台灣晚期
肺癌藥物治療共識

共同編撰

台灣胸腔暨重症加護醫學會

中華民國癌症醫學會

台灣肺癌學會

台灣臨床腫瘤醫學會

台灣免疫暨腫瘤學會

編撰委員

何肇基教授 / 吳尚俊醫師 編修

分組	組長	組員				
		台灣胸腔暨重症加護醫學會	台灣肺癌學會	台灣臨床腫瘤醫學會	中華民國癌症醫學會	台灣免疫暨腫瘤學會
小細胞肺癌	何肇基	蔡鎮良 蕭世欣	江起陸 賴建豪	施慧瑄 朱逸羣	徐偉勛	吳銘芳 張境夫
鱗狀細胞癌	賴俊良	張時杰 楊宗穎	蘇 健 羅永鴻	楊志仁 徐稟智	廖斌志	謝燿宇
非鱗狀細胞癌 有驅動基因	夏德椿	蘇 健 郭志熙	黃俊耀 廖唯昱	徐培菘 何明霖	廖斌志	王智亮 張家崙
非鱗狀細胞癌 無驅動基因	張文震	林建中 涂智彥	郭志熙 趙恒勝	林旻希 潘奕宏	徐偉勛	吳教恩

Levels of evidence

I. Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta–analyses of well–conducted randomized trials without heterogeneity

II. Small randomized trials or large randomized trials with a suspicion of bias (low methodological quality) or meta–analyses of such trials or of trials with demonstrated heterogeneity

III. Prospective cohort studies

IV. Retrospective cohort studies of case—control studies

V. Studies without control group, case reports, experts' opinions

Outline

NON-SQUAMOUS CELL CARCINOMA WITH DRUGGABLE ONCOGENIC DRIVERS

#Not Taiwan FDA approved.

EGFR mutation

■ Sensitizing *EGFR* mutation

▶ First–line treatment

- Osimertinib is preferred **(Category I)**[1].
- Gefitinib, erlotinib, afatinib, or dacomitinib are also recommended **(Category I)**[2–5].
- Erlotinib with bevacizumab or erlotinib with ramucirumab represent a front–line treatment option **(Category II)**[6, 7].

▶ *EGFR* S768I, L861Q, and/or G719X mutations

- Afatinib or osimertinib# is preferred **(Category II)**[8, 9].
- Gefitinib, erlotinib, or dacomitinib is also recommended **(Category II)**[2, 3, 5].

▶ Second–line treatment

- Progression on gefitinib, erlotinib, afatinib, or dacomitinib should be tested for the presence of the *EGFR* T790M mutation (tissue biopsy and/or liquid biopsy).
- Osimertinib is the standard therapy for T790M positive after first–line EGFR–TKI **(Category I)**[10].
- Systemic therapy including platinum–based doublet is the standard therapy for patients harboring tumors without acquired *EGFR* T790M.
- Combination of atezolizumab and bevacizumab with carboplatin and paclitaxel might be considered **(Category IV)**[11].

EGFR exon 20 insertion

▶ First–line treatment

- *EGFR*–A763_Y764insFQEA: Sensitive to first–, second–, and third–generation EGFR TKIs [12].
- Systemic therapy including platinum–based doublet is the standard therapy.

▶ Second–line treatment

- Amivantamab or mobocertinib# is preferred **(Category II)**[13, 14].

ALK–rearrangement

▶ **First–line treatment**

- Alectinib, brigatinib or lorlatinib is preferred **(Category I)**[15–17].
- Ceritinib is also recommended **(Category I)**[18].
- Crizotinib is also recommended **(Category I)**[19].

▶ **Second–line treatment**

- Ceritinib, alectinib, brigatinib or lorlatinib is preferred after progression on crizotinib or intolerant to crizotinib **(Category I)**[20–23].
- Lorlatinib is recommended in patients who progress after a second–generation ALK TKIs. **(Category II)**[23].
- Systemic therapy including platinum–based doublet should be considered if the next–generation ALK inhibitors are not available.
- Combination of atezolizumab and bevacizumab with carboplatin and paclitaxel might be considered **(Category IV)**[11].

ROS1 rearrangement

▶ **First–line treatment**

- Entrectinib or crizotinib is preferred **(Category II)**[24, 25].
- Ceritinib[#] is also recommended **(Category III)**[20].

▶ **Second–line treatment**

- Lorlatinib is preferred **(Category III)**[26].
- Systemic therapy including platinum–based doublet if the next–generation *ROS–1* inhibitors are not available

BRAF^{V600E} mutation

▶ **First–line treatment**

- Dabrafenib/trametinib is preferred **(Category II)**[27].

▶ **Second–line treatment**

- Systemic therapy including platinum–based doublet is recommended.

RET rearrangement

▶ **First-line treatment**
- Selpercatinib or pralsetinib[#] is preferred **(Category II)**[28, 29].

▶ **Second-line treatment**
- Systemic therapy including platinum-based doublet is recommended.

NTRK 1/2/3 gene fusion

▶ **First-line treatment**
- Larotrectinib or entrectinib are preferred **(Category II)**[30, 31].

▶ **Second-line treatment**
- Systemic therapy including platinum-based doublet is recommended.

METex14 skipping mutation

▶ **First-line treatment**
- Capmatinib or tepotinib is preferred **(Category II)**[32, 33].
- Crizotinib[#] is also recommended **(Category II)**[34].

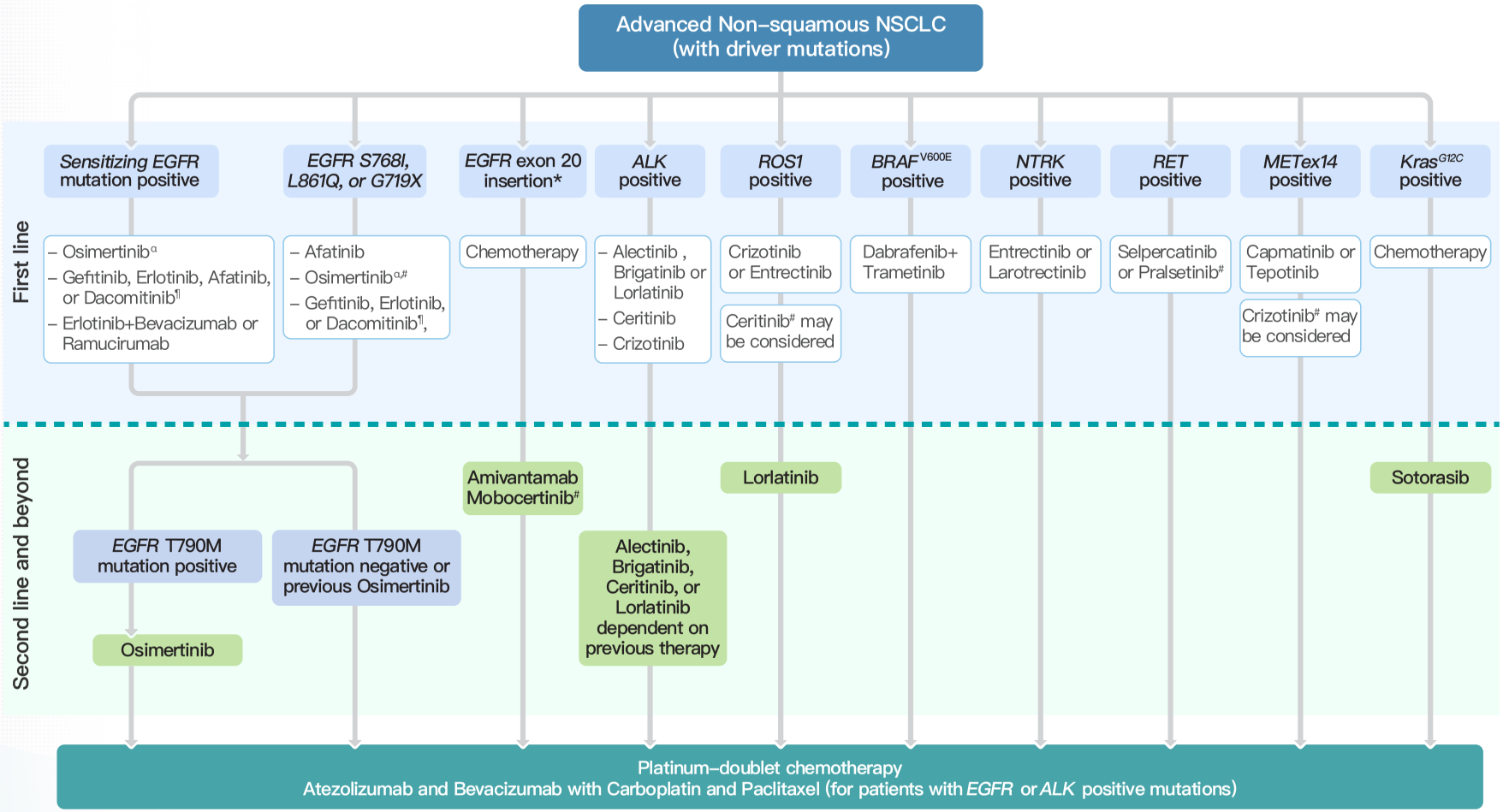
▶ **Second-line treatment**
- Systemic therapy including platinum-based doublet is recommended.

KRAS^{G12C} mutation

▶ **First-line treatment**
- Systemic therapy including platinum-based doublet is recommended.

▶ **Second-line treatment**
- Sotorasib is preferred **(Category II)**[35].

Non-squamous cell carcinoma with druggable oncogeneic drivers



[¶]Dacomitinib: No brain metastasis data; [α]Osimertinib: favor patients with brain metastasis or leptomeningeal carcinomatosis; *EGFR-A763_Y764insFQEA: Sensitive to first-, second-, and third-generation EGFR TKIs.
PS: Drug sequence by time to market; [#]Not Taiwan FDA approved.

NON-SQUAMOUS CELL CARCINOMA WITHOUT DRUGGABLE ONCOGENIC DRIVERS

#Not Taiwan FDA approved.

Immunotherapy should be considered for all non–squamous NSCLC patients without druggable oncogene drivers. In the patients unfit for PD–1 or PD–L1 inhibitors,† chemotherapy should be considered.

†**Unfit to the treatment of PD–1 or PD–L1 inhibitor [36, 37]**

- Active or previously documented autoimmune disease and/or current use of immunosuppressive agents.
- Presence of an oncogene (eg, *EGFR* [exon 19 deletions, or p.L858R point mutation in exon 21], *ALK*, *ROS1* or *RET* rearrangements), which would predict lack of benefit.
- If progression on PD–1/PD–L1 inhibitor, switching to another using a PD–1/PD–L1 inhibitor is not recommended.

First–line treatment

PD–L1 ≥ 50%

- Pembrolizumab, atezolizumab, or combination pembrolizumab with pemetrexed plus platinum, is preferred **(Category I)**[38–40].The other option is cemiplimab–rwlc#, but it is not available in Taiwan **(Category I)** [41].
- Atezolizumab in combination with bevacizumab, paclitaxel and carboplatin, combination atezolizumab with carboplatin and nab–paclitaxel, combination nivolumab and Ipilimumab with pemetrexed plus platinum, or nivolumab in combination with bevacizumab, paclitaxel and carboplatin is also recommended **(Category I)** [42–45].
- Combination nivolumab and ipilimumab represents a front–line treatment option **(Category I)**[46].

PD–L1 ≥ 1%—49%

- Pembrolizumab with pemetrexed plus platinum is preferred **(Category I)**[40].
- Atezolizumab in combination with bevacizumab, paclitaxel and carboplatin, combination atezolizumab with carboplatin and nab–paclitaxel, combination nivolumab and ipilimumab with pemetrexed plus platinum, or nivolumab in combination with bevacizumab, paclitaxel and carboplatin is also recommended **(Category I)**[42–45].
- Combination nivolumab and ipilimumab represents a front–line treatment option **(Category I)**[46]. The other option is pembrolizumab, especially for patients who are not suitable for chemotherapy **(Category I)**[47].

PD–L1 <1%

- Pembrolizumab with pemetrexed plus platinum is preferred. **(Category I)**[40].
- Atezolizumab in combination with bevacizumab, paclitaxel and carboplatin, combination atezolizumab with carboplatin and nab–paclitaxel, or combination nivolumab and ipilimumab with pemetrexed plus platinum are also recommended **(Category I)**[42–44]. Combination nivolumab and ipilimumab[#] is also effective in the post–hoc analysis **(Category II)** [46].

Contraindications to immunotherapy or immunotherapy are not available

- Maximum six cycles of platinum–based doublets chemotherapy is suggested **(Category I)** [48].
- Pemetrexed is preferred to gemcitabine or docetaxel for patients with non–squamous tumors **(Category I)**[49, 50].
- Less toxic maintenance monotherapy should be considered, and pemetrexed is preferred **(Category I)**[51].
- Combination bevacizumab with paclitaxel and carboplatin, or combination bevacizumab with pemetrexed and platinum may be offered in the absence of contraindications **(Category I)**[52–54].

Second–line treatment

PD–L1 ≥ 50%

- For patients with progression after first–line immunotherapy (pembrolizumab, atezolizumab, combination of nivolumab and ipilimumab, or cemiplimab–rwlc[#]), platinum–based chemotherapy is recommended as the second–line treatment option.
- PD–1 and PD– L1 inhibitors (nivolumab and atezolizumab) are the treatment of choice for PD–L1 inhibitor–naive NSCLC in second–line setting, irrespective of PD–L1 expression **(Category I)**[55, 56]. Pembrolizumab is indicated for second–line treatment of lung cancer with PD–L1 ≧ 1% **(Category I)**[57].
- In patients not suitable for immunotherapy, second–line chemotherapy is recommended.
- Docetaxel+/–Ramucirumab, or TS–1 is a treatment option in NSCLC patients progressing after first–line chemotherapy **(Category I)**[58–60].
- Erlotinib represents a potential second– or third–line treatment option in particular for patients not suitable for immunotherapy or second–line chemotherapy in unknown *EGFR* status or *EGFR–WT* tumors **(Category II)**[61].

Non-squamous cell carcinoma without druggable oncogenic drivers

ICIs are available and no contraindications to ICIs.†

First line

Yes

PD-L1 ≧ 50%

- Pembrolizumab
- Atezolizumab
- Pembrolizumab/Pemetrexed/Platinu
- Atezolizumab/Bevacizumab/Paclitaxel /Carboplatin
- Atezolizumab/nab-Paclitaxel/Carboplatin
- Nivolumab/Ipilimumab/Pemetrexed/ Platinum
- Nivolumab/Ipilimumab
- Nivolumab/Bevacizumab/Paclitaxel/ Carboplatin
- Cemiplimab-rwlc#

PD-L1 1-49%

- Pembrolizumab/Pemetrexed/Platinum
- Atezolizumab/Bevacizumab/ Carboplatin/Paclitaxel
- Nivolumab/Ipilimumab/Pemetrexed/ Platinum
- Nivolumab/Ipilimumab
- Nivolumab/Bevacizumab/Paclitaxel/ Carboplatin
- Pembrolizumab

PD-L1<1%

- Pembrolizumab/Pemetrexed/Platinum
- Atezolizumab/Bevacizumab/ Carboplatin/Paclitaxel
- Nivolumab/Ipilimumab/Pemetrexed/ Platinum
- Nivolumab/Ipilimumab#

No

- Platinum-based chemotherapy (Favor Pemetrexed)*
- Bevacizumab/Paclitaxel/ Carboplatin
- Bevacizumab/Pemetrexed/ Platinum

Second-line

For patients with 1st-line single ICI using:

- Platinum-based chemotherapy (Favor Pemetrexed)*

Other treatment options:

- Ramucirumab/Docetaxel
- Erlotinib
- Docetaxel
- TS-1

Platinum-based chemotherapy for 4-6 cycles*

- Platinum/Pemetrexed
- Platinum/Gemcitabine
- Platinum/Docetaxel
- Platinum/Paclitaxel
- Carboplatin/Albumin-bound paclitaxel
- Platinum/Etoposide

or

- Gemcitabine/Docetaxel
- Gemcitabine/Vinorelbine
- Bevacizumab/Paclitaxel/Carboplatin
- Bevacizumab/Pemetrexed/Platinum

- Nivolumab
- Pembrolizumab (PD-L1≧ 1%)
- Atezolizumab

Other treatment options:

- Ramucirumab/Docetaxel
- Erlotinib
- Docetaxel
- TS-1

*Maximum six cycles of platinum-based doublets followed by less toxic maintenance monotherapy should be considered (*N Engl J Med 2002; 346:92-98; Lancet. 2009;374:1432-40.*); #Not Taiwan FDA approved.
†Contraindications for treatment with PD-1/PD-L1 inhibitors may include active or previously documented autoimmune disease and/or current use of immunosuppressive agents, or presence of an oncogene (ie, EGFR exon 19 deletion or L858R, ALK, ROS1 or RET rearrangements), which would predict lack of benefit (NCCN guideline) ICI: Immune checkpoint inhibitors

SQUAMOUS CELL CARCINOMA WITHOUT DRUGGABLE ONCOGENIC DRIVERS

#Not Taiwan FDA approved.

Immunotherapy should be considered for all squamous NSCLC patients without druggable oncogene drivers. In the patients unfit for PD–1 or PD–L1 inhibitors,† chemotherapy should be considered.

†**Unfit to the treatment of PD–1 or PD–L1 inhibitor [36, 37]**

- Active or previously documented autoimmune disease and/or current use of immunosuppressive agents.
- Presence of oncogenic driver mutations, which would predict lack of benefit.
- If progression on PD–1/PD–L1 inhibitor, switching to another using a PD–1/PD–L1 inhibitor is not recommended.

(PS: Taiwan National Health Insurance (NHI) requests EGFR and ALK testing before using PD–1 or PD–L1 inhibitors.)

First–line treatment

PD–L1 ≥ 50%

- Monotherapy with pembrolizumab, atezolizumab, or combination pembrolizumab with paclitaxel or albumin bound paclitaxel plus carboplatin is preferred (Category I)[38, 39, 62].
- Combination nivolumab and ipilimumab with paclitaxel plus carboplatin is also recommended **(Category I)**[44].
- Combination nivolumab and ipilimumab represents a front–line treatment option **(Category I)**[46].
- The other option is cemiplimab–rwlc#, which is not available in Taiwan **(Category I)**[41].

PD–L1 ≥ 1%—49%

- Pembrolizumab with paclitaxel or albumin bound paclitaxel plus carboplatin is preferred **(Category I)**[62].
- Combination nivolumab and ipilimumab with paclitaxel plus carboplatin is also recommended **(Category I)**[44].
- Combination nivolumab and ipilimumab represents a front–line treatment option **(Category I)**[46].
- Monotherapy with pembrolizumab, especially for patients who are not suitable for chemotherapy **(Category II)**[47].

PD–L1 <1%

- Pembrolizumab with paclitaxel or albumin bound paclitaxel plus carboplatin is preferred **(Category I)**[62].
- Combination nivolumab and ipilimumab with paclitaxel plus carboplatin is also recommended **(Category I)**[44].
- The other option: Combination nivolumab and ipilimumab[#] is also effective according to the post–hoc analysis result, but it is not approved by TFDA **(Category II)**[46].

If immunotherapy is not available or contraindicative to immunotherapy

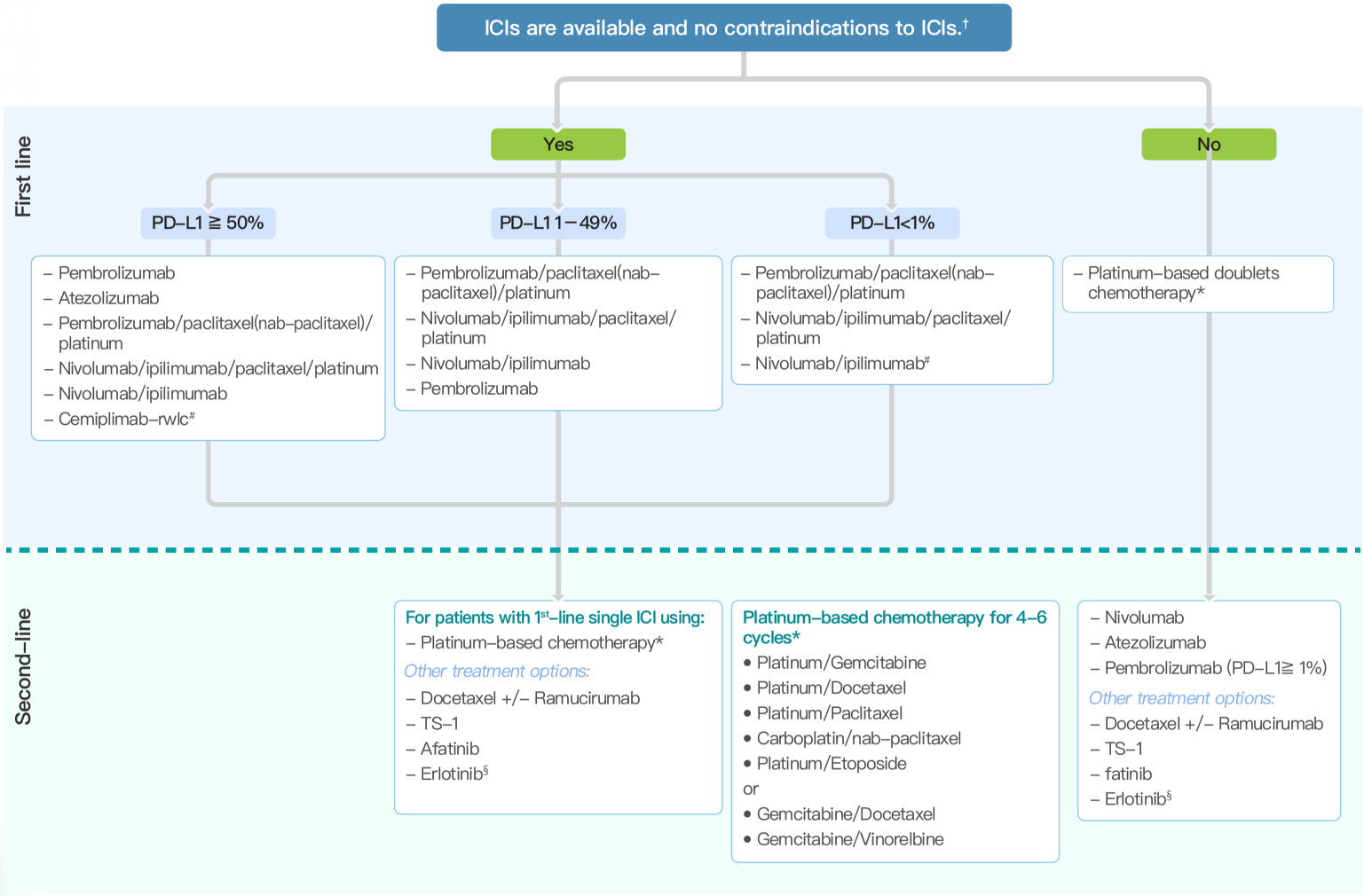
- Maximum six cycles of platinum–based doublets chemotherapy is suggested **(Category I)** [48].*

* Pemetrexed is not recommended for the treatment of squamous cell carcinoma [49].

Second–line treatment

- For patients with progression after first–line immunotherapy (pembrolizumab, atezolizumab, combination of nivolumab and ipilimumab), platinum–based chemotherapy is recommended as the second–line treatment option.
- PD–L1 and PD–1 inhibitors (nivolumab and atezolizumab) are the treatment of choice for PD–L1 inhibitor–naive NSCLC in the second–line setting, irrespective of PD–L1 expression **(Category I)**[55, 56]. Pembrolizumab is indicated for second–line treatment of lung cancer with PD–L1 ≧ 1% **(Category I)**[57].
- In patients not suitable for immunotherapy, second–line chemotherapy is recommended.
- Docetaxel+/–Ramucirumab, or TS–1 is a treatment option in lung squamous cell carcinoma patients progressing after first–line chemotherapy **(Category I)**[58–60].
- Afatinib is approved for the second–line treatment lung squamous cell carcinoma irrespective of the *EGFR* mutation status **(Category I)**[63]. Erlotinib is only reimbursed as the third–line treatment of squamous cell carcinoma **(Category II)**[61].

Squamous cell carcinoma without druggable oncogenic drivers



*Maximum six cycles of platinum–based doublets chemotherapy is suggested (*N Engl J Med 2002; 346:92–98*); #Not Taiwan FDA approved.
†Contraindications for treatment with PD–1/PD–L1 inhibitors may include active or previously documented autoimmune disease and/or current use of immunosuppressive agents, or presence of an oncogene (ie, EGFR exon 19 deletion or L858R, ALK, ROS1 or RET rearrangements), which would predict lack of benefit (NCCN guideline).
§ Erlotinib is reimbursed as the third–line treatment by Taiwan NHI. ICI: Immune checkpoint inhibitors

SMALL CELL LUNG CANCER CONSENSUS

#Not Taiwan FDA approved.

Limited-stage SCLC

1. Management of limited-stage SCLC should be discussed in a multidisciplinary committee.
2. Clinical stage I–IIA (T1–2, N0, M0) should consider pathological mediastinal staging, then Lobectomy and mediastinal lymph node dissection or sampling should be considered in pathologic mediastinal staging negative.
3. Limited stage IIB–IIIC (T3–4, N0, M0; T1–4, N1–3, M0) with good performance status (ECOG 0–2), systemic therapy with concurrent radiotherapy should be considered **(category 1)**. Poor performance status (ECOG 3–4), systemic therapy with/without radiotherapy (concurrent or sequential) should be considered.

Primary or adjuvant therapy for limited-stage SCLC

▶ **Preferred regimens**

- Combination of cisplatin and etoposide is preferred **(Category I)**[64].
- Combination of carboplatin and etoposide is also recommended **(Category I)**[64].

Extensive-stage SCLC

Primary therapy for extensive-stage SCLC

▶ **Preferred regimens**

- Carboplatin and etoposide and atezolizumab every 21 days x 4 cycles followed by maintenance atezolizumab every 21 days should be considered. **(Category I)**[65].
- Carboplatin / Cisplatin and etoposide and durvalumab every 21 days x 4 cycles followed by maintenance durvalumab every 28 days should be considered **(Category I)**[66].

▶ **Other recommended regimens**

- Carboplatin and etoposide 4—6 cycles [67].
- Cisplatin and etoposide 4—6 cycles [68–70].

Relapse SCLC or second-line therapy

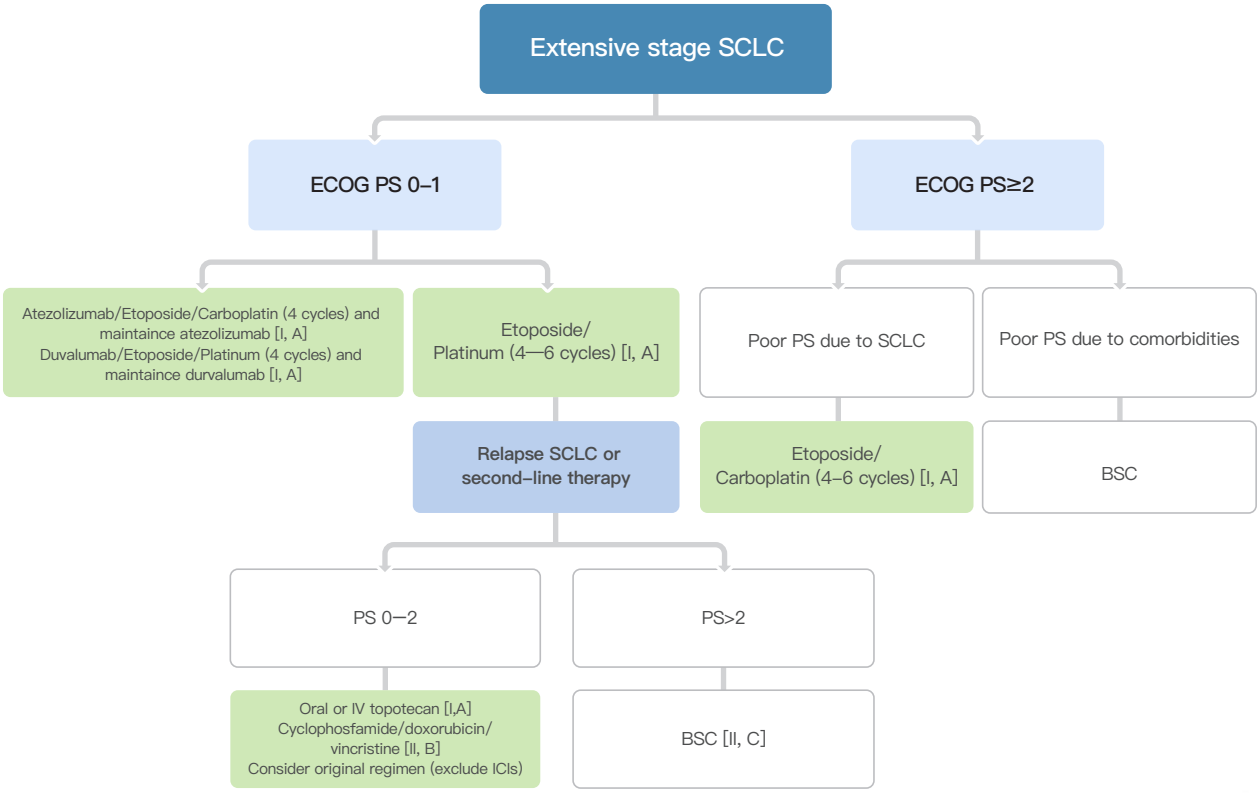
▶ **Preferred regimens**

- Topotecan PO or IV [71].
- The original regimen, excluding ICIs, is also considered [72].

▶ **Other recommended regimens**

- TFDA Approved
  - ✓ Cyclophosphamide/doxorubicin/vincristine (CAV) [71].
  - ✓ Oral etoposide [73, 74].
- No TFDA Approved[#]
  - ✓ Paclitaxel[#] [75, 76]
  - ✓ Docetaxel[#] [77]
  - ✓ Irinotecan[#] [78]
  - ✓ Temozolomide[#] [79, 80]
  - ✓ Vinorelbine[#] [81, 82]
  - ✓ Gemcitabine[#] [83, 84]
  - ✓ Nivolumab[#] [85, 86]
  - ✓ Bendamustine[#] [87]

Small cell lung cancer



[#]Not Taiwan FDA approved.

Modified from the ESMO Clinical Practice Guidelines Ann Oncol. 2021 Jul;32(7):839–853.

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