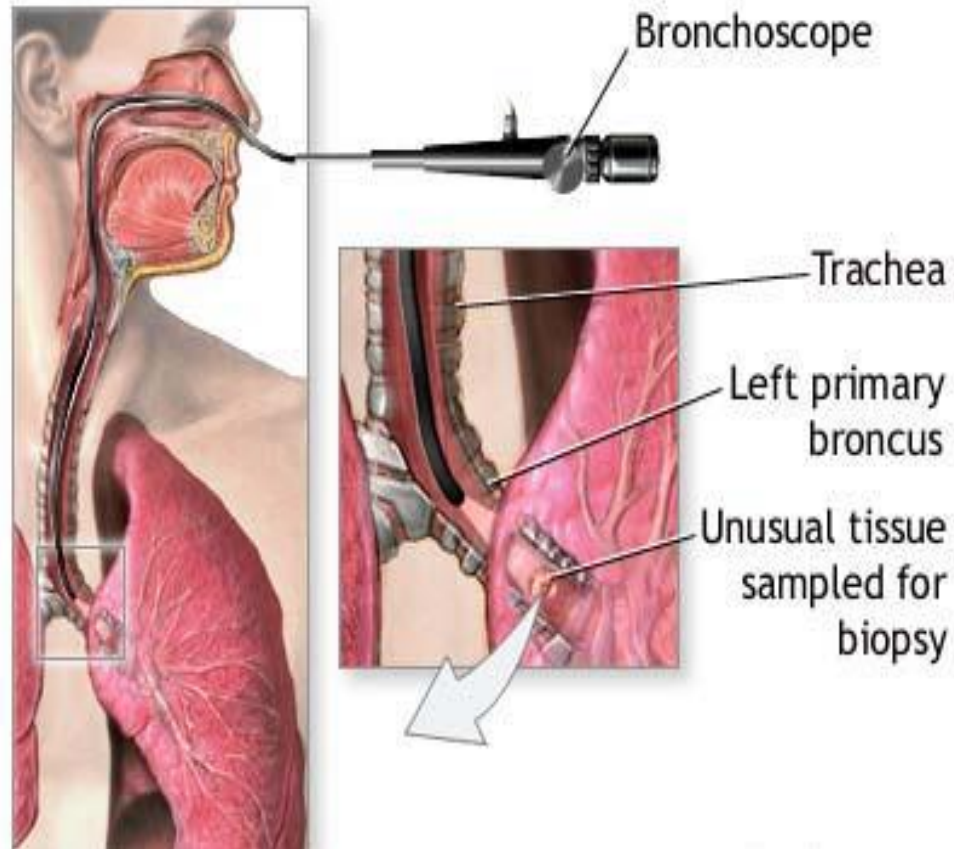
Tumor central:
Citologia, BRF, BAT, VATS

Diagnóstico do cancro do pulmão





Meios complementares de diagnóstico Broncofibroscopia





OLYMPUS KEYMED ENDOSCOPY TROLLEY KT-1

TECNOLOGIAS MEDICAS ENDOSCOPICAS

NaCl 0,9% B. BRAUN

Avopaine-gel 2%

Endoscopic tube and various medical instruments on a green sterile drape.

CAINA

PRODOS

TESOURAS

CANULA SPRAY

A GULMAS SISTUIS

SERINGAS 10ML 20ML

COMPRESSAS

NOT TO BE USED IN THE PRESENCE OF INFLAMMABLE ANAESTHETIC GASES



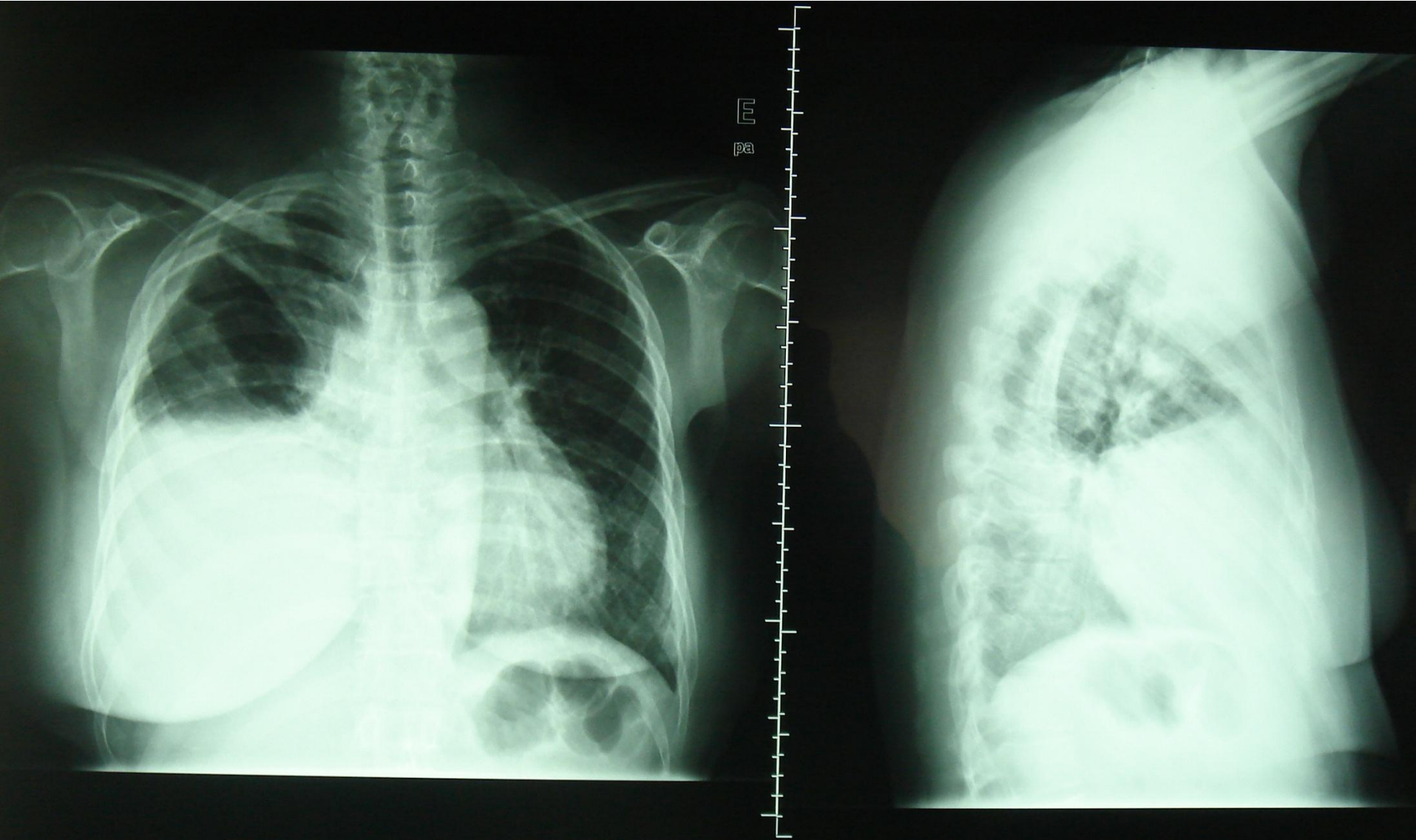


dacomo® ile



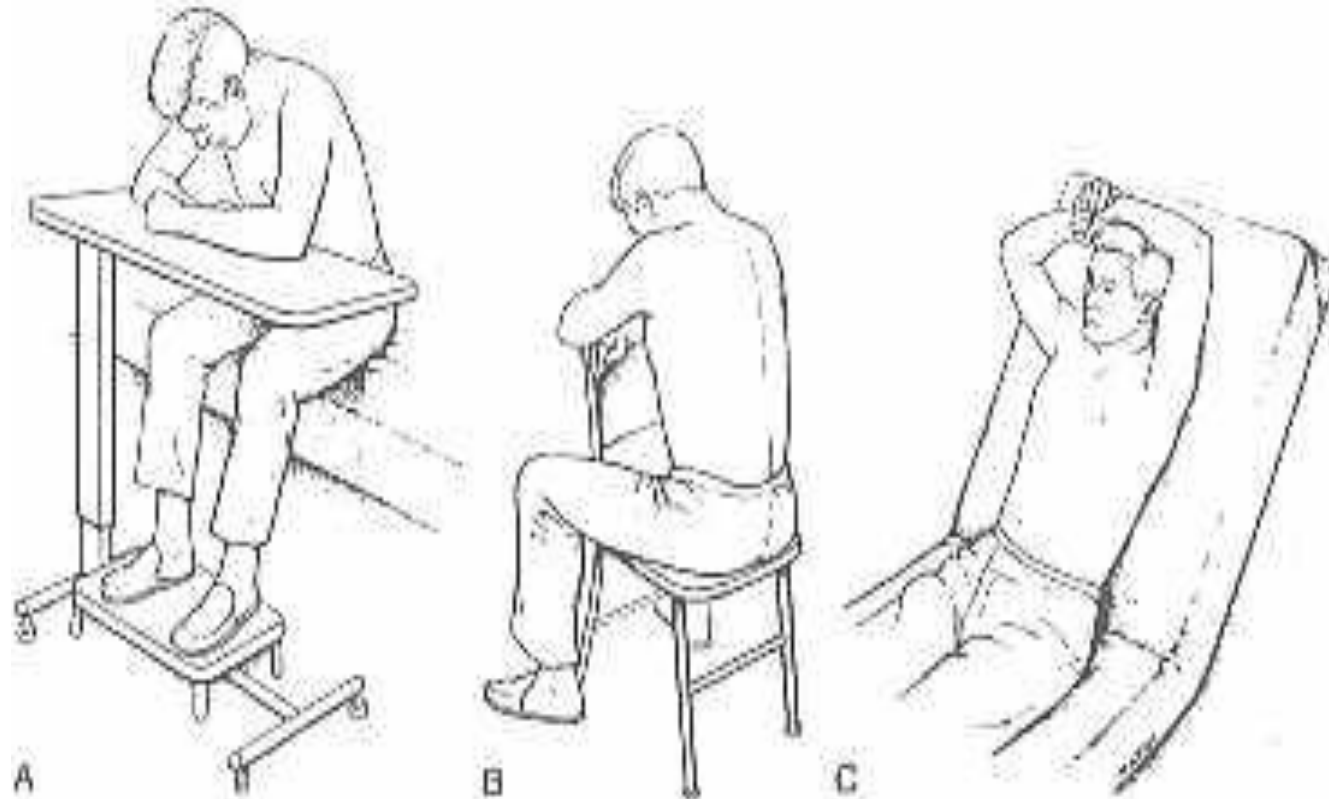
Meios complementares de diagnóstico

Toracocentese



Meios complementares de diagnóstico

Toracocentese



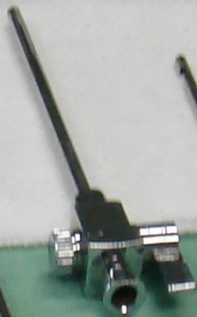
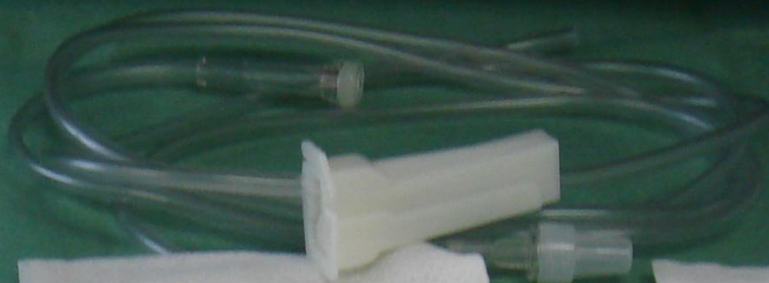
OLYMPUS
KEYMED

ENDOSCOPY TROLLEY KT-1

CE
B BR

TECNOLOGIAS MEDICAS ENDOSCÓPICAS
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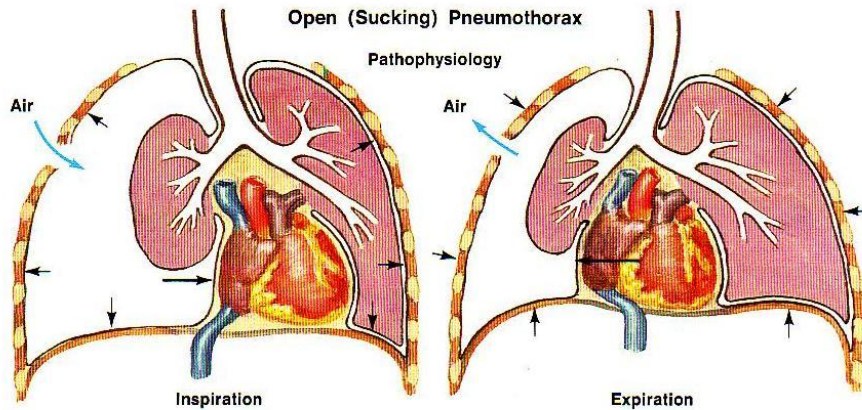






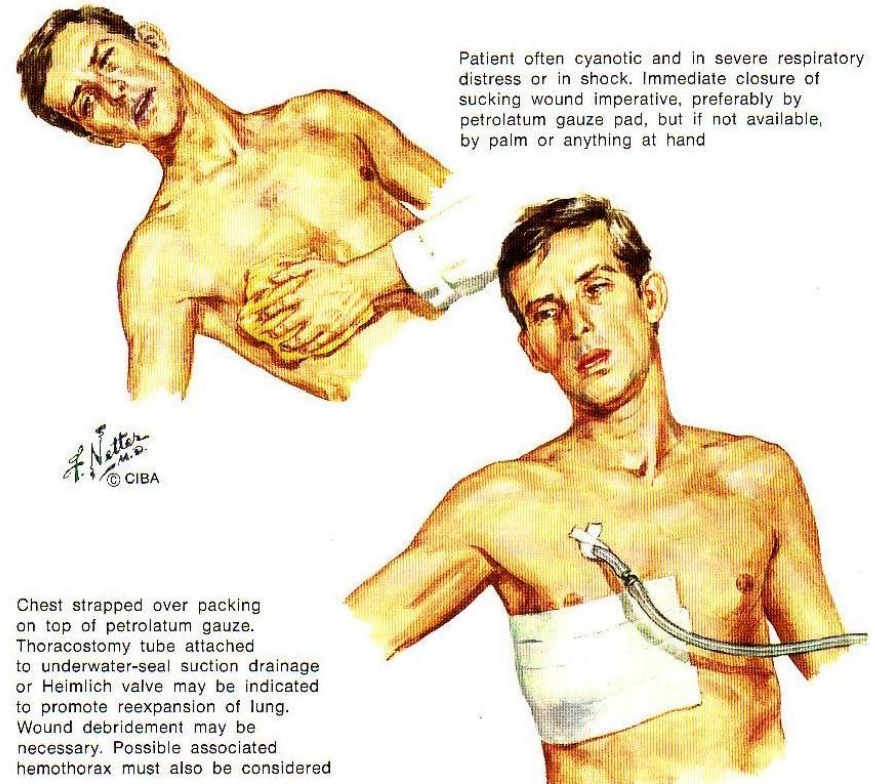
Meios complementares de diagnóstico

Dreno torácico



Air enters pleural cavity through open, sucking chest wound. Negative pleural pressure is lost, permitting collapse of ipsilateral lung and reducing venous return to heart. Mediastinum shifts, compressing opposite lung

As chest wall contracts and diaphragm rises, air is expelled from pleural cavity via wound. Mediastinum shifts to affected side and mediastinal flutter further impairs venous return by distortion of venae cavae

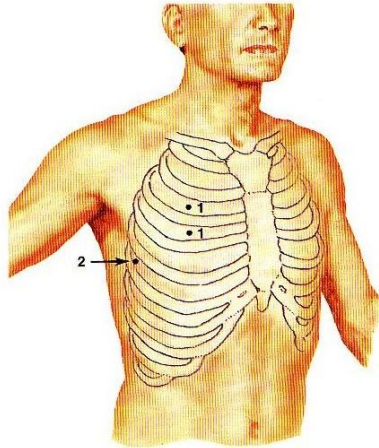


Patient often cyanotic and in severe respiratory distress or in shock. Immediate closure of sucking wound imperative, preferably by petrolatum gauze pad, but if not available, by palm or anything at hand

Chest strapped over packing on top of petrolatum gauze. Thoracostomy tube attached to underwater-seal suction drainage or Heimlich valve may be indicated to promote reexpansion of lung. Wound debridement may be necessary. Possible associated hemothorax must also be considered

Meios complementares de diagnóstico

Dreno torácico



Preferred sites

1. For pneumothorax (2nd or 3rd interspace at midclavicular line)
2. For hemothorax (5th interspace at midaxillary line)

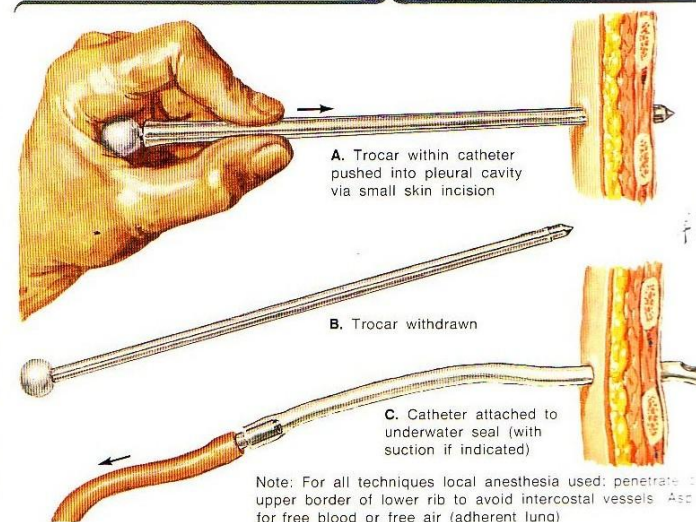
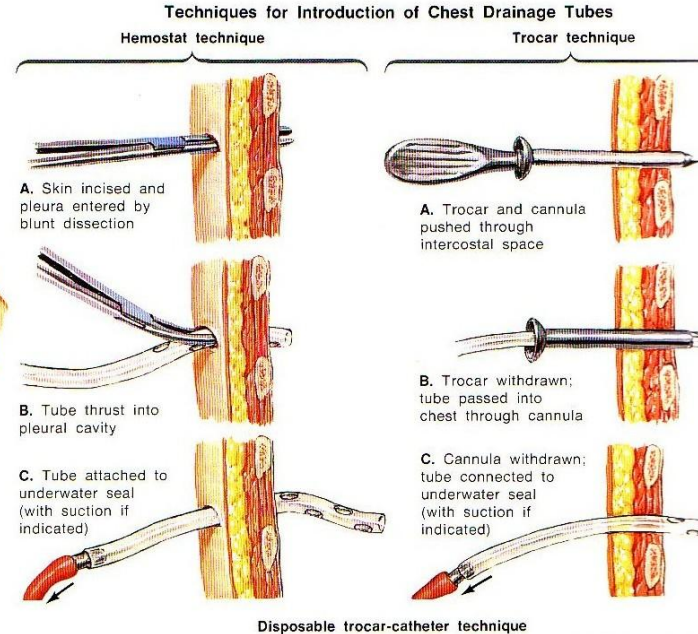
SECTION V PLATE 17

Introduction of Chest Drainage Tubes

Pleural drainage tubes are inserted for evacuation of air or fluid from the pleural space in pneumothorax or hemothorax.

Placement of an intercostal tube or catheter for *pneumothorax* can be readily accomplished under local or intercostal nerve block anesthesia, or both. It may be done at the bedside, but strict aseptic precautions need be observed. The site for tube insertion should be one that is away from adherent lung. Generally preferred is the second or third anterior intercostal space in the midclavicular line or the fourth or fifth intercostal space in the midaxillary line. To help select the optimal point of entry, chest x-ray films should be reviewed unless the clinical situation is one of extreme urgency.

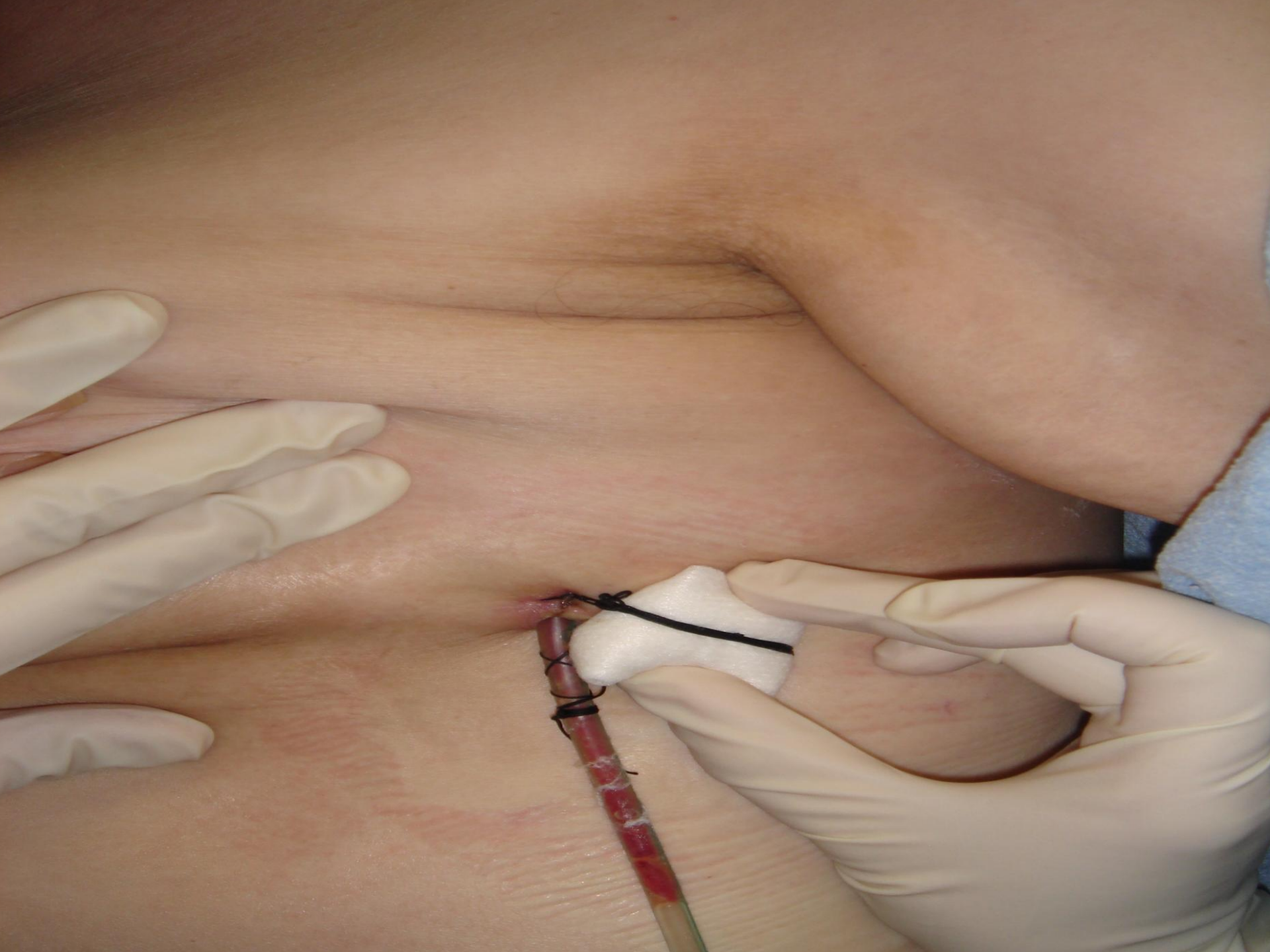
Under any circumstances, needle aspiration and ready withdrawal of air (or fluid) should precede any tube insertion. Such aspiration is simple and can be part of the process of local infiltration with an anesthetic agent. Failure to find a free



ENDOSCOPY TROLLEY KT-1

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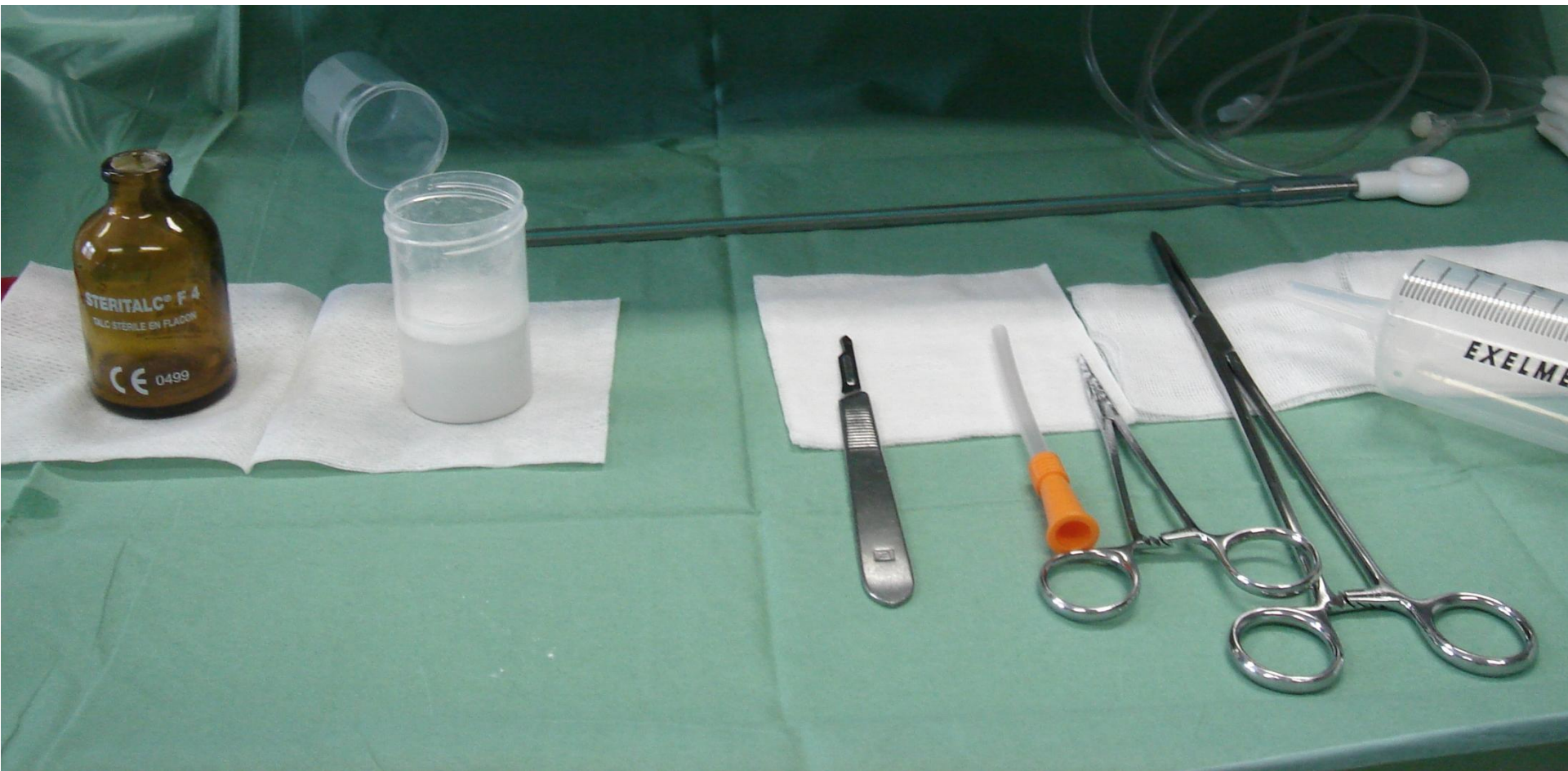














Estadiamento do CPNPC

- Estadiamento anatómico:

T – Tumor

N – Gânglios

M – Metástases

- Estadiamento fisiológico

Função respiratória

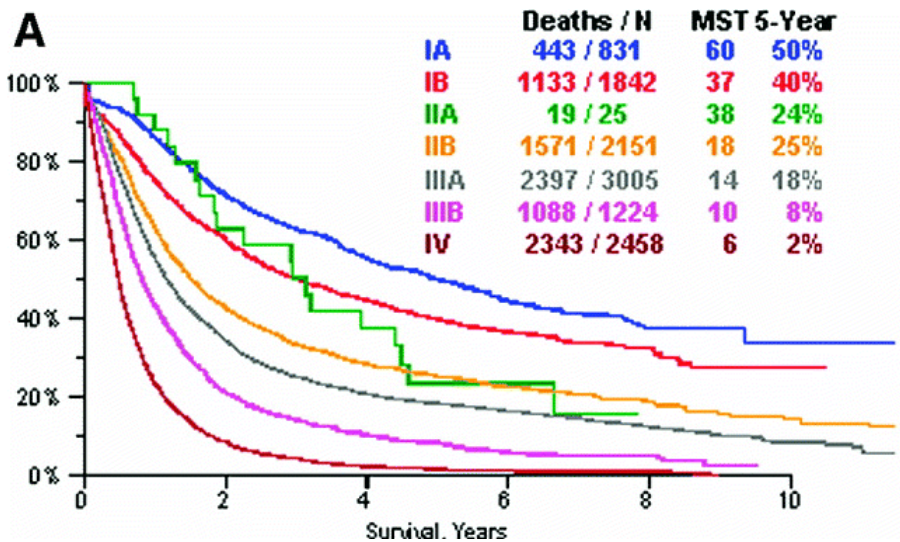
Função cardíaca

Co-morbilidades

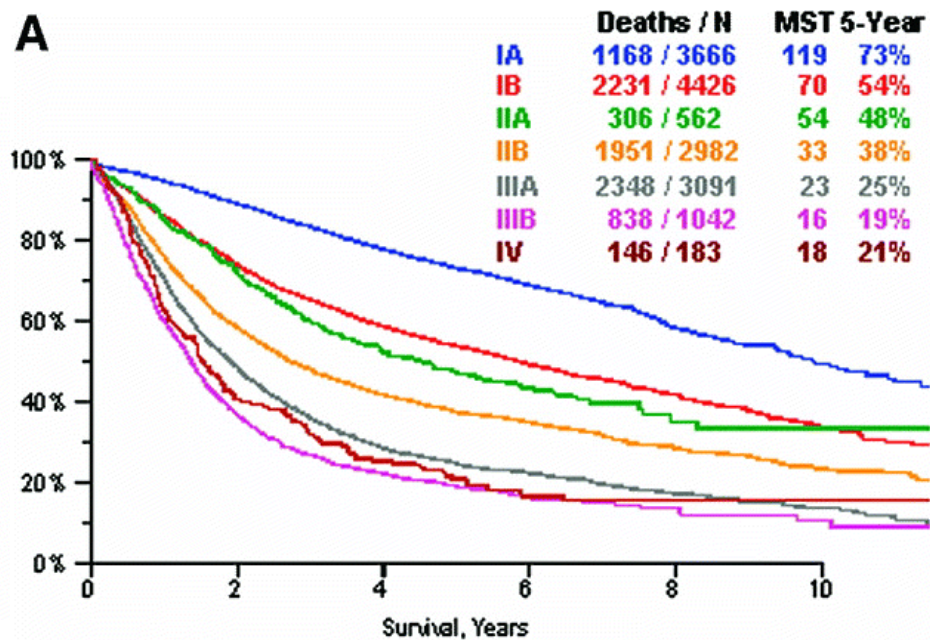
Estadiamento do CPNPC

Sobrevida global

6ª Edição do TNM

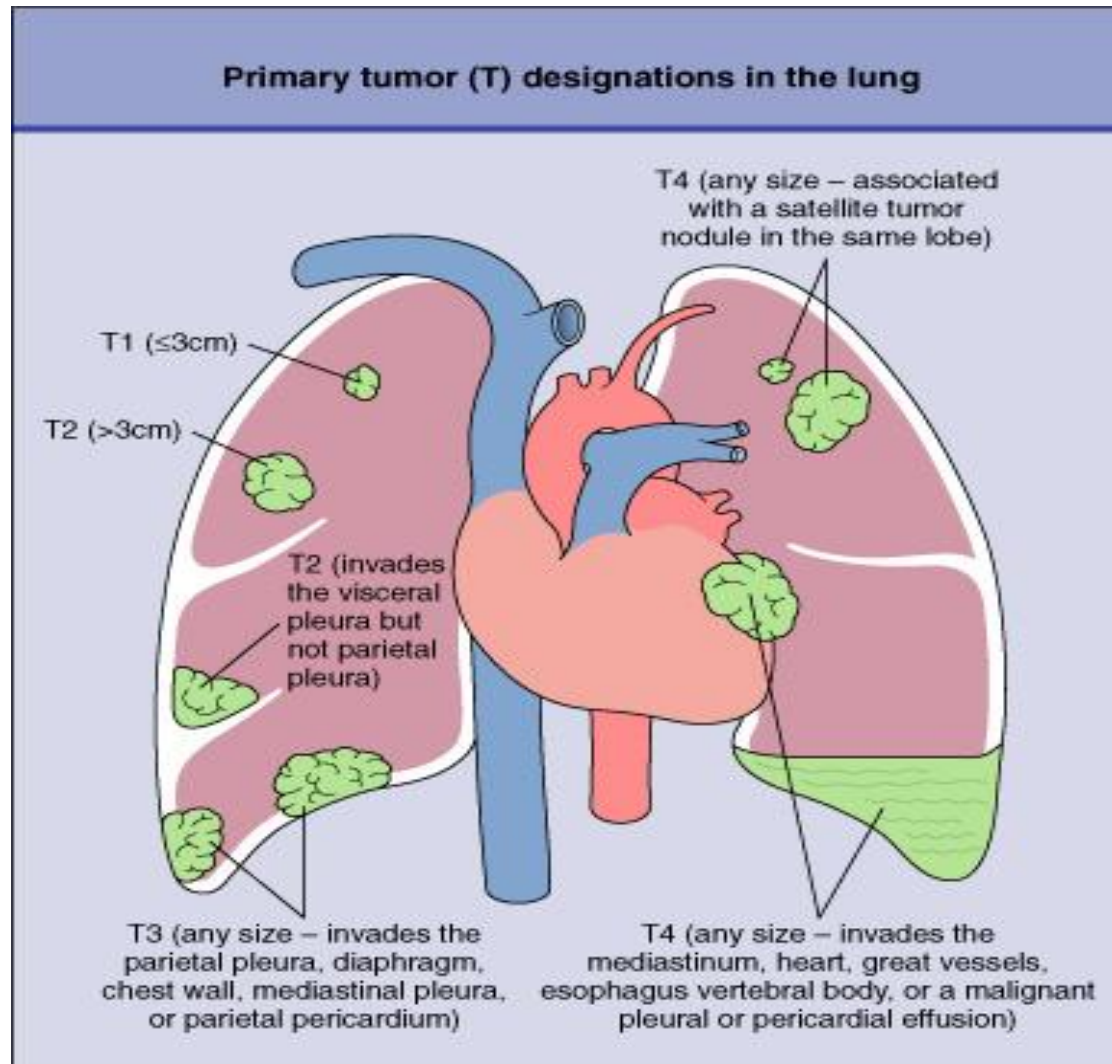


Estadiamento Clínico

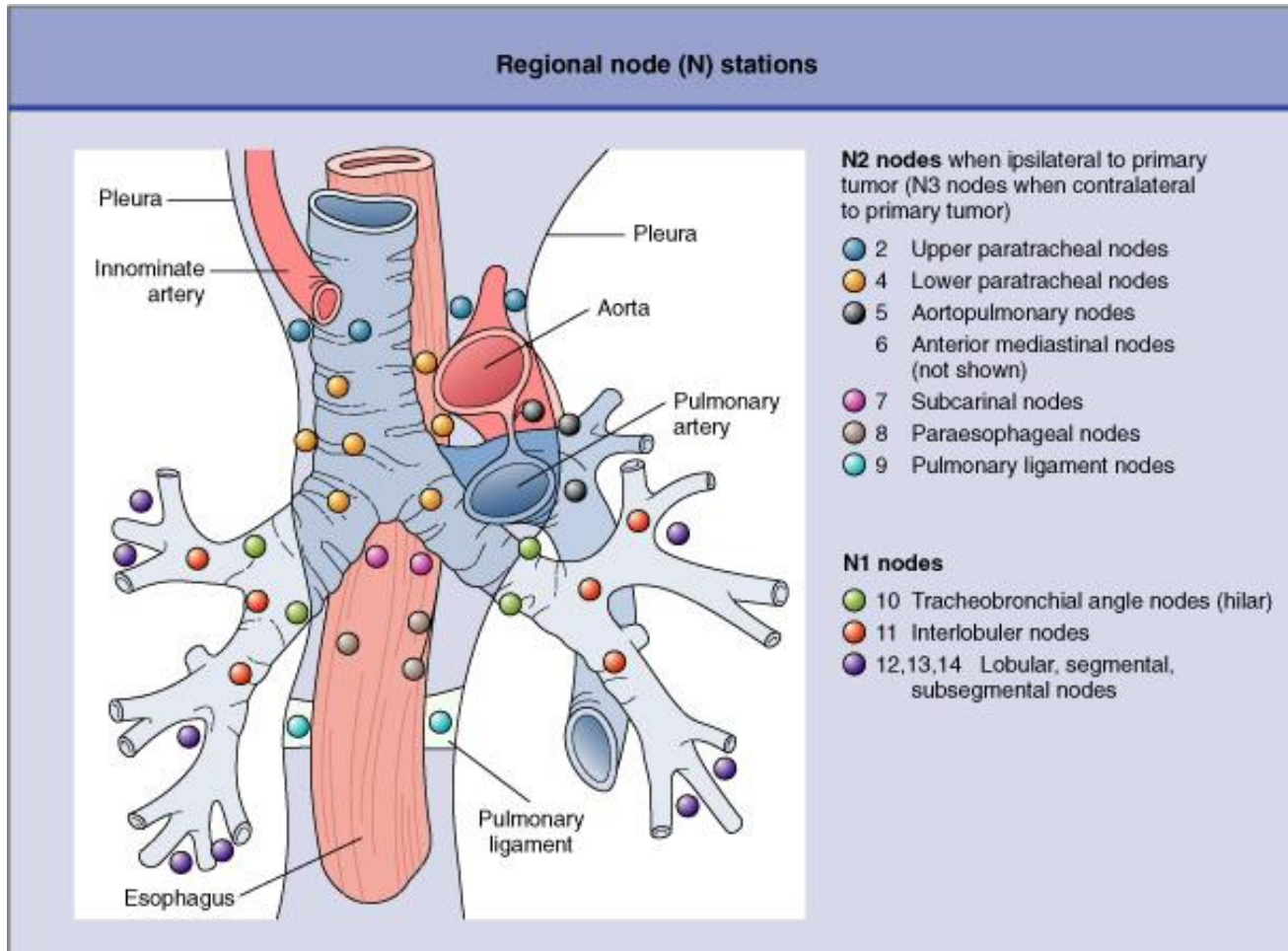


Estadiamento Patológico

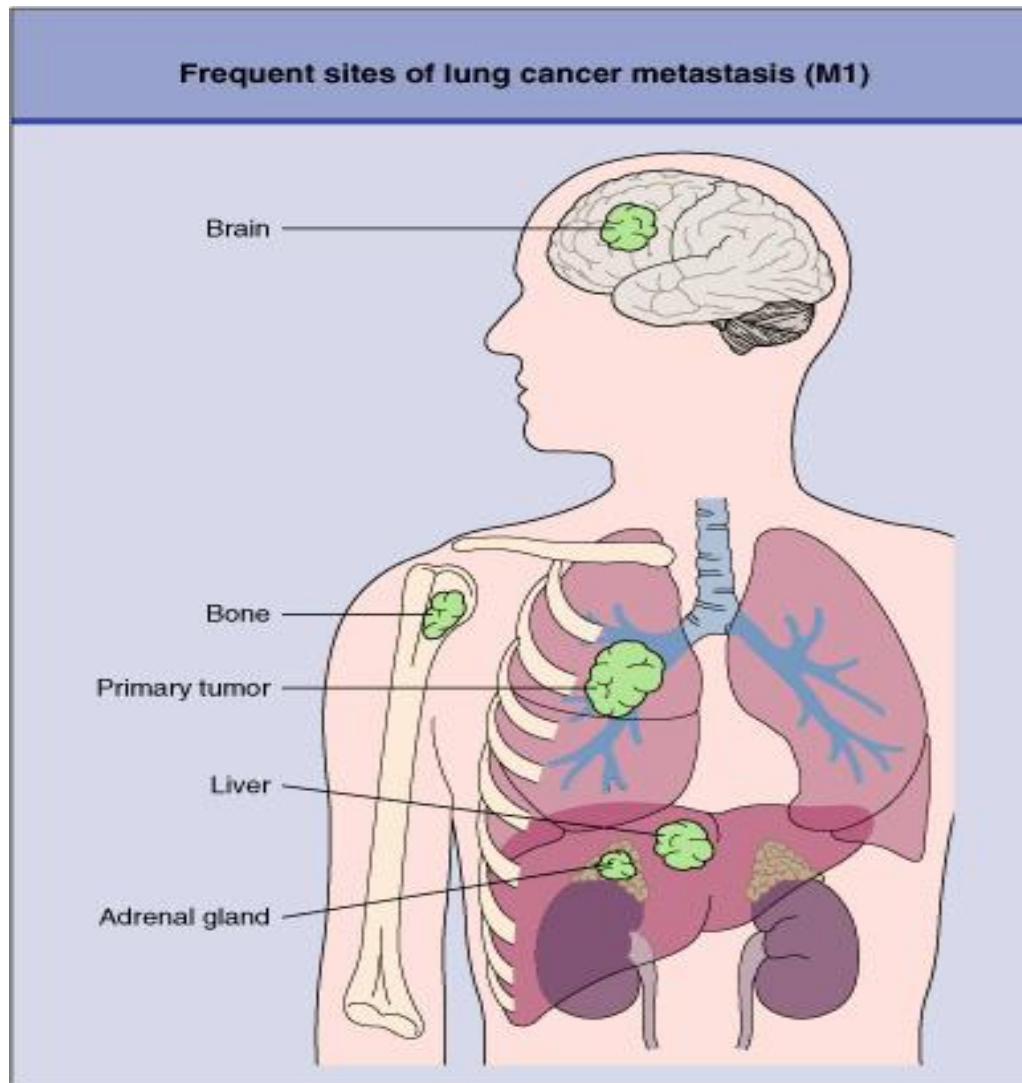
Estadiamento do CPNPC



Estadiamento do CPNPC

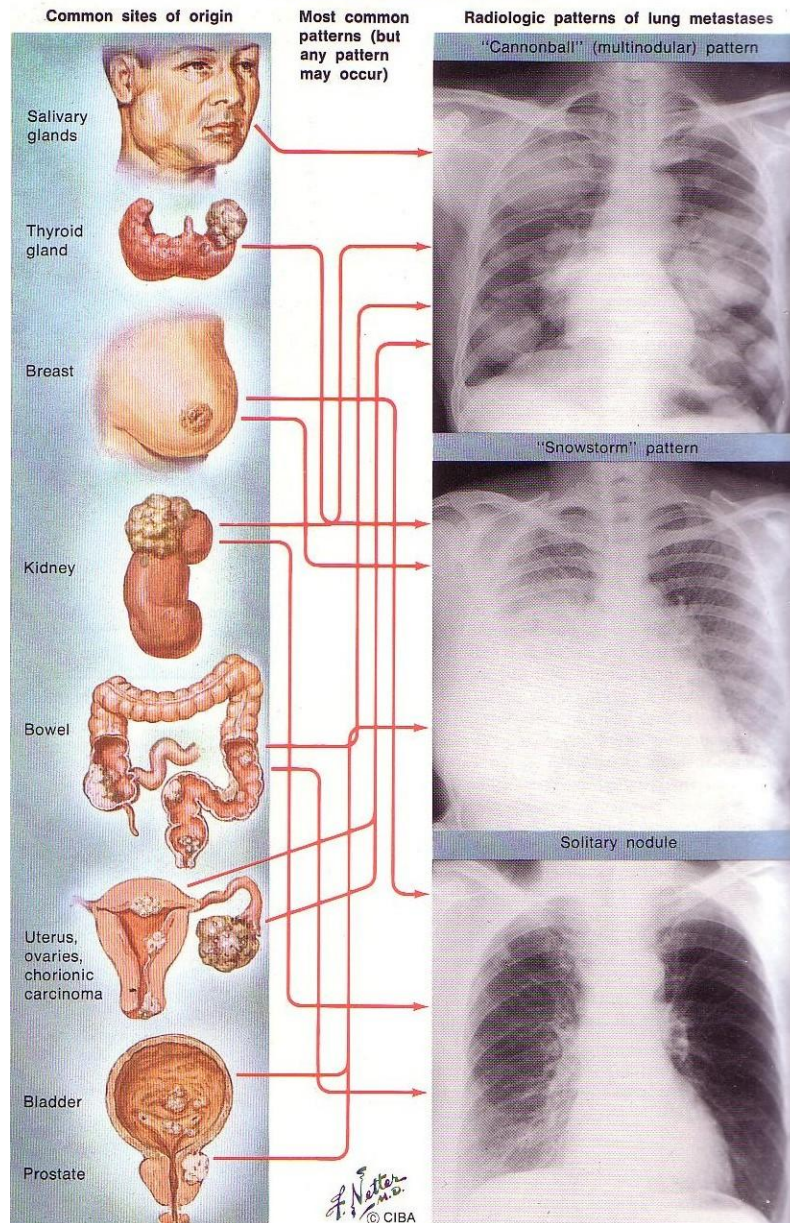


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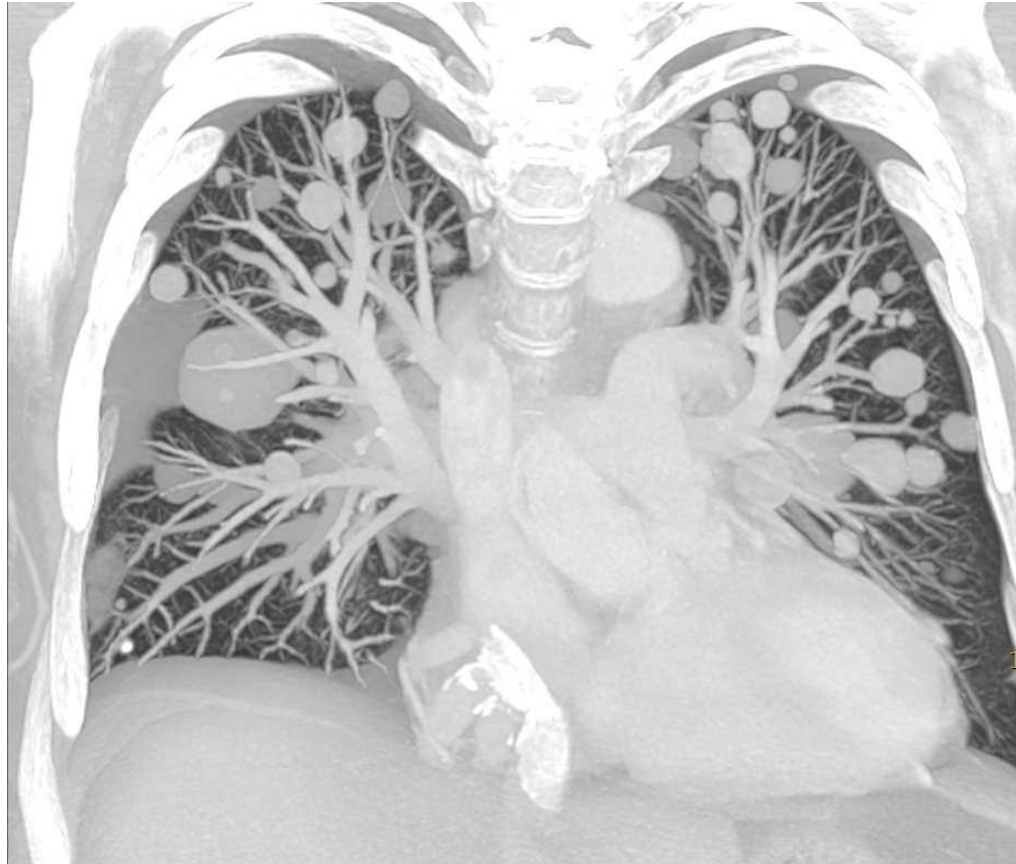


Estadiamento do CPNPC

Metastatic Carcinoma to Lung

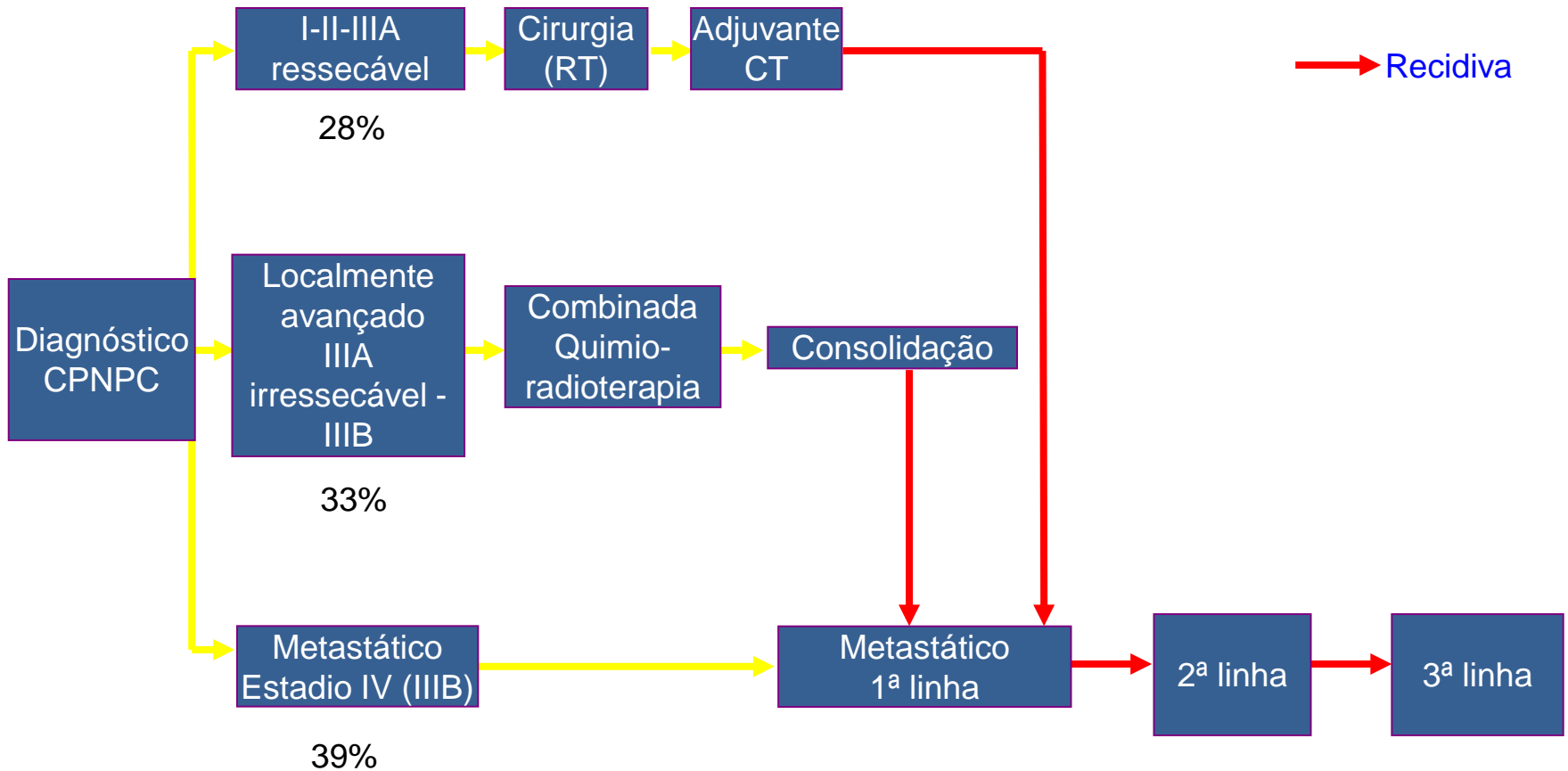


Cancro do Pulmão



Tratamento

Algoritmo de tratamento do CPNPC



CPNPC é uma doença rapidamente progressiva



Mau prognóstico ¹

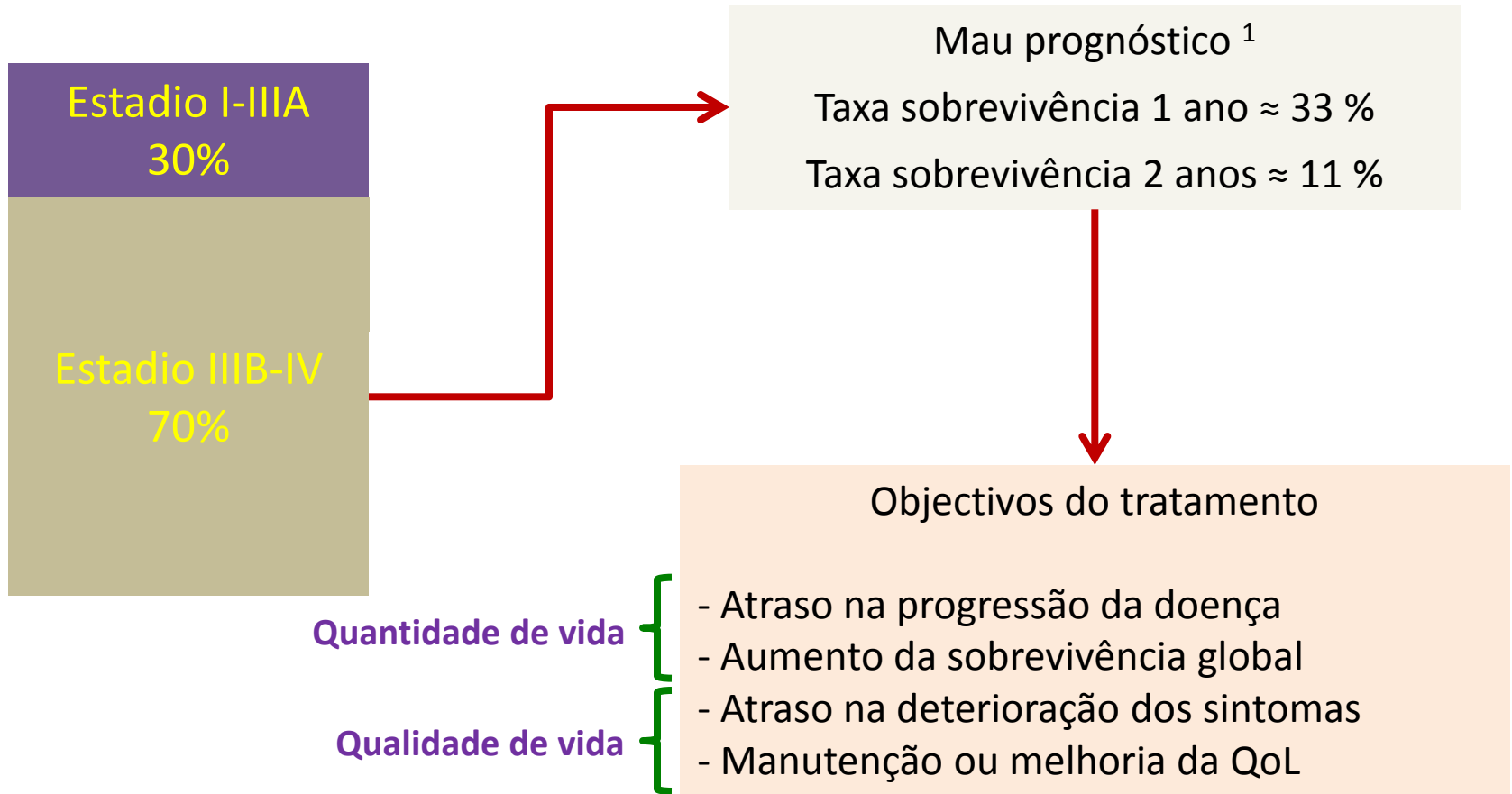
Taxa sobrevivência 1 ano \approx 33 %
Taxa sobrevivência 2 anos \approx 11 %

Objectivos do tratamento

- Atraso na progressão da doença
- Aumento da sobrevivência global
- Atraso na deterioração dos sintomas
- Manutenção ou melhoria da QoL

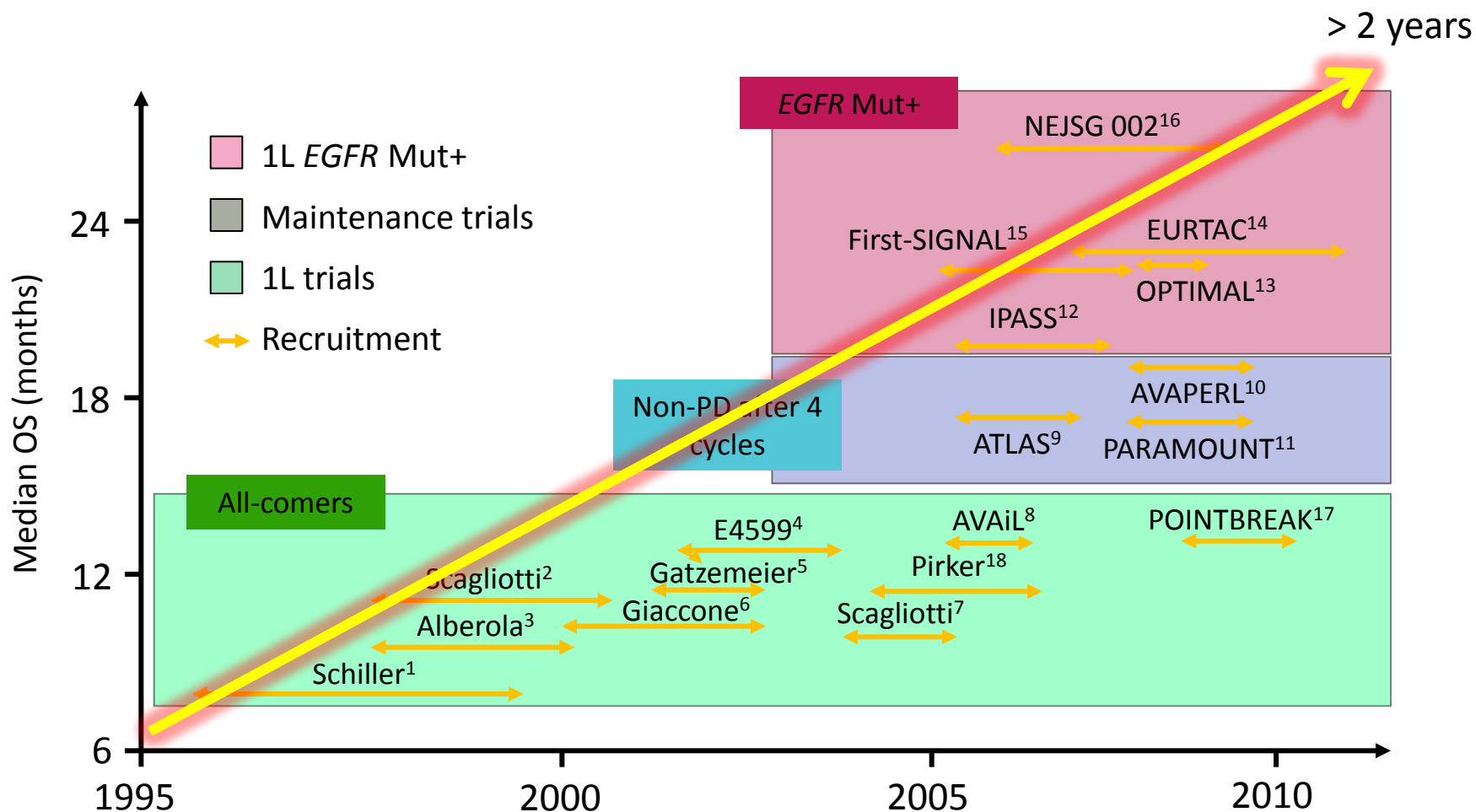
1. Schiller J et al, N Eng J Med 346:92-98, 2002

CPNPC é uma doença rapidamente progressiva



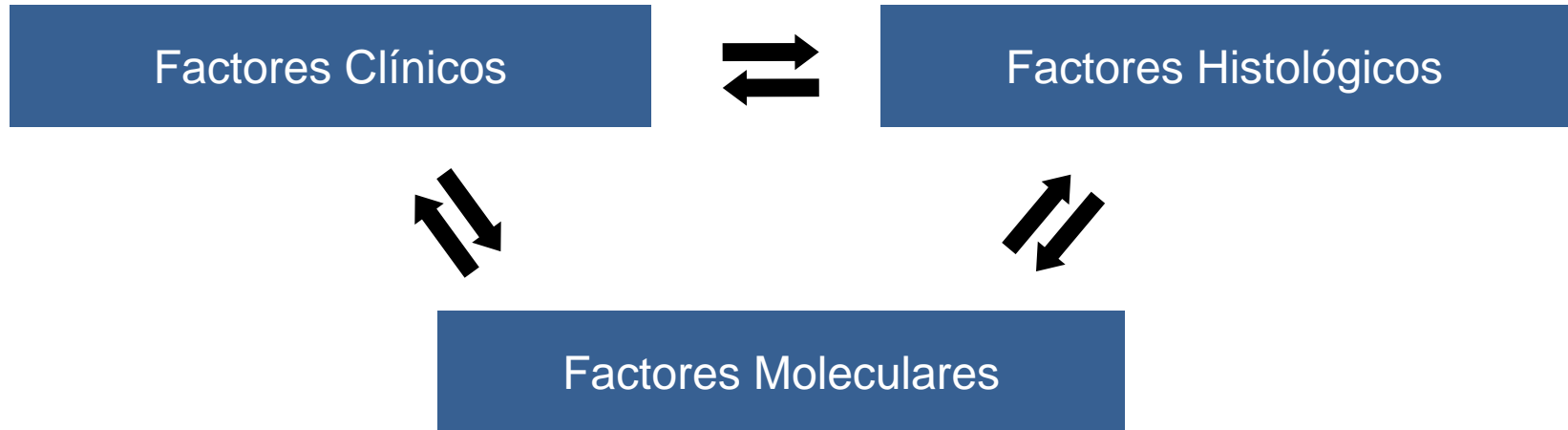
1. Schiller J et al, N Eng J Med 346:92-98, 2002

Ultrapassando os limites - O que conseguimos ?



1. Schiller, et al. NEJM 2002;
2. Scagliotti, et al. JCO 2002;
3. Alberola, et al. JCO 2003;
4. Sandler, et al. NEJM 2006;
5. Gatzemeier, et al. JCO 2007
6. Giaccone, et al. JCO 2004;
7. Scagliotti, et al. Clin Cancer Res 2005;
8. Reck, et al. Ann Oncol 2010;
9. Kabbinavar, et al. ASCO 2010
10. Barlesi, et al. EMCC 2011;
11. Paz-Ares, et al. ASCO 2012;
12. Fukuoka, et al. JCO 2011;
13. Zhou, et al. ASCO 2012
14. de Marinis, et al. EMCC 2011;
15. Han, et al. JCO 2012;
16. Maemondo NEJM 2010;
17. Patel, et al. IASLC 2012 (Chicago);
18. Pirker, et al. Lancet 2009.

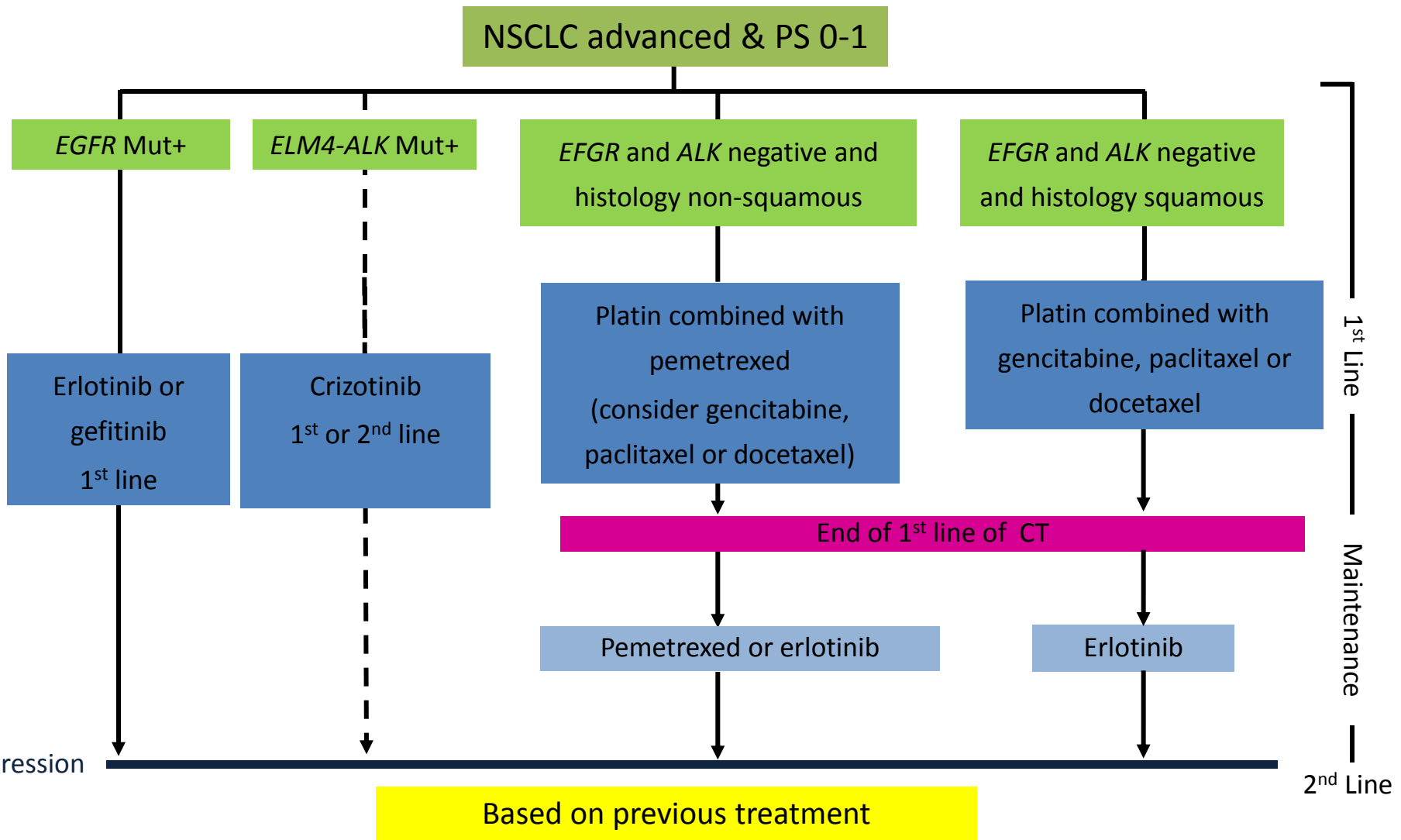
Terapêutica individualizada do cancro do pulmão



Factores estão interligados e não são independentes.

Da terapia “one size fits all” para “tailored”.

Algorithm for the treatment of advanced NSCLC in 2013



Targeted and biologic therapies for NSCLC

EGFR inhibitors

Class of Agent(s)	Trial Sponsoring Entity (ies)	Generic Name Trade Name Other Name(s)	Type	Targets	Current Phase of Development	Significant Side Effects
	Merrimack Pharmaceuticals	NA NA MM111	Bispecific antibody fusion protein	HER2-HER3 heterodimer	Phase I/II Phase I for lung cancer	
	Genmab	Zalutumumab NA HuMax-EGFr	Human MoAB	EGFR	No longer in clinical development	Rash, fatigue, and pyrexia
	Pfizer	Canertinib NA CI-1033	Irreversible small-molecule TKI	Pan-HER	No longer in clinical development	Rash, diarrhea, asthenia, and stomatitis
	Merck KGaA/EMD Serono	Matuzumab NA EMD 72000	Humanized MoAB	EGFR	No longer in clinical development	Rash and diarrhea
	AVEO Pharmaceuticals	NA NA AV-412	Irreversible small-molecule TKI	EGFR/HER2	No longer in clinical development	Diarrhea, nausea, and fatigue

Targeted and biologic therapies for NSCLC

VEGF and VEGFR inhibitors

Class of Agent(s)	Trial Sponsoring Entity (ies)	Generic Name Trade Name Other Name(s)	Type	Targets	Current Phase of Development	Significant Side Effects
	Exelixis/ GlaxoSmith-Kline	Foretinib NA GSK1363089/XL880	Small-molecule TKI	VEGFR-2, MET, Ron	Phase II	Hypertension, fatigue, nausea, diarrhea, and night blindness
	Novartis	NA NA AEE 788	Irreversible small-molecule TKI	VEGFR-2, EGFR, HER2	Phase I/II	Fatigue, diarrhea, nausea, and rash
	Exelixis	NA NA XL820	Small-molecule TKI	VEGFR-2, PDGFR β , KIT	Phase II No active lung trials	Nausea, fatigue, and rash
	Exelixis	NA NA XL999	Small-molecule TKI	VEGFR, PDGFR, FLT-3, Src, FGFR	Phase II (terminated due to safety concerns)	Cardiac toxicity, diarrhea, asthenia, and hypersensitivity
	Bayor	Telatinib NA BAY57-9352	Small-molecule TKI	VEGFR-2,3, PDGFR- β and KIT	Phase I (completed)	Hypertension, hoarseness, anorexia, and diarrhea
	Sanofi-Aventis	Ombretastatin NA AVE8062	Combretastatin A-4 derivative	Tubulin-binding agent that targets the immature neovasculature of tumors	Phase II	
	Genentech	NA NA MEGF0444A/RG7414	Humanized antibody against EGFL7	Targets EGFL7. A vascular-restricted secreted protein present in the tracks that surround tumor blood vessels	Phase I	

Targeted and biologic therapies for NSCLC

ALK inhibitors / BRAF / ROS

Class of Agent(s)	Trial Sponsoring Entity (ies)	Generic Name Trade Name Other Name(s)	Type	Targets	Current Phase of Development	Significant Side Effects
ALK inhibitors/ braf/ros	Pfizer	Crizotinib Xalkori PF-02341066	Dual small-molecule ATP competitive inhibitor	ALK, c-Met, ROS	FDA approved for ALK+ locally advanced or metastatic NSCLC	Nausea, diarrhea, visual disturbances, alanine aminotransferase elevation, and fatigue
	Xcovery	NA NA X-396	Small-molecule inhibitor	ALK	Phase I	
	Novartis	NA NA LDK378	Small-molecule inhibitor	ALK translocations	Phase I lung	
	Ariad Pharmaceuticals	NA NA AP26113	Small-molecule inhibitor	ALK/EGFR	Phase I/II	
	Chugai Pharmaceuticals	NA NA CHS424802/AF802	Small-molecule inhibitor	ALK	Phase I/II	
BRAF inhibitors	Plexxikon/Roche	Vemurafenib Zelboraf PLX4032/ RG7204	Small-molecule inhibitor	BRAF (V600E) mutation)	FDA approved for metastatic melanoma Phase I for NSCLC	Diarrhea, rash, fatigue, and skin squamous cell carcinoma
	GlaxoSmithKline	Dabrafenib NA GSK2118436	Small-molecule inhibitor	Mutant BRAF kinase	Phase III for melanoma Phase II for NSCLC	Pyrexia, rash, skin squamous cell carcinoma, and diarrhea
	Novartis	NA NA LGX818	Small-molecule inhibitor	BRAF kinase inhibitor	Phase I/II	
	ArQule	NA NA ArQ736	Small-molecule inhibitor	Pan-Raf inhibitor	Phase I	

Targeted and biologic therapies for NSCLC

BCL-2 inhibitors / BCR-ABL / STAT inhibitors

Class of Agent(s)	Trial Sponsoring Entity (ies)	Generic Name Trade Name Other Name(s)	Type	Targets	Current Phase of Development	Significant Side Effects
BCL-2 inhibitors	Abbott & Genentech	Navitoclax NA ABT-263/ ABT-737	Small-molecule inhibitor (ABT-263 is orally bio-available)	Bad-like BH3 mimetic	Phase II for SCLC	Diarrhea, back pain, and thrombocytopenia
	Genta	Oblimersom Genasense G3139	Antisense oligo-deoxyribonucleotide	Bcl-2	Phase II/III	Fever and elevated liver enzymes
	GeminX	Obatoclax NA GX15-070	Small-molecule inhibitor	Pan Bcl-2	Phase I/II	Neurotoxicity, cytopenias
	Ascenta	NA NA AT101	Negative enantiomer of gossypol	Pan Bcl-2	Phase II (NSCLC studies terminated, SCLC ongoing)	Gastrointestinal side effects
BCR-ABL/SRC tyrosine kinase / STAT inhibitors	Bristol-myers squibb	Dasatinib sprycel BMS-354825	Small-molecule TKI of SRC-family	Src, BCR-ABL, KIT, PDGFR, FMS or colony-stimulating factor 1 receptor CSF1R	FDA approved for chronic myelogenous leukemia Phase II for NSCLC	Fluid retention, pleural effusion, diarrhea, prolonged QTc, myelosuppression, and rash
	Novartis	Imatinib gleevec STI-571	Small-molecule TKI	KIT, PDGFR, BCR-ABL fusion protein	FDA approved for Gastrointestinal stromal tumor Dermatofibrosarcoma protuberans-Philadelphia chromosome positive chronic myelogenous leukemia Phase II for NSCLC	Fluid retention, diarrhea, myelosuppression, and rash
	AstraZeneca	Saracatinib NA AZD 0530	Small-molecule TKI of SRC-family binds the active conformation of the ATP binding pocket	Src, BCR-ABL (Inhibits Src kinase mediated osteoclast resorption)	Phase II	Leukopenia, febrile neutropenia, and asthenia
	Pfizer (Wyeth)	Bosutinib NA SKI-606	4-anilino-3-quinolinecarboxitrile dual Src/Abl kinase inhibitor	Src, ABL	Phase II Phase I for lung cancer	Diarrhea, anorexia, and nausea
	Kinex Pharmaceuticals	NA NA KX2-391	Small-molecule TKI targeting the substrate binding site	c-Src	Phase II Phase I for lung cancer	Hypokalemia, anemia, elevated AST, fatigue, dyspnea, fever, vomiting, constipation, hematuria, and lymphopenia
	Exelixis	NA NA XL228	Multitargeted TKI	Src, ABL, IGF-1R, AURORA, FGFR1-3	Phase I	Nausea, neutropenia, fatigue, and hypoglycemia
	Otsuka Beijing Research Institute	NA NA OPB 51602	inhibitor of signal transducer and activator of transcription 3	STAT 3	Phase I	

Targeted and biologic therapies for NSCLC

Epigenetic modulators of gene expression

Class of Agent(s)	Trial Sponsoring Entity (ies)	Generic Name Trade Name Other Name(s)	Type	Targets	Current Phase of Development	Significant Side Effects
		Valproic acid depakote	Aliphatic acid	Class I and IIa specific	Phase II	Anemia, neurological toxicity, nausea, and hepatic toxicity
		Sodium phenylbutyrate	Aliphatic acid	Class I and IIa specific	Phase II	Neuro-cortical toxicity, hypokalemia, hyponatremia, hyperuricemia, and nausea
	Novartis	Panobinostat Faridak LBH589	Hydroxamic acid-type	Pan-HDAC (all isoforms)	Phase II Phase I for lung cancer	Rash, QT interval prolongation, nausea, diarrhea, hypokalemia, and thrombocytopenia
	S*Bio	NA NA SB939	Small-molecule HDAC inhibitor	HDAC	Phase II Phase I for lung (no ongoing trials)	Fatigue, troponin elevation, and QTc prolongation
	Curis	NA NA CUDC-101	Hydroxamic acid	HDAC, HER2, EGFR	Phase Ib	Fatigue, increased creatinine, and increased hepatic enzymes
	Pharmacyclics	NA NA PCI-24781	Cyclic tetrapeptide	Class I and II	Phase I/II	
	Gloucester Pharmaceuticals	NA NA FK-228	Cyclic tetrapeptide(depsipeptide)	Class I	Phase IIb Phase I for lung	
	Chroma therapeutics	NA NA CHR-3996	Small-molecule inhibitor	Class I HDAC isoforms	Phase I	Fatigue, nausea, and vomiting
	Novartis	Dacinostat NA NVP-LAQ824	Hydroxamic acid derivative	Class I and II	Drug dropped from further development after phase I	
	Italfarmaco	Givinostat NA ITF2357	Hydroxamic acid derivative	Class I and II	Currently being studied in hematologic malignancies in phase II	

Targeted and biologic therapies for NSCLC

Proteasome and FGFR inhibitors

Class of Agent(s)	Trial Sponsoring Entity (ies)	Generic Name Trade Name Other Name(s)	Type	Targets	Current Phase of Development	Significant Side Effects
Proteasome inhibitors	Millennium Pharmaceuticals (takeda oncology)	Bortezomib velcade PS-341	Reversible inhibitor	26S proteasome and client proteins (i.e., p27, p53, NFkB, Bcl-2, Bax)	FDA approved for Multiple myeloma Mantle cell lymphoma Phase II for NSCLC	Asthenia, nausea, diarrhea, constipation, peripheral neuropathy, hypotension, and thrombocytopenia
	Onyx Pharmaceuticals	Carfilzomib NA PR-171	Irreversible inhibitor	20S proteasome subunit	Phase II Phase I for lung cancer	Pancytopenia, peripheral neuropathy
	Millennium Pharmaceuticals (takeda oncology)	NA NA MLN9708	Reversible inhibitor	20S proteasome subunit	Phase I/II Phase I for lung cancer	Anorexia, dehydration, fatigue, nausea, peripheral sensory neuropathy, macular rash, renal failure and thrombocytopenia
	Nereus Pharmaceuticals	Salinosporamide A NA NPI-0052	Irreversible inhibitor	20S catalytic core subunit of the proteasome	Phase I	Fatigue, nausea, and neurological toxicity
	Cephalon and ethical oncology science	NA NA CEP-18770	Slowly reversible	Inhibits chymotrypsin-like activity of proteasome	Phase I	
FCFR inhibitors	Bristol-Myers Squibb	Brivanib NA BMS-582664	Small-molecule TKI	FGFR and VEGFR-2	Phase III Phase II for NSCLC	Hypertension, and fatigue
	Novartis	Dovitinib NA TKI-258	Small-molecule inhibitor	FGFR-1,2,3, PDGFR, VEGFR-2	Phase II Phase I for lung cancer	Hypertension, anorexia, nausea, vomiting, fatigue, and headache
	Five prime therapeutics	FP-1039	Soluble fusion protein consisting of a portion of the FGFR1 linked to Fc portion of IgG1	FGF ligand trap (multiple FGF's)	Phase II Phase I including lung (completed)	Neutropenia, bowel perforation, urticaria, and atrial fibrillation
	AstraZeneca	NA NA AZD4547	Small-molecule inhibitor	FGFR1,2,3	Phase I/II Phase I for lung cancer	
	ARIAD	Ponatinib NA AP24534	Small-molecule inhibitor	Pan-FGFR inhibitor Pan-BCR ABL inhibitor	Phase II CML Currently no clinical trials in solid tumors initiated yet	Low platelet counts, headache, nausea, joint pain, fatigue, anemia, increased lipase, muscle spasms, rash, and pancreatitis
	Taiho Pharmaceutical	TSU-68	Small-molecule inhibitor	FGFR, PDGFR, VEGFR	Phase I/II No active trials for lung	Fatigue, AST/ALT elevation, and diarrhea
	Novartis	NA NA BGJ398	Small-molecule inhibitor	FGFR1,2,3	Phase I	

Targeted and biologic therapies for NSCLC

Hedgehog antagonists and hormone therapy

Class of Agent(s)	Trial Sponsoring Entity (ies)	Generic Name Trade Name Other Name(s)	Type	Targets	Current Phase of Development	Significant Side Effects
Hedgehog antagonists	Genentech	Vismodegib NA GDC-0449	Small-molecule inhibitor	Smoothed receptor in the sonic hedgehog pathway	Phase II	Dysgeusia, hyponatremia, fatigue, and muscle spasms
	Novartis	NA NA LDE 225	Small-molecule inhibitor	Smoothed receptor in the hedgehog pathway	Phase II Phase I for lung cancer	Fatigue, nausea, anorexia, muscle cramps, and dysgeusia
	Infinity	NA NA IPI-926	Small-molecule inhibitor	Smoothed receptor in the hedgehog pathway	Phase II Phase I for lung	Fatigue, nausea, and transaminitis
	Bristol-Myers Squibb/ exelixis	NA NA BMS-33923/ XL-1395	Small-molecule inhibitor	Smoothed receptor in the hedgehog pathway	Phase I	Dysgeusia, hypophosphatemia, muscle spasms, and increase in lipase
	Pfizer	NA NA PF04449913	Small-molecule inhibitor	Smoothed receptor in the hedgehog pathway	Phase I	
	Eli Lilly	NA NA LY2940680	Small-molecule inhibitor	Smoothed receptor in the hedgehog pathway	Phase I	
Hormone therapy	AstraZeneca	Fulvestrant Faslodex ICI 182780	Blocks estrogen activity through receptor	Estrogen receptor	FDA approved for hormone receptor positive breast cancer Phase II for postmenopausal women with NSCLC	Hot flashes, injection-site reaction, headache, gastrointestinal disturbances, and back pain
	AstraZeneca	Anastrozole Arimidex	Decreases estrogen in postmenopausal women	Aromatase inhibitor	FDA approved for hormone receptor positive breast cancer Phase II for postmenopausal women with NSCLC	Hot flashes, joint disorders, osteoporosis, nausea, mood changes, and hypertension
	GTx Inc	Enobosarm Osterine GTx-024	A selective androgen receptor modulator	aryl propionamides	Phase III	Hair growth/virilization, prostatic hyperplasia, elevated red blood cell counts, decrease in HDL cholesterol, and liver function abnormalities

Targeted and biologic therapies for NSCLC

Hypoxia activated prodrug

Class of Agent(s)	Trial Sponsoring Entity (ies)	Generic Name Trade Name Other Name(s)	Type	Targets	Current Phase of Development	Significant Side Effects
Hypoxia activated prodrug	Threshold Pharmaceuticals	NA NA TH-302	Tumor-selective hypoxia activated prodrug	2-Nitroimidazole moiety is triggered by hypoxic conditions to release DNA-alkylating dibromo isophosphoramidate mustard	Phase II Phase I/II for NSCLC	Skin lesions, mucositis, fatigue, and nausea,
	Proacta	NA NA PR-104	Tumor selective hypoxia activated preprodrug	Converted to a prodrug that is reduced under hypoxic conditions to a hydroxylaminemetabolite, PR-104H, which is a cytotoxic nitrogen mustard alkylating agent.	Phase II (phase II in NSCLC and SCLC terminated)	Cytopenias, nausea, vomiting, and fatigue
	Novacea	Banoxatrone NA AQ4N	Tumor-selective hypoxia-activated prodrug	Converted selectively under hypoxic conditions to the drug's active form, AQ4, a potent topoisomerase II inhibitor	Phase I/II No active trials for lung	
	SRI International	Tirapazamine NA SR-4233	Benzotriazine di-N-oxide, which acts as a hypoxia-activated cytotoxin	Forms free radicals in hypoxic cells that cause DNA damage. Also sensitizes hypoxic cells to ionizing radiation and inhibits the repair via inhibition of topoisomerase II	Phase III completed No longer underdevelopment for lung or other cancers	Ototoxicity, muscle cramps, nausea, and vomiting

Targeted and biologic therapies for NSCLC

HIF-1 inhibitor and immunomodulatory agents

Class of Agent(s)	Trial Sponsoring Entity (ies)	Generic Name Trade Name Other Name(s)	Type	Targets	Current Phase of Development	Significant Side Effects
HIF-1 inhibitor	Oncothyreon	PX-478	Small-molecule inhibitor	HIF-1 α	Phase I	Anemia, fatigue, nausea, elevated AST/ALT
Immunomodulatory agents	Eon Pharmaceuticals	EZN-2968	HIF-1α mRNA antagonist	HIF-1 α	Phase I	Vomiting and fatigue
	Celgene	Lenalidomide revlimid CC-5013		Immunomodulatory, anti-inflammatory, and antiangiogenic	FDA approved for Multiple myeloma, Myelodysplastic syndrome. Phase II completed for NSCLC	Myelosuppression, rash, and thrombosis
	Celgene	Thalidomide thalomid		Immunomodulatory, anti-inflammatory, and antiangiogenic	FDA approved for -multiple myeloma Phase II for NSCLC	Somnolence, peripheral neuropathy, dizziness, neutropenia, thrombosis, and rash
Immunomodulatory antibodies	Agennix	Talactoferrin NA rhLF	Recombinant human lactoferrin	Dendritic cell recruiter and activator	Phase III randomized trial vs. placebo negative for OS in previously treated NSCLC	Diarrhea
	Bristol-Myers Squibb	Ipilimumab Yervoy MDX 010	IgG1 Human MoAB	CTLA-4	FDA approved for metastatic melanoma Phase II for lung cancer.	Rash, diarrhea (autoimmune colitis), hypothyroidism, hypophysitis, and hepatitis
	MedImmune	Tremelimumab/ ticitimumab NA CP675,206	IgG2 monoclonal antibody	CTLA-4	Phase II (malignant mesothelioma)	
	Bristol-Meyers Squibb	NA NA MDX-1105	Human IgG4 MoAB	Inhibitor of PD-L1	Phase I	Rash, diarrhea, fatigue, hypothyroidism, hypophysitis, and hepatitis
	Bristol-Meyers Squibb	NA NA MDX-1106/ BMS936558/ ONO4538	Human IgG4 MoAB	Inhibitor of PD1 (a receptor expressed on activated T cells, and may suppress antitumor immunity)	Phase I	Rash, lymphopenia, arthralgia, and myalgia
	GlaxoSmithKline / Amplimmune	NA NA AMP-224	Fc-fusion protein	Targets PD-L2, which binds to PD-1	Phase I	
	Bristol-Myers Squibb	BMS-663513	Humanized MoAB	Agonist of CD-137, a TNF receptor	Phase II (terminated) Phase I in combination with chemoradiation in NSCLC (terminated)	Neutropenia, elevated liver enzymes, rash, pruritus, diarrhea

Targeted and biologic therapies for NSCLC

IAP antagonist and IGF-1R inhibitor

Class of Agent(s)	Trial Sponsoring Entity (ies)	Generic Name Trade Name Other Name(s)	Type	Targets	Current Phase of Development	Significant Side Effects
IAPs antagonist	Human Genome Sciences/Aegera	NA NA HGS 1029/ AEG 40826	Small-molecule Smac mimetic	IAPs antagonist	Phase I	Nausea, anorexia, diarrhea, fatigue, elevated amylase and lipase, and supraventricular tachycardia
	Tetralogic	NA NA TL32711	Small-molecule Smac mimetic	IAPs antagonist	Phase I/II	
	Ascenta Therapeutics	NA NA AT-406	Small-molecule Smac mimetic	Multi-IAP antagonist (XIAP, c-IAP1, c-IAP2, and ML-IAP)	Phase I	
	Genentech	NA NA GDC0917	Small-molecule peptide Smac mimetic	IAPs antagonist	Phase I	
	Novartis	NA NA LCL161	Small-molecule Smac mimetic	IAPs antagonist	Phase I	
IGF-1R inhibitor	Pfizer	Figitumumab CP-751871	IgG2 type human MoAB	IGF-1R	Phase III terminated (further development halted)	Cardiac toxicity, hyperglycemia, asthenia, anorexia, pneumonia, dehydration, and early death.
	OSI Pharmaceuticals/ Astellas	NA NA	Small-molecule inhibitor	IGF-1R and IR	Phase III Phase II for NSCLC	Nausea, vomiting, fatigue, hyperglycemia, and elevated liver enzymes
	Amgen	NA NA AM	IgG1-type human MoAB	IGF-1R	Phase III Phase I/II for lung was terminated based on results from similar study	Thrombocytopenia, neutropenia, hyperglycemia, fatigue, rash, elevated LFTs, and asymptomatic TSH increase
	ImClone	Cixutumumab NA IMC-A12	IgG1-type human MoAB	IGF-1R	Phase II	Pruritus, rash, anemia, hyperglycemia, and infusion-related reaction
	Merck	Dalotuzumab NA MK-0646	IgG1-type humanized MoAB	IGF-1R	Phase II	Fatigue, hyperglycemia, nausea, constipation, and diarrhea
	Biogen idec	BIB022	Human nonglycosylated IgG4 MoAB	IGF-1R	Phase II Phase I for NSCLC	Hypertension, fatigue, dyspnea, and QTc prolongation
	Bristol-Myers Squibb	NA NA BMS-754807	Small-molecule reversible inhibitor	IGF-1R and IR	Phase I	Fatigue and hyperglycemia
	Sanofi-Aventis	NA NA AVE1642	Humanized MoAB	IGF-1R	Phase I/II(no active trials. Company discontinued development)	Hyperglycemia, asthenia and hypersensitivity
	Genmab & Roche	Robatumumab NA R1507	IgG1-type human MoAB	IGF-1R	Phase II (development is halted)	Fatigue, anorexia, and weight loss
	Schering-Plough	Robatumumab NA SCH717454	IgG1-type human MoAB	IGF-1R	Phase II (development halted)	

Targeted and biologic therapies for NSCLC

Integrins and mTOR inhibitors

Class of Agent(s)	Trial Sponsoring Entity (ies)	Generic Name Trade Name Other Name(s)	Type	Targets	Current Phase of Development	Significant Side Effects
Integrins	Merck Serono	Cilengitide NA EMD121974	Cyclic peptide	$\alpha_v \beta_3$, and $\alpha_v \beta_5$ integrin	Phase III Phase I/II for NSCLC	Lymphopenia, thrombocytopenia, neutropenia, fatigue, nausea, anorexia
	PDL BioPharma and Biogen Idec	Volociximab NA M200	Chimeric MoAB	$\alpha 5 \beta 1$ integrin	Phase II	Fatigue, nausea, constipation, diarrhea, and arthralgia
	Pfizer	NA NA PF-04605412	Human IgG1 MoAB	$\alpha 5 \beta 1$ integrin	Phase I	
	MedImmune	Vitaxin NA MEDI-522	Humanized IgG1 MoAB	$\alpha 5 \beta 1$ integrin	Phase I	Chills, fever, and nausea
mTOR inhibitors	Pfizer (Wyeth)	Temsirolimus Torisel CCI-779	Ester analog of rapamycin	mTORC1	FDA approved for advanced renal cell carcinoma Phase II for NSCLC	Fatigue, rash, asthenia, hyperglycemia, hyperlipemia, hypophosphatemia, myelosuppression, nausea, and diarrhea
	Novartis	Everolimus Afinitor RAD001	Derivative of the natural macrocyclic lactone sirolimus	mTORC1	FDA approved for advanced renal cell carcinoma Phase II for NSCLC closed (Gefitinib + Everolimus)	Stomatitis, asthenia, pneumonitis, fatigue, infections, diarrhea, and neutropenia
	Merck/Ariad	Ridaforolimus Taltorvic (proposed) AP-23573	Small-molecule serine/threonine kinase inhibitor	mTOR	Phase III Phase II for NSCLC	Fatigue, anorexia, and mucositis
	Generic drug with multiple manufacturers	Sirolimus Rapamune Rapamycin	A macrolide derived from <i>Streptomyces hygroscopicus</i>	mTORC1	Phase I/II	Cytopenias, hypoalbuminemia, hyperglycemia, hypercholesterolemia, and hypertriglyceridemia
	AstraZeneca	NA NA AZD 8055	ATP competitive small-molecule inhibitor	mTOR C1,2	Phase I/II	Transaminitis,
	OSI Pharmaceuticals	NA NA OSI 027	Small-molecule inhibitor	mTORC1,2	Phase II	
	Novartis	NA NA BEZ 235	Small-molecule inhibitor	PI3K/mTORC1	Phase I/II	

Targeted and biologic therapies for NSCLC

c-MET/HGFR pathway inhibitors

Class of Agent(s)	Trial Sponsoring Entity (ies)	Generic Name Trade Name Other Name(s)	Type	Targets	Current Phase of Development	Significant Side Effects
c-MET/HGFR pathway inhibitors	ArQule	Tivantinib NA ARQ197	Small-molecule inhibitor	c-MET/ HGFR	Phase III	Hepatotoxicity
	Roche/Genentech	Onartuzumab NA MetMab/RG3638	Humanized monovalent MoAB	c-MET	Phase III	Peripheral edema
	Amgen	Rilotumumab NA AMG 102	Human IgG2 MoAB	HGF (ligand)	Phase I/II	Fatigue, constipation, anorexia, nausea, and dyspnea
	AVEO Pharmaceuticals	Ficlatuzumab NA AV-299/SCH900105	Humanized IgG1 MoAB	HGF (ligand)	Randomized phase II	Fatigue, peripheral edema, headache, and diarrhea
	Astex Pharmaceuticals//	Amuvatinib NA MP-470	Small-molecule inhibitor	KIT, c-MET, RET, PDGFR, FLT3	Phase II (SCLC)	
	MethylGene	NA NA MGCD265	Small-molecule inhibitor	c-MET, VEGFR1,2,3, Ron, Tie-2	Phase I/II	
	Merck	NA NA MK2461	Small-molecule inhibitor	c-MET	Phase I/II	
	Bristol-Myers Squibb	NA NA BMS777607	Small-molecule inhibitor	c-MET	Phase I/II	
	Incyte	NA NA INCB28060	Small-molecule inhibitor	c-MET	Phase I	
	Amgen	NA NA AMG 208	Small-molecule inhibitor	c-MET	Phase I	
	Eli Lilly	NA NA LY2875358	Humanized IgG4 MoAB	c-MET	Phase I	
	Pfizer	NA NA PF-4217903	Small-molecule inhibitor	c-MET/ HGFR	Phase I (terminated)	
	Johnson & Johnson	NA NA JNJ38877605	Small-molecule inhibitor	c-MET	Phase I (terminated)	Elevation in Creatinine
	SGX Pharmaceuticals	NA NA SGX523	Selective small-molecule inhibitor	Met	Phase I (terminated)	Nephrotoxicity, fatigue, pyrexia, nausea, and vomiting

Targeted and biologic therapies for NSCLC

MEK inhibitors

Class of Agent(s)	Trial Sponsoring Entity (ies)	Generic Name Trade Name Other Name(s)	Type	Targets	Current Phase of Development	Significant Side Effects
MEK inhibitors	AstraZeneca/Array BioPharma	Selumetinib NA AZD6244/ARRY142880	Allosteric inhibitor	MEK ½	Phase III Phase II completed in NSCLC (phase I ongoing in KRAS & BRAF mutants)	Rash, diarrhea, nausea, and emesis
	Merck KGaA/EMD Serono	NA NA AS 703026/ MSC1936369B	Noncompetitive small-mole- cule inhibitor	MEK 1/2	Phase I/II	Asthenia, diarrhea, constipa- tion, rash, nausea, and vomiting
	Ardea Biosciences	NA NA RDEA119/ BAY 869766	Allosteric inhibitor	MEK 1/2	Phase I/II	Rash, diarrhea, nausea, vomit- ing, fatigue, and peripheral edema
	GlaxoSmithKline	Trametinib NA GSK1120212	Allosteric small-molecule inhibitor	MEK 1/2	Phase I/ II	Rash, diarrhea, and central serous retinopathy
	Novartis	NA NA MEK162	Small-molecule inhibitor	MEK	Phase III/Phase I in lung cancer	
	Pfizer	NA NA PD325901	Small-molecule inhibitor	MEK 1/2	Phase I	Ocular toxicity, neurological toxicity
	AstraZeneca/Array BioPharma	NA NA AZD8330	Small-molecule inhibitor	MEK 1	Phase I	
	Genentech	NA NA GDC-0973/ XL518	Small-molecule inhibitor	MEK 1	Phase I	

Targeted and biologic therapies for NSCLC

Inhibitors of mitosis

Class of Agent(s)	Trial Sponsoring Entity (ies)	Generic Name Trade Name Other Name(s)	Type	Targets	Current Phase of Development	Significant Side Effects
Polo-like kinase inhibitor	Boehringer Ingelheim	NA NA BI-2536	ATP competitive small-molecule inhibitor	Plk1 (serine threonine kinase)	Phase II	Neutropenia, fatigue, and nausea
	Boehringer Ingelheim	Volasertib NA BI-6727	Dihydropteridinone derivative (binds to ATP-binding pocket)	Plk1 (serine threonine kinase)	Phase II	Anemia, neutropenia, thrombocytopenia, and fatigue
	GlaxoSmithKline	NA NA GSK461364	ATP competitive inhibitor	Plk1 (serine threonine kinase)	Phase I	Fatigue, anemia, abdominal pain
	Nerviano Medical Sciences	NA NA NMS1286937	Small-molecule inhibitor	Plk1 (serine threonine kinase)	Phase I	

Targeted and biologic therapies for NSCLC

Notch pathway inhibitors and osteoclast function modifiers

Class of Agent(s)	Trial Sponsoring Entity (ies)	Generic Name Trade Name Other Name(s)	Type	Targets	Current Phase of Development	Significant Side Effects
Notch pathway inhibitors	Roche	NA NA RO 4929097	Gamma secretase inhibitor	γ secretase inhibitor (Pan-notch)	Phase II	Asthenia, nausea, diarrhea, hypophosphatemia, and pruritus.
	Merck	NA NA MK0752	Gamma secretase inhibitor	γ secretase inhibitor (Pan-notch)	Phase I/II Phase I in lung cancer	Abdominal cramps, diarrhea, nausea, and fatigue
	Pfizer	NA NA PF03084014	Gamma secretase inhibitor	γ secretase inhibitor (Pan-notch)	Phase I	Gastrointestinal toxicity (reduced with steroids)
	Regeneron	NA NA REGN421	Human MoAB	Delta-4 ligand	Phase I	
Osteoclast function modifiers (important in bone metastasis)	Novartis	Zoledronate zometa NA	Farnesyl pyrophosphate	Osteoclast inhibitor	FDA approved for Osteoporosis Cancer-related bone metastases (multiple myeloma and solid tumors)	Hypocalcemia, osteonecrosis of jaw, and renal toxicity
	Amgen	Denosumab Xgeva/Prolia AMG-162	Fully human monoclonal antibody	RANK ligand inhibitor (transmembrane protein important for osteoclast activity and survival)	FDA approved for Osteoporosis Prevention of skeletal-related events in patients with bone metastases from solid tumors	Hypocalcemia, osteonecrosis of jaw, serious infections, and skin reactions
	Procter & Gamble Pharmaceuticals	Etidronate Didronel	Bisphosphonate-ATP requiring small molecule	Osteoclast inhibitor	FDA approved for symptomatic Paget's disease, and hypercalcemia from cancer Phase III for bone metastasis	Esophagitis, arthralgias, and hypersensitivity reactions
	Novartis	Alendronate Fosamax	Nitrogen containing bisphosphonate targets farnesyl pyrophosphate synthase	Osteoclast inhibitor	FDA approved for osteoporosis Phase III for bone metastasis	Esophagitis, osteonecrosis of jaw, delayed healing, hypersensitivity reaction, and bone/muscle pains
	Merck	NA NA L-000845704	Integrin antagonist- decreases bone resorption	$\alpha\beta3$	Phase III for osteoporosis. (not being pursued further)	
	Merck	Odanacatib NA MK-0822	Anti-cathepsin K, (decreases bone resorption)	Cathepsin K (osteoclast specific enzyme)	Phase III for osteoporosis No open cancer-specific trials	
	Novartis	Balicatib NA AAE-581	Anticathepsin K		Phase II for osteoporosis No open cancer trials	

Targeted and biologic therapies for NSCLC

PI-3K/AKT inhibitors

Class of Agent(s)	Trial Sponsoring Entity (ies)	Generic Name Trade Name Other Name(s)	Type	Targets	Current Phase of Development	Significant Side Effects
PI-3K/AKT inhibitors: AKT inhibitors	Merck	NA NA MK2206	Non-ATP competitive allosteric Akt	Akt	Phase II	Rash, mucositis, and gastrointestinal toxicity
	Agouron Pharmaceuticals	Nelfinavir Viracept AG 1343	Protease inhibitor	Akt	Phase II (Phase II for lung terminated due to poor accrual)	Diarrhea, rash, fatigue, leukopenia
	Keryx/AOI Pharmaceuticals	Perifosine NA KRX-0401	Alkylphospholipid	Akt	Phase I/II (NSCLC trial suspended)	Nausea, vomiting, diarrhea, and fatigue
PI-3K inhibitors	Novartis	NA NA BEZ235	Small-molecule inhibitor	PI-3K (pan-class 1), mTOR complexes 1/2	Phase I/II	Nausea, emesis, diarrhea, fatigue, and anemia
	Novartis	NA NA BKM120	Small-molecule ATP competitive inhibitor	PI-3K (pan-class 1)	Phase II	Rash, hyperglycemia, altered mood, and pruritus
	Onconova Therapeutics	Rigosertib estybon ON01910	Non-ATP competitive small-molecule inhibitor	PI-3K inhibitor down-regulates Cyclin D1, induces NOXA, BIM and JNK	Phase III Phase I in solid tumors including lung cancer	Fatigue and anorexia
	Exelixis	NA NA XL147	Small-molecule inhibitor	PI-3K (class I isoforms)	Phase II Phase I for lung cancer	Rash, arterial thrombosis, transaminitis, and hyperglycemia
	Novartis	NA NA NVP-BGT226	Dual small-molecule inhibitor	PI-3K and mTOR	Phase I/II (completed)	
	Oncothyreon	NA NA PX-866	Irreversible small-molecule inhibitor (Wortmanin analog)	PI-3K, lowers p-mTOR, p-S6 ribosomal protein	Phase I/II	Diarrhea, nausea, and vomiting
	Genentech	NA NA GDC-0941	Small-molecule inhibitor	PI-3K (class I isoforms)	Phase I	Nausea, fatigue, diarrhea, dysgeusia, headache, and pleural effusion
	Pfizer	NA NA PF-04691502	Dual molecule inhibitor	PI-3K and mTOR	Phase I	
	Exelixis	NA NA XL765	Dual selective oral inhibitor	PI-3K (Class I) and mTOR	Phase I	Nausea, diarrhea, transaminitis, rash, anorexia, and fatigue
	Bayer	BAY80-6946	Highly selective reversible inhibitor	Pan-class I PI-3K	Phase I	Fatigue, nausea, diarrhea, mucositis, dysgeusia, and anemia

Targeted and biologic therapies for NSCLC

PDGFR α and PARP inhibitors, SMAC mimetics, SURVIVIN and telomerase inhibitors

Class of Agent(s)	Trial Sponsoring Entity (ies)	Generic Name Trade Name Other Name(s)	Type	Targets	Current Phase of Development	Significant Side Effects
PDGFRα inhibitors	Imclone LLC	Ramucirumab NA IMC-3G3	Human IgG1 MoAB	PDGFR α	Phase II	Fatigue
	MedImmune	NA NA MEDI-575	MoAB	PDGFR α	Phase II	
PARP inhibitors	Sanofi-Aventis(BiPar Sciences)	Iniparib NA BSI-201	Small lipophilic molecule inhibitor	PARP-1	Phase III (squamous)	Nausea and fatigue
	Pfizer	Rucaparib NA AG014699/PF-01367338	Small-molecule inhibitor	PARP-1	Phase II Phase I for NSCLC	Fatigue, thrombocytopenia, hypophosphatemia, and lymphopenia
	Abbott	Veliparib NA ABT 888	Small-molecule inhibitor	PARP-1, 2	Phase II	Fatigue, neutropenia (with chemotherapy)
	AstraZeneca	Olaparib NA AZD2281	Small-molecule inhibitor	PARP	Phase II Phase I/II for lung cancer	Nausea, fatigue, and anemia
	Merck	NA NA MK4827	Small-molecule inhibitor	PARP -1, 2	Phase I	Fatigue, nausea, myelosuppression
SMAC mimetics	Tetralogic	Birinapant NA TL32711	Small-molecule Smac mimetic	Antagonizes IAPs	Phase I	
	Ascenta Therapeutics	NA NA AT-406	Small-molecule Smac mimetic	Antagonizes IAPs	Phase I	
SURVIVIN inhibitors	Isis Pharmaceuticals and Eli Lilly	NA NA LY2181308	Antisense oligonucleotide	Blocks survivin	Phase II	PTT prolongation, headache, lymphopenia, fever, fatigue, and nausea
	Astellas	NA NA YM155	Small-molecule inhibitor	Suppresses survivin	Phase II	Hypertension, neutropenia, fatigue, nausea, stomatitis, and fever.
TELOMERASE inhibitors	Geron Corporation	Imetelstat NA GRN163L	Competitive telomerase RNA template antagonist	Telomerase	Phase II	PTT prolongation, gastrointestinal side effects, fatigue, anemia, GGT elevation, and peripheral neuropathy
	University of Maryland	Sodium metaarsenite NA KML001	Oral arsenic agent	Telomerase	Phase I	

Targeted and biologic therapies for NSCLC

TRAIL receptor agonists and vascular disrupting agents

Class of Agent(s)	Trial Sponsoring Entity (ies)	Generic Name Trade Name Other Name(s)	Type	Targets	Current Phase of Development	Significant Side Effects
	MediciNova	NA NA MN-029	Binds reversibly to the colchicine-binding site on tubulin.	Disrupts the endothelial tubulin cytoskeleton	Phase I (completed)	Nausea, vomiting, hypotension, fatigue, diarrhea
	AstraZeneca	NA NA ZD6126	Small-molecule VDA	Disrupts the endothelial tubulin cytoskeleton	Phase I (completed)	Anorexia, constipation, dyspnea, and fatigue

Targeted and biologic therapies for NSCLC

Vaccines

Class of Agent(s)	Trial Sponsoring Entity (ies)	Generic Name Trade Name Other Name(s)	Type	Targets	Current Phase of Development	Significant Side Effects
	University of Miami, Sylvester Cancer Center	NA NA Ad100-gp96Ig-HLA A1	Irradiated NSCLC cells, manipulated to express and secrete heat shock protein gp96-Ig fusion protein	CTL response against NSCLC cells	Phase I	
	NCI	MAGE-12 peptide vaccine (emulsified in Montanide ISA-51) NA	Peptide vaccine	MAGE-12 Antigen-positive tumors	Phase I (all solid tumors-completed)	
	Corixa Corporation	pVAX/L523S and Ad/L523S NA	Recombinant DNA and adenovirus expressing L523S protein		Phase I (no updates available)	
	University of Pittsburgh	Semiallogeneic human fibroblasts (MRC-5) transfected NA	Fibroblasts transfected with DNA from autologous tumor	Autologous tumor cells	Phase I (suspended due to funding)	
	Memorial Sloan Kettering Cancer Center	WT-1 analog peptide vaccine NA	Peptide vaccine	WT-1 gene-expressing tumors	Phase II for mesothelioma	

Targeted and biologic therapies for NSCLC

Anti-sense oligonucleotides and anti-body engineering

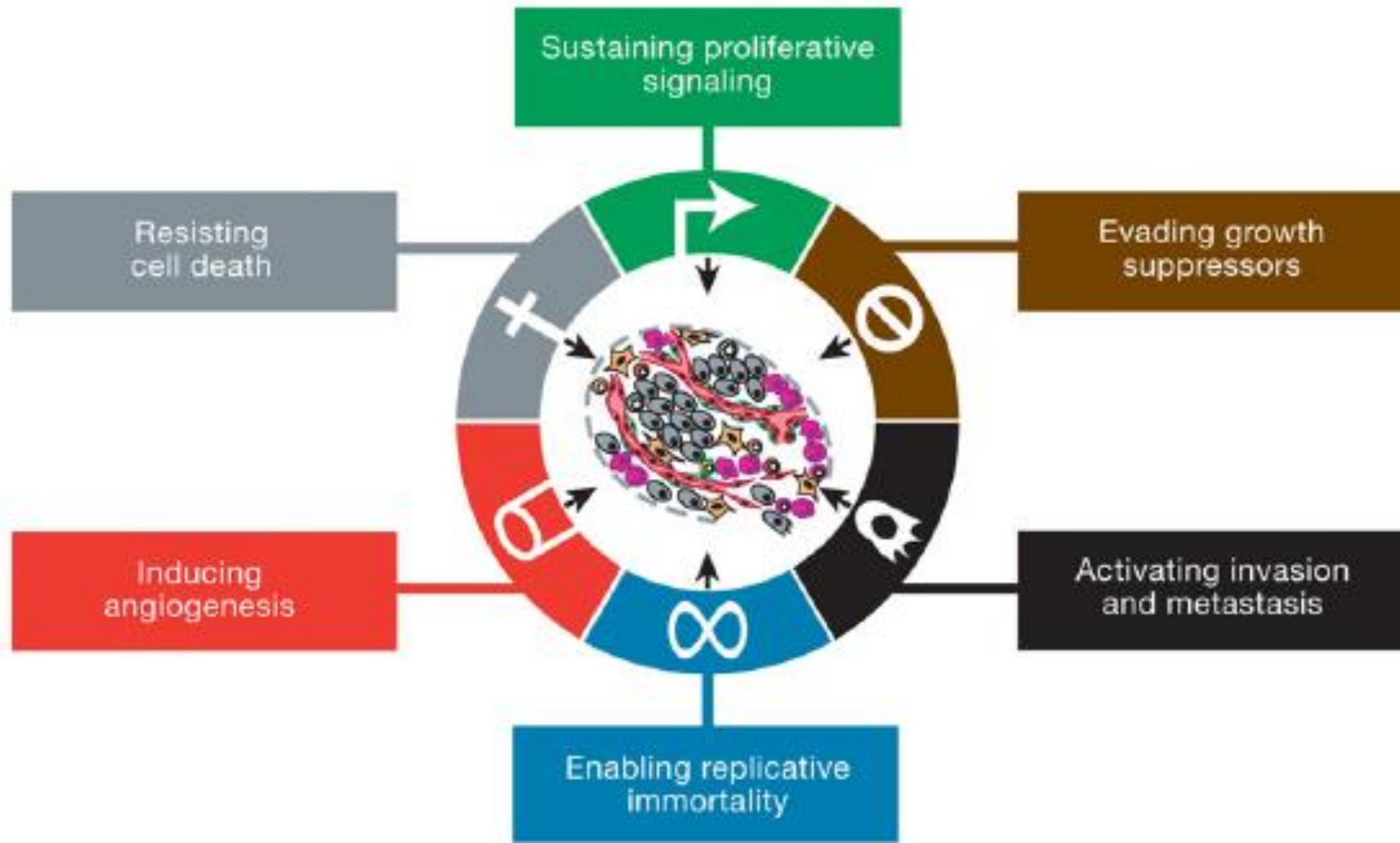
Class of Agent(s)	Trial Sponsoring Entity (ies)	Generic Name Trade Name Other Name(s)	Type	Targets	Current Phase of Development	Significant Side Effects
Anti-Sense Oligonucleotides	Genta	Oblimersen Genasense G3139	Antisense oligo-deoxyribonucleotide	Bcl-2	Phase II/III	Fever and elevated liver enzymes
	OncGenex	Custirsen NA OGX 011	ASO	Clusterin	Phase III (prostate) Phase I/II for NSCLC	
	Isis pharmaceuticals & Eli Lilly	NA NA LY2181308	ASO	Blocks survivin	Phase II	PTT prolongation, headache, lymphopenia, fever, fatigue, and nausea
	Isis pharmaceuticals	NA NA ISIS 2503	ASO	H-ras	Phase II (completed)	
	Isis pharmaceuticals	NA NA ISIS 5132	ASO against c-Raf kinase mRNA expression	Raf-1	Phase II	Mild hematologic toxicity, asthenia, fever
	Eli Lilly Isis Pharmaceuticals	Affinitac NA LY900003 /ISIS 3521	ASO	Protein kinase C alpha	Phase III completed. Further development discontinued.	
Therapeutic antibody engineering (novel targets, antibody-drug conjugates, antibody fragments)	Trion Pharma	Catumaxomab Removab	Rat-murine hybrid monoclonal antibody binding to EpCAM and CD3 antibody	EpCAM/CD3	Phase III(phase I/II for lung cancer)Approved in Europe for malignant ascites	Fever, Nausea, Vomiting
	Genzyme	NA NA	Human IgG4 MoAB	Pan-neutralizing TGF- β	Phase II (mesothelioma)	
	Peregrine Pharmaceuticals	Bavituximab Tarvacin UNII-Q16CT95N25 3G4	Chimeric IgG1 MoAB	Membrane phosphatidylerine complexed with β 2-glycoprotein I on tumor vasculature	Phase II	Nausea, fatigue, headache, alopecia, anemia, and hypertension
	Alder Pharmaceuticals	ALD518	Anti-IL-6 antibody	To treat anemia, cachexia, and fatigue	Phase II	
	Acceleron and Celgene	Sotatercept NA ACE-011	Fully human soluble activin receptor type 2A IgG-Fc fusion protein	Activin antagonist (increases hemoglobin and also increases bone mineral density)	Phase II	Headache, paresthesia, dizziness, fatigue, and hypertension
	Lpath/Merck-Sereno	Sonepizumab/ASONEP	Humanized MoAB	Shingosine-1-phosphate	Phase I	Infusion reaction
	Micromet AG	MT110	EpCAM/CD3 bispecific antibody construct (BiTE)	EpCAM/CD3	Phase I	Fever and elevated liver enzymes
	Pfizer	CVX-045	Human MoAB	Thrombospondin-1 Mimetic	Phase I	Fatigue, gastrointestinal upset, dyspnea, headache, dizziness and anemia

Targeted and biologic therapies for NSCLC

Therapeutic viruses and others

Class of Agent(s)	Trial Sponsoring Entity (ies)	Generic Name Trade Name Other Name(s)	Type	Targets	Current Phase of Development	Significant Side Effects
	Pfizer	PF-00562271	Reversible FAK inhibitor	FAK	Phase I	Headache, nausea, and peripheral neuropathy, diarrhea, fatigue, edema
	AstraZeneca	ZD4054	ETAR antagonist	ETAR	Phase II	
	AstraZeneca	AZD 6918	Small-molecule inhibitor	Tropomyosin-related kinases	Phase I (development discontinued)	
	Eisai Inc.	Eribulin mesylate E7389	Non-taxane microtubule dynamics inhibitor		Phase II	Fatigue and cytopenias
	Vion Pharmaceuticals, NCI	Triapine	Ribonucleotide reductase inhibitor (enhancing the activity of gemcitabine)		Phase II	
	Bristol-Meyers Squibb	Epopolate BMS-753493	Folate conjugate of epothilone analog BMS-748265		Phase I	Fatigue, nausea, elevated liver enzymes, and diarrhea
	Daiichi Sankyo	Efatutazone NA CS 7017/ RS5444	PPAR γ agonist	PPAR- γ	Phase II	Fluid retention
	Pfizer/Onyx	NA NA PD 0332991	Small-molecule inhibitor	CDK 4/6 inhibitor	Phase II	
	Pfizer	Celecoxib celebrex or celebra for arthritis; Onsenal for polyps	Eicosanoid	Cyclooxygenase-2 inhibitor	Phase II	
	Tragara Pharmaceuticals	Aprecoxib CS-706. TG01 Capoxigem	A benzenesulfonamide nonsteroidal anti-inflammatory drug	Small-molecule selective Cox-2 inhibitor	Phase II	
	Quintessence Biosciences	QBI-139	Variant of human pancreatic ribonuclease 1	Causes destruction of RNA	Phase I	
	Pfizer	CVX-060	Anti-Angiogenic COVX-Body	A selective angiopoietin-2 binding	Phase I	Fatigue and proteinuria
	AstraZeneca	NA NA AZD1480	Small-molecule inhibitor	JAK2 kinase	Phase I	
	NCI	4-(N-(S-glutathionylacetylamino) phenyl)arsinous acid	Synthetic tripeptide trivalent arsenical	Angiogenesis inhibitor that targets the mitochondria or actively dividing but not quiescent endothelial cells arresting their proliferation and causing apoptosis	Phase I	
	Introgen Therapeutics	DOTAP: chol-FUS1	Lipid-based nanoparticles	Fus1 tumor suppressor gene	Phase I	Fever and hypophosphatemia

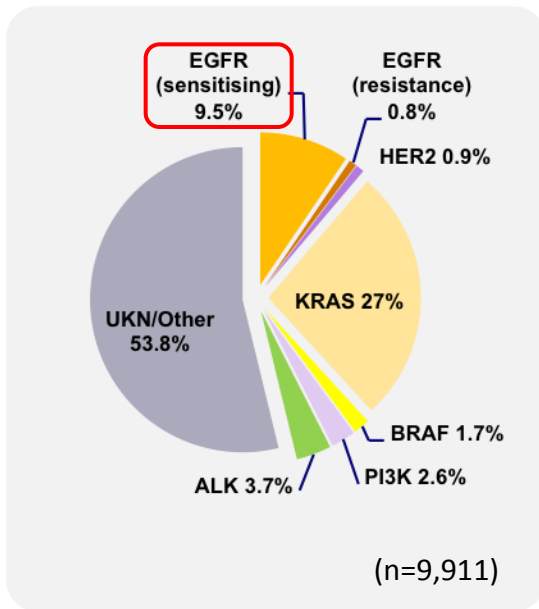
Characteristics of cancer cells



Molecular alterations in lung cancer

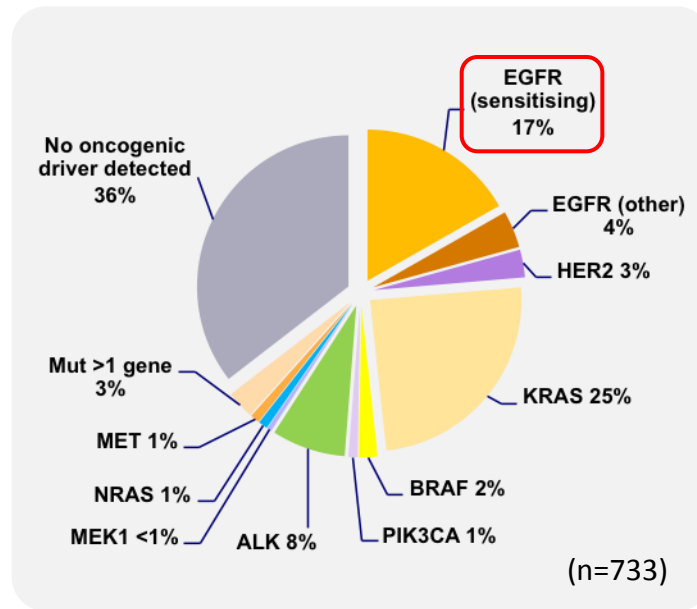
Europe

All histology



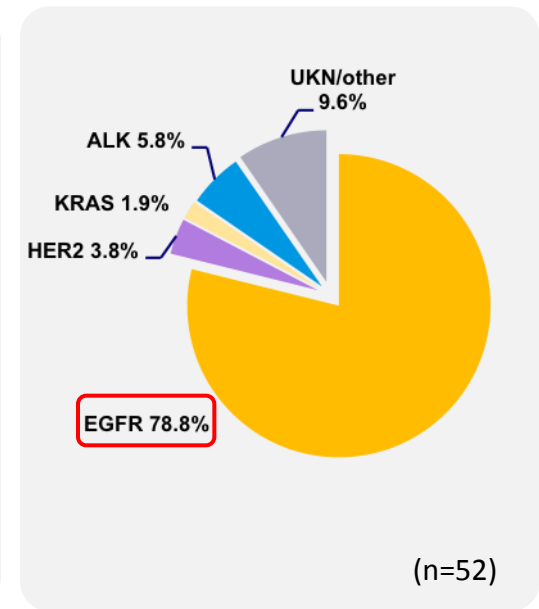
US

Adenocarcinoma

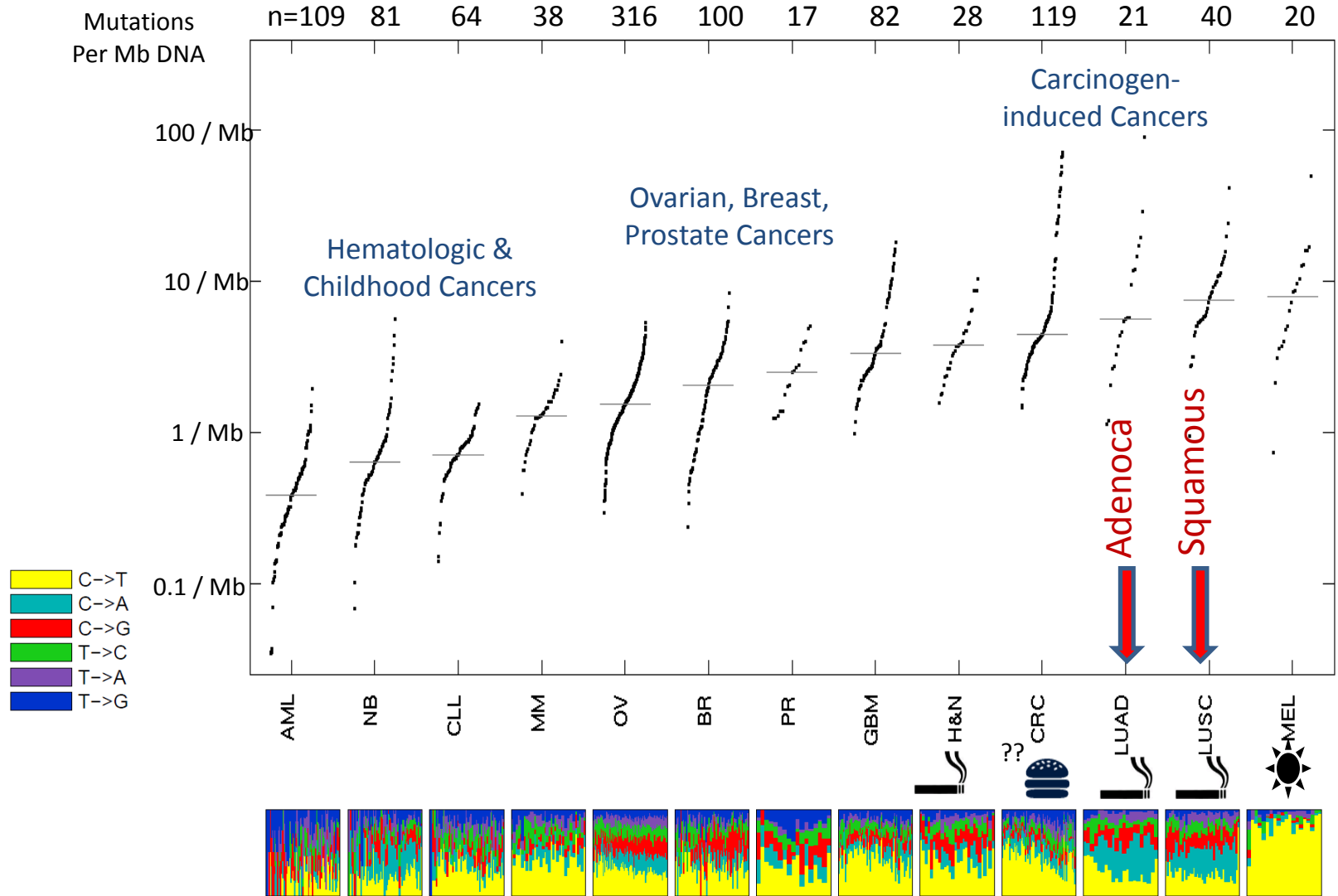


East Asia

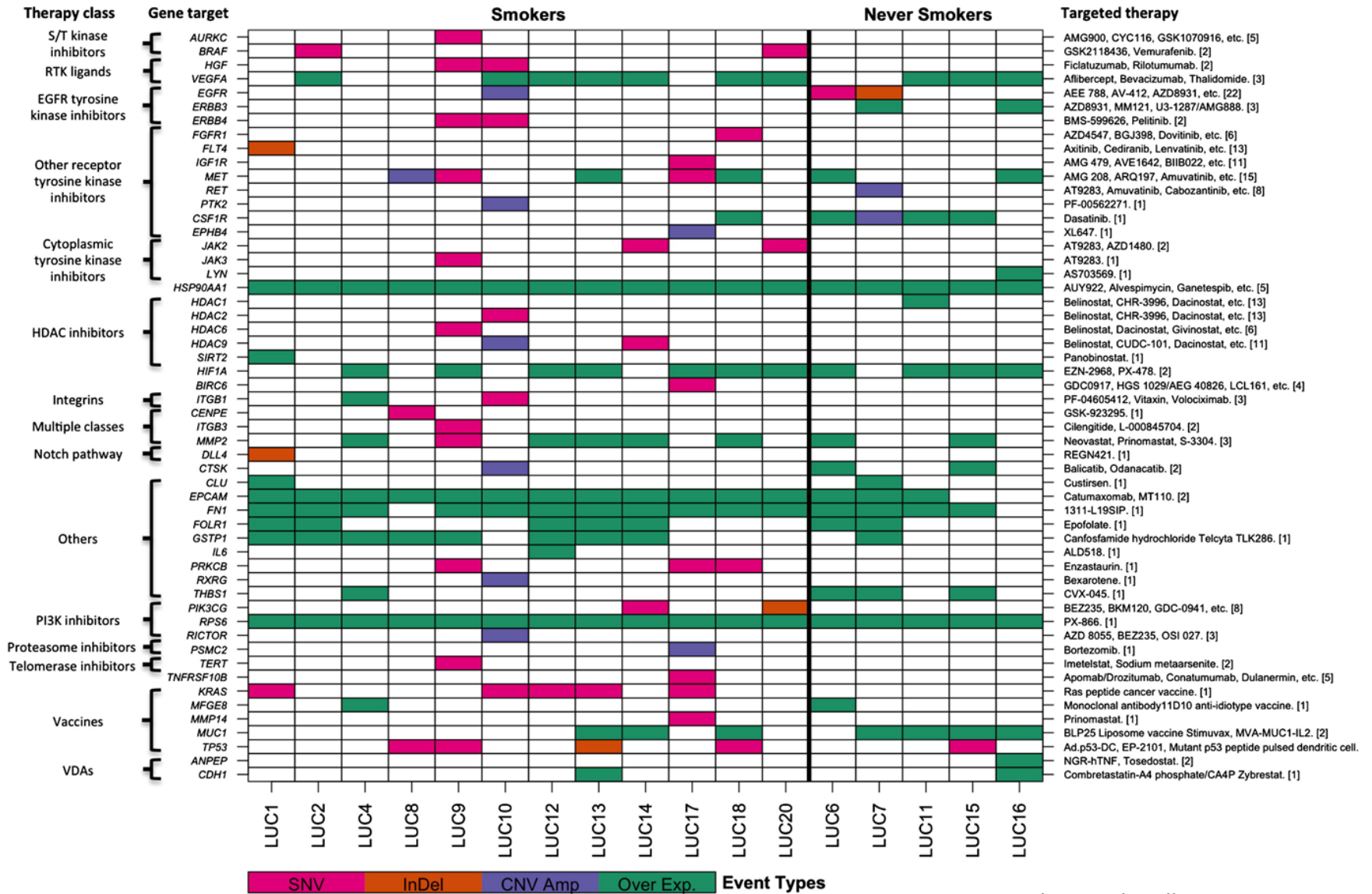
Adenocarcinoma, never smokers



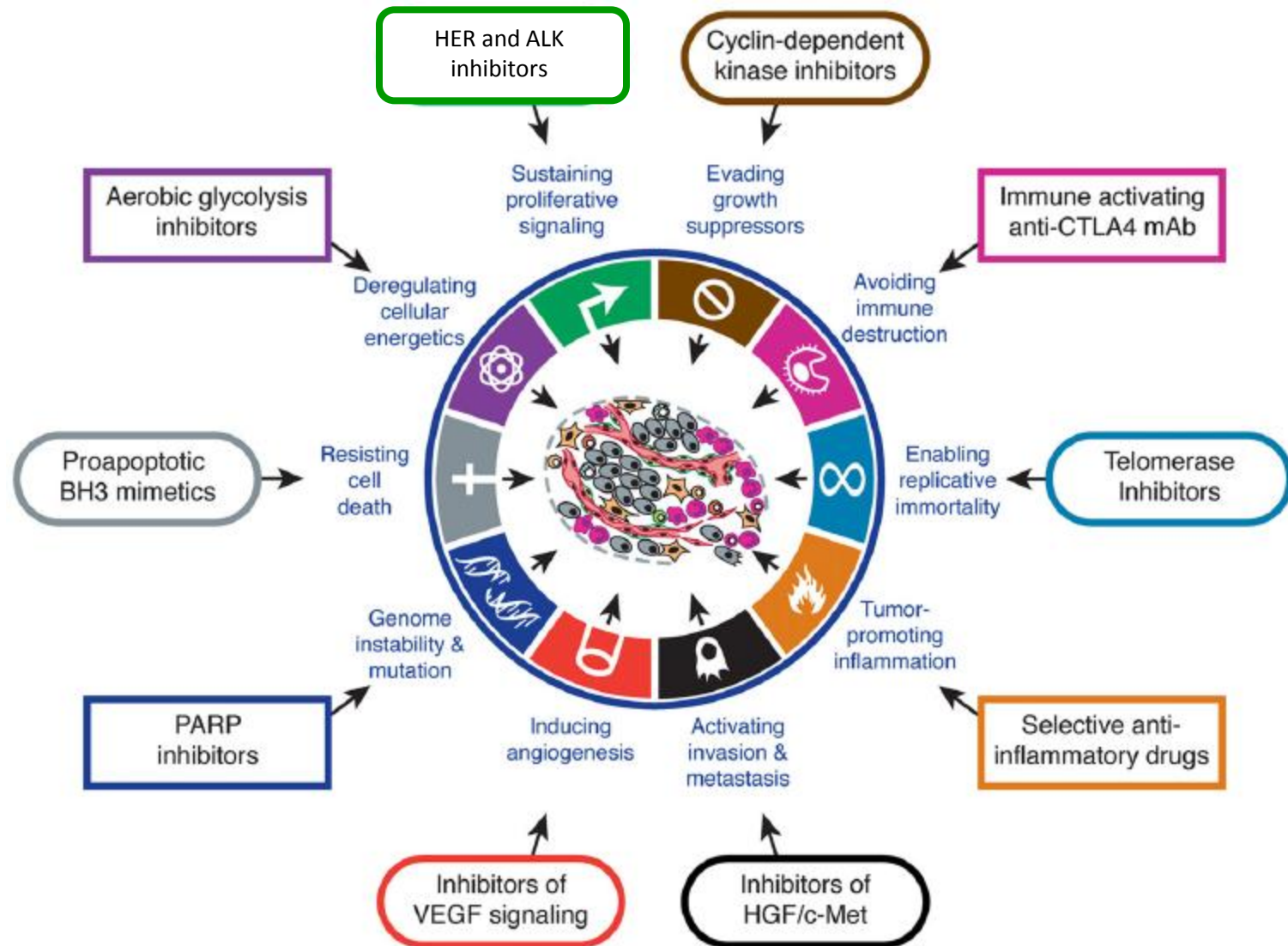
Magnitude of genomic derangement

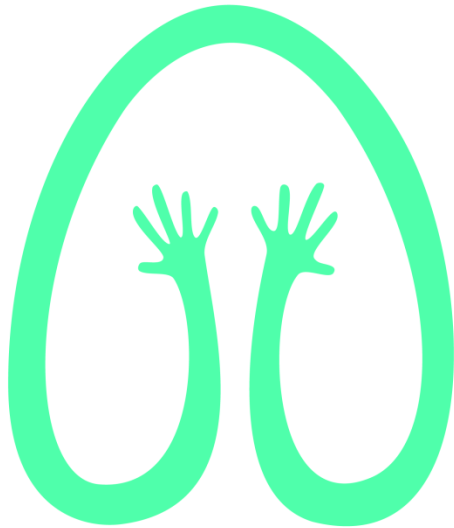


Drugable targets in smokers and never smokers



Characteristics of cancer cells





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