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ESMO, ASCO and NCCN: Common ground and differences - which one to follow?

Stage IV

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ESMO, ASCO, NCCN guidelines Outline

- Methodology
- Similarities and differences
  - Biomarker testing
  - First-line
  - Maintenance
  - Elderly
  - PS $\geq$ 2
  - Second-third line
  - Treatment of p with EGFR mutation
  - Treatment of p with ALK translocation
  - Other topics
- Weaknesses and strengths

ESMO guidelines, methodology

- **ESMO, "clinical practice guidelines"**
  - 3-5 authors (multidisciplinary) write the guidelines
  - Version reviewed by ≥ 5 ESMO faculty
  - Updated every 2 yrs

- **ESMO, "consensus conferences"**
  - 35-40 experts (multidisciplinary) in 4-5 working groups
  - Pre-conference, each group identifies clinically relevant questions and provides available literature
  - 2-day F2F meetings, recommendations from each group are presented to the whole group and a consensus is reached
  - All participants approve the final paper
  - Reviewed every 2-3 yrs

ESMO guidelines: methodology

- No systematic literature search carried out
- Levels of evidence and grades of recommendation included *(adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System)*

  - Metastatic NSCLC: 1st Consensus Conference on pathology and molecular tests, 1st-line, 2nd-line and 3rd-line ***(Felip et al Ann Oncol 11)***
  - Metastatic NSCLC: ESMO clinical practice guidelines ***(Peters et al Ann Oncol 12)***
  - 2st Consensus Conference Lugano 2013: NSCLC 1st-line/2nd and further lines in advanced disease ***(Besse et al Ann Oncol 14)***

ASCO guidelines: methodology

- An expert panel of professionals in lung cancer management involved
- Systematic review of available medical literature performed
- No levels of evidence, no grades of recommendation
- No specific review intervals; guidelines updated by a an Update Committee of the original expert panel

ASCO guidelines: methodology

- Scope changed for 2009 update to focus on CT, biologic therapy, and role of molecular analysis in stage IV
- In 2011
  - A focused update of “switch maintenance recommendation”
  - Provisional clinical opinion on EGFR mutation testing for p with stage IV

  - ASCO Clinical Practice Guideline update on CT for stage IV NSCLC ***(Azzoli et al JCO 09)***
  - 2011 focused update of 2009 ASCO clinical practice guideline update on CT ***(Azzoli et al JCO 11)***
  - ASCO provisional clinical opinion: EGFR mutation testing considering 1st line EGFRTKI therapy ***(Keedy VL et al JCO 11)***

NCCN guidelines: methodology

- NCCN panel: chair, vice chair, multidisciplinary panel members
- Comprise recommendations on prevention, diagnosis, and management of malignancies
- Process based on critical review of best available evidence and recommendation by panel members
- Recommendations: 4 categories (1, 2A, 2B, 3); 2A unless otherwise specified
- Algorithms included
- Incorporate real-time updates (at least, annually)
- **NSCLC: NCCN,** Version 3.2014

Biomarker testing: EGFR

ESMO	• EGFR mut status should be systematically analyzed-with sequencing as a standard-in advanced NSCLC with non-SCC histology [II,A] • Testing is not recommended in p with confident diagnosis of SCC, except in never/former light smokers (<15 pack/year) [II,A]
ASCO	• P with NSCLC who are being considered for 1st-line therapy with an EGFRTKI should have their tumor tested for EGFR mut to determine whether and EGFRTKI or CT is the appropriate 1st line therapy
NCCN	• In ADC, LCC, NOS, EGFR mut testing (1) • In SCC, consider EGFR mut testing, specially in never smokers, small biopsies specimens or mixed histology ○ Testing should be conducted as part of multiplex/next generation sequencing

Biomarker testing: ALK

ESMO	• ALK testing may focus on non-SCC histology and never/former light smokers in absence of EGFR or KRAS mut [II,A] • Detection of translocation by FISH is standard, but IHC may have a role in screening out negative cases
ASCO	• No recommendation
NCCN	• In ADC, LCC, NOS, ALK testing (1) • In SCC, consider ALK testing, specially in never smokers, small biopsies specimens or mixed histology • The current standard method for detecting ALK is FISH, although other methods are currently being evaluated, including PCR and IHC

First-line I

ESMO	• Systemic therapy should be offered to p with PS 0-2 [II, B]
ASCO	• Evidence supports the use of CT in p with PS 0, 1, and possibly 2
NCCN	• Unfit of any age (PS 3-4) do not benefit from cytotoxic treatment (except for EGFR mut positive p)

First-line II

ESMO	• In non-SCC and in p treated with 3rd-generation regimens, cis should be the treatment of choice [I, B] • Pem is preferred to gem in p with non-SCC [II, B]
ASCO	• Either cis or carbo is acceptable. Drugs that may be combined with platinum include the 3rd generation drugs doc, gem, irinotecan, paclitaxel, pem and vin
NCCN	• Cis or carbo proven effective in combination with: paclitaxel, doc, gem, etoposide, vinblastine, vin, pem, or albumin-bound paclitaxel • Superior efficacy for cis/pem in non-SCC in comparison to cis/gem • Superior efficacy for cis/gem in SCC in comparison to cis/pem

First-line III

ESMO	• Non-platinum-based combination CT with 3rd-generation agents should be considered only if platinum therapy is contraindicated [I, A]
ASCO	• Non-platinum therapy combinations are reasonable in p who have contraindications to platinum therapy
NCCN	• New agent/non-platinum combinations are reasonable alternatives if available data show activity and tolerable toxicity (eg, gem/doc, gem/vin)

First-line IV

ESMO	• Bev combined with pac/carbo may be offered to p with non-SCC and PS0-1 after exclusion of contraindications [I, A] • Combination of bev and other platinum based CT may be considered in eligible p with non-SCC [I, A]
ASCO	• Recommended: addition of bev (15 mg/kg every 3 wks), to carbo/pac, except for p with SCC, brain metastases, clinically significant hemoptysis, inadequate organ function, PS>1, therapeutic anticoagulation, clinically significant cardiovascular disease, or medically uncontrolled hypertension
NCCN	• Bev+CT or CT alone is indicated in PS 0-1 p

First-line V

ESMO	• No recommendation for cetuximab in the table
ASCO	• Clinicians may consider the addition of cetuximab to cis/vin in p with an EGFR positive tumor (IHC)
NCCN	• Cetuximab + cis/vin is an option for p with PS 0-1

Switch maintenance

ESMO	• In non-SCC p, improvements in PFS and OS observed with pem switch maintenance *vs* placebo following 4 cycles of platinum-based CT • Switch maintenance with erlotinib *vs* placebo demonstrated PFS and OS benefit in all histologies, with greatest efficacy in p with SD after induction
ASCO	• For p with SD or response after 4 cycles, immediate treatment with alternative, single agent CT such as pem in p with non-SCC, doc in unselected p, or erlotinib in unselected p may be considered
NCCN	• Initiation of pem in non-SCC (2B), erlotinib (2B), doc in SCC (2B) after 4-6 cycles of 1st-line CT

Continuous maintenance

ESMO	• Continuing pem following completion of 1st line cis/pem recommended in p with non-SCC [I,B]
ASCO	• Bev may be continued as tolerated until PD • Cetuximab may be continued, as tolerated, until PD
NCCN	• Bev and cetuximab in combination with CT should be continued until PD or unacceptable toxicity • Continuation of pem in non-SCC after 4-6 cycles of cis/pem (1) • Continuation of pem/bev after 4-6 cycles of bev/pem/carbo or cis for p with histologies other than SCC • Continuation of gem after 4-6 cycles of platinum doublet (2B)

Maintenance

ESMO	• Decisions about maintenance must take into account histology, response to platinum-doublet CT, remaining toxicity after 1st-line, PS and p preference [I, B]
ASCO	• Limitations are such that break from CT after fixed course is also acceptable, with initiation of 2nd line at disease PD
NCCN	• Close surveillance without therapy, a reasonable alternative to maintenance

Elderly

ESMO	• Platinum-based CT preferred option for elderly p with PS 0-1—as well as selected PS 2—and adequate organ function. A single-agent approach might remain the recommended treatment of elderly unfit or comorbid p who are more likely to present with more treatment-related Aes [I, B]
ASCO	• Evidence does not support selection of specific CT drug or combination based on age alone
NCCN	• Single-agent therapy or platinum-based combination, reasonable alternatives

PS ≥ 2

ESMO	• Single-agent with gem, vin, and taxanes, an option. Platinum-based combinations possible alternative [II, B] • PS 3-4 p should be offered BSC [II, B] in the absence of tumors with activating EGFR mut
ASCO	• Available data support the use of single-agent in p with PS 2. Insufficient data to make a recommendation for / against using a combination of two cytotoxic drugs in p with PS 2
NCCN	• Single-agent therapy or platinum-based combination, reasonable alternatives • PS 3-4 do not benefit from cytotoxic treatment, except for EGFR-mut p

Second-line

ESMO	• P clinically or radiologically progressing after 1st-line with PS 0-2 should be offered 2nd-line • Comparable options as 2nd-line consist of pem—for non-SCC only—or doc [I, B]. Erlotinib, additional option in EGFR WT p with PS 0-3 [II, B]
ASCO	• Doc, erlotinib, gefitinib or pem, acceptable for p with adequate PS when the disease has progressed during or after 1st-line, platinum-based therapy
NCCN	• In p with PD either during / after 1st-line therapy, single agent doc, pem or erlotinib, established 2nd line agents

Third-line

ESMO	• Erlotinib indicated for EGFR WT p who have not yet received EGFRTKIs, with PS 0-3 [II, B]
ASCO	• When disease progresses on or after 2nd-line CT, treatment with erlotinib may be recommended for p with PS 0-3 who have not received prior erlotinib or gefitinib • Data are not sufficient to make recommendation for / against using a cytotoxic drug as 3rd-line. These p should consider clinical trials, experimental treatment, and BSC
NCCN	• If not already given, options for PS 0-2 include doc, pem (non-SCC), erlotinib or gem (category 2B for all options)

Treatment of p with EGFR mutation

ESMO	• 1st-line erlotinib or gefitinib should be prescribed to p with tumors bearing activating EGFR mut [I, A] • P with PS 3-4 may also be offered an EGFRTKI [II, A]
ASCO	• 1st-line gefitinib may be recommended for p with activating EGFR mut (2009) • NSCLC p being considered for 1st-line with an EGFRTKI should be tested for EGFR mut to determine whether an EGFRTKI or CT is the appropriate 1st line therapy (2011)
NCCN	• Erlotinib or afatinib recommended as 1st-line in p with EGFR mut (1) • In areas of the world where gefitinib is available, it may be used in place of erlotinib

Treatment of p with ALK translocation

ESMO	• P harboring an ALK rearrangement should be considered for crizotinib, a dual ALK and MET TKI, during the course of their disease
ASCO	• No recommendation
NCCN	• Crizotinib indicated for p with ALK rearrangements

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Other topics

ESMO	• Recommendations on the role of ○ Minimally invasive procedures ○ Palliative surgery ○ Biphosphonate administration ○ Palliative-care early intervention ○ Treatment in oligometastatic disease
ASCO	• Comments on ○ Future directions of research ○ Patient-physician communication ○ Health disparities
NCCN	• Recommendations on ○ Cancer survivorship care ○ Targeted agents for p with other molecular alterations than EGFR and ALK

2nd ESMO Consensus Conference on Lung Cancer: NSCLC first-line/second and further lines in advanced disease (*Besse et al Ann Oncol 14*)

- **NSCLC all-comers**
  - *Should we use cis or carbo-based CT?*
  - *Is there a single platinum-based doublet standard CT in SCC and non-SCC NSCLC?*
  - *How many cycles of platinum-based CT?*
  - *Which CT for elderly p?*
- **NSCLC without driver mut (i.e. mut of EGFR or ALK rearrangement)**
  - *Should platinum based CT be offered to PS 2 p?*
  - *Which p should receive 2nd- or 3rd-line therapy?*
  - *What kind of treatment should be offered in 2nd-line?*

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2nd ESMO Consensus Conference on Lung Cancer: NSCLC first-line/second and further lines in advanced disease (*Besse et al Ann Oncol 14*)

- **EGFR mut NSCLC**
  - *What is the preferred 1st-line treatment?*
  - *What is the optimal management of brain metastases at diagnosis?*
  - *What kind of treatment should be offered in 2nd-line? and in 3rd-line?*
- ***ALK* rearranged NSCLC**
  - *What is the preferred 1st-line treatment?*
  - *What kind of treatment should be offered in 2nd-line? and in 3rd-line?*
- **Emerging biomarkers and secondary resistance**
  - *Do we need to re-biopsy a p on disease PD after a targeted treatment for a tumour with a targetable genomic driving alteration (i.e. EGFR mut)*
  - *What is the optimal treatment for p with ROS1, RET, BRAF or HER2 genomic alterations after standard treatment?*

ESMO, ASCO and NCCN guidelines Weaknesses and strengths

- **ESMO**
  - No systematic literature review
  - Face-to-face meeting at Consensus allows real interaction
  - Good update intervals
- **ASCO**
  - Long update intervals
  - Well-defined systematic literature review
  - Recommendations have strong literature support
- **NCCN**
  - No systematic literature review
  - Difficult to apply elsewhere
  - Optimal update intervals
  - Algorithms help clinicians

ESMO, ASCO and NCCN: Common ground and differences - which one to follow?

- There is common ground but there are differences
  - Differences in methodology
  - Differences in format
  - Differences in update intervals
  - Slight differences in content

- All three, **ESMO, ASCO, NCCN** guidelines should be taken into consideration by clinicians

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Thanks!!

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