Il trattamento del NSCLC WT:linee guida AIOM ed internazionali

Dott. Vincenzo Picece
Ospedale Sacro Cuore - Don G. Calabria
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LINEE GUIDA

AIOM Associazione Italiana Oncologi Medici

ESMO European Society for Medical Oncology

ASCO American Society of Clinical Oncology

NCCN National Comprehensive Cancer Network

Linee guida

NEOPLASIE DEL POLMONE

Allo stato attuale la scelta del trattamento medico da proporre al paziente con malattia metastatica si basa sulle caratteristiche del paziente e sulle caratteristiche biologiche della malattia, e si rende necessaria una stratificazione in rapporto allo stato di EGFR e all'istologia. L'informazione relativa allo stato di ALK è al momento utile per la decisione relativa al trattamento di pazienti in progressione dopo chemioterapia di prima linea, in quanto crizotinib è approvato per l'impiego in seconda linea nei casi con traslocazione di ALK.

In assenza di mutazione attivante di EGFR, o nei pazienti in cui lo stato mutazionale di EGFR non sia noto, i regimi a due farmaci contenenti cisplatino per 4-6 cicli costituiscono la terapia di scelta nella prima linea.

Nei pazienti con NSCLC avanzato ad istologia diversa dalla squamosa, la combinazione cisplatino-pemetrexed o l'impiego di bevacizumab in associazione alla chemioterapia nei pazienti eleggibili possono essere valutati come opzioni terapeutiche di prima scelta.

La terapia di mantenimento è un' opzione terapeutica da discutere con il paziente, tenendo comunque presente che, a luglio 2013, nessuno dei farmaci è rimborsato in Italia per tale indicazione.

La terapia radiante svolge un ruolo di pura palliazione, peraltro estremamente importante nel controllo delle metastasi cerebrali, delle sindromi mediastiniche da ostruzione della cava superiore, nelle metastasi ossee e in particolare nelle compressioni midollari da metastasi vertebrali.

Grado di raccomandazione SIGN	Raccomandazione clinica	Forza della raccomandazione clinica
A	Per i pazienti in stadio IV vanno prese in considerazione la chemioterapia e la terapia di supporto, comprensiva della radioterapia ad intento palliativo. Il trattamento chemioterapico di prima linea va riservato a pazienti ambulatoriali, senza considerevole calo ponderale ed in buone condizioni generali.	**Positiva forte**
A	In assenza di mutazioni attivanti dell'EGFR, i regimi a due farmaci contenenti platino rappresentano il trattamento standard di prima linea del NSCLC avanzato. Il cisplatino deve essere considerato il farmaco di prima scelta, e il carboplatino rappresenta un valida alternativa in presenza di controindicazioni all'impiego del cisplatino.	**Positiva forte**
A	Nelle istologie non squamose, sulla base dell'analisi per sottogruppi di un solo studio randomizzato, il regime cisplatino + pemetrexed rappresenta una scelta preferenziale come trattamento di prima linea rispetto al regime cisplatino-gemcitabina, per il suo migliore rapporto rischio/beneficio.	**Positiva debole**

A	Il bevacizumab può essere impiegato in associazione a carboplatino + paclitaxel, unico regime con il quale ha documentato un vantaggio di sopravvivenza, pur essendo in indicazione con qualunque regime a 2 farmaci contenente platino.	**Positiva debole**
A	In pazienti anziani non selezionati, la monochemioterapia deve essere considerata il trattamento standard.	**Positiva forte**
A	In pazienti anziani selezionati, una doppietta con carboplatino o cisplatino (a dosi ridotte) possono rappresentare un'opzione terapeutica.	**Positiva debole**
A	Pazienti in progressione di malattia dopo trattamento di prima linea sono candidati a ricevere un trattamento di seconda linea. Farmaci di possibile impiego sono il docetaxel (per i pazienti che non abbiano ricevuto il farmaco in prima linea), il pemetrexed (per i soli tumori ad istologia non-squamosa, che non abbiano ricevuto il farmaco in prima linea), l'erlotinib.	**Positiva forte**

A	Pazienti in progressione di malattia dopo trattamento di seconda linea dovrebbero essere valutati per ricevere un trattamento di terza linea con erlotinib (se non hanno ricevuto precedentemente il farmaco).	**Positiva debole**

clinical practice guidelines

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

S. Peters[1], A.A. Adjei[2], C. Gridelli[3], M. Reck[4], K. Kerr[5] & E. Felip[6] on behalf of the ESMO Guidelines Working Group*

[1]Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland; [2]Department of Medicine, Roswell Park Cancer Institute, Buffalo, NY, USA; [3]Department of Medical Oncology, 'S.G. Moscati' Hospital, Avellino, Italy; [4]Department of Thoracic Oncology, Hospital Grosshansdorf, Grosshansdorf, Germany; [5]Aberdeen Royal Infirmary, Aberdeen, UK; [6]Vall d'Hebron University Hospital, Barcelona, Spain

Treatment strategy	• The treatment strategy should take into account the histology, molecular pathology, age, PS, comorbidities, and patient's preferences. • Treatment decisions should be discussed within a multidisciplinary tumor board. • Systemic therapy should be offered to all stage IV patients with PS 0–2 [I, A]. • In any stage of NSCLC, smoking cessation should be highly encouraged because it improves the outcome.

First-line treatment

- In the subgroup of non-squamous tumors and in patients treated with third-generation regimens, including gemcitabine and taxanes, cisplatin should be the treatment of choice [I, B].
- Pemetrexed is preferred to gemcitabine in patients with non-squamous tumors [II, B]. Pemetrexed use should be restricted to non-squamous NSCLC in any line of treatment.
- Bevacizumab combined with a paclitaxel–carboplatin regimen may be offered to patients with non-squamous histology NSCLC and PS0–1 after exclusion of contraindications [I, A].
- The combination of bevacizumab and other platinum based chemotherapies may be considered in eligible patients with non-squamous NSCLC [I, A].
- Non-platinum-based combination chemotherapy with third-generation agents should be considered only if platinum therapy is contraindicated [I, A].
- The timing and duration of palliative first-line treatment: chemotherapy should be initiated while the patient has a good PS. For most patients, four cycles of chemotherapy are recommended, with a maximum of six cycles [II, B].

PS ≥2 patients:

- Chemotherapy prolongs survival and possibly improves the QoL in NSCLC patients with a PS of 2, when compared with BSC [I, B]. Single-agent chemotherapy with gemcitabine, vinorelbine, and taxanes represents an option. Platinum-based combinations may also be considered as an alternative [II, B].
- Poor PS (3–4) patients should be offered best supportive care [II, B] in the absence of tumors with activating (sensitizing) EGFR mutations.

Elderly patients:

- Single-agent chemotherapy is the standard of care for first-line therapy for clinically unselected elderly advanced NSCLC patients.
- A survival advantage has been seen for combination therapy in patients aged 70–89 with PS0-2.
- Platinum-based chemotherapy is the preferred option for elderly patients with PS 0–1—as well as selected PS2—and adequate organ function. A single-agent approach might remain the recommended treatment of elderly unfit or comorbid patients who are more likely to present with more treatment-related adverse events [I, B].

Maintenance treatment	• In patients with a non-squamous histology, improvements in PFS and OS were observed with pemetrexed switch maintenance versus placebo following four cycles of platinum-based chemotheraphy. • Switch maintenance with erlotinib versus placebo demonstrated PFS and OS benefit in all histologies, with a greatest benefit in efficacy in patients with stable disease (SD) after induction treatment leading to a label restriction for such patients. • Decisions about maintenance must take into account the histology, response to platinum-doublet chemotherapy, remaining toxicity after first-line chemotherapy, PS, and patient preference [I, B]. • Any patient with a tumor bearing an activating (sensitizing) EGFR mutation should receive an EGFR TKI as maintenance, if not received as the first-line therapy [II, A]. • Continuing pemetrexed following completion of first-line cisplatin plus pemetrexed chemotherapy is recommended in patients with a non-squamous histology [I, B].

Second-line treatment	• Patients clinically or radiologically progressing after first-line chemotherapy with PS 0–2 should be offered second-line chemotherapy. • Comparable options as the second-line therapy consist of pemetrexed—for a non-squamous histology only—or docetaxel [I, B]. Erlotinib is an additional option in EGFR WT patients with PS 0–3 [II, B]. • Any patient with a tumor bearing an activating (sensitizing) EGFR mutation should receive an EGFR TKI as the second-line therapy, if not received previously [I, A]. • Treatment may be prolonged if the disease is controlled and the toxicity acceptable [II, B].
Subsequent lines of treatment	• Erlotinib is indicated for EGFR WT patients who have not yet received EGFR TKIs, with PS 0–3 [II, B]. • Any patient with a tumor bearing an activating (sensitizing) EGFR mutation should receive an EGFR TKI in any line of therapy, if not received previously [I, A].

Treatment of oligometastatic NSCLC	• Stage IV NSCLC patients presenting with solitary metastases, if localized to brain, adrenals, or lung, can be treated with curative intent. • In the case of solitary brain metastasis, surgical resection followed by WBRT or alternatively radiosurgery ± WBRT might be beneficial. Further options include surgical resection of the primary lung combined with systemic chemotherapy [II; B], or definitive chemoradiotherapy, preferred in the case of locally advanced primary, such as solitary station N2 disease [III; B]. • In cases of solitary—histological proven—adrenal metastasis, prolonged survival after resection of the adrenal and the primary tumor has been suggested in selected patients [II; B]. • Solitary lesions in the contralateral lung should, in most cases, be considered as synchronous secondary primary tumors and treated, if possible, with surgery and adjuvant chemotherapy (if indicated), definitive radiotherapy or chemoradiotherapy [II;A].

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ASCO SPECIAL ARTICLE

2011 Focused Update of 2009 American Society of Clinical Oncology Clinical Practice Guideline Update on Chemotherapy for Stage IV Non–Small-Cell Lung Cancer

Christopher G. Azzoli, Sarah Temin, Timothy Aliff, Sherman Baker Jr, Julie Brahmer, David H. Johnson, Janessa L. Laskin, Gregory Masters, Daniel Milton, Luke Nordquist, William Pao, David G. Pfister, Steven Piantadosi, Joan H. Schiller, Reily Smith, Thomas J. Smith, John R. Strawn, David Trent, and Giuseppe Giaccone

Recommendation	Summary
A. First-line chemotherapy	
A1	Evidence supports use of chemotherapy in patients with stage IV* NSCLC with ECOG/Zubrod performance status of 0, 1, possibly 2
A2	In patients with performance status of 0 or 1, evidence supports using combination of two cytotoxic drugs for first-line therapy; platinum combinations are preferred over nonplatinum combinations because they are superior in response rate and marginally superior in OS; nonplatinum therapy combinations are reasonable in patients who have contraindications to platinum therapy; recommendations A8 and A9 address whether to add bevacizumab or cetuximab to first-line cytotoxic therapy
A3	Available data support use of single-agent chemotherapy in patients with performance status of 2; data are insufficient to make recommendation for or against using combination of two cytotoxic drugs in patients with performance status of 2
A4	Evidence does not support selection of specific first-line chemotherapy drug or combination based on age alone
A5	Choice of either cisplatin or carboplatin is acceptable; drugs that may be combined with platinum include third-generation cytotoxic drugs docetaxel, gemcitabine, irinotecan, paclitaxel, pemetrexed, and vinorelbine; evidence suggests cisplatin combinations result in higher response rates than carboplatin and may improve survival when combined with third-generation agents; carboplatin is less likely to cause nausea, nephrotoxicity, and neurotoxicity than cisplatin but more likely to cause thrombocytopenia
A6	In patients with stage IV NSCLC, first-line cytotoxic chemotherapy should be stopped at disease progression or after four cycles in patients whose disease is **stable but** not responding to treatment; two-drug cytotoxic combinations should be administered for no more than six cycles; **for patients with stable disease or response after four cycles, immediate treatment with alternative, single-agent chemotherapy such as pemetrexed in patients with nonsquamous histology, docetaxel in unselected patients, or erlotinib in unselected patients may be considered; limitations of this data are such that break from cytotoxic chemotherapy after fixed course is also acceptable, with initiation of second-line chemotherapy at disease progression**

A7	In unselected patients, erlotinib or gefitinib should not be used in combination with cytotoxic chemotherapy as first-line therapy; in unselected patients, evidence is insufficient to recommend single-agent erlotinib or gefitinib as first-line therapy; first-line use of gefitinib may be recommended for patients with activating *EGFR* mutations; if *EGFR* mutation status is negative or unknown, cytotoxic chemotherapy is preferred (see A2)
A8	On basis of results of one large phase III RCT, update committee recommends addition of bevacizumab (15 mg/kg every 3 weeks) to carboplatin/paclitaxel, except for patients with squamous cell carcinoma histologic type, brain metastases, clinically significant hemoptysis, inadequate organ function, ECOG performance status > 1, therapeutic anticoagulation, clinically significant cardiovascular disease, or medically uncontrolled hypertension; bevacizumab may be continued as tolerated until disease progression
A9	On basis of results of one large phase III RCT, clinicians may consider addition of cetuximab to cisplatin/vinorelbine in first-line therapy in patients with EGFR-positive tumor as measured by immunohistochemistry; cetuximab may be continued as tolerated until disease progression

B. Second-line chemotherapy	
B1	Docetaxel, erlotinib, gefitinib, or pemetrexed is acceptable as second-line therapy for patients with advanced NSCLC with adequate performance status when disease has progressed during or after first-line platinum-based therapy
B2	Evidence does not support selection of specific second-line chemotherapy drug or combination based on age alone
C. Third-line chemotherapy	
C1	When disease progresses on or after second-line chemotherapy, treatment with erlotinib may be recommended as third-line therapy for patients with performance status of 0 to 3 who have not received prior erlotinib or gefitinib
C2	Data are not sufficient to make recommendation for or against using cytotoxic drug as third-line therapy; patients should consider experimental treatment, clinical trials, and best supportive care

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Non-Small Cell Lung Cancer

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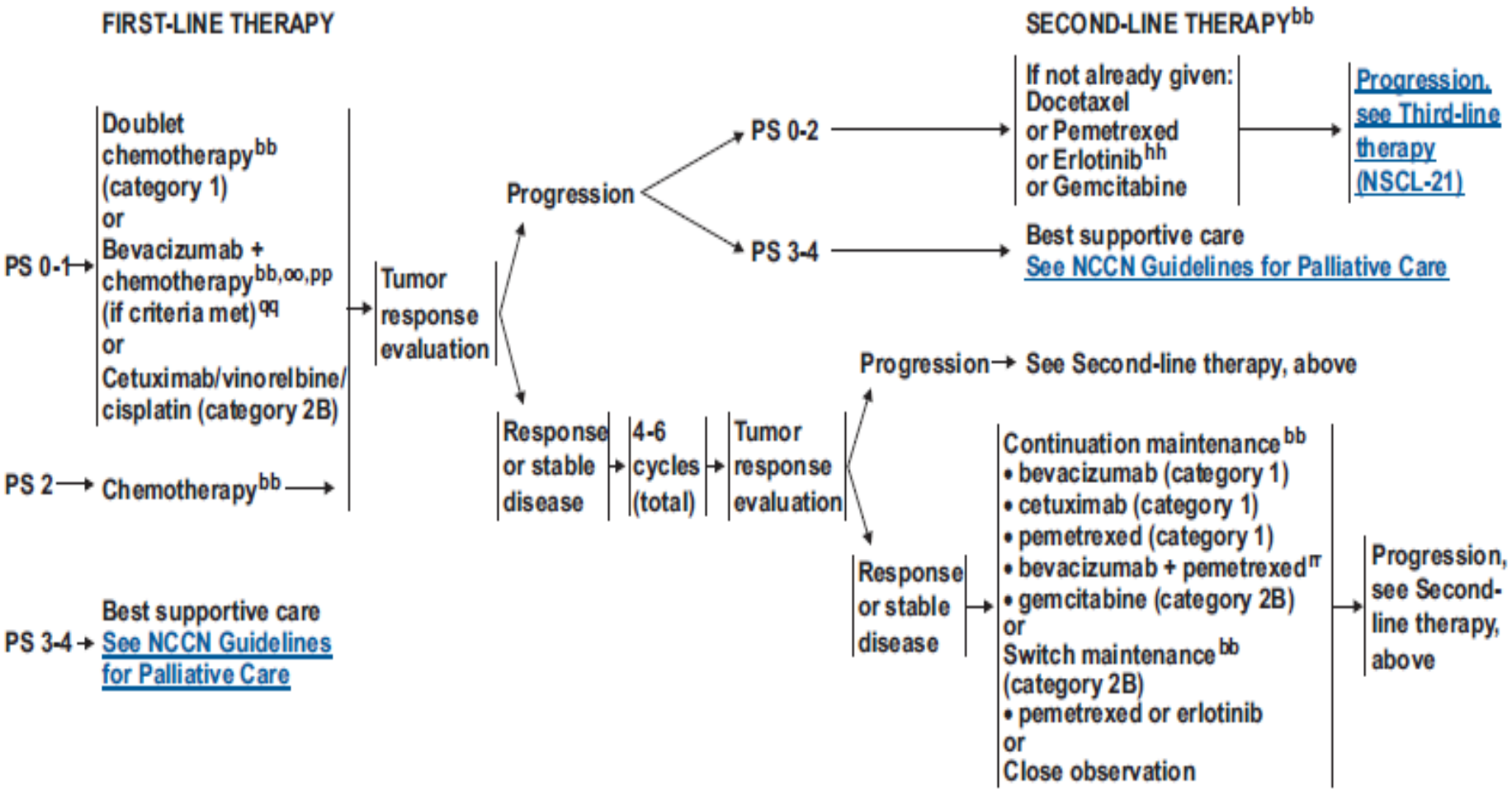
ADENOCARCINOMA, LARGE CELL, NSCLC NOS: EGFR MUTATION AND ALK NEGATIVE OR UNKNOWN[nn]



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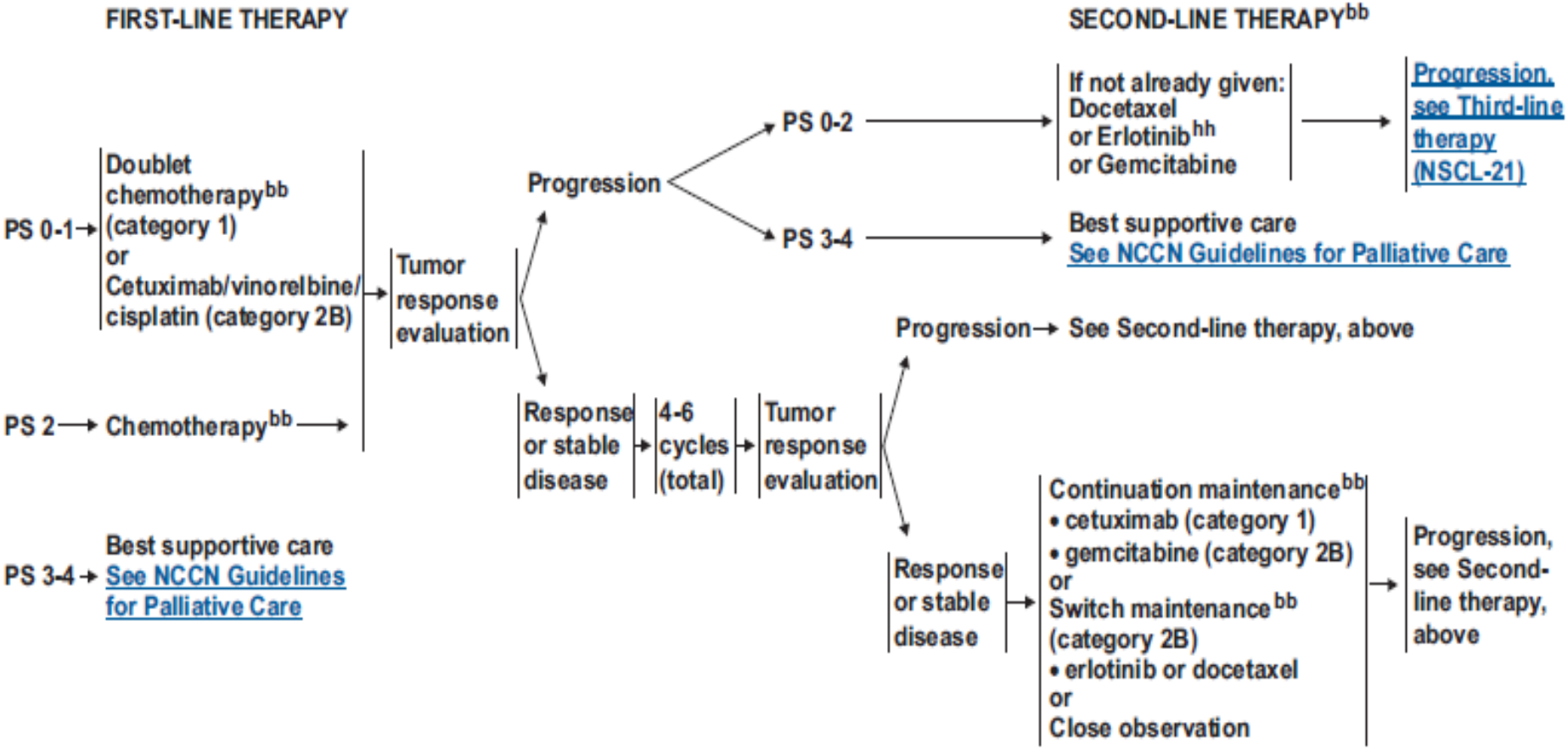
SQUAMOUS CELL CARCINOMA



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ADENOCARCINOMA, LARGE CELL, NSCLC NOS, or SQUAMOUS CELL CARCINOMA

THIRD-LINE THERAPY