Prise en charge thérapeutique des CBNPC

M Gamaz
HDJ Oncologie Médicale CPMC

Traitement

But :

1. Guérir le malade, / obtenir une rémission la plus longue possible.
2. Augmenter la survie.
3. Améliorer et garder une bonne QOL

Armes :

1. Chirurgie
2. Radiothérapie
3. Traitement médicamenteux
4. Traitement symptomatique

Stratégie thérapeutique :

1. Traitement de maintenance
2. Traitement de deuxième ligne ,
3. traitement de 3eme ligne et au delà.

Eléments d'évaluation :

1. Réponse au traitement
2. Survie globale ,
3. Survie sans progression
4. Qualité de vie

Pré requis au traitement

1

RCP

- Age / Comorbidités.
- PS
- L'extension de la maladie (TNM)
- Le type histologique
- Les drivers moléculaires

- âge, [< 70 ans, 70 – 89 ans]
- Comorbidités tel que insuffisance rénale, cardiopathies, neuropathies importantes….
- PS = 0, 1 / PS = 2 / PS = 3, 4.

Choix du protocole thérapeutique médicale

- Cisplatine / carboplatine
- Monothérapie / bithérapie
- Chimiothérapie / Thérapie ciblée (TKI / antiangiogénique) / Immunothérapie.

Pré requis au traitement

2

RCP

- Age / Comorbidités.
- PS
- L'extension de la maladie (TNM)
- Le type histologique
- Les drivers moléculaires

On aura 3 grands groupes :

- Stades localisés opérables
- Stades localement avancés non opérables
- Stades métastatiques

Classification par stade

		Tis	N0	M0
I	IA1	T1mi, T1a	N0	M0
	IA2	T1b	N0	M0
	IA3	T1c	N0	M0
	IB	T2a	N0	M0
II	IIA	T2b	N0	M0
	IIB	T1a, T1b, T1c, T2a, T2b T3	N1 N0	M0 M0
III	IIIA	T1a, T1b, T1c, T2a, T2b T3 IIIA T4	N2 N1 N0, N1	M0 M0 M0
	IIIB	T1a, T1b, T1c, T2a, T2b T3, T4	N3 N2	M0 M0
	IIIC	T3, T4	N3	
IV	IVA	Quel que soit T	Quel que soit N	M1a, M1b
	IVB	Quel que soit T	Quel que soit N	M1c

Stades opérables			
I	IA1	T1mi, T1a	N0
	IA2	T1b	N0
	IA3	T1c	N0
	IB	T2a	N0
II	IIA	T2b	N0
	IIB	T1a, T1b, T1c, T2a, T2b T3	N1 N0
III	IIIA	T1a, T1b, T1c, T2a, T2b T3	N2 N1

Stades localement avancés				
III	IIIA	T4	N0, N1	M0
	IIIB	T1a, T1b, T1c, T2a, T2b T3, T4	N3 N2	M0 M0
	IIIC	T3, T4	N3	M0

Stades métastatiques				
IV	IVA	Quel que soit T	Quel que soit N	M1a, M1b
	IVB	Quel que soit T	Quel que soit N	M1c

BUT du traitement

Guérir le patient
Eviter les récidives

Obtenir une rémission
Eviter les récidives

Obtenir une rémission
Prolonger la SSP et SG
Améliorer et maintenir QOL

Stades opérables			
I	IA1	T1mi, T1a	N0
	IA2	T1b	N0
	IA3	T1c	N0
	IB	T2a	N0
II	IIA	T2b	N0
	IIB	T1a, T1b, T1c, T2a, T2b T3	N1 N0
III	IIIA	T1a, T1b, T1c, T2a, T2b T3	N2 N1

Stades localement avancés				
III	IIIA	T4	N0, N1	M0
	IIIB	T1a, T1b, T1c, T2a, T2b T3, T4	N3 N2	M0 M0
	IIIC	T3, T4	N3	M0

Stades métastatiques				
IV	IVA	Quel que soit T	Quel que soit N	M1a, M1b
	IVB	Quel que soit T	Quel que soit N	M1c

Armes thérapeutique

Chirurgie
+ Chimiothérapie
+/- Radiothérapie

CT/RT concomitante ou séquentielle

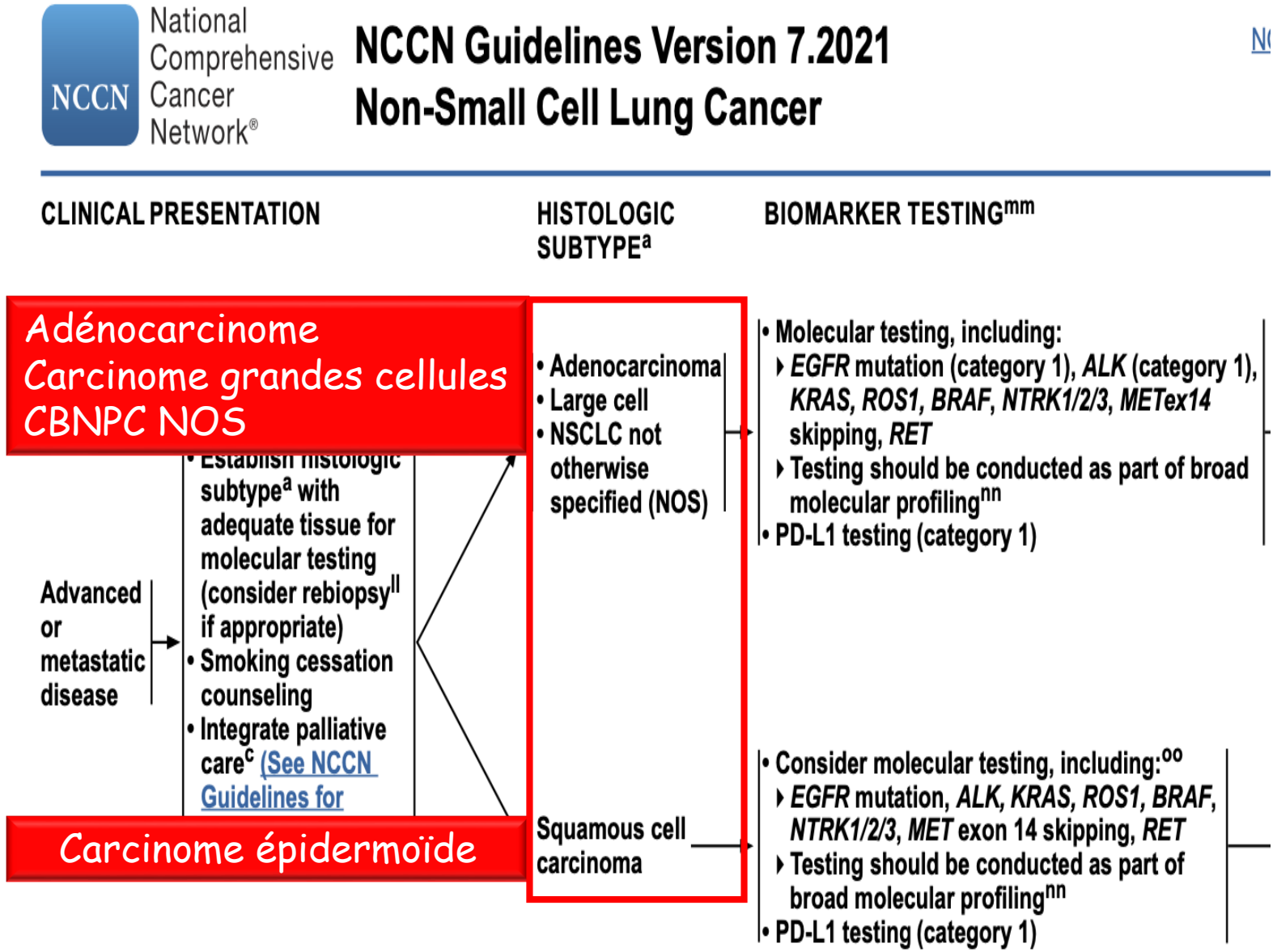
Chimiothérapie (1970)
Thérapie ciblée (2004)
Immunothérapie (2016)
Traitement symptomatique

Pré requis au traitement

3

RCP

- Age / Comorbidités.
- PS
- L'extension de la maladie (TNM)
- Le type histologique
- Les drivers moléculaires



Diagnostic Histologique

NCCN Guidelines Version 7.2021
Non-Small Cell Lung Cancer

PRINCIPLES OF PATHOLOGIC REVIEW

sification

types of NSCLC are: adenocarcinoma, squamous cell carcinoma, adenosquamous carcinoma, large cell carcinoma, and sarcomatoid carcinoma.

- **Squamous cell carcinoma: A malignant epithelial tumor that either shows keratinization and/or intercellular bridges, or a morphologically undifferentiated NSCC that expresses immunohistochemical markers of squamous cell differentiation.**
- **Adenocarcinoma:**
  - **For small (<3 cm), resected lesions, determining extent of invasion is critical.**
    - **Adenocarcinoma in situ (AIS; formerly BAC): A small (≤3 cm) localized nodule with lepidic growth, mostly non-mucinous, although mucinous types can occur. Multiple synchronous AIS tumors can also occur.**
    - **Minimally invasive adenocarcinoma (MIA): A small (≤3 cm) solitary adenocarcinoma with a predominantly lepidic pattern and ≤5 mm invasion in greatest dimension. MIA is usually non-mucinous, but rarely may be mucinous. MIA is, by definition, solitary and discrete.**
    - **Invasive adenocarcinoma: A malignant epithelial tumor with glandular differentiation, mucin production, or pneumocyte marker expression. The tumors show an acinar, papillary, micropapillary, lepidic, or solid growth pattern, with either mucin or pneumocyte marker expression. The invasive adenocarcinoma component should be present in at least one focus measuring >5 mm in greatest dimension.**
    - **Invasive adenocarcinoma variants: invasive mucinous aden adenocarcinoma.**
    - **Refer to College of American Pathologists Protocols for add**
- **Adenosquamous carcinoma: A carcinoma showing components component constituting at least 10% of the tumor. Definitive dia on findings in small biopsies, cytology, or excisional biopsies. F otherwise squamous should trigger molecular testing.**
- **Large cell carcinoma: Undifferentiated NSCC that lacks the cyto adenocarcinoma, or squamous cell carcinoma. The diagnosis re resection or cytology specimens.**
- **Sarcomatoid carcinoma is a general term that includes pleomor it is best to use the specific term for these entities whenever pos**
  - **Pleomorphic carcinoma is a poorly differentiated NSCC that c only of spindle and giant cells. Spindle cell carcinoma consis carcinoma consists almost entirely of tumor giant cells.**
  - **Carcinosarcoma is a malignant tumor that consists of a mixtu rhabdomyosarcoma, chondrosarcoma, osteosarcoma).**
  - **Pulmonary blastoma is a biphasic tumor that consists of fetal**

Classification histologique OMS 2015	
Carcinome épidermoïde	Pont d'union +/- Kératine
Adénocarcinome	Différenciation glandulaire Production mucine (BA +)
Carcinome adéno-squameux	Double composante épidermoïde et adénocarcinome avec pour chaque composante au moins 10 % de la Tumeur
Carcinome à grandes cellules	Pas de différenciation Diagnostic sur pièce opératoire
Carcinome	Pléiomorphe / carcino-sarcome /

Diagnostic Histologique

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Non-Small Cell Lung Cancer

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PRINCIPLES OF PATHOLOGIC REVIEW

Immunohistochemistry

- Judicious use of IHC is strongly recommended to preserve tissue for molecular testing, most notably in small specimens. When adenocarcinoma or squamous cell carcinomas are poorly differentiated, the defining morphologic criteria that would allow for specific diagnosis may be inconspicuous or absent. In this case, IHC or mucin staining may be necessary to determine a specific diagnosis.
- In small specimens, a limited number of immunostains with one lung adenocarcinoma marker (TTF1, napsin A) and one squamous carcinoma marker (p40, p63) should suffice for most diagnostic problems. Virtually all tumors that lack squamous cell morphology and show co-expression of p63 and TTF1 are preferably classified as adenocarcinoma. A simple panel of TTF1 and p40 may be sufficient to classify most NSCC-NOS cases.
- Testing for NUT expression by IHC should be considered in all poorly differentiated carcinomas that lack glandular differentiation or specific etiology, particularly in non-smokers or in patients presenting at a young age, for consideration of a pulmonary NUT carcinoma.
- IHC should be used to differentiate primary lung adenocarcinoma from squamous cell carcinoma, large cell carcinoma, metastatic carcinoma, and primary pleural mesothelioma (particularly for pleural specimens).
- Primary pulmonary adenocarcinoma:
  - In patients for whom the primary origin of the carcinoma is uncertain, an appropriate panel of immunohistochemical stains is recommended to assess for metastatic carcinoma to the lung.
  - TTF1 is a homeodomain-containing nuclear transcription protein of t
    embryonal and mature lung and thyroid. TTF1 immunoreactivity is se
    of non-mucinous adenocarcinoma subtypes. Metastatic adenocarcin
    thyroid malignancies, in which case thyroglobulin and PAX8 are also
    (gynecologic tract, pancreatobiliary) have been noted, and may be de
    of correlation with clinical and radiologic features.
  - Napsin A—an aspartic proteinase expressed in normal type II pneum
    expressed in >80% of lung adenocarcinomas and may be a useful adjunct to TTF1.
  - The panel of TTF1 (or alternatively napsin A) and p40 (or alternatively p63) may be useful in refining the diagnosis to either adenocarcinoma or squamous cell carcinoma in small biopsy specimens previously classified as NSCC NOS.

	C épidermoïde	Adénocarcinome
Morphologie	- Pont d'union - +/- kératine	Morphologie glandulaire Mucine (BA +)
IHC	P63 ou p40	TTF1 ou Napsin A

Pré requis au traitement

4

RCP

- Age / Comorbidités.
- PS
- L'extension de la maladie (TNM)
- Le type histologique
- Les drivers moléculaires

Stade Avancé / métastatique

Tous stades

- EGFR
- ALK
- ROS-1
- BRAF
- NTRK 1/2/3
- MET exon 14
- RET
- KRAS
- PDL-1

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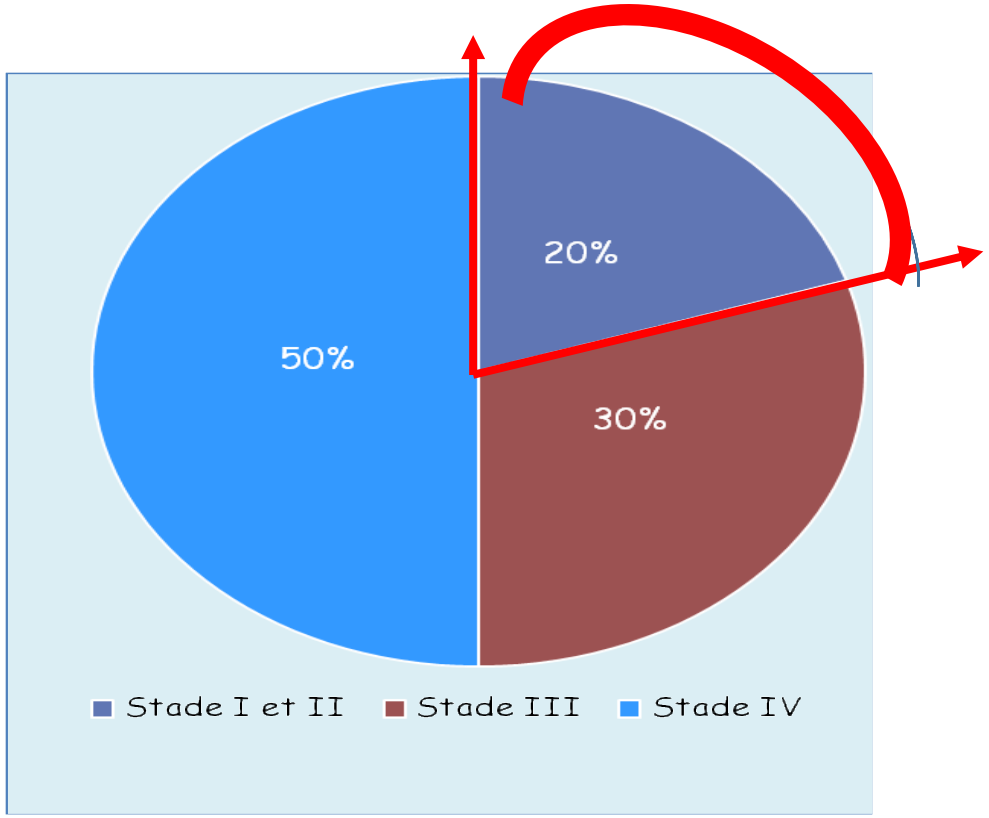
CLINICAL PRESENTATION	HISTOLOGIC SUBTYPE[a]	BIOMARKER TESTING[mm]
	• Adenocarcinoma • Large cell • NSCLC not otherwise specified (NOS)	• Molecular testing, including: ‣ *EGFR* mutation (category 1), *ALK* (category 1), *KRAS, ROS1, BRAF, NTRK1/2/3, METex14* skipping, *RET* ‣ Testing should be conducted as part of broad molecular profiling[nn] • PD-L1 testing (category 1)
	Squamous cell carcinoma	• Consider molecular testing, including:[oo] ‣ *EGFR* mutation, *ALK, KRAS, ROS1, BRAF, NTRK1/2/3, MET* exon 14 skipping, *RET* ‣ Testing should be conducted as part of broad molecular profiling[nn] • PD-L1 testing (category 1)

Stades localisés

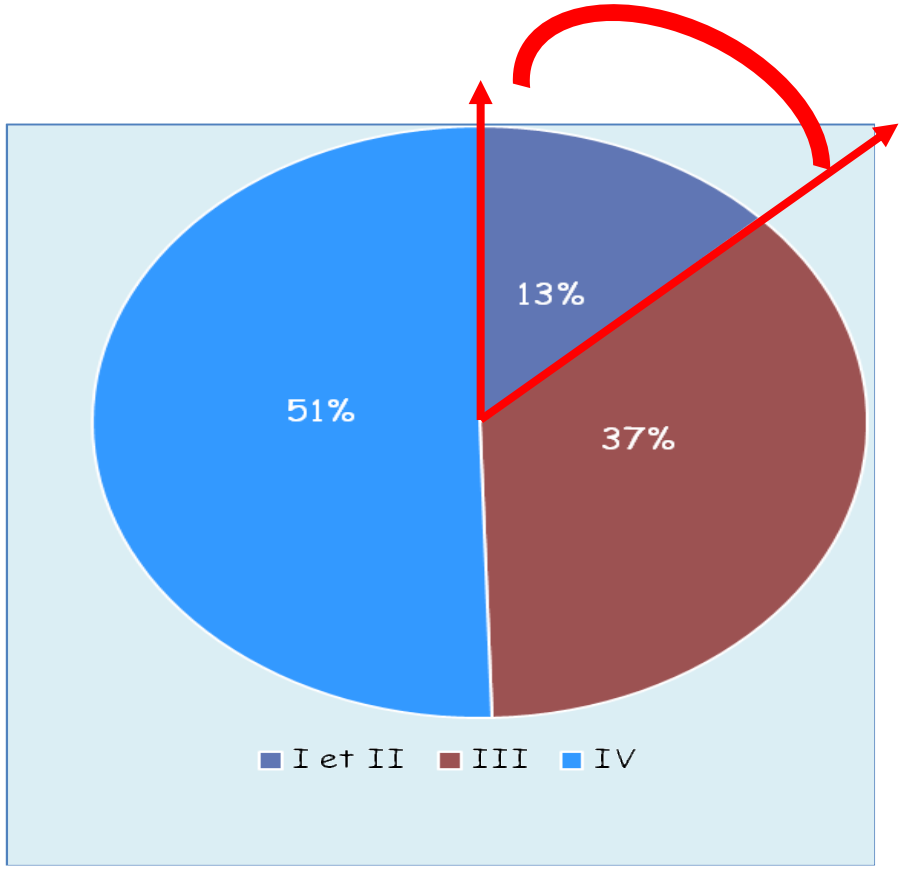
Les indispensables

Dans le monde



Fry WA, et al. Cancer. 1996;77:1949–1995

Algérie



CPMC, HDJ Oncologie médicale. 2000

Les indispensables

Stades localisés			
I	IA1	T1mi, T1a	N0
	IA2	T1b	N0
	IA3	T1c	N0
	IB	T2a	N0
II	IIA	T2b	N0
	IIB	T1a, T1b, T1c, T2a, T2b T3	N1 N0
III	IIIA	T1a, T1b, T1c, T2a, T2b T3	N2 N1

=

Stade opérable

=

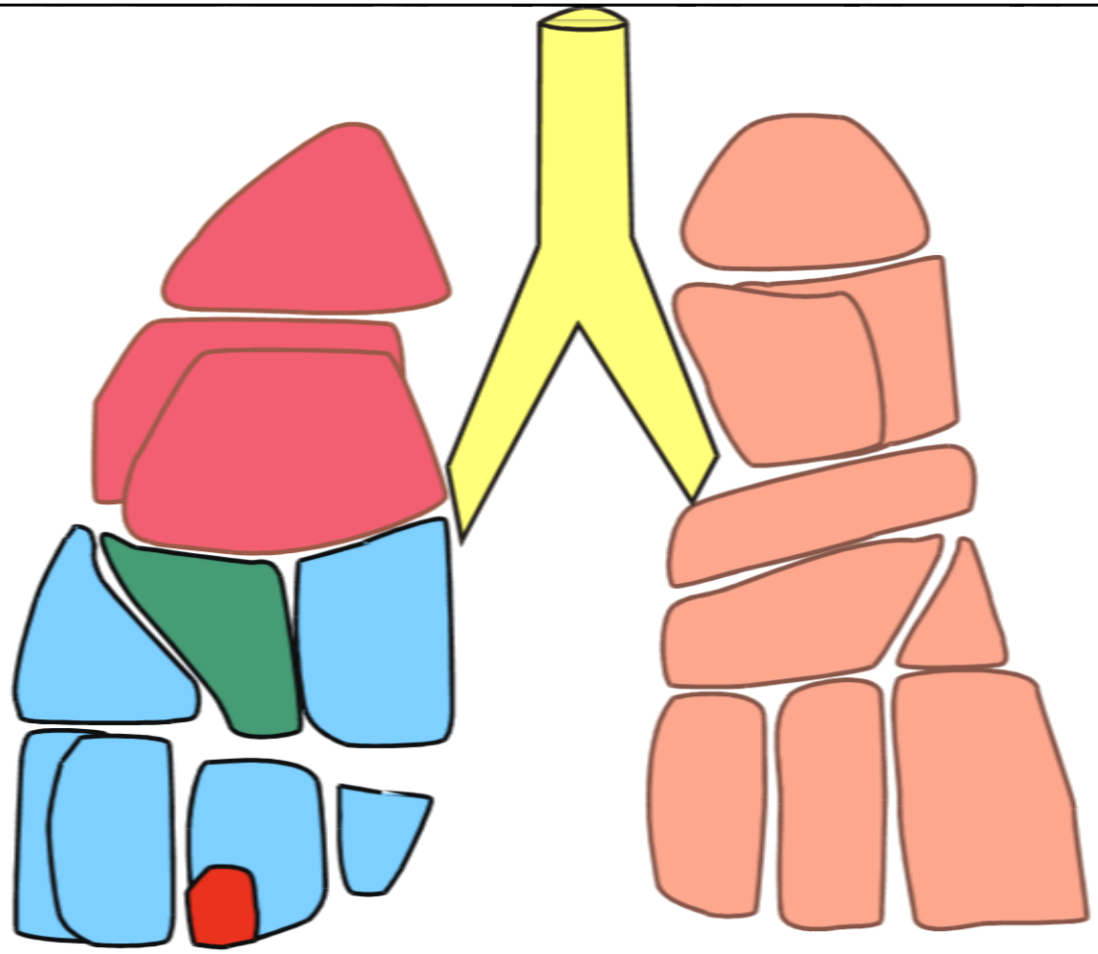
Chirurgie
+/- Chimiothérapie
+/- Radiothérapie

1

Chirurgie = 1- Résection Tumorale
2- Curage ganglionnaire

Chrurgie
=
Seul traitement curateur

- Pneumonectomie
- Lobectomie
- Segmentectomie
- Résection atypique
  Wedge résection



Résection tumorale

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Non-Small Cell Lung Cancer

PRINCIPLES OF SURGICAL TH

ation

- Determination of resectability, surgical staging, and ***pulmonary resection should b***
  cancer surgery as a prominent part of their practice.
- CT and PET/CT used for staging should be within 60 days before proceeding with s
- For medically operable disease, resection is the preferred local treatment modality
  as radiofrequency ablation, and cryotherapy). Thoracic surgical oncology consulta
  considered for curative local therapy. In cases where SABR is considered for high-
  evaluation including a radiation oncologist is recommended.
- The overall plan of treatment as well as needed imaging studies should be determi
- Thoracic surgeons should actively participate in multidisciplinary discussions and
  multidisciplinary clinic and/or tumor board).
- Patients who are active smokers should be provided counseling and smoking cess
  While active smokers have a mildly increased incidence of postoperative pulmona
  a prohibitive risk for surgery. Surgeons should not deny surgery to patients solely
  predominant therapy for patients with early-stage lung cancer.

Resection

- Anatomic pulmonary resection is preferred for the majority of patients with NSCLC
- Sublobar resection - Segmentectomy and wedge resection should achieve parench
- Sublobar resection should also sample appropriate N1 and N2 lymph node stations
  increasing the surgical risk.
- Segmentectomy (preferred) or wedge resection is appropriate in selected patients
  - Poor pulmonary reserve or other major comorbidity that contraindicates lobector
  - Peripheral nodule[1] ≤2 cm with at least one of the following:
    - ◊ Pure AIS histology
    - ◊ Nodule has ≥50% ground-glass appearance on CT
    - ◊ Radiologic surveillance confirms a long doubling time (≥400 days)
- VATS or minimally invasive surgery (including robotic-assisted approaches) shoul
  surgical contraindications, as long as there is no compromise of standard oncolog
- In high-volume centers with significant VATS experience, VATS lobectomy in selec
  decreased pain, reduced hospital length of stay, more rapid return to function, few
  outcomes.
- Lung-sparing anatomic resection (sleeve lobectomy) is preferred over pneumonec
  resection is achieved.
- T3 (invasion) and T4 local extension tumors require en-bloc resection of the involv
  is uncertain about potential complete resection, consider obtaining an additional s

Margins and Nodal Assessment (see NSCL-B 2 of 4)

[1]Peripheral is defined as the outer one third of the lung parenchyma.

Principes généraux pour une bonne chirurgie cancer bronchique

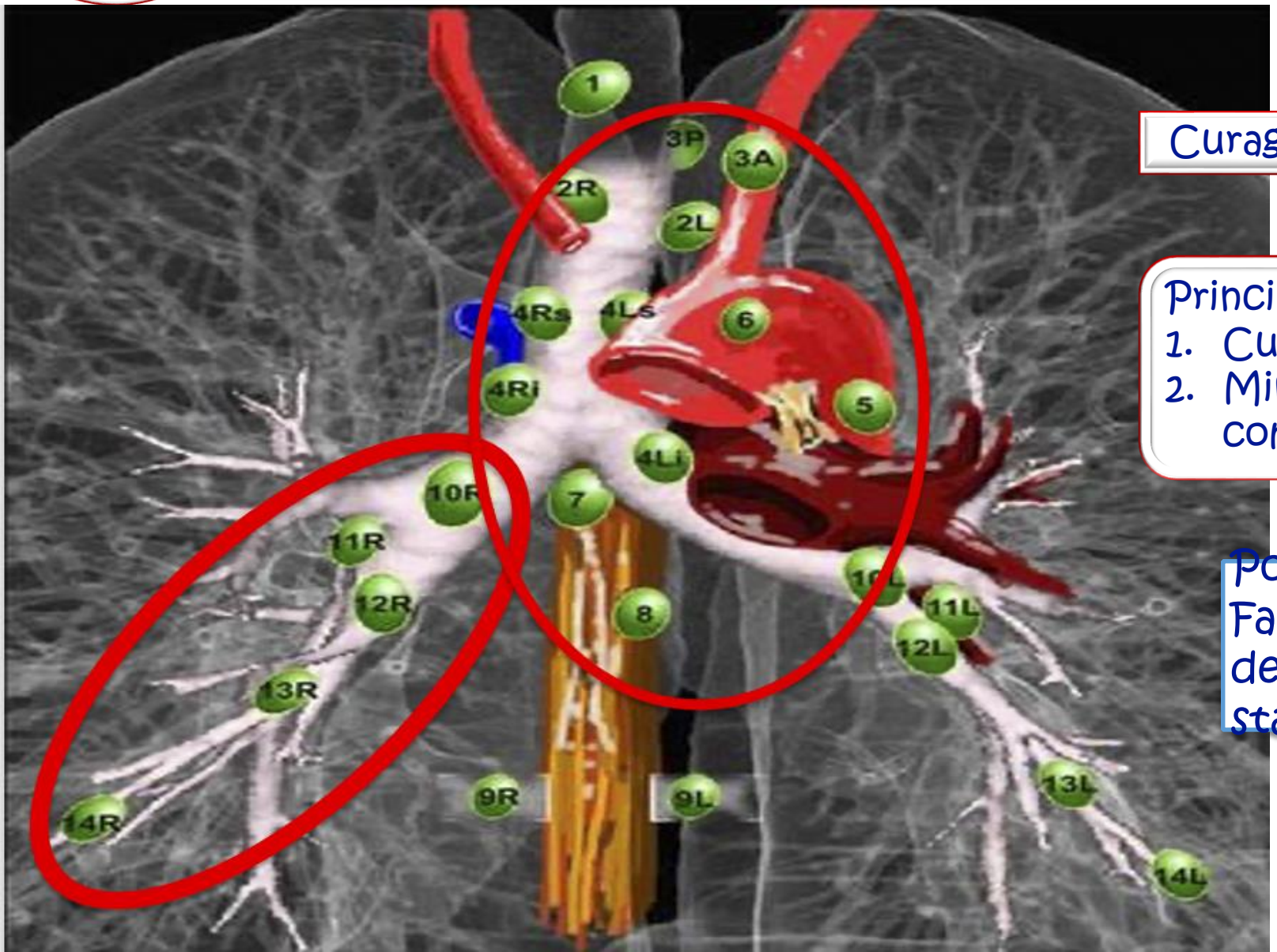
1- Chirurgien expert
2- TDM et Pet-scan ≤ 60 jours

3-Résection anatomique
4-Si résection sub-lobaire, segmentaire ou wedge ➔ marge de résection ≥ 2 cm ou ≥ taille du nodule.
5- Curage gg stations N1 et N2
6- Segmentectomie ou wedge :

- Si comorbidités et Fonction respiratoire CI lobectomie
- Si nodule périphérique ≤ 2 cm avec au moins un des éléments suivant :
  - histo = ADK in situ
  - nodule ≥ 50 % composante en verre dépoli à la TDM.
  - si surveillance radiologique confirme un temps de dédoublement ≥ 400 jours.

1

Chirurgie = 1- Résection Tumorale
2- Curage ganglionnaire



Curage ganglionnaire doit être systématique

Principe d'un bon curage gg

1. Curage N1 et N2 / routine
2. Minimum de 3 stations N2, curage gg complet.

Pour les patients No ou N1 =
Faire un prélèvement systématique de 1 à 2 ganglions de chaque station gg

Curage ganglionnaire

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mediastinal lymph node dissection did not improve survival.[348,349] Thus, systematic lymph node sampling is appropriate during pulmonary resection; one or more nodes should be sampled from all mediastinal stations. For right-sided cancers, an adequate mediastinal lymphadenectomy should include stations 2R, 4R, 7, 8, and 9. For left-sided cancers, stations 4L, 5, 6, 7, 8, and 9 should be sampled.[348] Patients should have N1 and N2 node resection and mapping (American Thoracic Society map) with a minimum of 3 N2 stations sampled or a complete lymph node dissection.[135] The lymph node map from the IASLC may be useful.[350] Formal ipsilateral mediastinal lymph node dissection is indicated for patients undergoing resection for stage IIIA (N2) disease. For patients undergoing sublobular resection, the appropriate N1 and N2 lymph node stations should be sampled unless not technically feasible because sampling would substantially increase the surgical risk.

A gauche :
- 4L para trachéaux inférieur
- 5 sous aortique
- 6 para aortique
- 7 sous carènaire
- 8 para œsophagien
- 9 ligament pulmonaire

A droite :
- 2R para trachéaux supérieur
- 4R para trachéaux inférieur
- 7 sous carènaire
- 8 para œsophagien
- 9 ligament pulmonaire

Stades localisés

ASCO 2004

Pourquoi traitement adjuvant ?

La survie a long terme des patients ayant bénéficie d'une chirurgie est décevante du fait de **rechutes soit locale ou à distance**

TNM	Survie a 5 ans % cTNM	Survie a 5 ans % pTNM	Récidive locale %	Récidive a distance %
IA = T1a, b No Mo	50	73	10	15
IB = T2a No Mo	43	58	10	30
IIA = T1a, b N1 Mo T2 N1 Mo	36	46		
IIB = T2b N1 Mo T3 No Mo	25 22	36 38	12	40
IIIA = T1, 2 N2 Mo T3 N1 N2 Mo	19	24 25	15	60

Pour améliorer ces résultats et éviter les récidives locale et à distance, l'idée est née d'associer un traitement adjuvant par CT et/ou RT.

Stades localisés

But du traitement adjuvant

Eviter les récidives à distance ⟺ Chimiothérapie

Eviter les récidives locales ⟺ Radiothérapie

Stades localisés

Essais	n	Stades	Médiane de survie Contrôle	Médiane de survie Experimental	Survie a 5 ans Contrôle	Survie a 5 ans Experimental	p
Intergroupe 0115	488	II, IIIA	37,9	38,8	33	39	0.56
Big Lung Trial	381	I, II, IIIA	24,7	27	-	-	NS
ALPI-EORTC	1209	I, II, IIIA	48	55,2	-	-	0,58
IALT	1867	I, II, IIIA	44,4	50,8	40,4	44,5	< 0,03
UFT	999	I					
Intergroupe JBR10	482	IB, II	73	94	54	69	0,009
CALBG 9633	344	IB	78	95	57	59	0,37
ANITA	840	IB, II, IIIA	43,7	65,7	42,6	51,2	0,017
Rosell et al	140	IB	41,6	94,8	30	78	0,003

Stades localisés

CT adjuvante Stade I

- Pour les tumeurs stade IA = aucun bénéfice n'est démontré
- Pour les tumeurs stade IB =

➔ Deux études de sous groupes (ANITA et Intergroupe JBR 10) ne démontrent pas de bénéfice.

➔ La méta-analyse LACE montre une tendance au bénéfice mais qui est non significative.

➔ L'étude CALGB 9633 montre un bénéfice pour les tumeurs de 4 cm

Ces résultats ne sont pas suffisant pour faire une CT adjuvante dans les tumeurs stade IB.

Mais il semble être raisonnable de la proposer pour les **tumeurs de plus de 4 cm**

Stades localisés

CT adjuvante
Stade II IIIA

Plusieurs essais sont franchement positive et montrent un bénéfice absolu en terme de survie à 5 ans variant entre 4 à 15 % avec les CT à base de platine

- Etude IALT (I II et III, CT avec CDDP)
  Bénéfice de survie à 5 ans de 4,1 %
- Etude NCIC JBR 10 (IB et II, CDDP + VNR)
  Gain de survie à 5 ans de 15 %

  Etude CALGB 9633 (IB, Carbo + TXL)
  Gain de survie à 4 ans de 12 %
- Essai ANITA
  SM 43,7 mois -------- 65, 7 mois (CDDP VNR)

Deux grandes méta-analyses :
- Medical research Council portant sur 8147 patients , 30 essais
- Lung Adjuvant Cisplatin Evaluation LACE portant sur 4584 patients, 5 essais

Confirme ce bénéfice en survie entre de 4 à 5,3 % en faveur du bras CT adjuvante

Mais ce gain de survie, concerne essentiellement les stades qui s'accompagnent d'une extension ganglionnaire stade II et IIIA

RT adjuvante

Stades localisés

- Le risque de **récidive locorégionale** est compris entre 15 à 40 % selon les stades
- D'où l'intérêt de la radiothérapie adjuvante
- De nombreuses études randomises ont évalué cette option.
- La méta-analyse PORT a montré que la RT adjuvante bien qu'elle diminue le risque de récidive locale de prés de 25 %, a un effet défavorable sur la survie globale.
- Cet effet défavorable était plus prononcé en cas de tumeur de stade I II et N0 N 1.

RT adjuvante

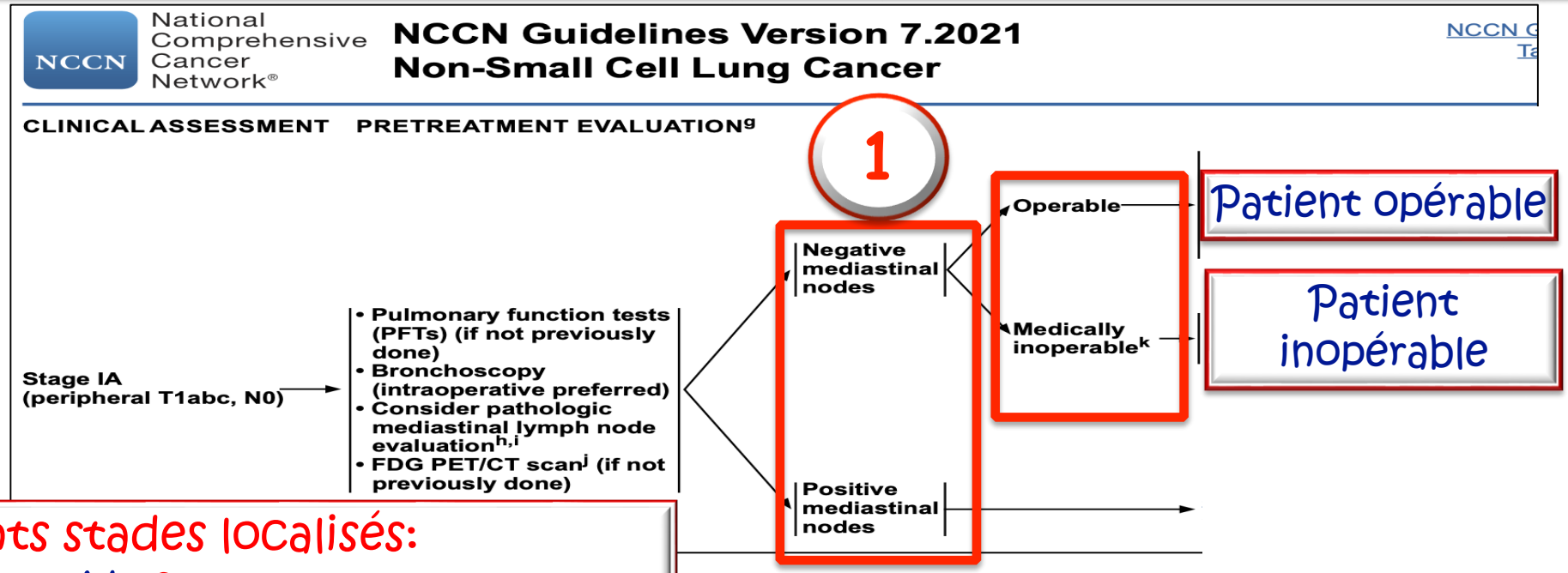
Stades localisés

- Pas d'indication de radiothérapie adjuvante (post-opératoire) pour les N0 et N1.

- RT adjuvante post-opératoire pour les stades IIIA N2 :
  - ➔ Diminue le risque de rechute locale.
  - ➔ mais pas d'amélioration de la survie.

Mais…

Stades localisés

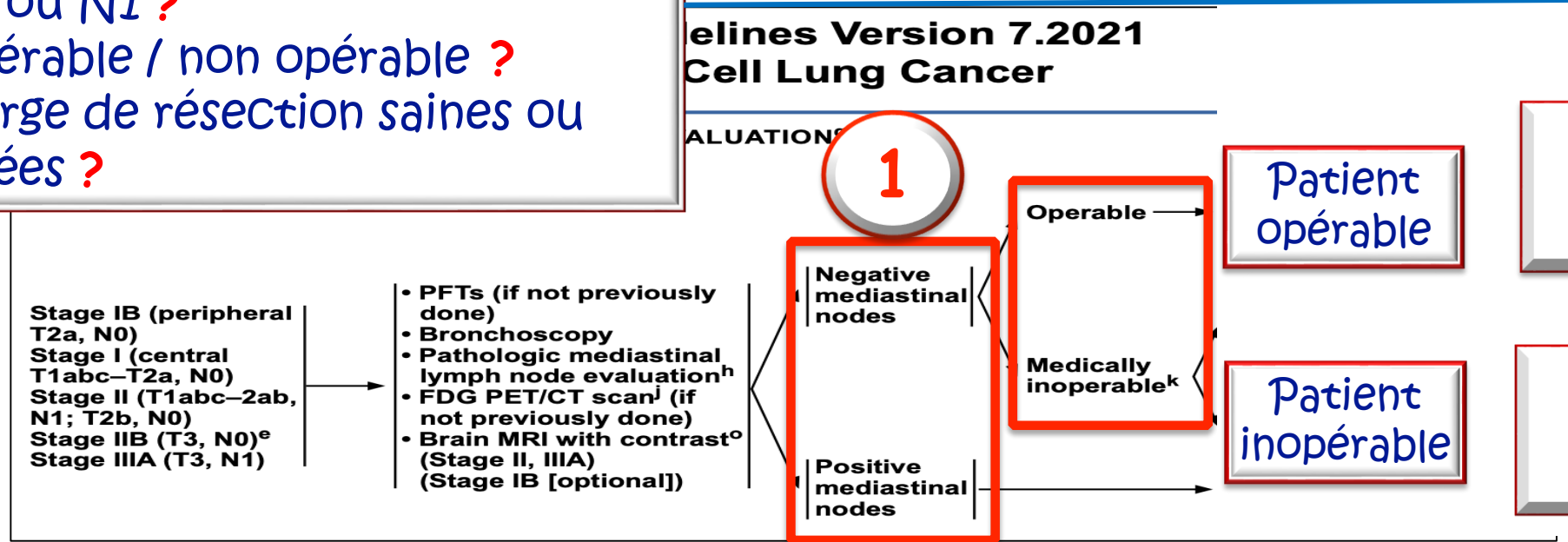


Patient opérable

Patient inopérable

Résection tumorale
+ curage gg
Radiothérapie

Patients stades localisés:
1- No ou N1 ?
2- Opérable / non opérable ?
3- Marge de résection saines ou infiltrées ?



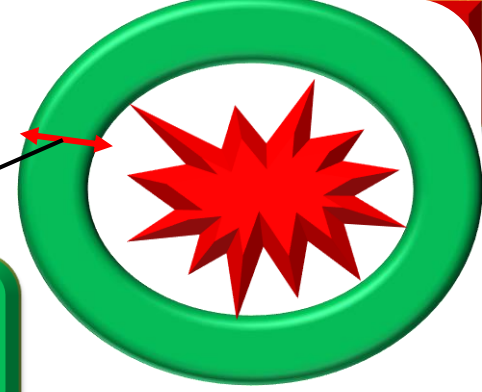
Patient opérable

Patient inopérable

Résection tumorale
+ curage gg
Suivi de CT adjuvante

No = RT suivi CT adj
Haut risque Ib-IIB
N1 = RTCT suivi
Durvalumab

Stades localisés



Marges négative =
Surveillance ou traitement adjuvant

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FINDINGS AT SURGERY — **ADJUVA**

- **Stage IA (T1abc, N0)**
  - Margins negative (R0)[v] → Observe
  - Margins positive (R1, R2)[v] → Reresection (preferred) or RT[l] (category 2B)
- **Stage IB (T2a, N0)** / **Stage IIA (T2b, N0)**
  - Margins negative (R0)[v] → Observe or Chemotherapy[r] for high-risk patients[s] and atezolizumab[r,w] (Stage IIA) or osimertinib[r,x]
  - Margins positive (R1, R2)[v] → Reresection (preferred) ± chemotherapy[r,y] or RT[l] ± chemotherapy[r] (chemotherapy for stage IIA)
- **Stage IIB (T1abc–T2a, N1)** / **Stage IIB (T3, N0; T2b, N1)**
  - Margins negative (R0)[v] → Chemotherapy[r] (category 1) and atezolizumab[r,w] or osimertinib[r,x]
  - Margins positive
    - R1[v] → Reresection + chemotherapy[r] or Chemoradiation[l] (sequential[r] or concurrent[t])
    - R2[v] → Reresection + chemotherapy[r] or Concurrent chemoradiation[l,t]
- **Stage IIIA (T1–2, N2; T3, N1)** / **Stage IIIB (T3, N2)**
  - Margins negative (R0)[v] → Chemotherapy[r] (category 1) and atezolizumab[r,w] or osimertinib[r,x] or Sequential chemotherapy[r] + RT[l] (N2 only)
  - Margins positive
    - R1[v] → Chemoradiation[l] (sequential[r] or concurrent[t])
    - R2[v] → Concurrent chemoradiation[l,t]

R0 = Pas de résidu tumoral
R1 = Résidu tumoral microscopique
R1 = Résidu tumoral macroscopique

R1 = Reprise Xie +/- CT
R2 = Reprise chirurgicale ou RT-CT concomitante / séquentielle

Stades localisés

National Comprehensive Cancer Network

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- T > 4 cm
- T peu differenciee
- Invasion vasculaire
- Wedge resection
- Atteinte plèvre viscerale
- Statut ganglionnaire Nx

FINDINGS AT SURGERY		ADJUVANT TREATMENT	
Stage IA (T1abc, N0) T1a ≤ 1 cm T1b > 1 ≤ 2 cm T1b > 2 ≤ 3 cm	Margins negative (R0)[v]	Observe	Surveillance
	Margins positive (R1, R2)[v]	Reresection (preferred) or RT[l] (category 2B)	Xie ou RT
Stage IB (T2a, N0) Stage IIA (T2b, N0) T2a > 3 ≤ 4 cm T1b > 4 ≤ 5 cm	Margins negative (R0)[v]	Observe or Chemotherapy[r] for high-risk patients[s] and atezolizumab[r,w] (Stage IIA) or osimertinib[r,x]	Surveillance CT si F risque + Atezolizumab ou Osimertinib
	Margins positive (R1, R2)[v]	Reresection (preferred) ± chemotherapy[r,y] or RT[l] ± chemotherapy[r] (chemotherapy for stage IIA)	Xie +/-CT RT +/-CT
Stage IIB (T1abc–T2a, N1) Stage IIB (T3, N0; T2b, N1) T3 > 5 ≤ 7 cm	Margins negative (R0)[v]	Chemotherapy[r] (category 1) and atezolizumab[r,w] or osimertinib[r,x]	CT + Atezo ou Osimertinib
	Margins positive, R1[v]	Reresection + chemotherapy[r] or Chemoradiation[l] (sequential[r] or concurrent[t])	RT + CT RT-CT sequentielle ou concomitante
	Margins positive, R2[v]	Reresection + chemotherapy[r] or Concurrent chemoradiation[l,t]	Xie + CT RT-CT concomitante

Essai ADAURA

Phase III en adjuvant chez les patients atteints de CBNPC EGFR muté

Patients atteints d'un CBNPC réséqué de stade IB, II, IIIA, ayant reçu ou non une chimiothérapie adjuvante

- Âge ≥ 18 ans (Japon/Taïwan : ≥ 20 ans)
- Performance OMS status : 0/1
- CBNPC non épidermoïde avec del exon 19/L858R
- Imagerie cérébrale, si non réalisée en préopératoire
- Résection complète avec marges négatives
- Délai maximal entre la chirurgie et la randomisation
  - 10 semaines sans chimiothérapie adjuvante
  - 26 semaines si chimiothérapie adjuvante

Schéma de l'étude

Stratification :
stade (IB vs II vs IIIA)
EGFRm (del exon 19 vs L858R)
Ethnie : Asiatiques vs non-Asiatiques

Randomisation 1:1 (n = 682)

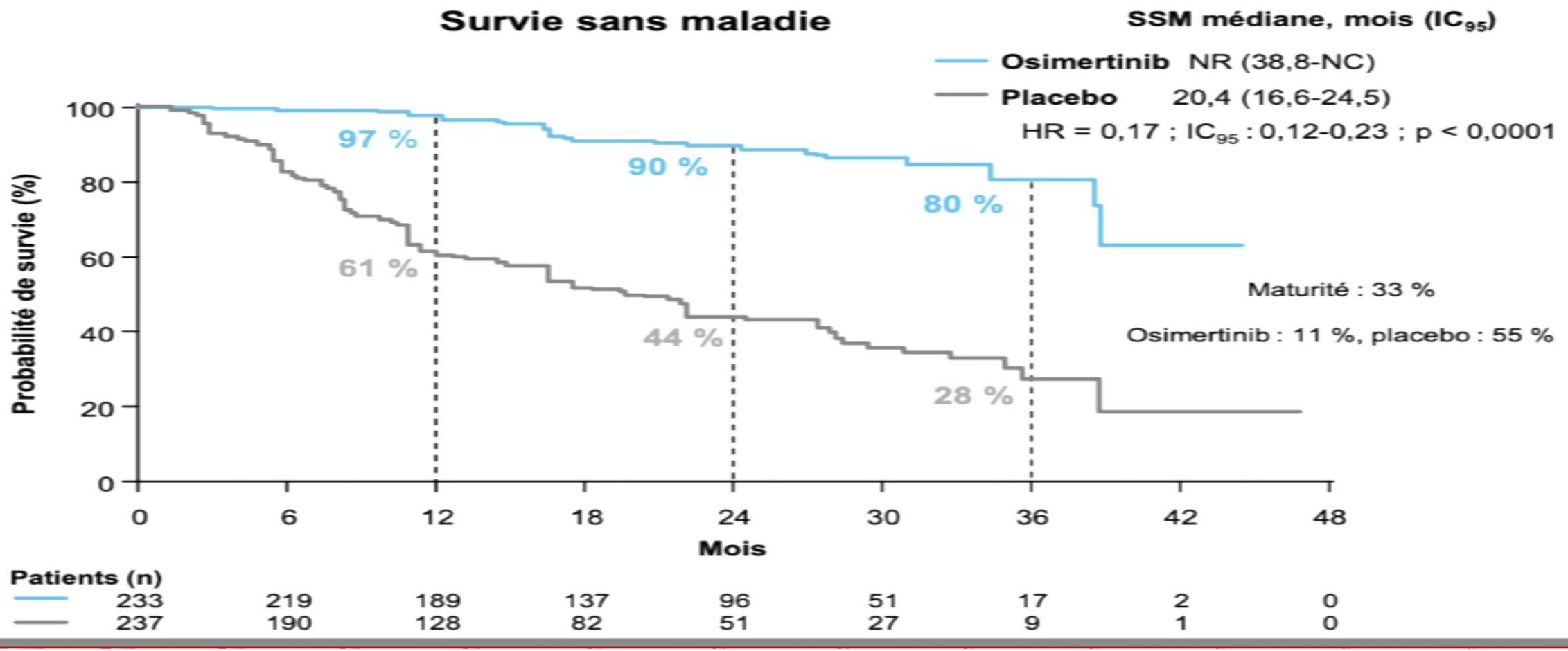
- **Osimertinib** 80 mg/j
- **Placebo** 1/j

- Plan de durée de traitement : 3 ans
- Traitement poursuivi jusqu'à :
  - rechute de la maladie
  - fin du traitement
  - arrêt selon critères de l'étude
- **Suivi :**
  - jusqu'à rechute : S12 et S24, puis toutes les 24 semaines pendant 5 ans, puis tous les ans
  - après la rechute : toutes les 24 semaines pendant 5 ans, puis tous les ans

- **Critères d'évaluation**
  - Principal : survie sans maladie (SSM), évaluée par les investigateurs, chez les patients de stade II-IIIA
  - Secondaires : SSM dans la population globale, taux de SSM à 2, 3, 4 et 5 ans, SG, tolérance, qualité de vie
  - **Levée de l'aveugle du fait de l'efficacité observée, réalisée après les recommandations de l'IDMC ; analyse non planifiée**
  - **Au moment de la levée d'aveugle, tous les patients avaient été inclus et suivis pendant au moins 1 an**

L'essai randomisé de phase III ADAURA a randomisé 682 patients opérés d'un CBNPC de stade IB à IIIA, avec mutation activatrice de l'EGFR L858R ou délétion dans l'exon 19.
L'étude comparait un groupe traité par un placebo et un traitement de 3 ans maximum par osimertinib (80 mg/j).

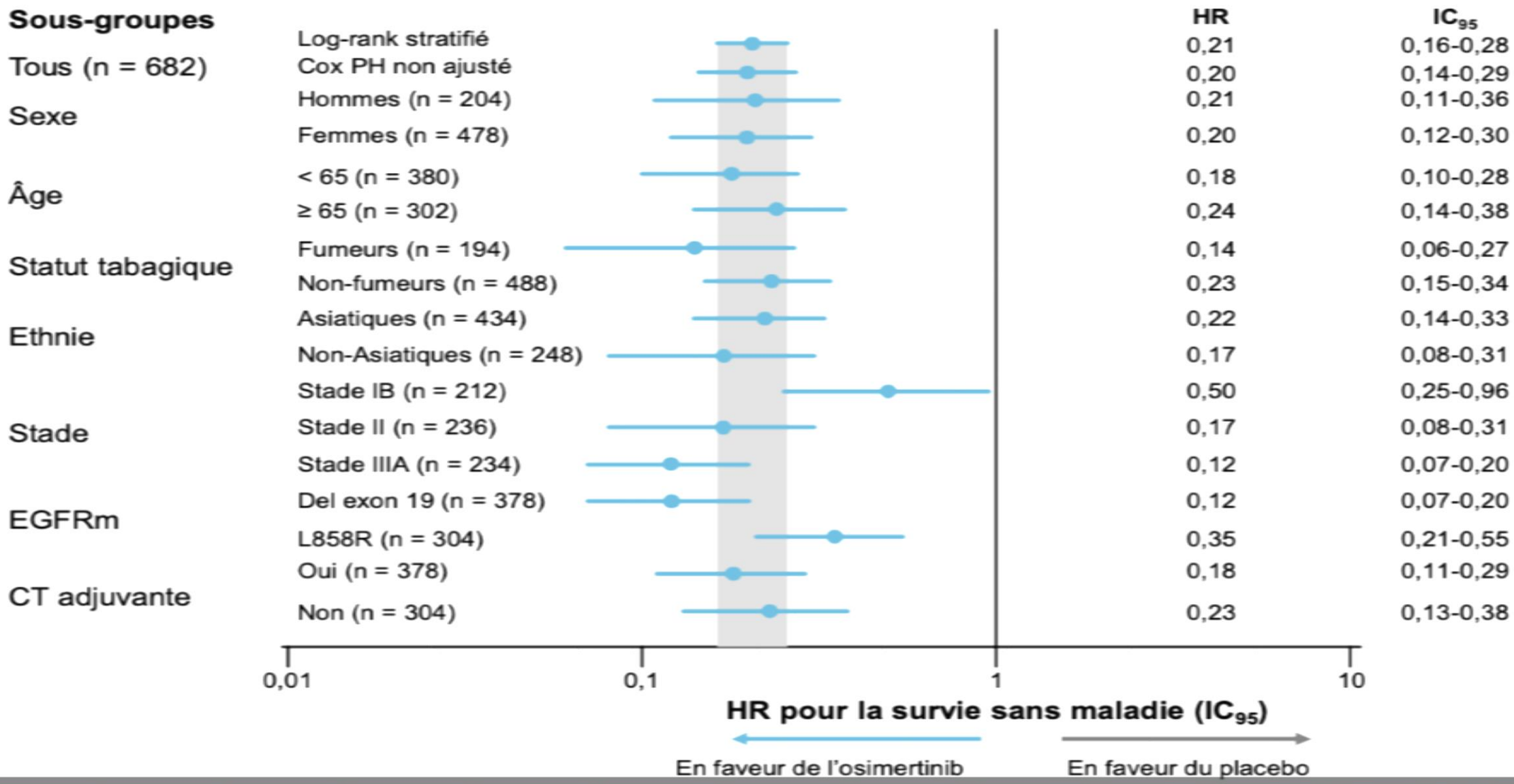
Essai ADAURA



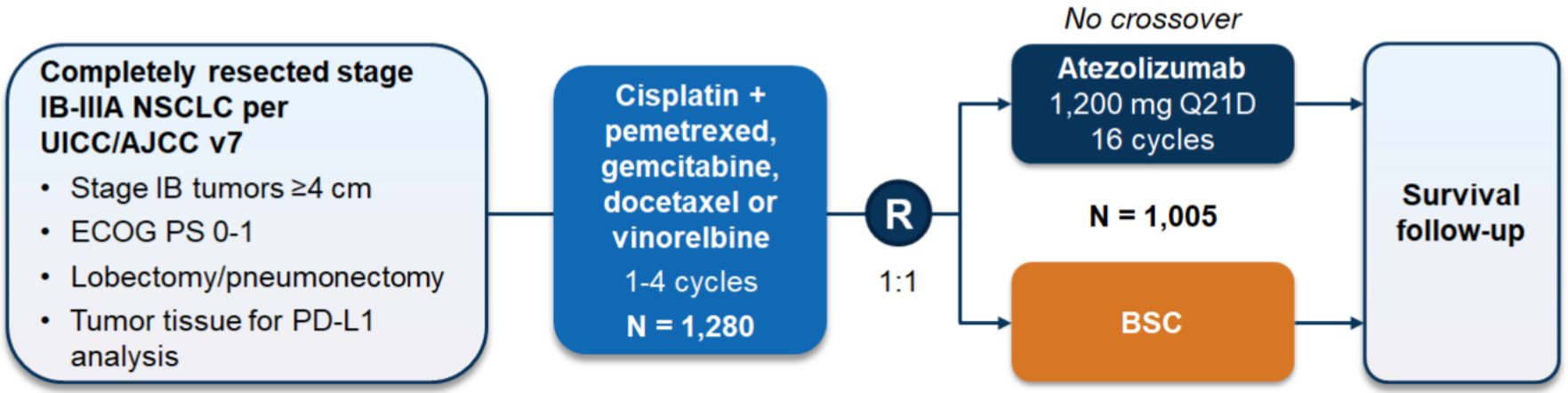
Les résultats montrent un bénéfice majeur de l'osimertinib, avec une réduction du risque de récidive pour les tumeurs de stades II et IIIA de 83 % par rapport au placebo (HR = 0,17 ; IC95 : 0,12-0,23 ; p < 0,0001).

Ce niveau de bénéfice est l'un des plus élevés rapportés en oncologie thoracique ; la survie sans récidive à 2 ans était de 90 % avec l'osimertinib et de 44 % avec le placebo

Essai ADAURA



Phase 3 IMpower010 Study: Schema[1]



Stratification factors

- Sex
- Stage (IB vs II vs IIIA)
- Histology
- PD-L1 tumor expression status[a]: TC2/3 and any IC vs TC0/1 and IC2/3 vs TC0/1 and IC0/1

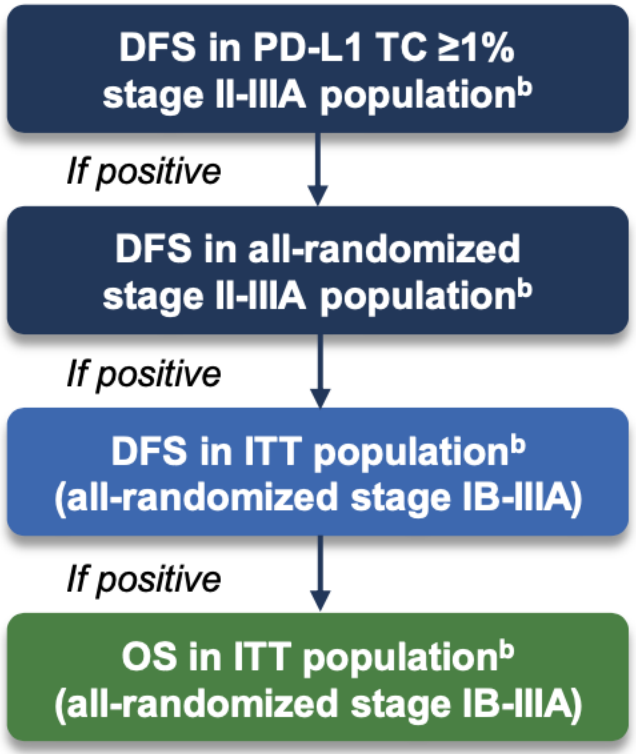
Primary endpoints

- Investigator-assessed DFS tested hierarchically:
  - PD-L1, TC ≥1% (per SP263) stage II-IIIA population
  - All-randomized stage II-IIIA population
  - ITT population (stage IB-IIIA)

Exploratory endpoints

- OS in ITT population
- DFS in PD-L1 TC ≥50% (per SP263) stage II-IIIA population
- 3-year and 5-year DFS in all 3 populations

Hierarchical statistical testing



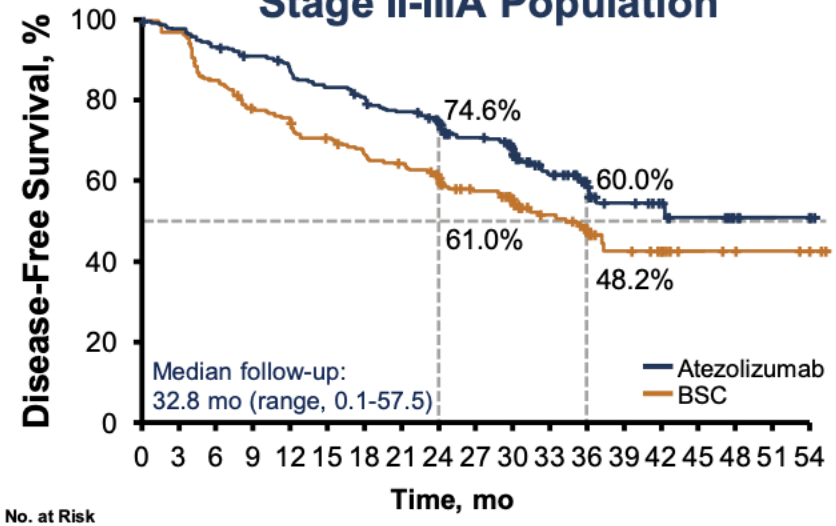
- Endpoint was met at DFS IA
- Endpoint was not met at DFS IA, and follow-up is ongoing
- OS data were immature, and endpoint was not formally tested

Both arms included observation and regular scans for disease recurrence on the same schedule. [a] Per SP142 assay. [B] Two-sided α = .05.

1. Wakelee HA et al. ASCO 2021. Abstract 8500.

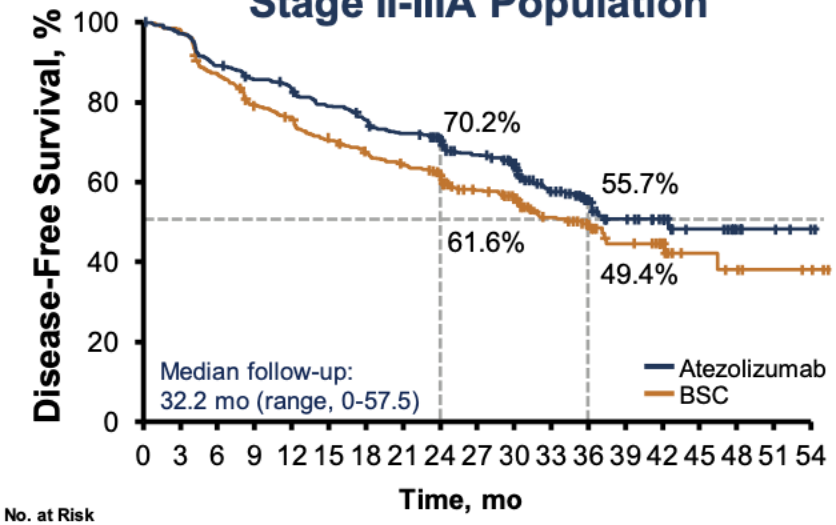
IMpower010: DFS in PD-L1 TC ≥1%[a] Stage II-IIIA, All-Randomized, Stage II-IIIA, and ITT Populations[1]

PD-L1 TC ≥1% Stage II-IIIA Population



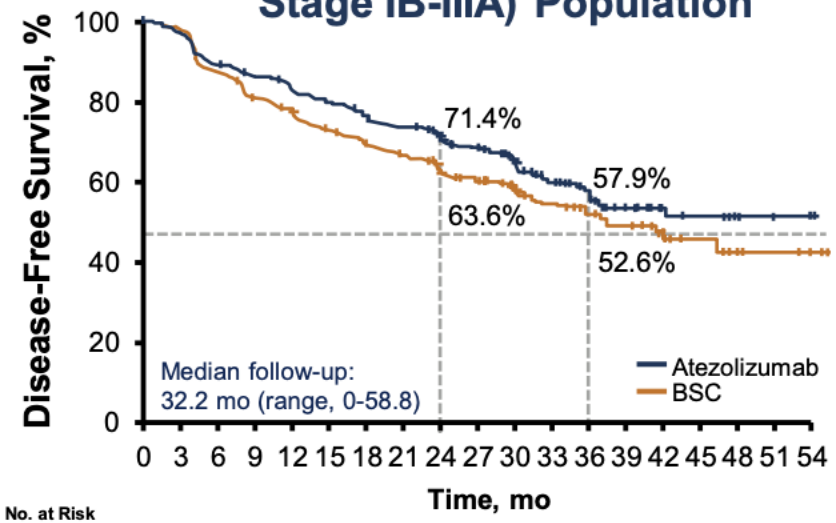
No. at Risk																			
Atezolizumab	248	235	225	217	206	198	190	181	159	134	111	76	54	31	22	12	8	3	3
BSC	228	212	186	169	160	151	142	135	117	97	80	59	38	21	14	7	6	4	3

All-Randomized Stage II-IIIA Population



No. at Risk																			
Atezolizumab	442	418	384	367	352	337	319	305	269	225	185	120	84	48	34	16	11	5	3
BSC	440	412	366	331	314	292	277	263	230	182	146	102	71	35	22	10	8	4	3

ITT (Randomized Stage IB-IIIA) Population



No. at Risk																			
Atezolizumab	507	478	437	418	403	387	367	353	306	257	212	139	97	53	38	19	14	8	4
BSC	498	467	418	383	365	342	324	309	269	219	173	122	90	46	30	13	10	5	4

	Atezolizumab (n = 248)	BSC (n = 228)
Median DFS (95% CI), mo	NE (36.1,NE)	35.3 (29.0,NE)
Stratified HR (95% CI)	0.66 (0.50, 0.88)	
P[b]	.004[c]	

	Atezolizumab (n = 442)	BSC (n = 440)
Median DFS (95% CI), mo	42.3 (36.0, NE)	35.3 (30.4, 46.4)
Stratified HR (95% CI)	0.79 (0.64, 0.96)	
P[b]	.02[c]	

	Atezolizumab (n = 507)	BSC (n = 498)
Median DFS (95% CI), mo	NE (36.1, NE)	37.2 (31.6, NE)
Stratified HR (95% CI)	0.81 (0.67, 0.99)	
P[b]	.04[d]	

Clinical cutoff: 21 January 2021. [a] Per SP263 assay. [b] Stratified log-rank. [c] Crossed the significance boundary for DFS.
[d] The statistical significance boundary for DFS was not crossed.

1. Wakelee HA et al. ASCO 2021. Abstract 8500.

FDA Approval

On October 15, 2021, the FDA approved atezolizumab for adjuvant treatment following resection and platinum-based chemotherapy in patients with stage II to IIIA NSCLC whose tumors have PD-L1 expression on ≥ 1% of tumor cells, as determined by an FDA-approved test

The FDA also approved the VENTANA PD-L1 (SP263) Assay as a companion diagnostic device to select patients with NSCLC for adjuvant treatment with atezolizumab

National Comprehensive Cancer Network®

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Non-Small Cell Lung Cancer

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Discussion

SYSTEMIC THERAPY REGIMENS FOR NEOADJUVANT AND ADJUVANT THERAPY

Preferred (nonsquamous)
- Cisplatin 75 mg/m² day 1, pemetrexed 500 mg/m² day 1 every 21 days for 4 cycles[1]

Preferred (squamous)
- Cisplatin 75 mg/m² day 1; gemcitabine 1250 mg/m² days 1 and 8, every 21 days for 4 cycles[2]
- Cisplatin 75 mg/m² day 1; docetaxel 75 mg/m² day 1 every 21 days for 4 cycles[3]

Other Recommended
- Cisplatin 50 mg/m² days 1 and 8; vinorelbine 25 mg/m² days 1, 8, 15, and 22, every 28 days for 4 cycles[4]
- Cisplatin 100 mg/m² day 1; vinorelbine 30 mg/m² days 1, 8, 15, and 22, every 28 days for 4 cycles[5,6]
- Cisplatin 75–80 mg/m² day 1; vinorelbine 25–30 mg/m² days 1 and 8, every 21 days for 4 cycles
- Cisplatin 100 mg/m² day 1; etoposide 100 mg/m² days 1–3, every 28 days for 4 cycles[5]

Useful in Certain Circumstances

Chemotherapy Regimens for Patients with Comorbidities or Patients Not Able to Tolerate Cisplatin
- Carboplatin AUC 6 day 1, paclitaxel 200 mg/m² day 1, every 21 days for 4 cycles[7]
- Carboplatin AUC 5 day 1, gemcitabine 1000 mg/m² days 1 and 8, every 21 days for 4 cycles[8]
- Carboplatin AUC 5 day 1, pemetrexed 500 mg/m² day 1 for nonsquamous every 21 days for 4 cycles[9]

All chemotherapy regimens listed above can be used for sequential chemotherapy/RT.

Protocole de chimiothérapie :
PS 0, 1 = platine + drogue 3eme génération (GMZ, VNB, TXT, PMT) ou VP16
PS = 2 ➔ Carboplatine + Paclitaxel / GMZ / PMT

Nombre de cure = 4
Délai entre 4eme semaine et 8eme semaine post chirurgie

Previous Adjuvant Chemotherapy
- Osimertinib 80 mg daily[10]
  - Osimertinib for patients with completely resected stage IIB-IIIA or high risk stage IB-IIA *EGFR* mutation-positive NSCLC who received previous adjuvant chemotherapy or are ineligible to receive platinum-based chemotherapy.
- Atezolizumab 840 mg every 2 weeks, 1200 mg every 3 weeks, or 1680 mg every 4 weeks for up to 1 year[11]
  - Atezolizumab for patients with completely resected stage IIB-IIIA or high risk stage IIA PD-L1 ≥1% NSCLC who received previous adjuvant chemotherapy.

Au total

Stades localisés			
I	IA1	T1mi, T1a < 1 cm	N0
	IA2	T1b > 1 cm ≤ 2 cm	N0
	IA3	T1c > 2 cm ≤ 3 cm	N0
	IB	T2a > 3 cm ≤ 4 cm	N0
II	IIA	T2b > 4 cm ≤ 5 cm	N0
	IIB	T1a, T1b, T1c, T2a, T2b T3	N1 N0
III	IIIA	T1a, T1b, T1c, T2a, T2b T3	N2 N1

- T > 4 cm
- T peu differenciee
- Invasion vasculaire
- Wedge resection
- Atteinte plèvre viscerale
- Statut ganglionnaire Nx

Chirurgie

Chirurgie +
R0 = CT adjuvante si F risque /osimertinib ou Atézo
R1-R2 = Reresection + CT
ou RT + CT

Chirurgie
R0 = CT adjuvante /osimertinib ou Atézolizumab
ou RT-CT séquentielle
R1 = re resection + CT
Ou RT-CT séquentielle ou concomitante
R2 = re resection + CT
RT + CT concomitante.

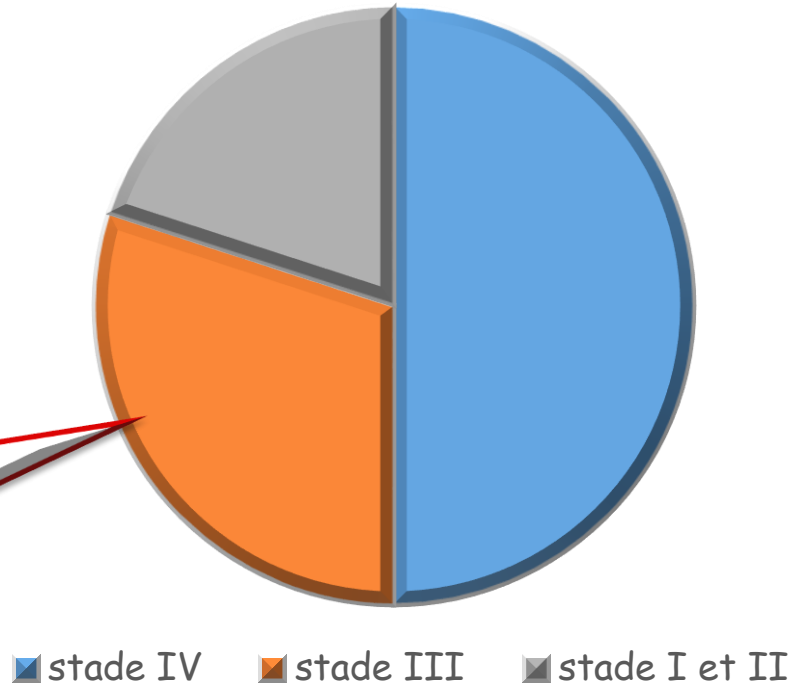
Chirurgie
R0 = CT adjuvante /osimertinib ou Atézolizumab
ou RT-CT séquentielle (N2)
R1 = RT-CT séquentielle ou concomitante
R2 = RT + CT concomitante.

Stades localement avancés

Les indispensables

Stades localement avancés

Groupe de patients très hétérogène avec un pronostic très variable



30 % des patients sont au stade localement avancé IIIA N2, IIIB, IIIC

60 à 70 % des patients décèdent de rechute métastatique

Les indispensables

Stades localement avancés

Stades localement avancés				
III	IIIA	T4	N0 N1	M0
	IIIB	T1a, T1b, T1c, T2a,T2b T3, T4	N3 N2	M0 M0
	IIIC	T3, T4	N3	M0

=

Radio-chimiothérapie concomitante

Stades localement avancés

Objectif du traitement

Obtenir le contrôle locale de la maladie ⟺ **Radiothérapie**

Prévenir l'évolution métastatique en contrôlant la maladie micro métastatique ⟺ **Chimiothérapie**

Stades localisés

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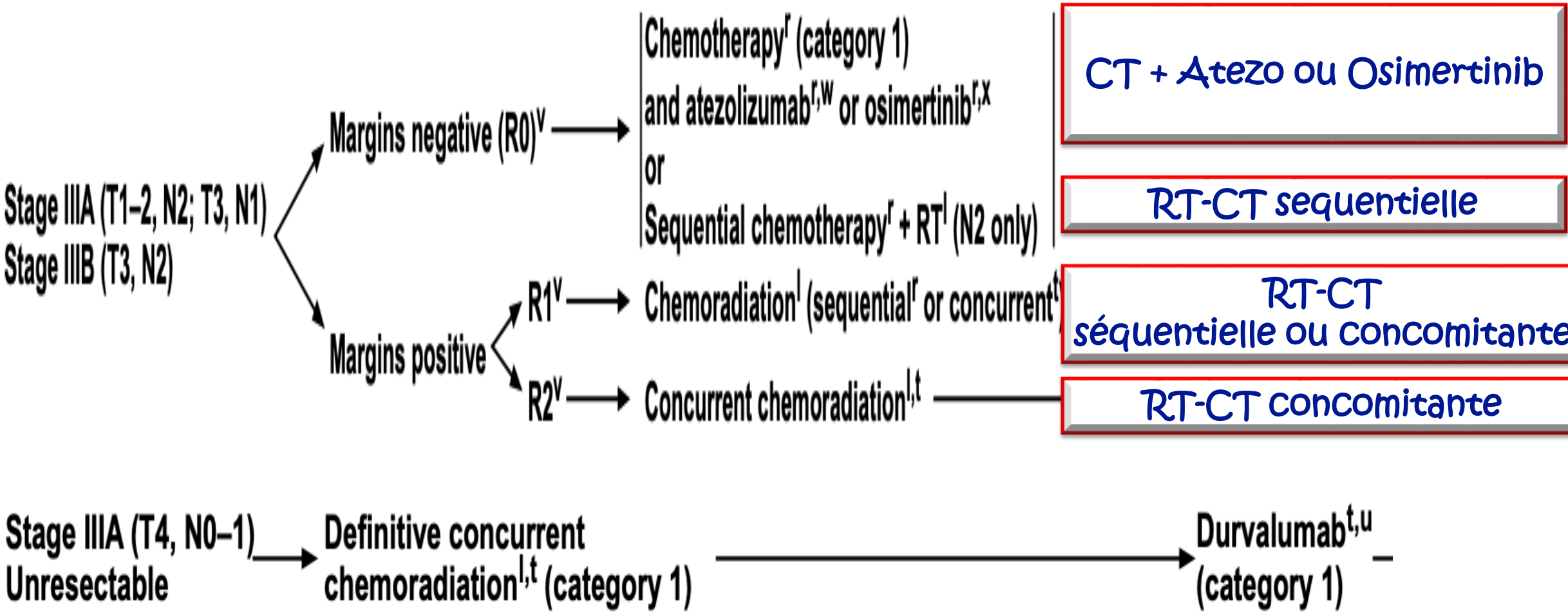
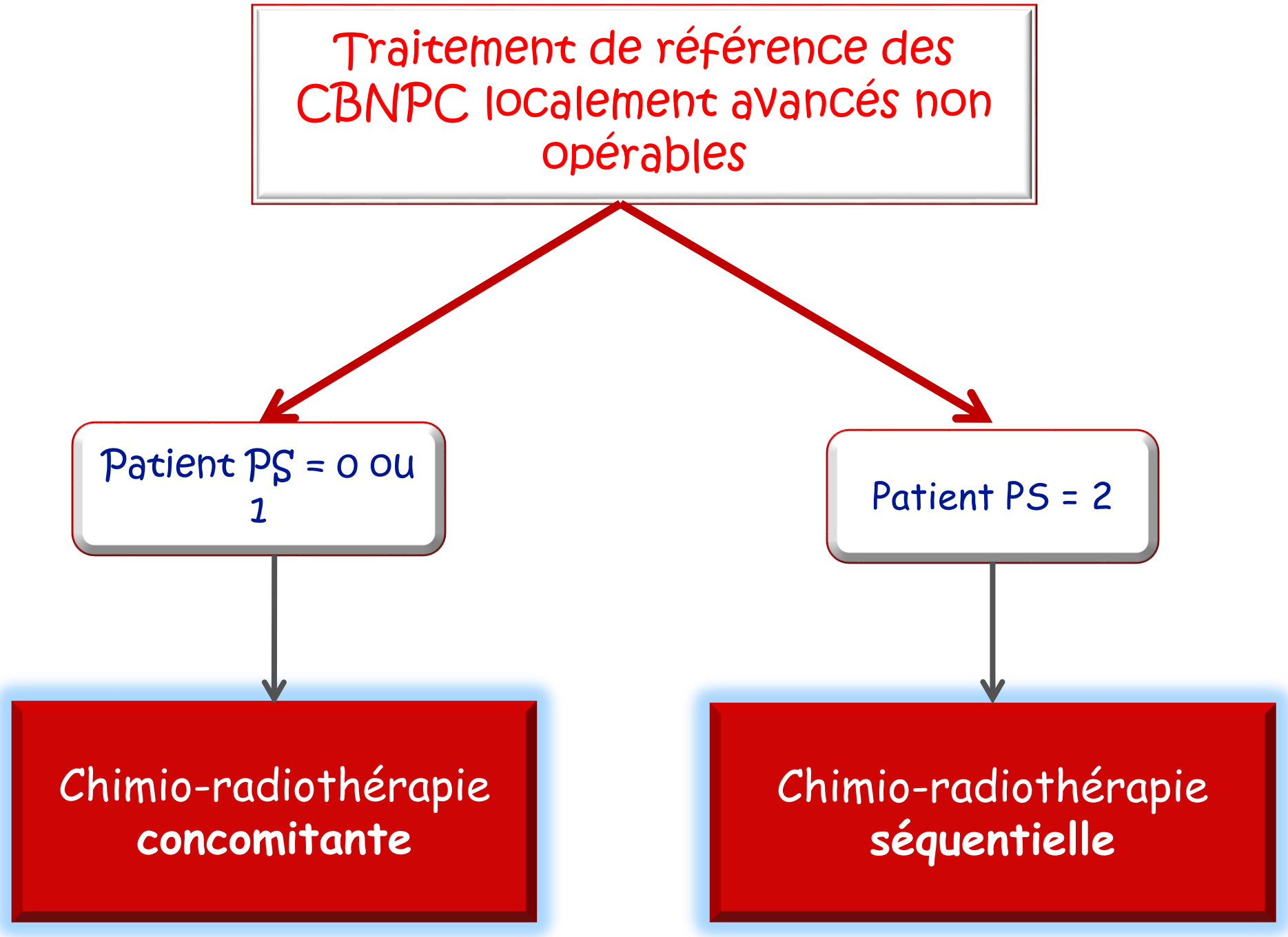
Non-Small Cell Lung Cancer




Traitement de référence des CBNPC localement avancés non opérables
Patient PS = 0 ou 1
Patient PS = 2
Chimio-radiothérapie **concomitante**
Chimio-radiothérapie **séquentielle**

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Non-Small Cell Lung Cancer

Protocole de chimiothérapie : platine + PMT ou Paclitaxel ou VP16.

CONCURRENT CHEMORADIATION REGIMENS

Concurrent Chemoradiation Regimens[€]

Preferred (nonsquamous)

- Carboplatin AUC 5 on day 1, pemetrexed 500 mg/m^2 on day 1 every 21 days for 4 cycles; concurrent thoracic RT[1,*,†,‡]
- Cisplatin 75 mg/m^2 on day 1, pemetrexed 500 mg/m^2 on day 1 every 21 days for 3 cycles; concurrent thoracic RT[2,3,*,†,‡] ± additional 4 cycles of pemetrexed 500 mg/m^2[†,§]
- Paclitaxel 45–50 mg/m^2 weekly; carboplatin AUC 2, concurrent thoracic RT[4,*,†,‡] ± additional 2 cycles every 21 days of paclitaxel 200 mg/m^2 and carboplatin AUC 6[†,§]
- Cisplatin 50 mg/m^2 on days 1, 8, 29, and 36; etoposide 50 mg/m^2 days 1–5 and 29–33; concurrent thoracic RT[5,6,*,†,‡]

Preferred (squamous)

- Paclitaxel 45–50 mg/m^2 weekly; carboplatin AUC 2, concurrent thoracic RT[6,*,†,‡] ± additional 2 cycles every 21 days of paclitaxel 200 mg/m^2 and carboplatin AUC 6[†,§]
- Cisplatin 50 mg/m^2 on days 1, 8, 29, and 36; etoposide 50 mg/m^2 days 1–5 and 29–33; concurrent thoracic RT[5,6,*,†,‡]

Consolidation Immunotherapy for Patients with Unresectable Stage II/III NSCLC, PS 0–1, and No Disease Progression After 2 or More Cycles of Definitive Concurrent Chemoradiation

Durvalumab 10 mg/kg IV every 2 weeks or 1500 mg every 4 weeks for up to 12 months (patients with a body weight of ≥30 kg)[7,8] (category 1 for stage III; category 2A for stage II)

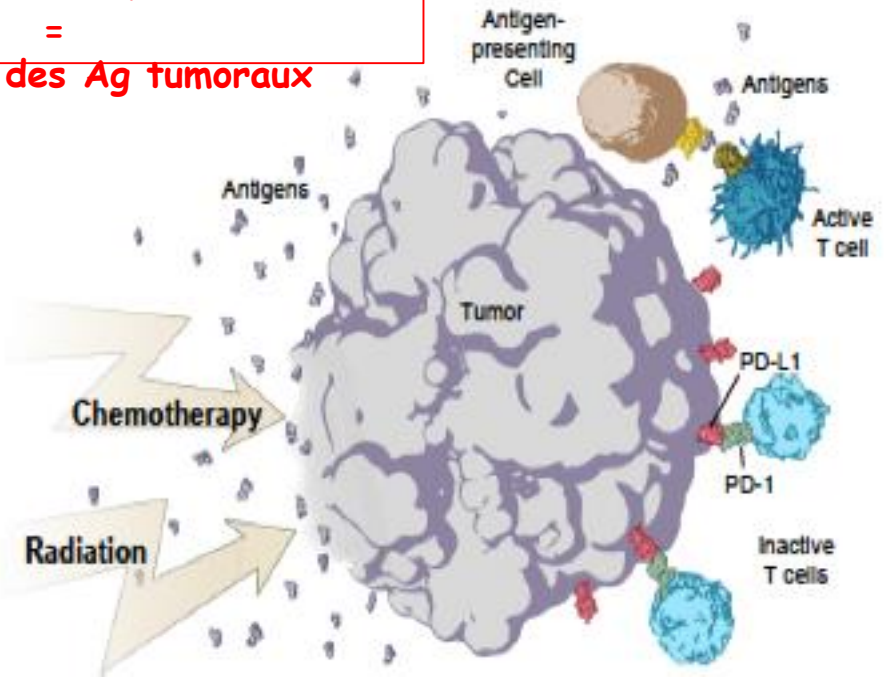
Traitement de consolidation / stades localements avancés

PACIFIC Regimen – Mechanism of Action[1–6]

CHEMORADIATION

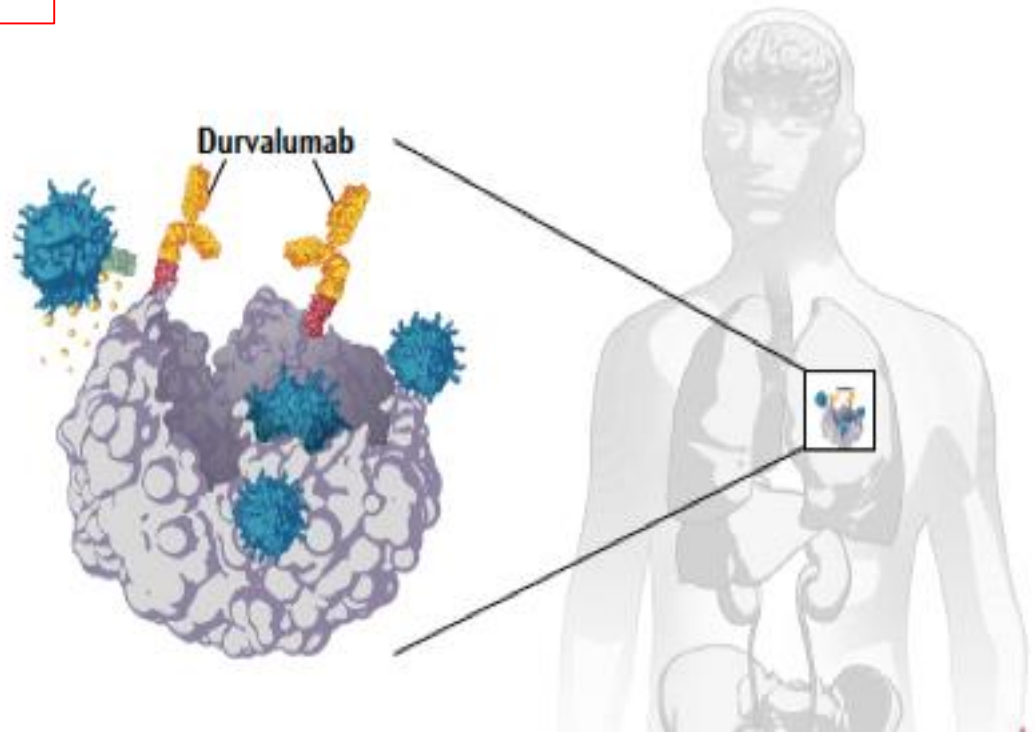
La RT-CT concomitante entraine la lyse
des cellules tumorales
=
Relargages des Ag tumoraux

Réaction immunitaire



DURVALUMAB

Annule l'immuno-suppression



PACIFIC: Study Design

Phase 3, Randomized, Double-blind, Placebo-controlled, Multicenter, International Study[1]

- Unresectable, Stage III NSCLC without progression after definitive platinum-based cCRT (≥2 cycles)
- 18 years or older
- WHO PS score 0 or 1
- If available, archived pre-cCRT tumor tissue for PD-L1 testing*

All-comers population (i.e. irrespective of PD-L1 status)

N=713 randomized

1–42 days post-cCRT

R

2:1 randomization, stratified by age, sex, and smoking history

Durvalumab
10 mg/kg q2w for up to 12 months
N=476

Placebo
10 mg/kg q2w for up to 12 months
N=237

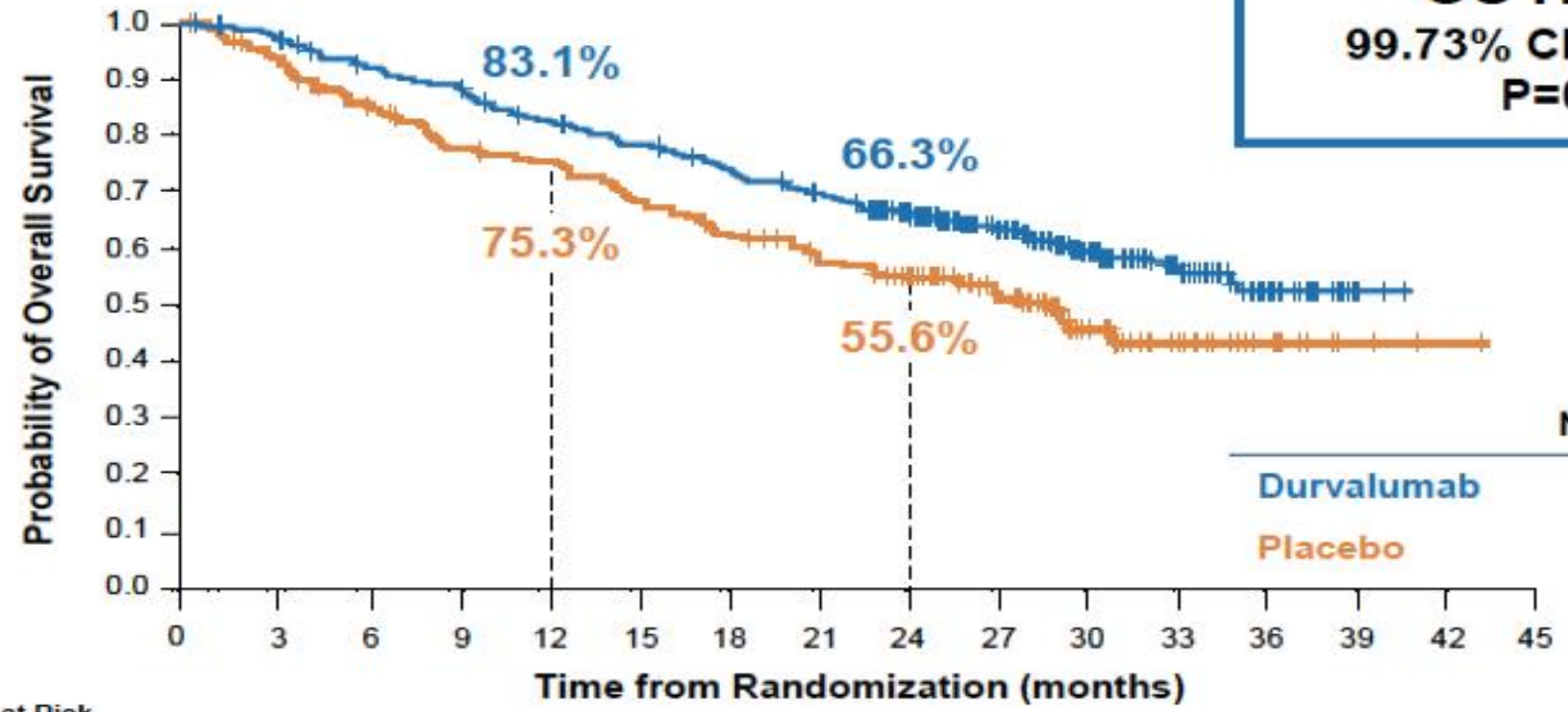
Primary endpoints
- PFS by BICR using RECIST v1.1†
- OS

Key secondary endpoints
- ORR, DoR and TTDM by BICR
- PFS2 by investigator
- Safety
- PROs

*Using the Ventana SP263 immunohistochemistry assay
†Defined as the time from randomization until the date of objective disease progression or death by any cause in the absence of progression. BICR, blinded independent central review; cCRT, concurrent CRT; PFS2, time to second progression; RECIST, Response Evaluation Criteria in Solid Tumors; TTDM, time to death or distant metastasis. ClinicalTrials.gov number: NCT02125461

1. Antonia SJ, et al. N Engl J Med 2017;377:1919–29.

Overall Survival* (ITT)



OS HR = 0.68
99.73% CI, 0.469–0.997†
P=0.00251

	No. of events / No. of patients (%)	Median OS (95% CI) months
Durvalumab	183/476 (38.4)	NR (34.7–NR)
Placebo	116/237 (48.9)	28.7 (22.9–NR)

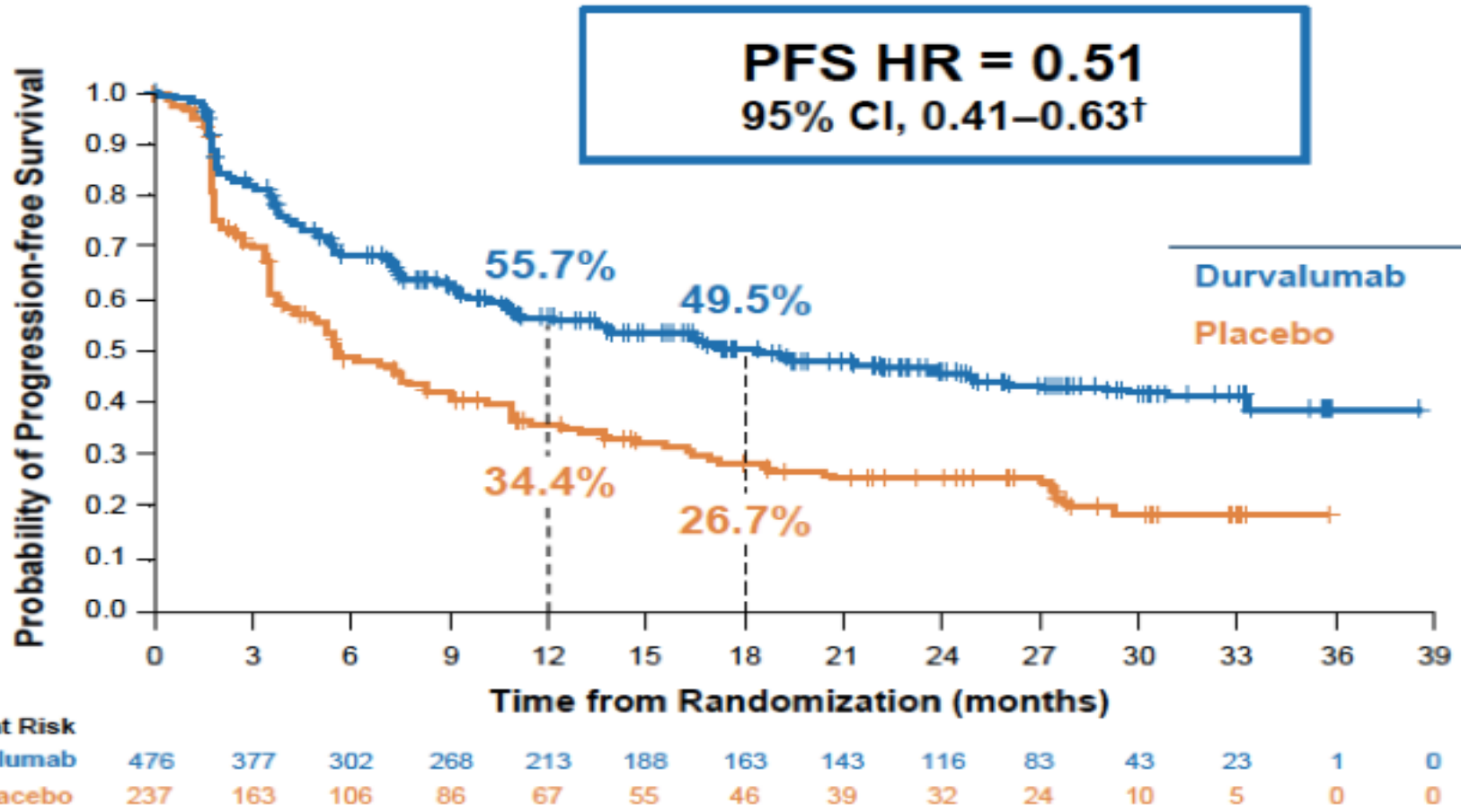
No. at Risk																
Durvalumab	476	464	431	415	385	364	343	319	274	210	115	57	23	2	0	0
Placebo	237	220	198	178	170	155	141	130	117	78	42	21	9	3	1	0

*Median duration of follow-up for OS was 25.2 months (range 0.2–43.1)
†Adjusted for interim analysis

NR, not reached

WCLC 2018

Updated Progression-free Survival by BICR* (ITT)

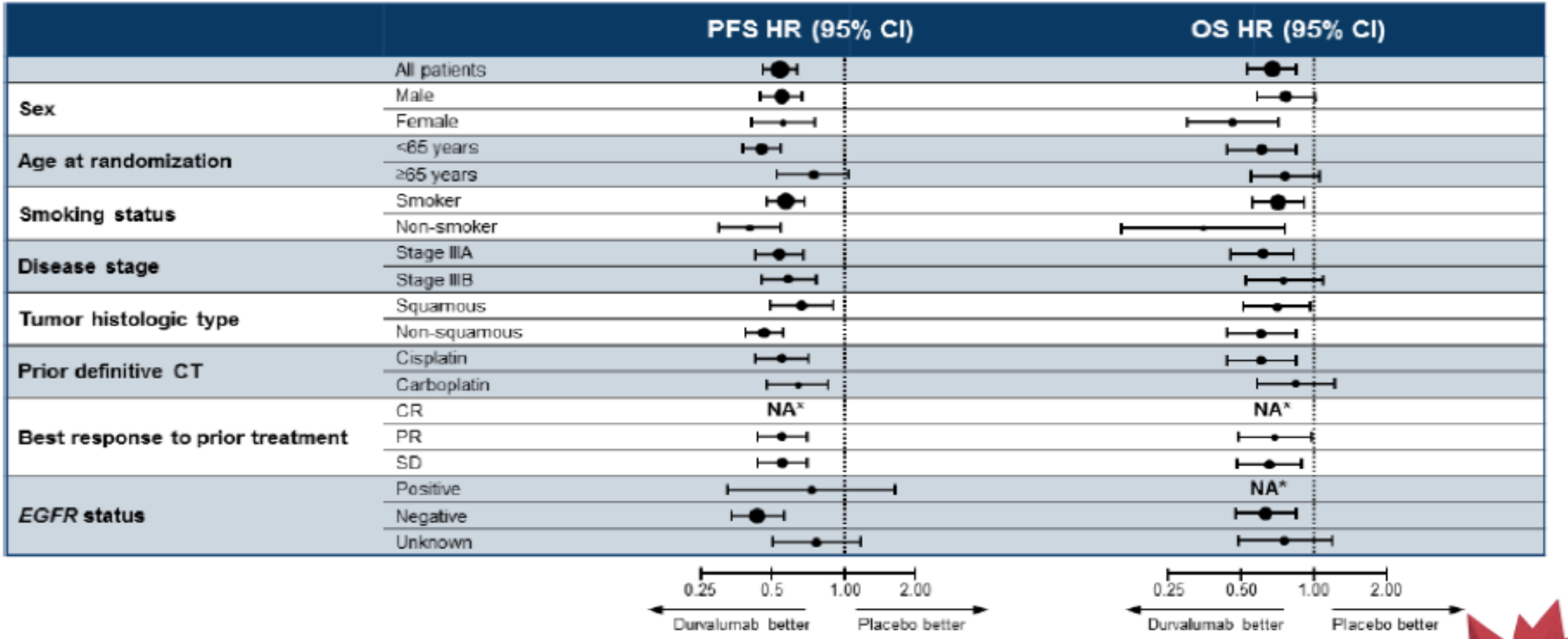


	No. of events / No. of patients (%)	Median PFS (95% CI) months
Durvalumab	243/476 (51.1)	17.2 (13.1–23.9)
Placebo	173/237 (73.0)	5.6 (4.6–7.7)

*Median duration of follow-up was 25.2 months (range 0.2–43.1)
†No formal statistical comparison was made because the study had achieved significance for PFS at the first planned IA (data cutoff of Feb 13, 2017)

WCLC 2018

Progression-free and Overall Survival by Subgroup (ITT)



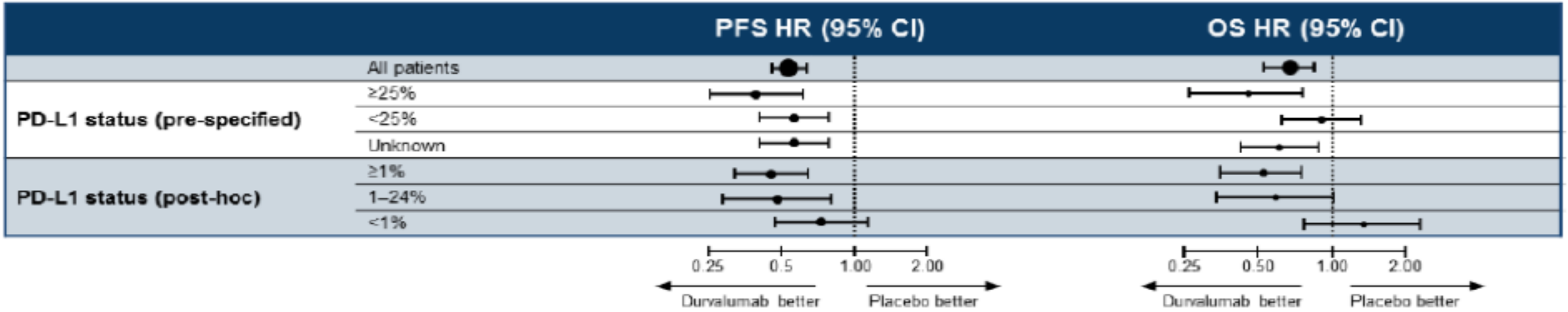
*Not calculated if subgroup has <20 events

Note: PFS data based on data cutoff of Feb 13, 2017, and OS data based on data cutoff of March 22, 2018

NA, not available

WCLC 2018

Subgroup Analysis by PD-L1 Status



- Important facts regarding PD-L1 status:
  - PD-L1 testing was not required
  - 37% of patients with unknown PD-L1 status
  - PD-L1 status was obtained pre-CRT (getting a sample post-CRT medically not feasible)
  - PD-L1 expression-level cutoff of 1% was part of an unplanned post-hoc analysis requested by a health authority

Note: PFS data based on data cutoff of Feb 13, 2017, and OS data based on data cutoff of March 22, 2018

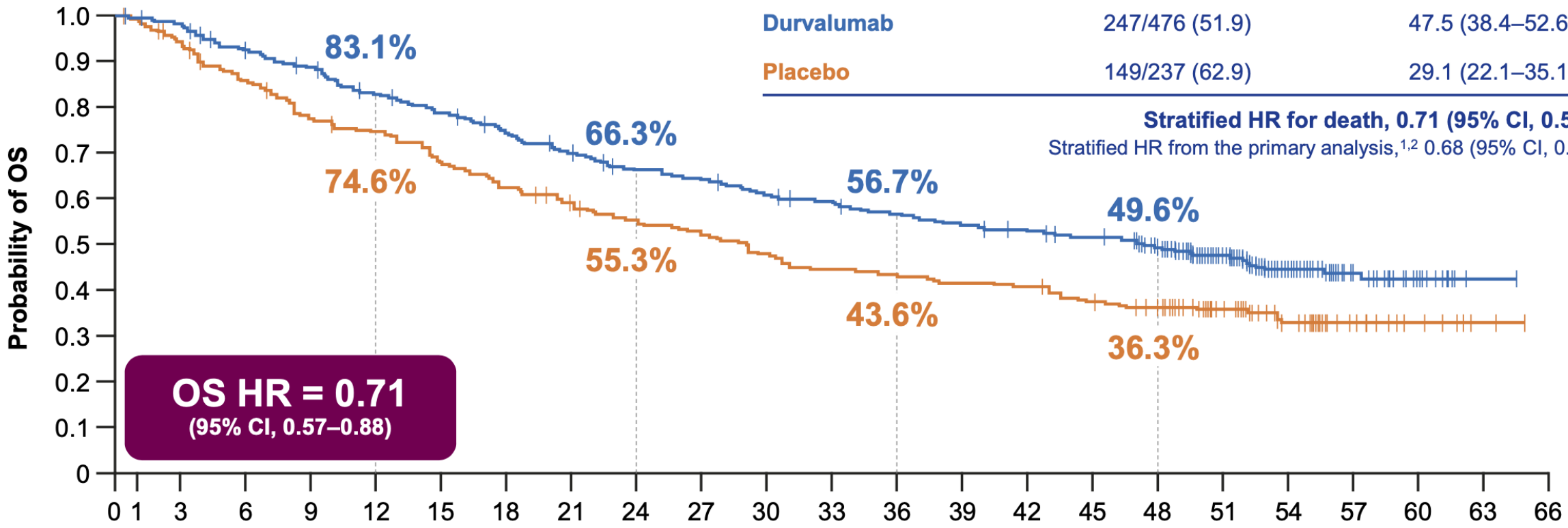
Survie globale

PACIFIC: Updated OS

	No. of events/ total no. of patients (%)	Median OS (95% CI), months
Durvalumab	247/476 (51.9)	47.5 (38.4–52.6)
Placebo	149/237 (62.9)	29.1 (22.1–35.1)

Stratified HR for death, 0.71 (95% CI, 0.57–0.88)

Stratified HR from the primary analysis,[1,2] 0.68 (95% CI, 0.53–0.87)



No. at risk

Durvalumab	476	464	431	414	385	364	343	319	299	290	274	265	252	241	235	225	195	138	75	36	15
Placebo	237	220	199	179	171	156	143	133	123	116	107	99	97	93	91	83	75	53	29	15	7

Faivre-Finn et al, ESMO 2020

WCLC 2020

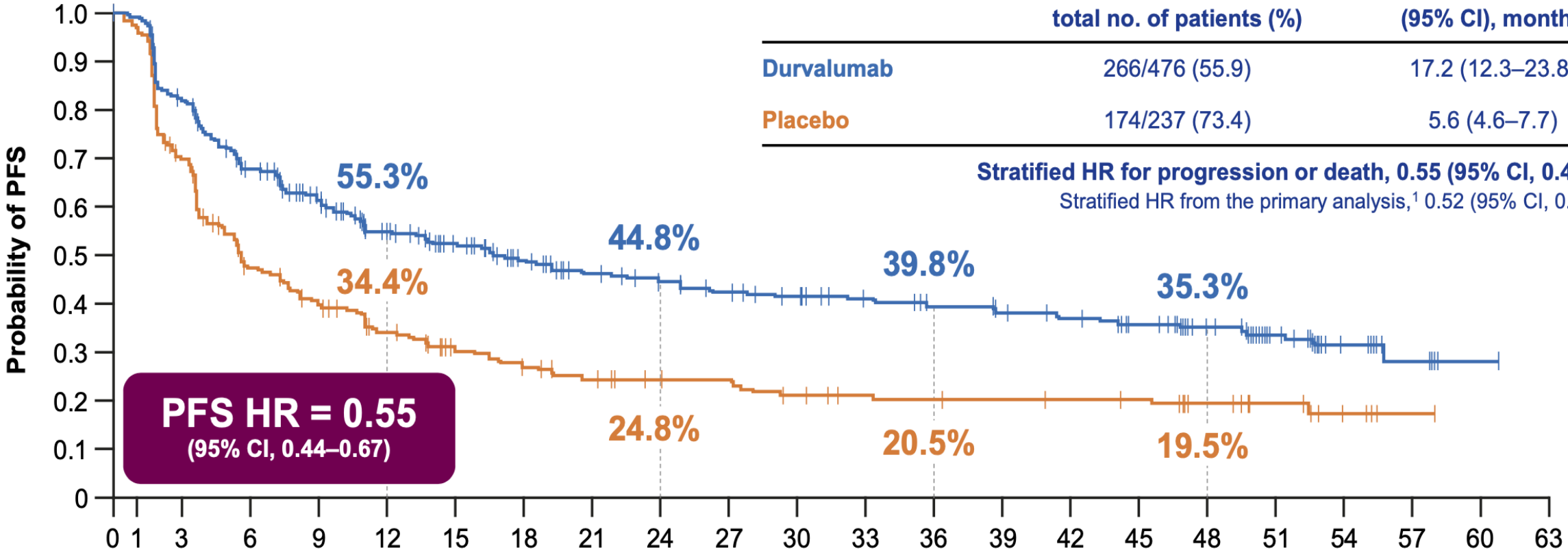
Survie sans progression

CIFIC: Updated PFS (BIRC)

	No. of events/ total no. of patients (%)	Median PFS (95% CI), months
Durvalumab	266/476 (55.9)	17.2 (12.3–23.8)
Placebo	174/237 (73.4)	5.6 (4.6–7.7)

Stratified HR for progression or death, 0.55 (95% CI, 0.44–0.67)

Stratified HR from the primary analysis,[1] 0.52 (95% CI, 0.42–0.65)



No. at risk

Durvalumab	476	377	301	266	213	189	165	146	136	127	119	110	103	97	92	80	59	37	18	8
Placebo	237	163	105	86	67	55	47	40	36	35	29	26	25	24	23	22	16	11	5	1

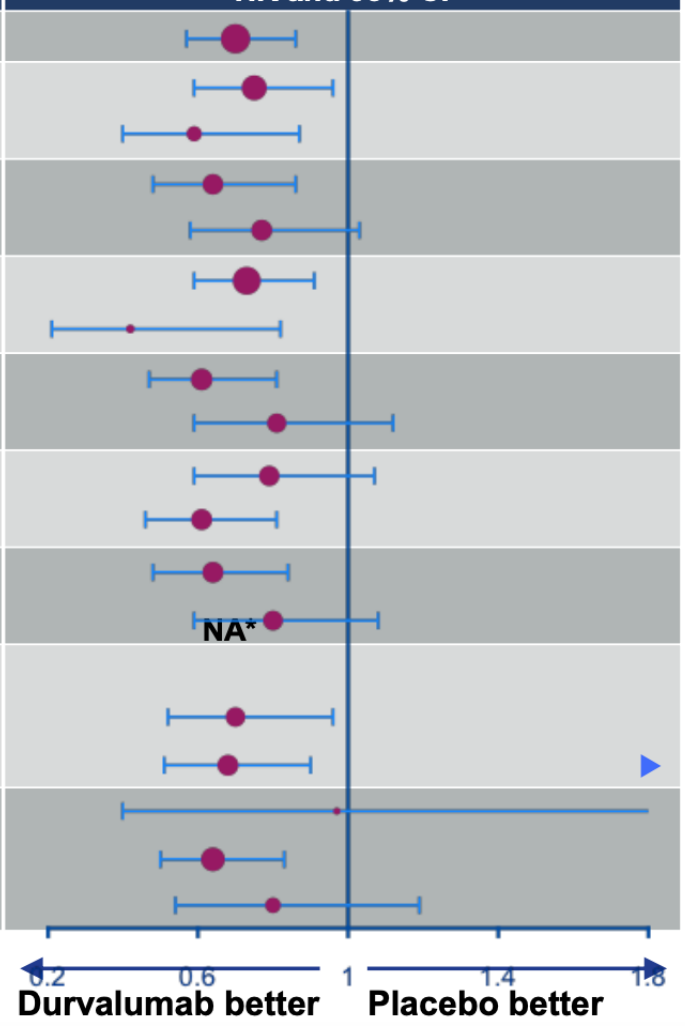
WCLC 2020

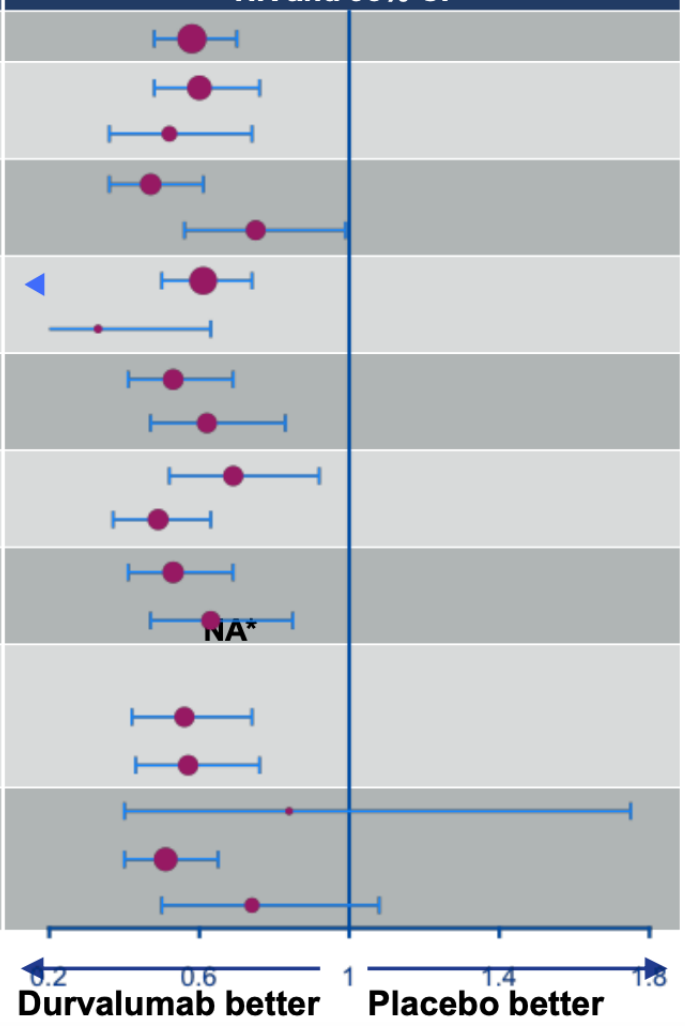
Faivre-Finn et al, ESMO 2020

WCLC 2020

PACIFIC: Subgroup Analysis

		OS		PFS (BICR)	
		# events / # patients (%)	HR and 95% CI	# events / # patients (%)	HR and 95% CI
All patients		396/713 (55.5)		440/713 (61.7)	
Sex	Male	290/500 (58.0)		313/500 (62.6)	
	Female	106/213 (49.8)		127/213 (59.6)	
Age at randomisation	<65 years	195/391 (49.9)		235/391 (60.1)	
	≥65 years	201/322 (62.4)		205/322 (63.7)	
Smoking status	Smoker	361/649 (55.6)		401/649 (61.8)	
	Non-smoker	35/64 (54.7)		39/64 (60.9)	
NSCLC disease stage	Stage IIIA	216/377 (57.3)		223/377 (59.2)	
	Stage IIIB	170/319 (53.3)		208/319 (65.2)	
Tumour histologic type	Squamous	192/326 (58.9)		212/326 (65.0)	
	All other	204/387 (52.7)		228/387 (58.9)	
Prior definitive CT	Cisplatin	203/395 (51.4)		238/395 (60.3)	
	Carboplatin	179/301 (59.5)	NA*	189/301 (62.8)	NA*
Best response to prior therapy	Complete response	8/16 (50.0)		9/16 (56.3)	
	Partial response	177/349 (50.7)		211/349 (60.5)	
	Stable disease	203/338 (60.1)		214/338 (63.3)	
***EGFR* mutation**	Positive	24/43 (55.8)		32/43 (74.4)	
	Negative	261/482 (54.1)		290/482 (60.2)	
	Unknown	111/188 (59.0)		118/188 (62.8)	





Faivre-Finn et al, ESMO 2020

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NCCN Guidelines Version 7.2021
Non-Small Cell Lung Cancer

Protocole de chimiothérapie : platine + PMT ou Paclitaxel ou VP16.

CONCURRENT CHEMORADIATION REGIMENS

Concurrent Chemoradiation Regimens[€]

Preferred (nonsquamous)

- Carboplatin AUC 5 on day 1, pemetrexed 500 mg/m^2 on day 1 every 21 days for 4 cycles; concurrent thoracic RT[1,*,†,‡]
- Cisplatin 75 mg/m^2 on day 1, pemetrexed 500 mg/m^2 on day 1 every 21 days for 3 cycles; concurrent thoracic RT[2,3,*,†,‡] ± additional 4 cycles of pemetrexed 500 mg/m^2[†,§]
- Paclitaxel 45–50 mg/m^2 weekly; carboplatin AUC 2, concurrent thoracic RT[4,*,†,‡] ± additional 2 cycles every 21 days of paclitaxel 200 mg/m^2 and carboplatin AUC 6[†,§]
- Cisplatin 50 mg/m^2 on days 1, 8, 29, and 36; etoposide 50 mg/m^2 days 1–5 and 29–33; concurrent thoracic RT[5,6,*,†,‡]

Preferred (squamous)

- Paclitaxel 45–50 mg/m^2 weekly; carboplatin AUC 2, concurrent thoracic RT[6,*,†,‡] ± additional 2 cycles every 21 days of paclitaxel 200 mg/m^2 and carboplatin AUC 6[†,§]
- Cisplatin 50 mg/m^2 on days 1, 8, 29, and 36; etoposide 50 mg/m^2 days 1–5 and 29–33; concurrent thoracic RT[5,6,*,†,‡]

Consolidation Immunotherapy for Patients with Unresectable Stage II/III NSCLC, PS 0–1, and No Disease Progression After 2 or More Cycles of Definitive Concurrent Chemoradiation

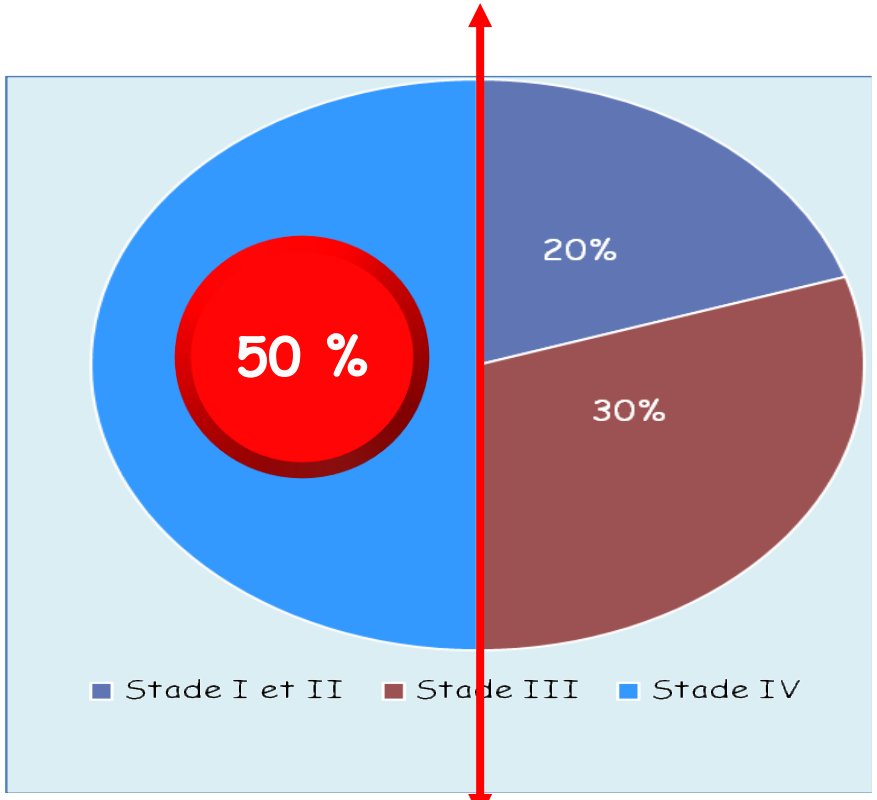
Durvalumab 10 mg/kg IV every 2 weeks or 1500 mg every 4 weeks for up to 12 months (patients with a body weight of ≥30 kg)[7,8]
(category 1 for stage III; category 2A for stage II)

Stades métastatiques

Les indispensables

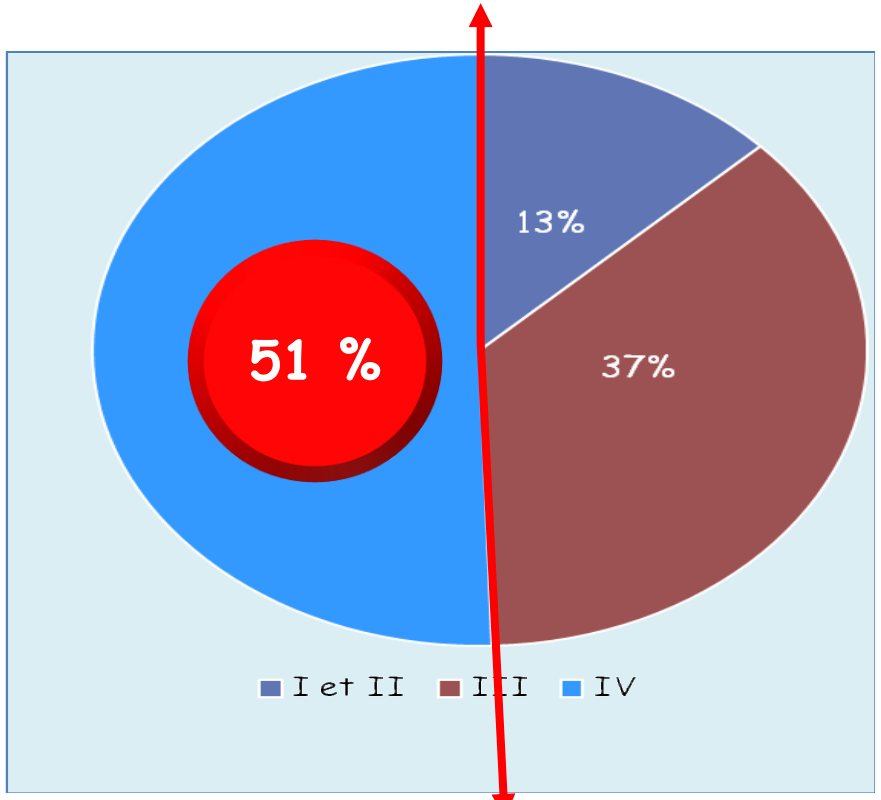
Stades métastatiques

Dans le monde



Fry WA, et al. Cancer. 1996;77:1949–1995

Algérie



CPMC, HDJ Oncologie médicale. 2000

Les indispensables

Stades métastatiques

Stades métastatiques				
IV	IVA	Quel que soit T	Quel que soit N	M1a, M1b
	IVB	Quel que soit T	Quel que soit N	M1c

=

1. Traitement symptomatique
2. La chimiothérapie
3. Les thérapies ciblées
4. L'immunothérapie

1. Prolonger la survie des patients « Survie Globale SG » tout en améliorant la qualité de vie.
2. Augmenter le temps jusqu'à progression SSP.

Pré requis au traitement

RCP

- Age / Comorbidités.
- PS
- L'extension de la maladie (TNM)
- Le type histologique
- Les drivers moléculaires

- âge, [< 70 ans, 70 – 89 ans]
- Comorbidités tel que insuffisance rénale, cardiopathies, neuropathies importantes….
- PS = 0, 1 / PS = 2 / PS = 3, 4.

Choix du protocole thérapeutique médicale

- Cisplatine / carboplatine
- Monothérapie / bithérapie
- Chimiothérapie / Thérapie ciblée (TKI / antiangiogenique) / Immunothérapie.

Classification TNM et Stade

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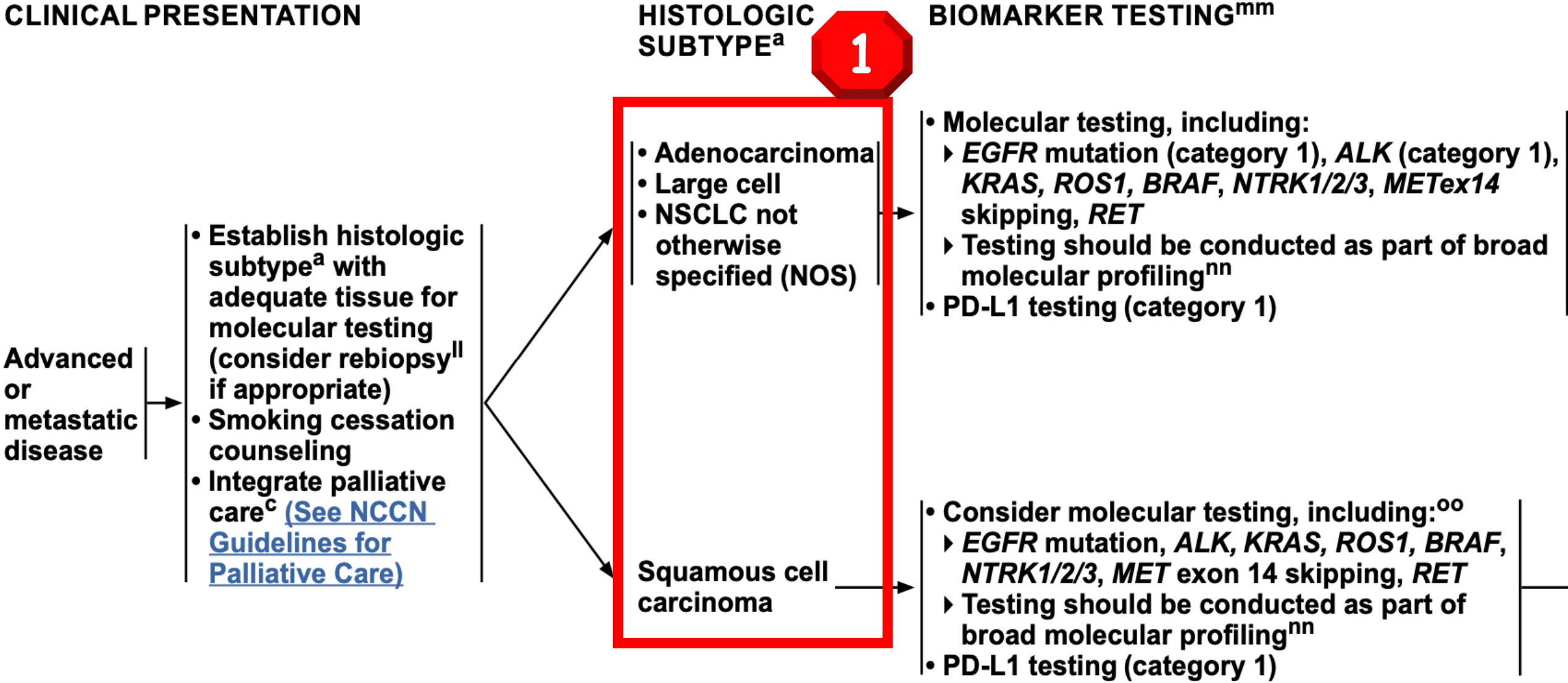

Diagnostic Histologique

NCCN Guidelines Version 7.2021
Non-Small Cell Lung Cancer

PRINCIPLES OF PATHOLOGIC REVIEW

sification

types of NSCLC are: adenocarcinoma, squamous cell carcinoma, adenosquamous carcinoma, large cell carcinoma, and sarcomatoid carcinoma.

- **Squamous cell carcinoma: A malignant epithelial tumor that either shows keratinization and/or intercellular bridges, or a morphologically undifferentiated NSCC that expresses immunohistochemical markers of squamous cell differentiation.**
- **Adenocarcinoma:**
  - **For small (<3 cm), resected lesions, determining extent of invasion is critical.**
    - **Adenocarcinoma in situ (AIS; formerly BAC): A small (≤3 cm) localized nodule with lepidic growth, mostly non-mucinous, although mucinous types can occur. Multiple synchronous AIS tumors can also occur.**
    - **Minimally invasive adenocarcinoma (MIA): A small (≤3 cm) solitary adenocarcinoma with a predominantly lepidic pattern and ≤5 mm invasion in greatest dimension. MIA is usually non-mucinous, but rarely may be mucinous. MIA is, by definition, solitary and discrete.**
    - **Invasive adenocarcinoma: A malignant epithelial tumor with glandular differentiation, mucin production, or pneumocyte marker expression. The tumors show an acinar, papillary, micropapillary, lepidic, or solid growth pattern, with either mucin or pneumocyte marker expression. The invasive adenocarcinoma component should be present in at least one focus measuring >5 mm in greatest dimension.**
    - **Invasive adenocarcinoma variants: invasive mucinous aden adenocarcinoma.**
    - **Refer to College of American Pathologists Protocols for add**
- **Adenosquamous carcinoma: A carcinoma showing components component constituting at least 10% of the tumor. Definitive dia on findings in small biopsies, cytology, or excisional biopsies. F otherwise squamous should trigger molecular testing.**
- **Large cell carcinoma: Undifferentiated NSCC that lacks the cyto adenocarcinoma, or squamous cell carcinoma. The diagnosis re resection or cytology specimens.**
- **Sarcomatoid carcinoma is a general term that includes pleomor it is best to use the specific term for these entities whenever pos**
  - **Pleomorphic carcinoma is a poorly differentiated NSCC that c only of spindle and giant cells. Spindle cell carcinoma consis carcinoma consists almost entirely of tumor giant cells.**
  - **Carcinosarcoma is a malignant tumor that consists of a mixtu rhabdomyosarcoma, chondrosarcoma, osteosarcoma).**
  - **Pulmonary blastoma is a biphasic tumor that consists of fetal**

Classification histologique OMS 2015	
Carcinome épidermoïde	Pont d'union +/- Kératine
Adénocarcinome	Différenciation glandulaire Production mucine (BA +)
Carcinome adéno-squameux	Double composante épidermoïde et adénocarcinome avec pour chaque composante au moins 10 % de la Tumeur
Carcinome à grandes cellules	Pas de différenciation Diagnostic sur pièce opératoire
Carcinome	Pléiomorphe / carcino-sarcome /

Diagnostic Histologique

NCCN Guidelines Version 7.2021
Non-Small Cell Lung Cancer

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Discussion

PRINCIPLES OF PATHOLOGIC REVIEW

Immunohistochemistry

- Judicious use of IHC is strongly recommended to preserve tissue for molecular testing, most notably in small specimens. When adenocarcinoma or squamous cell carcinomas are poorly differentiated, the defining morphologic criteria that would allow for specific diagnosis may be inconspicuous or absent. In this case, IHC or mucin staining may be necessary to determine a specific diagnosis.
- In small specimens, a limited number of immunostains with one lung adenocarcinoma marker (TTF1, napsin A) and one squamous carcinoma marker (p40, p63) should suffice for most diagnostic problems. Virtually all tumors that lack squamous cell morphology and show co-expression of p63 and TTF1 are preferably classified as adenocarcinoma. A simple panel of TTF1 and p40 may be sufficient to classify most NSCC-NOS cases.
- Testing for NUT expression by IHC should be considered in all poorly differentiated carcinomas that lack glandular differentiation or specific etiology, particularly in non-smokers or in patients presenting at a young age, for consideration of a pulmonary NUT carcinoma.
- IHC should be used to differentiate primary lung adenocarcinoma from squamous cell carcinoma, large cell carcinoma, metastatic carcinoma, and primary pleural mesothelioma (particularly for pleural specimens).
- Primary pulmonary adenocarcinoma:
  - In patients for whom the primary origin of the carcinoma is uncertain, an appropriate panel of immunohistochemical stains is recommended to assess for metastatic carcinoma to the lung.
  - TTF1 is a homeodomain-containing nuclear transcription protein of t
    embryonal and mature lung and thyroid. TTF1 immunoreactivity is se
    of non-mucinous adenocarcinoma subtypes. Metastatic adenocarcin
    thyroid malignancies, in which case thyroglobulin and PAX8 are also
    (gynecologic tract, pancreatobiliary) have been noted, and may be de
    of correlation with clinical and radiologic features.
  - Napsin A—an aspartic proteinase expressed in normal type II pneum
    expressed in >80% of lung adenocarcinomas and may be a useful adjunct to TTF1.
  - The panel of TTF1 (or alternatively napsin A) and p40 (or alternatively p63) may be useful in refining the diagnosis to either adenocarcinoma or squamous cell carcinoma in small biopsy specimens previously classified as NSCC NOS.

	C épidermoïde	Adénocarcinome
Morphologie	- Pont d'union - +/- kératine	Morphologie glandulaire Mucine (BA +)
IHC	P63 ou p40	TTF1 ou Napsin A

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Non-Small Cell Lung Cancer

CLINICAL PRESENTATION

HISTOLOGIC SUBTYPE[a]

BIOMARKER TESTING[mm]

2

Advanced or metastatic disease

- Establish histologic subtype[a] with adequate tissue for molecular testing (consider rebiopsy[ll] if appropriate)
- Smoking cessation counseling
- Integrate palliative care[c] (See NCCN Guidelines for Palliative Care)

Adenocarcinoma
- Large cell
- NSCLC not otherwise specified (NOS)

→

- Molecular testing, including:
  - *EGFR* mutation (category 1), *ALK* (category 1), *KRAS, ROS1, BRAF, NTRK1/2/3, METex14* skipping, *RET*
  - Testing should be conducted as part of broad molecular profiling[nn]
- PD-L1 testing (category 1)

Squamous cell carcinoma →

- Consider molecular testing, including:[oo]
  - *EGFR* mutation, *ALK, KRAS, ROS1, BRAF, NTRK1/2/3, MET* exon 14 skipping, *RET*
  - Testing should be conducted as part of broad molecular profiling[nn]
- PD-L1 testing (category 1)

Marqueurs moléculaires

PRINCIPLES OF MOLECULAR AND BIOMARKER ANALYSIS

Molecular Diagnostic Studies in Non-Small Cell Lung Cancer

- Numerous gene alterations have been identified that impact therapy selection. Testing of lu
  identification of potentially efficacious targeted therapies, as well as avoidance of therapies
- Some selection approaches for targeted therapy include predictive immunohistochemical a
  studies utilized to identify tumor type and lineage.
- Major elements of molecular testing that are critical for utilization and interpretation of mol
  - Use of a laboratory that is properly accredited, with a minimum of CLIA accreditation
  - Understanding the methodologies that are utilized and the major limitations of those meth
  - Understanding the spectrum of alterations tested (and those not tested) by a specific ass
  - Knowledge of whether a tumor sample is subjected to pathologic review and tumor enrich
  - The types of samples accepted by the testing laboratory
- Specimen Acquisition and Management:
  - Although tumor testing has been primarily focused on use of FFPE tissues, increasingly,
    cytopathology preparations not processed by FFPE methods. Although testing on cell blo
    companion diagnostic assays, testing on these specimen types is highly recommended v
  - A major limitation in obtaining molecular testing results for NSCLC occurs when minimall
    yield may be insufficient for molecular, biomarker, and histologic testing. Therefore, bron
    sufficient tissue to enable all appropriate testing.
  - When tissue is minimal, laboratories should deploy techniques to maximize tissue for mo
    protocols for small biopsies, including "up-front" slide sectioning for diagnostic and prec
- Testing Methodologies
  - Appropriate possible testing methodologies are indicated below for each analyte separately; however, several methodologies are generally considerations for use:
    - ◊ Next-generation sequencing (NGS) is used in clinical laboratories. Not all types of alterations are detected by individual NGS assays and it is important to be familiar with the types of alterations identifiable in individual assays or combination(s) of assays.
    - ◊ It is recommended at this time that when feasible, testing be performed via a broad, panel-based approach most typically performed by NGS. For patients who, in broad panel testing don't have identifiable driver oncogenes (espe
      already performed, to maximize detection of fusion events.
    - ◊ Real-time polymerase chain reaction (PCR) can be used in a highly targeted fashion (sp
      deployed, only those specific alterations that are targeted by the assay are assessed.
    - ◊ Sanger sequencing requires the greatest degree of tumor enrichment. Unmodified San
      in tumor samples with less than 25% to 30% tumor after enrichment and is not appropr
      (eg, resistance mutations) is important. If Sanger sequencing is utilized, tumor enrichm
    - ◊ Other methodologies may be utilized, including multiplex approaches not listed above
    - ◊ Fluorescence in situ hybridization (FISH) analysis is utilized for many assays examinin
      such as gene rearrangements.
    - ◊ IHC is specifically utilized for some specific analytes, and can be a useful surrogate or screening assay for others.

Plusieurs marqueurs :

- ➔ Mutation EGFR (2009)
  Mutation exon 20 (2019)
- ➔ Translocation ALK (2011)
- ➔ Translocation ROS-1 (2012)
- ➔ Mutation BRAF V600E
- ➔ Fusion NTRK
- ➔ Mutation KRAS G12C
- ➔ NTRK
- ➔ MET perte exon 14
- ➔ RET

Plusieurs méthodes :

NGS = Next Generation Sequencing
PCR = Real-Time Polymerase Chain Reaction
FISH = Hybridation In Situ par Fluorescence
IHC = Immuno Histo Chimie

EGFR

PRINCIPLES OF MOLECULAR AND BIOMARKER ANALYSIS

rgets for Analysis

n general, the mutations/alterations described below are seen in a non-overlapping fashion, although between 1%–3% of NSCLC may harbor concurrent alterations.

- ***EGFR* (Epidermal Growth Factor Receptor) Gene Mutations: EGFR is a receptor tyrosine kinase normally found on the surface of epithelial cells and is often overexpressed in a variety of human malignancies.**
  - ◊ **The most commonly**
    to oral EGFR tyrosin
    should not be treate
  - ◊ **Molecular testing for**
    are available for adju
  - ◊ **Many of the less co**
    ***exon 19* insertions,**
    studied patients is l
  - ◊ ***EGFR exon 20 (EGFR***
    knowledge of the spe
    - – ***EGFR p.T790M* is m**
      generation EGFR T
      third-generation TK
      possible germline
    - – **Most other *EGFRex***
      - ▪ **These are generally associated with lack of response to EGFR TKI therapy, with select exceptions:**
        ***p.A763_Y764insFQEA* is associated with sensitivity to TKI therapy**
        p. A763_Y764insL
      - ▪ **For this reason, t**
        ***EGFRex20* inserti**
        indicated.
  - ◊ **As use of NGS testing increases, additional *EGFR* variants are increasingly identified; however, the clinical implications of individual alterations are unlikely to be well established.**
  - ◊ **Some clinicopathologic features—such as smoking status, ethnicity, and histology—are associated with the presence of an *EGFR* mutation; however, these features should not be utilized in selecting patients for testing.**
  - ◊ **Testing Methodologies: Real-time PCR, Sanger sequencing (ideally paired with tumor enrichment), and NGS are the most commonly deployed methodologies for examining *EGFR* mutation status.**

- **Plusieurs mutations** ont été individualisées ayant une fonction activatrice répondant au TKI anti-EGFR
  - Délétion au niveau de l'**exon 19** (environ 45% des mutations) au niveau des amino-acides 747-749,
  - Substitution sur un seul nucléotide de l'**exon 21**, substituant une arginine à la place d'une leucine au codon 858 (**L858R**), (ceci représente environ 40% des mutations),
  - Mutations **exon 18**, plus rares (10 %)
  - Insertion **exon 19** ***P.L861Q, P.G719X, P.S768I***

Méthodes de recherche = Real time PCR, Sanger sequencing, NGS

EGFR

PRINCIPLES OF MOLECULAR AND BIOMARKER ANALYSIS

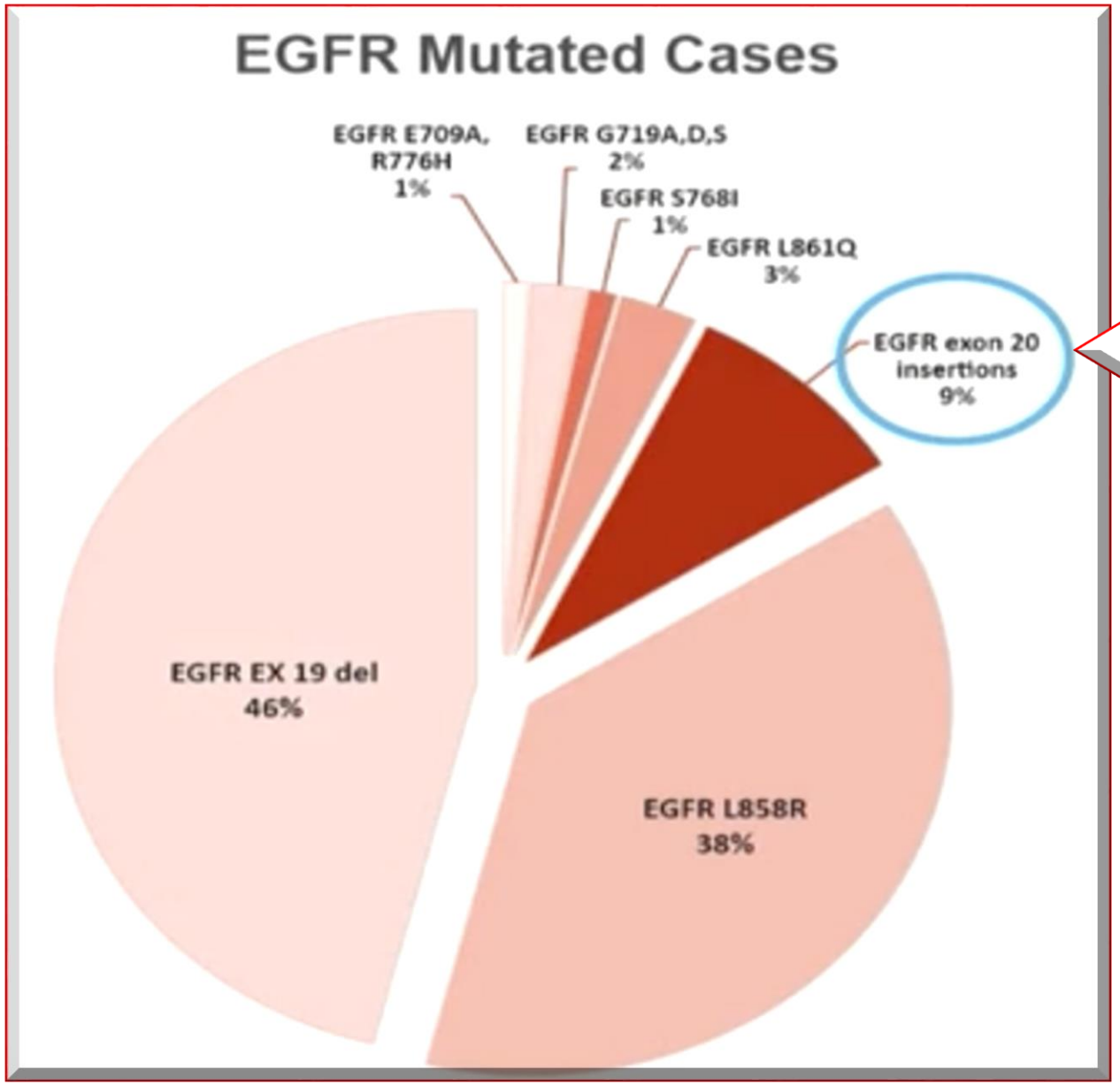
Mutation résistance aux TKI = Anomalie exon 20 :

- Insertion exon 20, ***p.A763_Y764insFQEA, p. A763_Y764insLQEA***
- Mutation T790M (résistance acquise, secondaire après prise TKI…)

Targets for Analysis

In general, the mutations/alterations des
concurrent alterations.

- ***EGFR*** **(Epidermal Growth Factor Recepto**
  and is often overexpressed in a variety o
  - ◊ **The most commonly described mutati**
    to oral EGFR tyrosine kinase inhibitor
    should not be treated with EGFR TKI i
  - ◊ **Molecular testing for *EGFR* mutation t**
    are available for adjuvant treatment de
  - ◊ **Many of the less commonly observed alterations in EGFR, which cumulatively account for ~10% of *EGFR*-mutation positive NSCLC (ie, *exon 19* insertions, *p.L861Q, p.G719X, p.S768I*) are also associated with responsiveness to EGFR TKI therapy, although the number of studied patients is lower.**
  - ◊ ***EGFR exon 20 (EGFRex20)*** **mutations are a heterogeneous group, some of which are responsive to targeted therapy and that require detailed knowledge of the specific alteration.**
    - ***EGFR p.T790M*** **is most commonly observed as a mutation that arises in response to and as a mechanism of resistance to first- and second-generation EGFR TKI. In patients with progression on first- or second-generation TKI with *p.T790M* as the primary mechanism of resistance, third-generation TKIs are typically efficacious. If *p.T790M* is observed in the absence of prior EGFR TKI therapy, genetic counseling and possible germline genetic testing is warranted.**
    - **Most other *EGFRex20* alterations are a diverse group of in-frame duplication or insertion mutations.**
      - **These are generally associated with lack of response to EGFR TKI therapy, with select exceptions:**
        p.A763_Y764insFQEA **is associated with sensitivity to TKI therapy**
        p. A763_Y764insLQEA **may be associated with sensitivity to TKI therapy**
      - **For this reason, the specific sequence of *EGFRex20* insertion mutations is important, and some assays will identify the presence of an *EGFRex20* insertion without specifying the sequence. In this scenario, additional testing to further clarify the *EGFRex20* insertion is indicated.**
  - ◊ **As use of NGS testing increases, additional *EGFR* variants are increasingly identified; however, the clinical implications of individual alterations are unlikely to be well established.**
  - ◊ **Some clinicopathologic features—such as smoking status, ethnicity, and histology—are associated with the presence of an *EGFR* mutation; however, these features should not be utilized in selecting patients for testing.**
  - ◊ **Testing Methodologies: Real-time PCR, Sanger sequencing (ideally paired with tumor enrichment), and NGS are the most commonly deployed methodologies for examining *EGFR* mutation status.**



- Amivantamab
- Mobocetinib
- Osimertinib
- Poziotinib

PRINCIPLES OF MOLECULAR AND BIOMARKER ANALYSIS

- **Molecular Targets for Analysis (continued)**
  - ***ALK*** **(Anaplastic Lymphoma Kinase) Gene Rearrangements:** **...lation and inappropriate signaling through the ALK ... ost common fusion partner seen with ALK is echino... ...rs have been identified. ...resence of an *ALK* rearrangement is associated with...**
    - ◊ **Some clinicopathologic features—such as smoking status... however, these features should not be utilized in selecting...**
    - ◊ **Testing Methodologies: FISH break-apart probe methodol... screening strategy. FDA-approved IHC (ALK [D5F3] CDx A... Numerous NGS methodologies can detect *ALK* fusions. T... fusions with novel partners.**
  - ***ROS1*** **(ROS proto-oncogene 1) Gene Rearrangements: ROS1 is a receptor tyrosine kinase that can be rearranged in NSCLC, resulting in dysr...ulation and inappropriate signaling through the ROS1 kinase domain. ...erous fusion partners are seen with *ROS1*, and common fusion pa... ...resence of a *ROS1* rearrangement is associated with responsiven... ...clinicopathologic features—such as smoking status and histolog... ...ver, these features should not be utilized in selecting patients for ...esting Methodologies: FISH break-apart probe methodology can be de... approaches can be deployed; however, IHC for *ROS1* fusions has low s... utilizing ROS1 IHC as a screening modality. Numerous NGS methodologies can detect *ROS1* fusions, although DNA-based NGS may under-detect *ROS1* fusions. Targeted real-time PCR assays are utilized in some settings, although they are unlikely to detect fusions with novel partners.**
  - ***BRAF*** **(B-Raf proto-oncogene) point mutations: BRAF is a serine/threonine kinase that is part of the canonical MAP/ERK signaling pathway. Activ...g mutations in BRAF result in unregulated signaling through the MAP/ERK pathway. ...ons in *BRAF* can be seen in NSCLC. The presence of a specific mutation resulting in a change i... ...ated with responsiveness to combined therapy with oral inhibitors of BRAF and MEK. ...at other mutations in *BRAF* are observed in NSCLC, and the impact of those mutations on ther...**

    ...esting Methodologies: Real-time PCR, Sanger sequencing (ideally paired with tumor enrichment), and NGS are the most commonly deployed methodologies for examining *BRAF* mutation status. While an anti-BRAF p.V600E-specific monoclonal antibody is commercially available, and some studies have examined utilizing this approach, it should only be deployed after extensive validation.
  - ***KRAS*** **(KRAS proto-oncogene) point mutations: KRAS is a G-protein with intrinsic GTPase activity, and activating mutations result in unregulated sign...g through the MAP/ERK pathway. ...ions in *KRAS* are most commonly seen at codon 12,... ...resence of a *KRAS* mutation is prognostic of poor su... ...ions in *KRAS* have been associated with reduced re... ...g to the low probability of overlapping targetable alte... unlikely to benefit from further molecular testing.**

ALK

Translocation ALK-EML4:
FISH : méthode de detection standard = Hybridation in situ par fluorescence (FISH break-apart probe)
IHC : validé avec Ac D5F3
2019, utiliser comme pre screening et si + varifier avec FISH
2020, pas de confirmation par FISH.

ROS 1

Tanslocation ROS-1
Méthode de detection standard = IHC a confirmer
FISH (Hybridation in situ par fluorescence).

BRAF

Mutation BRAF V600E
PCR, Sanger sequencing, NGS

KRAS

Mutation KRAS = Plus fréquente des mutations, F mauvais pronostic
F de non réponse aux TKI classique

PRINCIPLES OF MOLECULAR AND BIOMARKER ANALYSIS

- Molecular Targets for Analysis (continued)
  - *MET* (mesenchymal-epithelial transition) *exon 14 (METex14)* skipping variants: MET is a receptor tyrosine kinase. A mutat
    - in NSCLC. Loss of *METex14* leads to dysregulation and inappropriate signaling.
    - ence of *METex14* skipping mutation is associated with responsiveness to oral MET TKIs.
    - A broad range of molecular alterations lead to *METex14* skipping.
    - ◊ Testing Methodologies: NGS-based testing is the primary method for detection of *METex14* skipping events, with RNA-based NGS demonstrating improvement in detection. IHC is not a method for detection of *METex14* skipping.
  - *RET* (rearranged during transfection) Gene Rearrangements: RET is a receptor tyrosine kinase that can be rearranged in NSCLC, resulting in
    - ulation and inappropriate signaling through the RET kinase domain.
    - mon fusion partners are *KIF5B, NCOA4*, and *CCDC6*; however, numerous other fusion partners have been identifie
    - ◊ The presence of a *RET* rearrangement is associated with responsiveness to oral RET TKIs regardless of fusion partner.
    - ◊ Testing Methodologies: FISH break-apart probe methodology can be deployed; however, it may under-detect some fusi reverse-transcriptase PCR assays are utilized in some settings, although they are unlikely to detect fusions with novel partners. NGS-based methodology has a high specificity, and RNA-based NGS is preferable to DNA-based NGS for fusion detection.
  - *NTRK1/2/3* (neurotrophic tyrosine receptor kinase) gene fusions
    - ◊ e tyrosine receptor kinases that are rarely rearranged in NSCLC as well as in other tumor types, resulting in dysregulation and e signaling.
    - us fusion partners have been identified.
    - ◊ To date, no specific clinicopathologic features, other than absence of other driver alterations, have been identified in as fusions.
    - ◊ Point mutations in *NTRK1/2/3* are generally non-activating and have not been studied in association with targeted therapy.
    - ◊ Testing Methodologies: Various methodologies can be used to detect *NTRK1/2/3* gene fusions, including: FISH, IHC, PCR, and NGS; false negatives may occur. IHC methods are complicated by baseline expression in some tissues. FISH testing may require at least 3 probe sets for full analysis. NGS testing can detect a broad range of alterations. DNA-based NGS may under-detect *NTRK1* and *NTRK3* fusions.

MET exon 14

MET exon 14 =
- NGS
- RNA NGS

RET

Rearrangement RET =
- FISH
- RNA NGS

NTRK 1, 2, 3

Fusion NTRK = FISH, IHC, PCR, NGS

En cas de progression s/TKI

PRINCIPLES OF MOLECULAR AND BIOMARKER ANALYSIS

- Testing in the Setting of Progression on Targeted Therapy:
  - For many of the above listed analytes, there is growing recognition of the molecular mechanisms of resistance to therapy. Re-testing of a sample from a tumor that is actively progressing while exposed to targeted therapy can shed light on appropriate next therapeutic steps:
    - ◊ For patients with an underlying *EGFR* sensitizing mutation who have been treated with EGFR TKI, minimum appropriate testing includes high-sensitivity evaluation for *p.T790M*; when there is no evidence of *p.T790M*, testing for alternate mechanisms of resistance (*MET* amplification, *ERBB2* amplification) may be used to direct patients for additional therapies. The presence of *p.T790M* can direct patients to third-generation EGFR TKI therapy.
      - – Assays for the detection of *EGFR p.T790M* should be designed to have an analytic sensitivity of a minimum of 5% allelic fraction. The original sensitizing mutation can be utilized as an internal control in many assays to determine whether a *p.T790M* is within the range of detection if present as a sub-clonal event.
    - ◊ For patients with underlying *ALK* rearrangement who have been treated with ALK TKI, it is unclear whether identification of specific tyrosine kinase domain mutation can identify appropriate next steps in therapy, although some preliminary data suggest that specific kinase domain mutations can impact next line of therapy.

PD-L1

PRINCIPLES OF MOLECULAR AND BIOMARKER ANALYSIS

- PD-L1 (Programmed Death Ligand 1): PD-L1 is a co-regulatory molecule that can be expressed on tumor cells and inhibit T-cell–mediated cell death. T-cells express PD-1, a negative regulator, which binds to ligands including PD-L1 (CD274) or PD-L2 (CD273). In the presence of PD-L1, T-cell activity is suppressed.
  - Checkpoint inhibitor antibodies block the PD-1 and PD-L1 interaction, thereby improving the antitumor effects of endogenous T cells.
  - IHC for PD-L1 can be utilized to identify disease most likely to respond to first-line anti PD-1/PD-L1.
    - Various antibody clones have been developed for IHC analysis of PD-L1 expression, and while several show relative equivalence, some do not.
    - Interpretation of PD-L1 IHC in NSCLC is typically focused on the proportion of tumor cells expressing membranous staining at any level and therefore is a linear variable; scoring systems may be different in other tumor types.
    - The FDA-approved companion diagnostic for PD-L1 guides utilization of pembrolizumab in patients with NSCLC and is based on the tumor proportion score (TPS). TPS is the percentage of viable tumor cells showing partial or complete membrane staining at any intensity.
    - The definition of positive and negative testing is dependent on the individual antibody and platform deployed, which may be unique to each checkpoint inhibitor therapy. The potential for multiple different assays for PD-L1 has raised concern among both pathologists and oncologists.
    - Although PD-L1 expression can be elevated in patients with an oncogenic driver, targeted therapy for the oncogenic driver should take precedence over treatment with an immune checkpoint inhibitor.

Testing PDL-1 :
==> IHC
==> cut of > 50 % L1
> 1 - 49 %

TPS :
% de cellules cancéreuses viables qui exprime une fixation partielle ou complète au niveau de la membrane cellulaire quelle que soit

PRINCIPLES OF MOLECULAR AND BIOMARKER ANALYSIS

- **Plasma Cell-Free/Circulating Tumor DNA Testing:**
  - Cell-free/circulating tumor DNA testing should not be used in lieu of a histologic tissue diagnosis.
  - Some laboratories offer testing for molecular alterations examining nucleic acids in peripheral circulation, most commonly in processed plasma (sometimes referred to as "liquid biopsy").
  - Studies have demonstrated cell-free tumor DNA testing to generally have very high specificity, but significantly compromised sensitivity, with up to 30% false-negative rate.
  - Standards for analytical performance characteristics of cell-free tumor DNA have not been established, and in contrast to tissue-based testing, no guidelines exist regarding the recommended performance characteristics of this type of testing.
  - Cell-free tumor DNA testing can identify alterations that are unrelated to a lesion of interest, for example, clonal hematopoiesis of indeterminate potential (CHIP).
  - The use of cell-free/circulating tumor DNA testing can be considered in specific clinical circumstances, most notably:
    - ◊ If a patient is medically unfit for invasive tissue sampling
    - ◊ In the initial diagnostic setting, if following pathologic confirmation of a NSCLC diagnosis there is insufficient material for molecular analysis, cell-free/circulating tumor DNA should be used only if follow-up tissue-based analysis is planned for all patients in which an oncogenic driver is not identified (see NSCL-18 for oncogenic drivers with available targeted therapy options).

ADN tumoral circulant:
A utiliser si :
- Patient ne pouvant pas supporter un geste invasive

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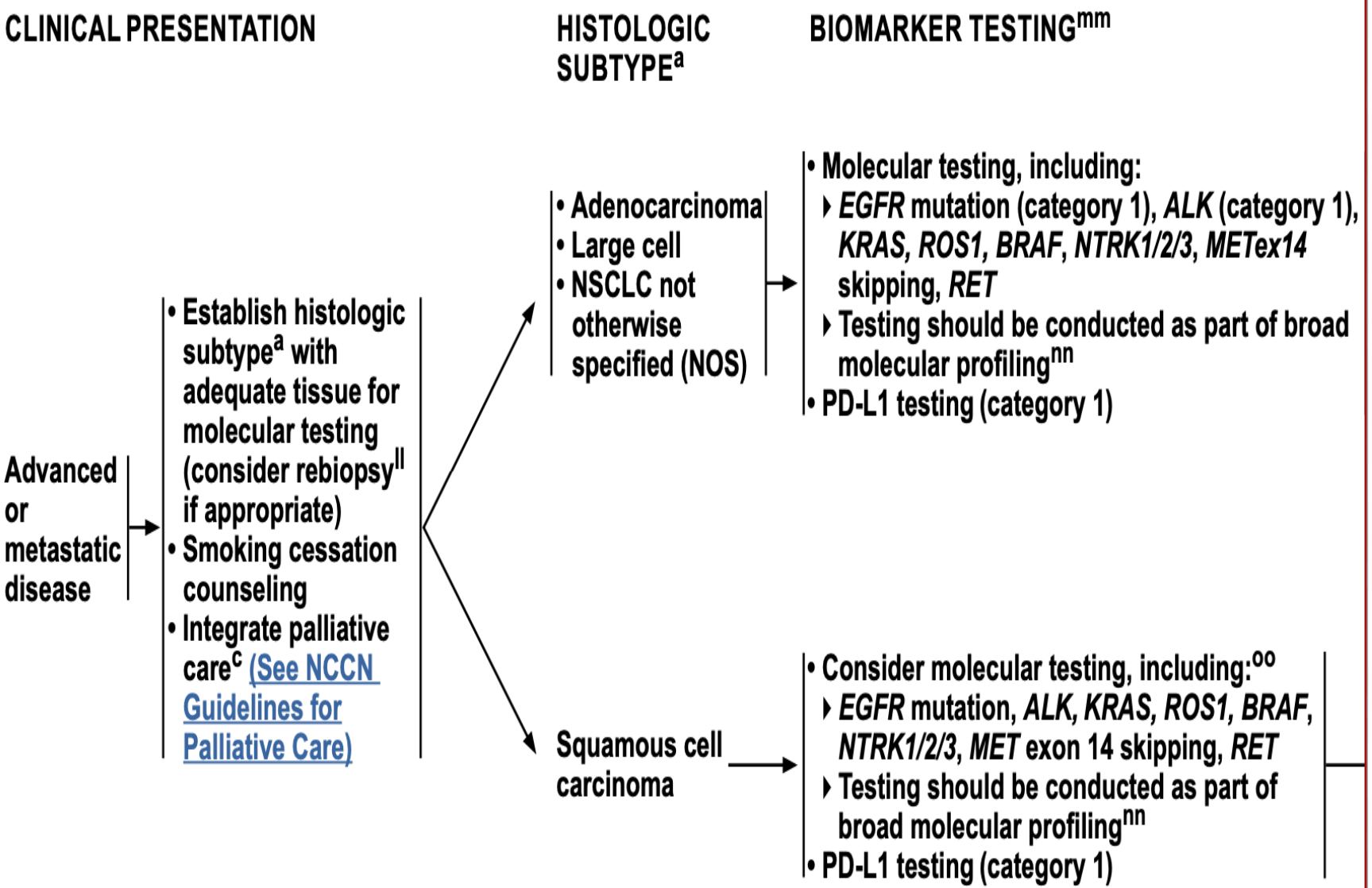
Non-Small Cell Lung Cancer



Quels tests moléculaires :

- Mutation EGFR
- Translocation ALK
- Translocation ROS1
- Mutation BRAF V600E
- perte MET exon 14
- Réarrangement RET
- Fusion gènes NTRK 1, 2, 3
- KRAS G12C
- Surexpression PDL1

Pour qui :

- ADK
- Carcinome à grandes cellules
- CBNPC NOS
- Carcinome épidermoïde :

si non ou peu fumeur < 15 p/a,
si petite Bx.
si histologie mixte.

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Non-Small Cell Lung Cancer

1 2 3 4

CLINICAL PRESENTATION

HISTOLOGIC SUBTYPE[a]

BIOMARKER TESTING[ll]

TESTING RESULTS[jj]

Advanced or metastatic disease

- Establish histologic subtype[a] with adequate tissue for molecular testing (consider rebiopsy[kk] if appropriate)
- Smoking cessation counseling
- Integrate palliative care[c] (See NCCN Guidelines for Palliative Care)

Adenocarcinoma
- Large cell
- NSCLC not otherwise specified (NOS)

Squamous cell carcinoma

Molecular testing, including:
- *EGFR* mutation (category 1), *ALK* (category 1), *ROS1*, *BRAF*, *NTRK1/2/3*, *METex14* skipping, *RET*
- Testing should be conducted as part of broad molecular profiling[mm]

PD-L1 testing (category 1)

Consider molecular testing, including:[nn]
- *EGFR* mutation, *ALK*, *ROS1*, *BRAF*, *NTRK1/2/3*, *MET* exon 14 skipping, *RET*
- Testing should be conducted as part of broad molecular profiling[mm]

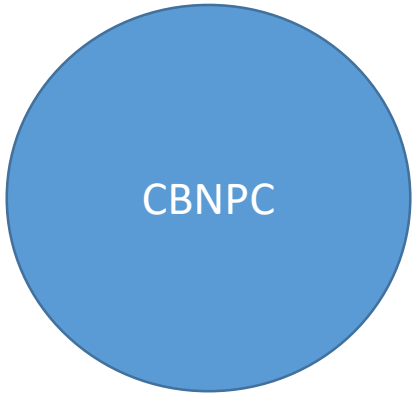
PD-L1 testing (category 1)

TESTING RESULTS[jj]

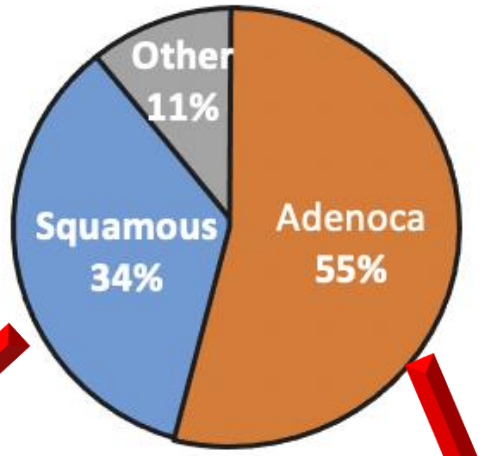
- Sensitizing *EGFR* mutation positive (see NSCL-19)
- *ALK* positive (see NSCL-22)
- *ROS1* positive (see NSCL-25)
- *BRAF* V600E positive (see NSCL-26)
- *MET* exon 14 skipping mutation positive (see NSCL-28)
- *RET* positive (see NSCL-29)
- PD-L1 ≥1% and *EGFR*, *ALK*, *ROS1*, *BRAF*, *MET* exon 14 skipping mutation, and *RET* negative[ii] (see NSCL-30)
- PD-L1 <1% and *EGFR*, *ALK*, *ROS1*, *BRAF*, *MET* exon 14 skipping mutation, and *RET* negative[ii] (see NSCL-32)

- Sensitizing *EGFR* mutation positive (see NSCL-19)
- *ALK* positive (see NSCL-22)
- *ROS1* positive (see NSCL-25)
- *BRAF* V600E positive (see NSCL-26)
- *MET* exon 14 skipping mutation positive (see NSCL-28)
- *RET* positive (see NSCL-29)
- PD-L1 ≥1% and *EGFR*, *ALK*, *ROS1*, *BRAF*, *MET* exon 14 skipping mutation, and *RET* negative[ii] (see NSCL-30)
- PD-L1 <1% and *EGFR*, *ALK*, *ROS1*, *BRAF*, *MET* exon 14 skipping mutation, and *RET* negative[ii] (see NSCL-33)

Drivers moléculaires

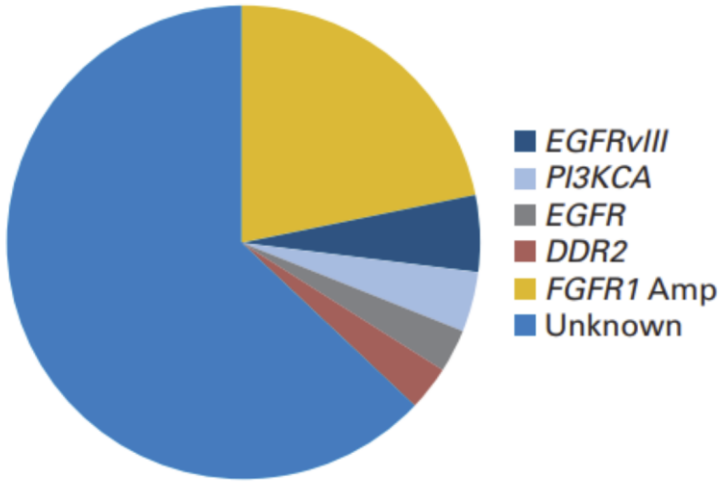


1990 - 2004

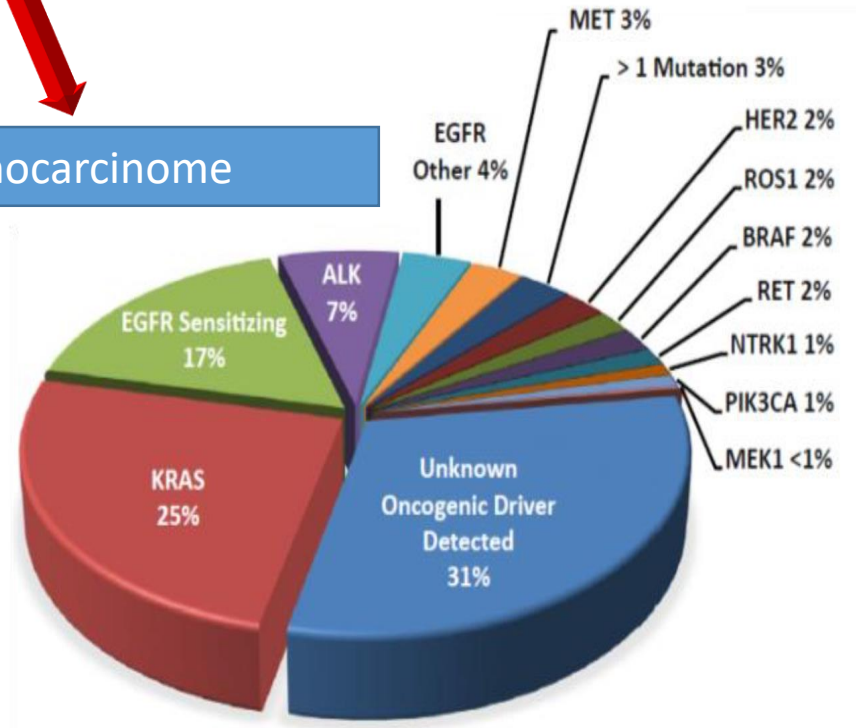


2004 - 2009

Carcinome épidermoïde



Adénocarcinome



2020

PDL-1

- Adénocarcinome
- Carcinome à grandes cellules
- CBNPC NOS
- Carcinome épidermoïde :
  si non ou peu fumeur < 15 p/a
  si petite biopsie
  si histologie mixte

Drivers moléculaires

Carcinome épidermoïde

Patients Avec drivers moléculaires PDL-1 < 1 %, ≥ 1–49 %, ≥ 50 %	=	**Thérapies ciblées** +/- anti-angiogènique
Patients sans drivers moléculaires PDL-1 < 1 %	=	**Chimiothérapie +/- anti-angiogèniques**
Patients sans drivers moléculaires PDL-1 ≥ 1-49 %	=	**Immunothérapie + Chimiothérapie** +/- Anti-angiogènique
Patients sans drivers moléculaires PDL-1 ≥ 50 %	=	**Immunothérapie** IO + CT +/- anti-angiogènique

Arbre décisionnel 2021, 1ere ligne de traitement

Patients
Avec drivers moléculaires
PDL-1 < 1 %, ≥ 1-49 %, ≥ 50 %

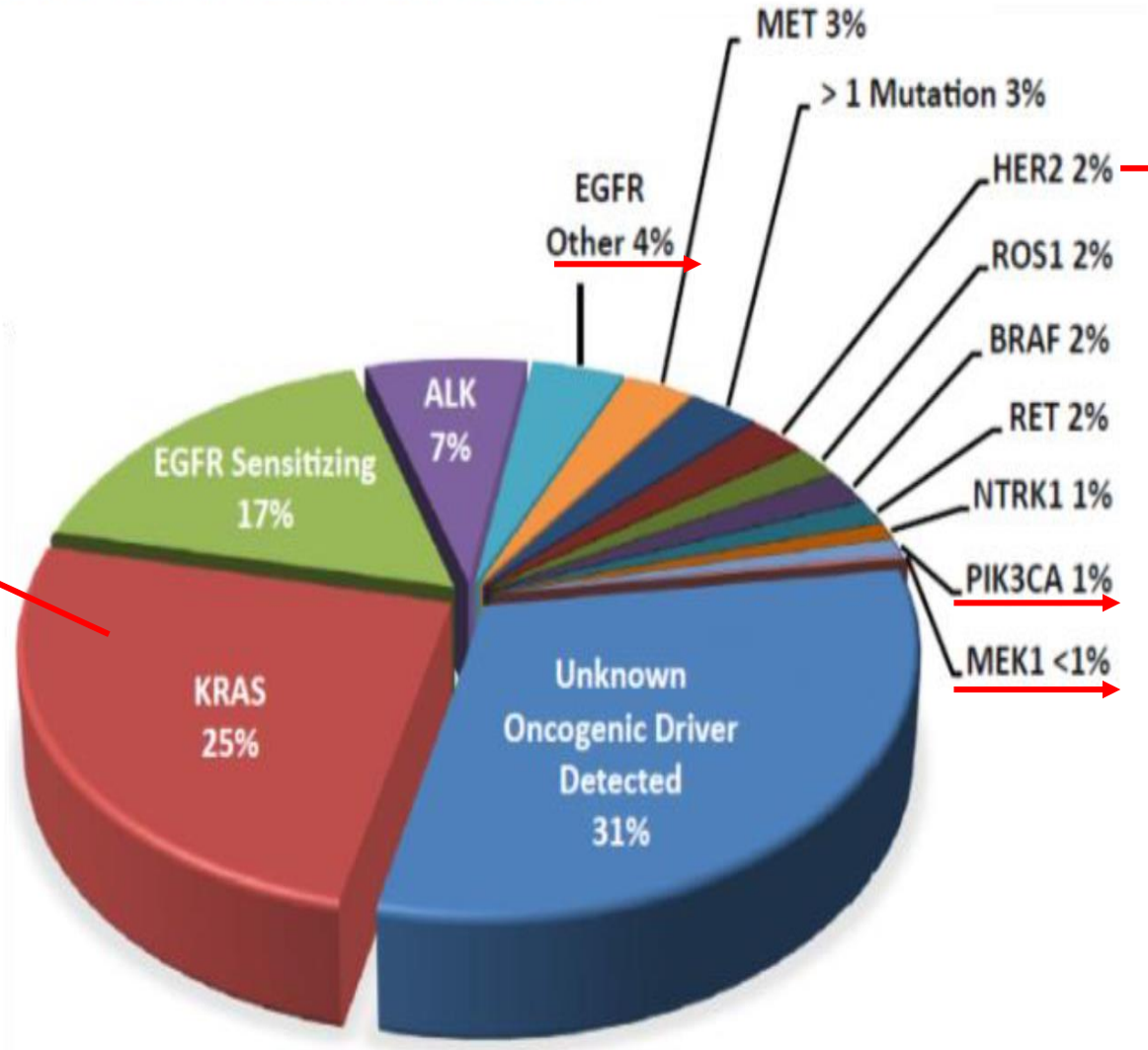
C non épidermoïde

C épidermoïde

- EGFR Exon 19 → Osimertinib, Erlotinib, Afatinib, Gefitinib, Dacomitinib, Erlo + Ramu, Erlo + Beva
- ALK → Alectinib, Brigatinib, Lorlatinib, Ceritinib, Crizotinib
- ROS-1 → Entrectinib, Crizotinib, Ceritinib
- BRAF → Dabrafenib + Trametinib, Vemurafenib
- NTRK → Larotrectinib, Entrectinib
- MET → Capmatinib, Tepotinib, crizotinib
- RET → Selpercatinib, Pralsetinib, Cabozantinib, Vandetanib

- EGFR Exon 20 → L1 = CT → L2 = Amivantamab ou Mobocertinib
- KRAS G12C → L1 = CT → L2 = Sotorasib

Adenocarcinoma



Inhibiteur de la mutation KRAS G12C :
- Sotorasib (AMG 510)
- Adagrasib

Anti-Her2:
- Poziotinib
- Trastuzumab Deruxtecan

Patients
sans drivers moléculaires
PDL-1 < 1 %

Arbre décisionnel 2021, 1ere ligne de traitement

C non épidermoïde

Contraindications to PD-1 or PD-L1 inhibitors[c]

Useful in Certain Circumstances

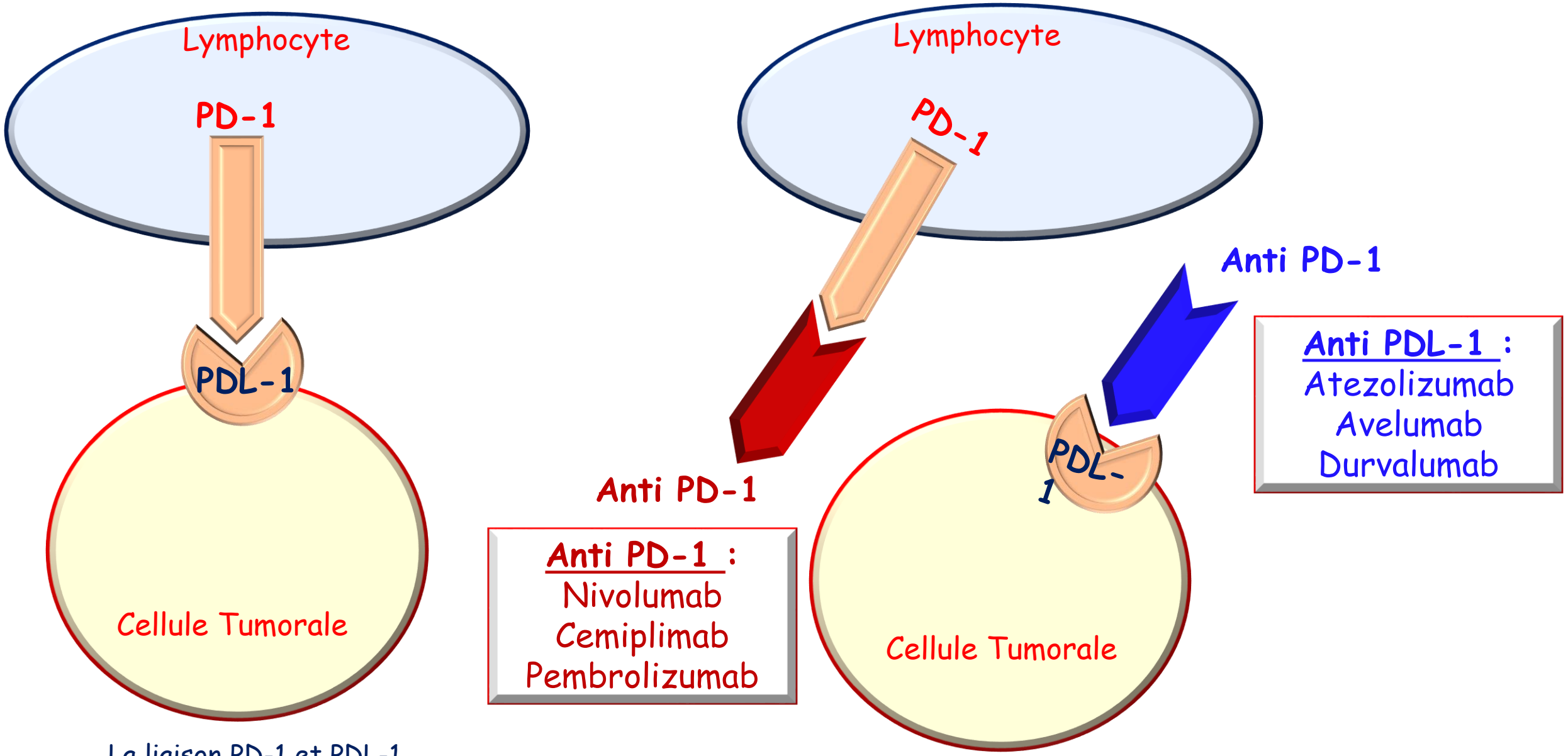
- Bevacizumab[e]/carboplatin/paclitaxel (category 1)[7,f,g,h]
- Bevacizumab[e]/carboplatin/pemetrexed[7,8,f,g,h]
- Bevacizumab[e]/cisplatin/pemetrexed[9,f,g,h]
- Carboplatin/albumin-bound paclitaxel (category 1)[10]
- Carboplatin/docetaxel (category 1)[11]
- Carboplatin/etoposide (category 1)[12,13]
- Carboplatin/gemcitabine (category 1)[14]
- Carboplatin/paclitaxel (category 1)[15]
- Carboplatin/pemetrexed (category 1)[16]
- Cisplatin/docetaxel (category 1)[11]
- Cisplatin/etoposide (category 1)[17]
- Cisplatin/gemcitabine (category 1)[15,18]
- Cisplatin/paclitaxel (category 1)[19]
- Cisplatin/pemetrexed (category 1)[18]
- Gemcitabine/docetaxel (category 1)[20]
- Gemcitabine/vinorelbine (category 1)[21]

C épidermoïde

Contraindications to PD-1 or PD-L1 inhibitors[c]

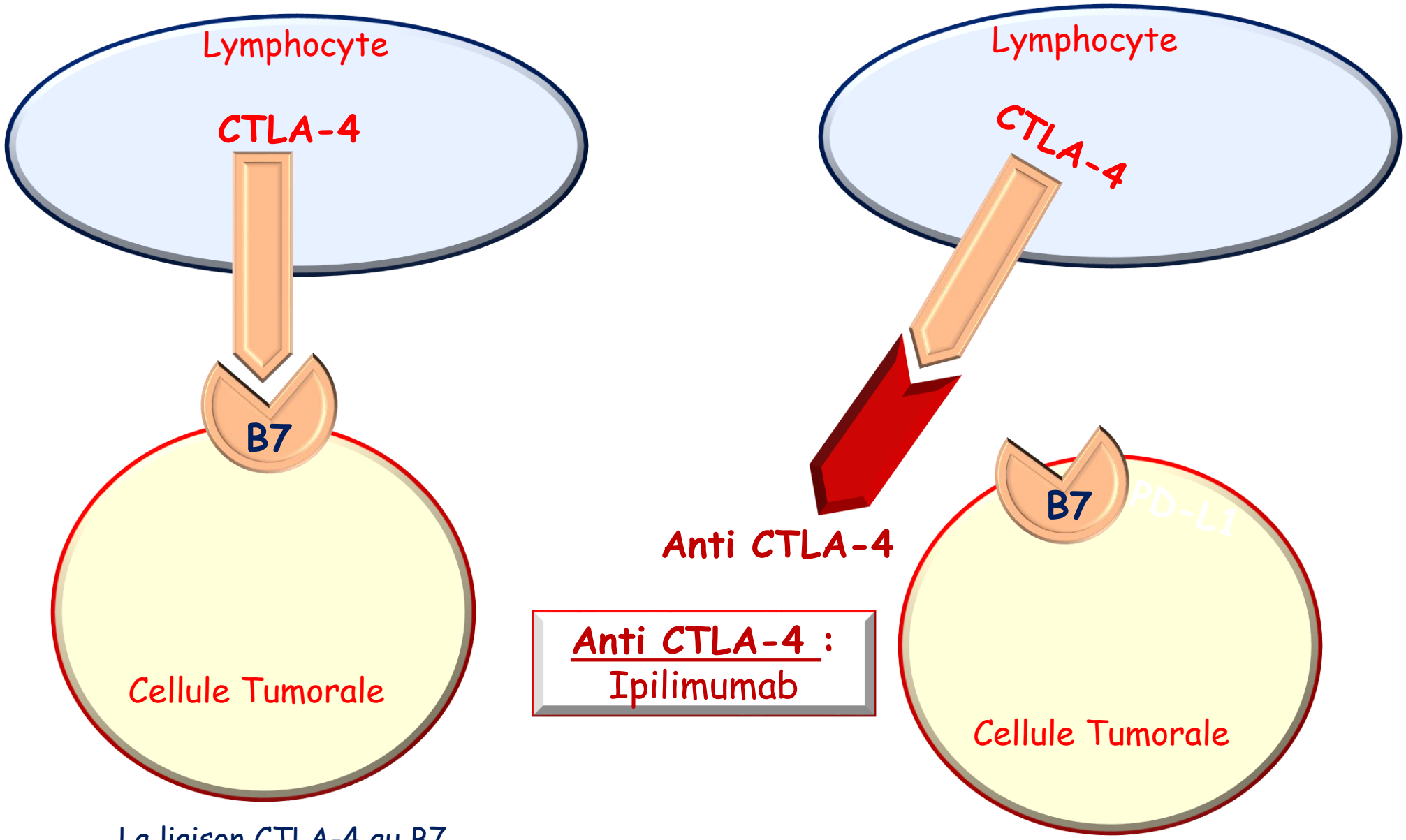
Useful in Certain Circumstances

- Carboplatin/albumin-bound paclitaxel (category 1)[9]
- Carboplatin/docetaxel (category 1)[11]
- Carboplatin/gemcitabine (category 1)[14]
- Carboplatin/paclitaxel (category 1)[15]
- Cisplatin/docetaxel (category 1)[11]
- Cisplatin/etoposide (category 1)[17]
- Cisplatin/gemcitabine (category 1)[15,18]
- Cisplatin/paclitaxel (category 1)[19]
- Gemcitabine/docetaxel (category 1)[20]
- Gemcitabine/vinorelbine (category 1)[21]



La liaison PD-1 et PDL-1 empêche l'activation lymphocytaire.

En bloquant la liaison PDL-1 et PD-1 Le lymphocyte est réactivé.



Anti CTLA-4 :
Ipilimumab

La liaison CTLA-4 au B7
empêche l'activation lymphocytaire.

En bloquant la liaison CTLA-4 au B7
Le lymphocyte est réactivé.

Patients
sans drivers moléculaires
PDL-1 ≥ 1- 49 %

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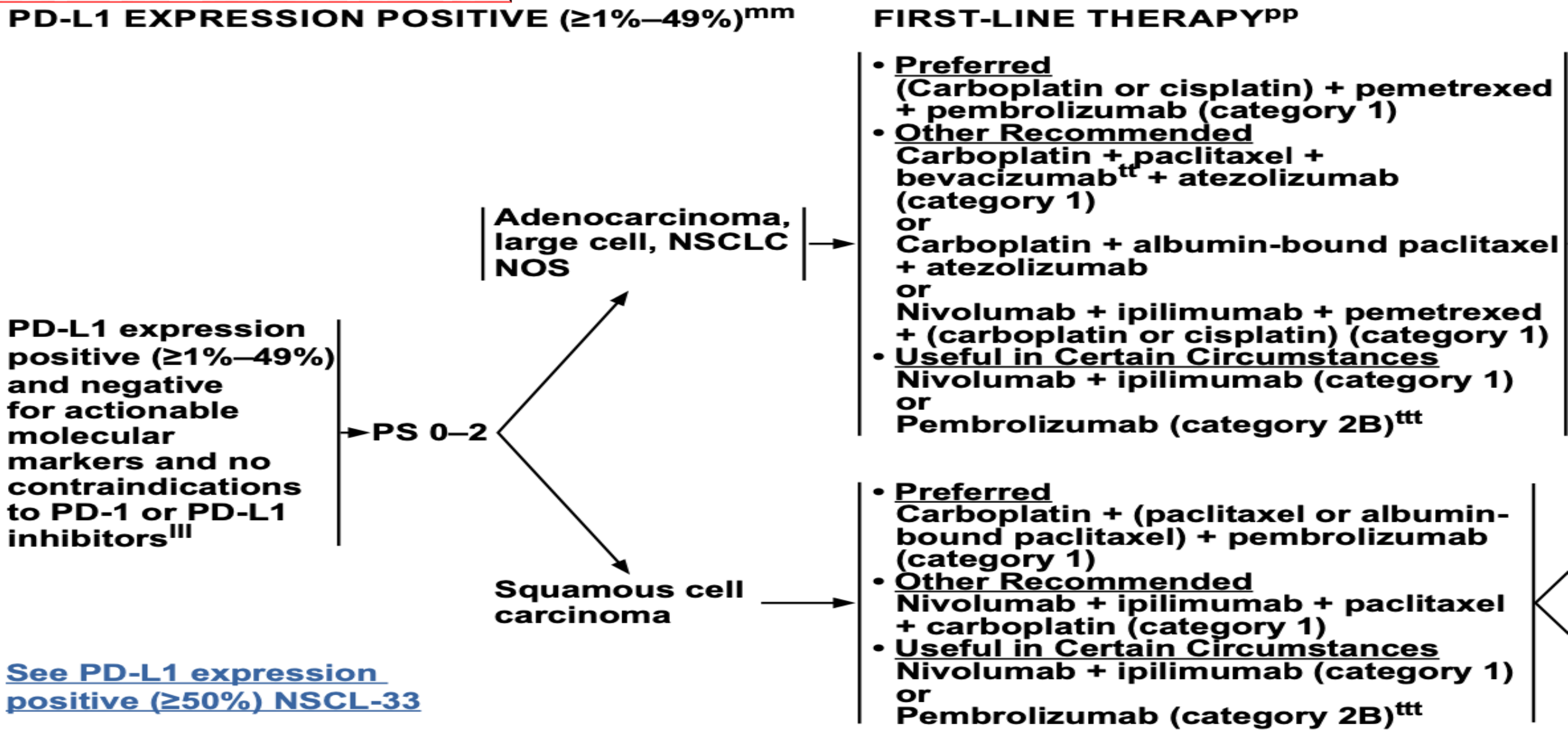

Patients sans drivers moléculaires
PDL-1 ≥ 1- 49 %

ines Version 7.2021
ell Lung Cancer

PD-L1 EXPRESSION POSITIVE (≥1%–49%)[mm]

FIRST-LINE THERAPY[pp]

PD-L1 expression positive (≥1%–49%) and negative for actionable molecular markers and no contraindications to PD-1 or PD-L1 inhibitors[lll]

→ **PS 0–2**

Adenocarcinoma, large cell, NSCLC NOS →

- **Preferred**
  (Carboplatin or cisplatin) + pemetrexed + pembrolizumab (category 1)
- **Other Recommended**
  Carboplatin + paclitaxel + bevacizumab[ttt] + atezolizumab (category 1)
  or
  Carboplatin + albumin-bound paclitaxel + atezolizumab
  or
  Nivolumab + ipilimumab + pemetrexed + (carboplatin or cisplatin) (category 1)
- **Useful in Certain Circumstances**
  Nivolumab + ipilimumab (category 1)
  or
  Pembrolizumab (category 2B)[ttt]

Response or stable disease →
- **Continuation maintenance[pp]**
- Pembrolizumab (category 1)[mmm]
- Pembrolizumab + pemetrexed (category 1)[nnn]
- Atezolizumab and bevacizumab (category 1)[ooo]
- Atezolizumab[ppp]
- Nivolumab + ipilimumab (category 1)[qqq]

Progression → **See Systemic Therapy[rrr]** (NSCL-K 1 of 5) or **Subsequent Therapy[rrr]** (NSCL-K 4 of 5)

Squamous cell carcinoma →

- **Preferred**
  Carboplatin + (paclitaxel or albumin-bound paclitaxel) + pembrolizumab (category 1)
- **Other Recommended**
  Nivolumab + ipilimumab + paclitaxel + carboplatin (category 1)
- **Useful in Certain Circumstances**
  Nivolumab + ipilimumab (category 1)
  or
  Pembrolizumab (category 2B)[ttt]

Response or stable disease →
- **Continuation maintenance[pp]**
- Pembrolizumab[mmm,sss]
- Nivolumab + ipilimumab (category 1)[qqq]

Progression → **See Systemic Therapy[rrr]** (NSCL-K 2 of 5) or **Subsequent Therapy[rrr]** (NSCL-K 4 of 5)

See PD-L1 expression positive (≥50%) NSCL-33

Patients
sans drivers moléculaires
PDL-1 ≥ 50 %

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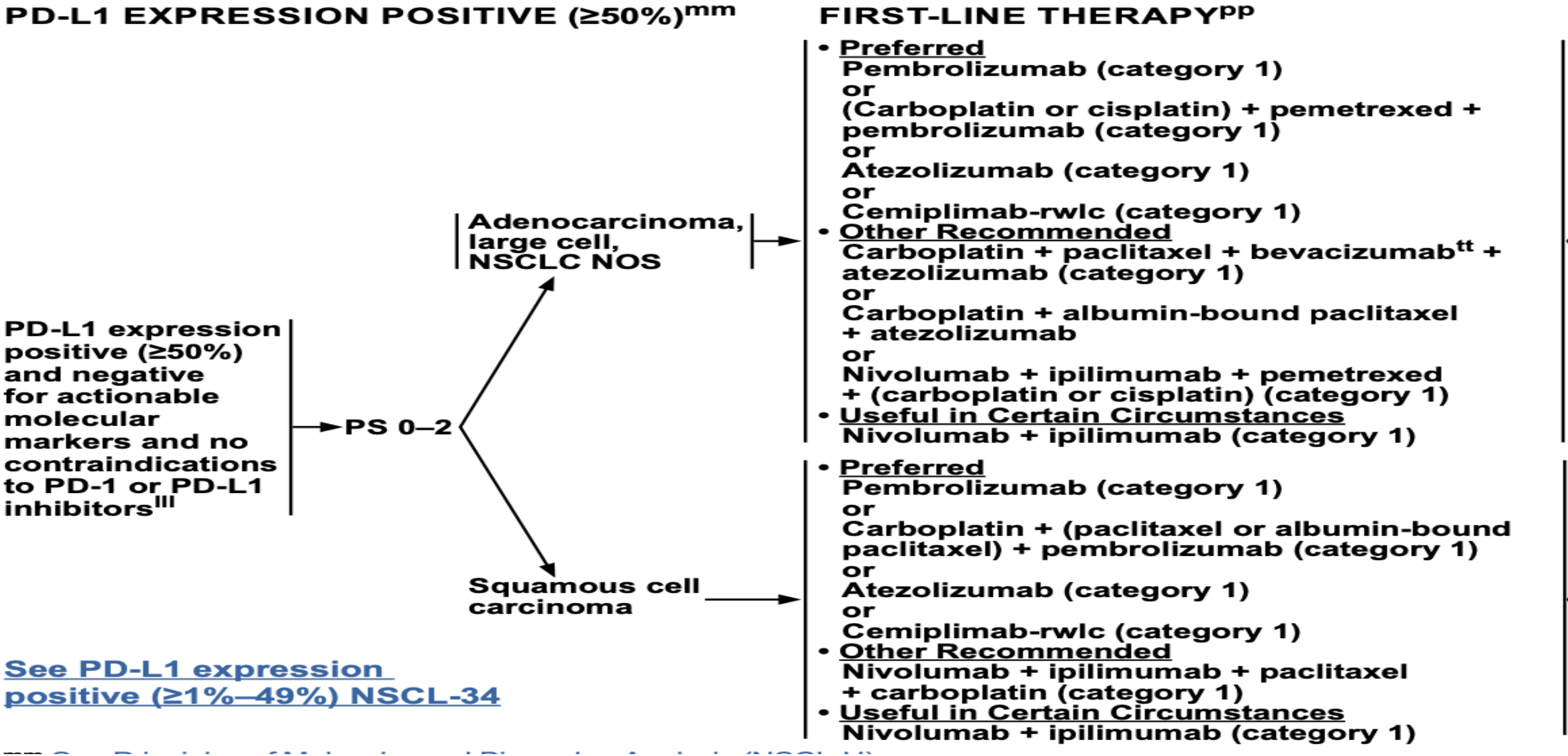
Non-Small Cell Lung Cancer



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Non-Small Cell Lung Cancer

NCCN Guidelines Index
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Discussion

PD-L1 EXPRESSION POSITIVE (≥50%)[mm]

PD-L1 expression positive (≥50%) and negative for actionable molecular markers and no contraindications to PD-1 or PD-L1 inhibitors[lll]

→ PS 0–2

Adenocarcinoma, large cell, NSCLC NOS

→ FIRST-LINE THERAPY[pp]

- **Preferred**
  - Pembrolizumab (category 1)
  - or
  - (Carboplatin or cisplatin) + pemetrexed + pembrolizumab (category 1)
  - or
  - Atezolizumab (category 1)
  - or
  - Cemiplimab-rwlc (category 1)
- **Other Recommended**
  - Carboplatin + paclitaxel + bevacizumab[tt] + atezolizumab (category 1)
  - or
  - Carboplatin + albumin-bound paclitaxel + atezolizumab
  - or
  - Nivolumab + ipilimumab + pemetrexed + (carboplatin or cisplatin) (category 1)
- **Useful in Certain Circumstances**
  - Nivolumab + ipilimumab (category 1)

Squamous cell carcinoma

→ FIRST-LINE THERAPY[pp]

- **Preferred**
  - Pembrolizumab (category 1)
  - or
  - Carboplatin + (paclitaxel or albumin-bound paclitaxel) + pembrolizumab (category 1)
  - or
  - Atezolizumab (category 1)
  - or
  - Cemiplimab-rwlc (category 1)
- **Other Recommended**
  - Nivolumab + ipilimumab + paclitaxel + carboplatin (category 1)
- **Useful in Certain Circumstances**
  - Nivolumab + ipilimumab (category 1)

See PD-L1 expression positive (≥1%–49%) NSCL-34

Response or stable disease

→ Continuation maintenance[pp]

- Pembrolizumab (category 1)[mmm]
- Pembrolizumab + pemetrexed (category 1)[nnn]
- Atezolizumab and bevacizumab (category 1)[ooo]
- Atezolizumab[ppp]
- Nivolumab + ipilimumab (category 1)[qqq]
- Cemiplimab-rwlc (category 1)

Progression

→ See Systemic Therapy[rrr] (NSCL-K 1 of 5) or Subsequent Therapy[rrr] (NSCL-K 4 of 5)

Response or stable disease

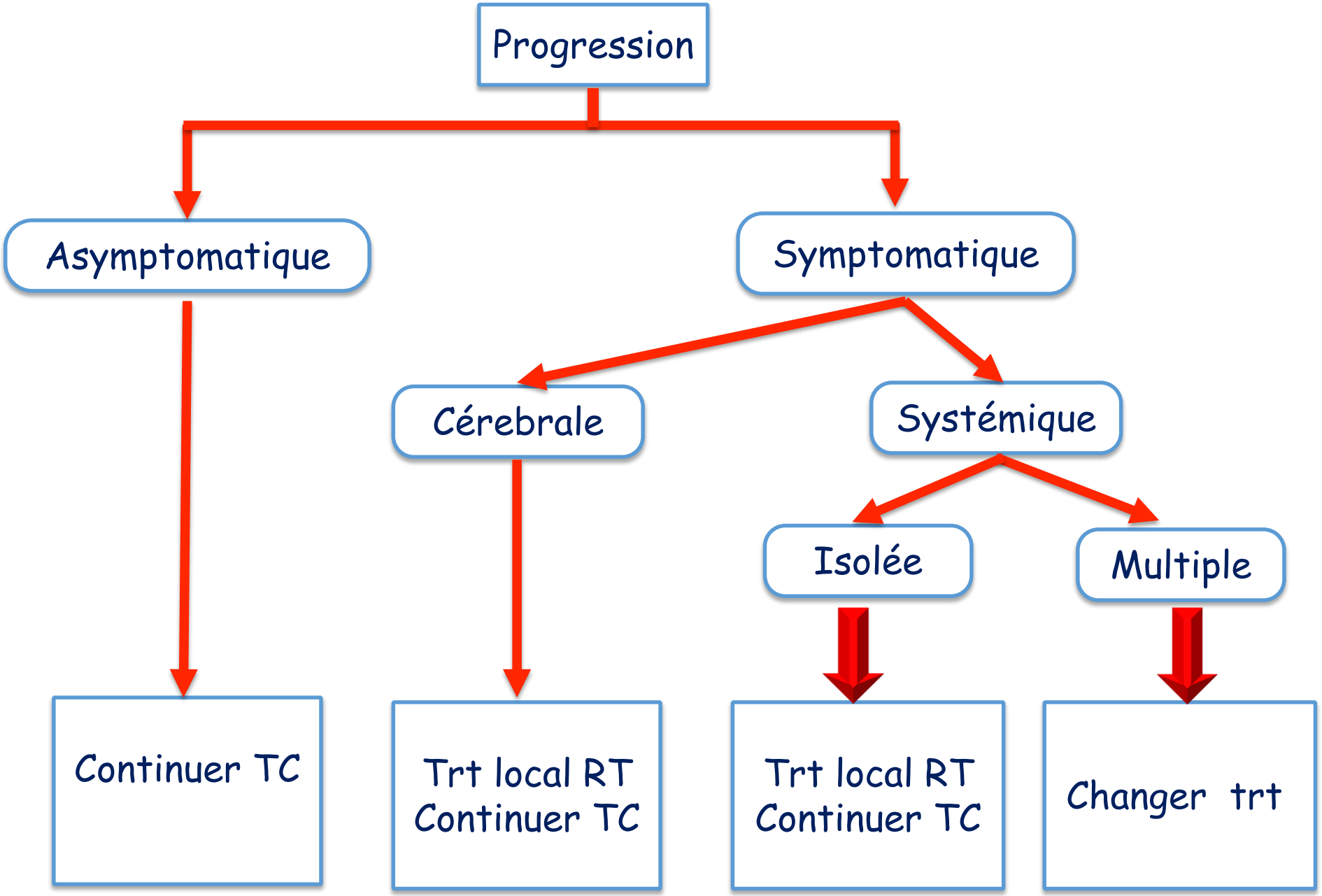
→ Continuation maintenance[pp]

- Pembrolizumab (category 1)[ooo,sss]
- Atezolizumab[ppp]
- Nivolumab + ipilimumab (category 1)[qqq]
- Cemiplimab-rwlc (category 1)

Progression

→ See Systemic Therapy[rrr] (NSCL-K 2 of 5) or Subsequent Therapy[rrr] (NSCL-K 4 of 5)

Stratégie thérapeutique / patient sous T Ciblée



Conclusion