New standardised features

Gastric Cancer (Adenocarcinoma)

Operable Stage T1N0
- Consider endoscopic / limited resection
- Surgery
  - Postoperative chemotherapy

Operable Stage >T1N0
- Preoperative chemotherapy
  - Surgery
    - Adjuvant chemoradiotherapy
    - Adjuvant chemotherapy

Inoperable or metastatic
- Palliative chemotherapy
  - Re-assess
  - HER2-negative: Platinum + fluoropyrimidine-based doublet or triplet regimen
  - HER2-positive: Trastuzumab + CF/CX
  - Second-line chemotherapy

Best supportive care if unfit for treatment

Preferred pathway
New standardised features

Personalised medicine synopsis table for metastatic NSCLC

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Method</th>
<th>Use</th>
<th>LOE, GOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR mutation</td>
<td>Any appropriate validated method, subject to external quality assurance.</td>
<td>Used to select patients for EGFR TKI therapy, identifying those, with sensitizing mutations, most likely to respond</td>
<td>V, A</td>
</tr>
<tr>
<td>ALK gene rearrangement</td>
<td>Any appropriate validated method, subject to external quality assurance. Standard approach has been FISH, or less often, multiplex PCR or RT-PCR. Certain IHC approaches may be used as a substitute primary test. IHC may also be used to screen patients, positive cases confirmed by an orthogonal method (FISH, PCR)</td>
<td>Used to select patients for ALK tyrosine kinase inhibitor therapy, identifying those, with a positive test, most likely to respond</td>
<td>V, A</td>
</tr>
</tbody>
</table>
Factors taken into account for ESMO-MCBS

- HR, Long term survival, RR
- Overall survival, Progression free survival
- Quality of Life
- Prognosis of the condition
- Magnitude of Clinically Benefit
- Toxicity
- Costs

Not analyzed in view of significant “Heterogeneity” across Europe

Presented By Lowell Schnipper at 2016 ASCO Annual Meeting
ESMO-MCBS substantial improvements

- Curative setting A & B or non-curative setting 5 & 4

Presented By Lowell Schnipper at 2016 ASCO Annual Meeting
# ESMO Magnitude of Clinical Benefit Scale

**Form 2a:** for therapies that are not likely to be curative with primary endpoint of OS

| Name of study: |  |
| Study drug: |  |
| Indication: |  |
| First author: |  |
| Year: |  |
| Journal: |  |

## IF median OS with the standard treatment is ≤ 1 year

### Grade 4

- HR ≤ 0.65 AND Gain ≥ 3 months
- Increase in 2 year survival alone ≥ 10%

### Grade 3

- HR ≤ 0.65 AND Gain 2.5-2.9 months
- Increase in 2 year survival alone 5 - <10%

### Grade 2

- HR > 0.65-0.70 AND Gain 1.5-2.4 months
- Increase in 2 year survival alone ± <5%

### Grade 1

- HR > 0.70 OR Gain <1.5 months
- Increase in 2 year survival alone <3%

---

## IF median OS with the standard treatment is > 1 year

### Preliminary magnitude of clinical benefit grade (highest grade scored)

<table>
<thead>
<tr>
<th>Grade</th>
<th>4</th>
<th>3</th>
<th>2</th>
<th>1</th>
</tr>
</thead>
</table>

### Quality of Life assessment/grade 3-4 toxicities assessment *

- Does secondary endpoint quality of life show improvement
- Are there statistically significantly less grade 3-4 toxicities impacting on daily well-being*

*This does not include alopecia, myelosuppression, but rather chronic nausea, diarrhea, fatigue, etc.

### Adjustments

Upgrade 1 level if improved quality of life and/or less grade 3-4 toxicities impacting daily well-being are shown

---

## Final adjusted magnitude of clinical benefit grade

<table>
<thead>
<tr>
<th>Grade</th>
<th>5</th>
<th>4</th>
<th>3</th>
<th>2</th>
<th>1</th>
</tr>
</thead>
</table>

---

## NON CURATIVE OS

### Grade 3

- HR ≤ 0.70 AND Gain 3.4-4.9 months
- Increase in 3 year survival alone 5 - <10%

### Grade 2

- HR > 0.70-0.75 AND Gain 1.5-2.9 months
- Increase in 3 year survival alone 3 - <5%

### Grade 1

- HR > 0.75 OR Gain <1.5 months
- Increase in 3 year survival alone <3%

---

## Final adjusted magnitude of clinical benefit grade

<table>
<thead>
<tr>
<th>Grade</th>
<th>5</th>
<th>4</th>
<th>3</th>
<th>2</th>
<th>1</th>
</tr>
</thead>
</table>

---

*This does not include alopecia, myelosuppression, but rather chronic nausea, diarrhea, fatigue, etc.

### Adjustments

Upgrade 1 level if improved quality of life and/or less grade 3-4 toxicities impacting daily well-being are shown

---
## ESMO-MCBS – inclusion of scores in Guidelines
Metastatic NSCLC (continued)

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Disease setting</th>
<th>Trial</th>
<th>Control</th>
<th>Absolute survival gain</th>
<th>HR (95% CI)</th>
<th>QoL/toxicity</th>
<th>MCBS score&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nivolumab</strong></td>
<td>Advanced</td>
<td>Nivolumab versus docetaxel in advanced squamous-cell NSCLC [98]</td>
<td>Docetaxel in patients with advanced SCC who have disease progression during or after 1&lt;sup&gt;st&lt;/sup&gt;-line chemotherapy. Control OS 6 months</td>
<td>OS gain: 3.2 months. 2-year survival gain 15%</td>
<td>OS: HR for death 0.59 (0.44-0.79)</td>
<td>Improved toxicity profile</td>
<td>5 (Form 2a)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Phase III</td>
<td></td>
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<td>NCT01642004</td>
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</tr>
<tr>
<td><strong>Nivolumab</strong></td>
<td>Advanced</td>
<td>Nivolumab versus docetaxel in advanced non-squamous NSCLC [104]</td>
<td>Docetaxel in patients with NSCC who progressed during or after platinum-based doublet chemotherapy. Control OS 9.4 months</td>
<td>OS gain: 2.8 months. 2-year survival gain 16%</td>
<td>OS: HR for death 0.73 (0.59-0.89)</td>
<td>Improved toxicity profile</td>
<td>5 (Form 2a)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Phase III</td>
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</tr>
<tr>
<td><strong>Pembrolizumab</strong></td>
<td>Advanced</td>
<td>Pembrolizumab vs docetaxel for previously treated, PD-L1-positive, advanced NSCLC (KEYNOTE-010): a randomised controlled trial [96]</td>
<td>Docetaxel in patients with previously treated, PD-L1-positive, advanced NSCLC. Control OS 8.5 months</td>
<td>In PD-L1 &gt;1%:&lt;sup&gt;d&lt;/sup&gt; OS gain: 1.9 months In PD-L1 &gt;50%:&lt;sup&gt;d&lt;/sup&gt; OS gain: 6.7 months</td>
<td>In PD-L1 &gt;1%:&lt;sup&gt;d&lt;/sup&gt; OS: HR for death 0.71 (0.58–0.88) In PD-L1 &gt;50%:&lt;sup&gt;d&lt;/sup&gt; OS: HR for death 0.54 (0.38–0.77)</td>
<td>Improved toxicity profile</td>
<td>In PD-L1 &gt;1%: 3 (Form 2a) In PD-L1 &gt;50%: 5 (Form 2a)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Phase III</td>
<td></td>
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</tbody>
</table>
ESMO Clinical Practice Guidelines News

2016 Clinical Practice Guidelines
NEW AND UPDATED

Line or two of intro text Line or two of intro test Line or two of intro text

- New Algorithms
  12 September 2016: New algorithms for diagnostic work-up, staging and treatment of Prostate Cancer

- New Consensus Guidelines
  5 July 2016: Online publication of the ESMO Consensus Guidelines for the Management of Patients with Metastatic Colorectal Cancer

- New Clinical Practice Guidelines
  4 July 2016: ESMO Clinical Practice Guidelines: Extramedullary Diffuse Large B-Cell Lymphoma and Primary Mediastinal B-Cell Lymphoma

- New Clinical Practice Guidelines
  7 April 2016: New ESMO Clinical Practice Guidelines: Acute Lymphoblastic Leukaemia
eUpdate - Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up


Section and Text

In a double-blinded prospective randomised trial, nivolumab was compared with ipilimumab and the ipilimumab/nivolumab combination. Nivolumab monotherapy compared to ipilimumab was scored with an ESMO Magnitude of Clinical Benefit Scale (MCBS) score of 4, as it resulted in a statistically and clinically significant progression-free survival (PFS) benefit, without increased toxicity. The nivolumab+ipilimumab combination was scored with an ESMO-MCBS score of 2, the lower score reflecting the presence of only PFS data as well as the increased toxicity of the combination. Programmed death ligand 1 (PD-L1) expression may be a relevant marker in this context, however data are not available nor mature for the ESMO-MCBS scoring of the nivolumab+ipilimumab combination compared to ipilimumab in the PD-L1-negative melanoma subgroup of patients.

Recommendation

For patients with metastatic melanoma, treatment options for first-line setting include the anti-PD-1 antibody nivolumab which showed a clinically and statistically significant PFS benefit over ipilimumab, with a high MCBS score of 4 [11, 6].

Reference


Magnitude of Clinical Benefit Scale (MCBS) table for new therapies/indications in Cutaneous Melanoma*

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Disease setting</th>
<th>Trial</th>
<th>Control</th>
<th>Absolute survival</th>
<th>HR (95% CI)</th>
<th>QoL/toxicity</th>
<th>MCBS score***</th>
</tr>
</thead>
</table>
**eUpdate – Neuroendocrine Tumours Treatment Recommendations**

**Published: 20 September 2016, Authors: ESMO Guidelines Committee**

**Clinical Practice Guidelines**


**Section**

Management of advanced/metastatic disease

**Text update**

In the randomised, double-blind, placebo-controlled, phase III RADIANT-4 trial, 320 patients with advanced, progressive, well-differentiated, non-functional neuroendocrine tumours of lung or gastrointestinal origin were randomised in a 2:1 ratio to everolimus 10 mg per day orally or placebo, both with supportive care. The primary endpoint was progression-free survival (PFS), while overall survival (OS) and quality of life were secondary endpoints. Median PFS was 11.0 months (95% CI 9.2–13.3) in the everolimus group and 3.9 months (1.6–7.4) in the placebo group (hazard ratio [HR] 0.46 [95% CI 0.36–0.67], p=0.0001). Although not statistically significant, the results of the first pre-planned interim OS analysis indicated that everolimus might be associated with a reduction in the risk of death (HR 0.84 [95% CI 0.46–1.68], one-sided p=0.027). Grade 3 or 4 drug-related adverse events were infrequent and manageable, though more numerous in the everolimus group.

**Recommendation**

In patients with unresectable or metastatic, well-differentiated (Grade 1 or Grade 2) non-functional neuroendocrine tumours of gastrointestinal or lung origin with progressive disease, everolimus, as compared with placebo, is associated with a statistically and clinically significant improvement in PFS. In the absence of mature OS and quality of life data, the observed PFS benefit is associated with an ESMO Magnitude of Clinical Benefit Scale (MCBS) score of 3.

**Magnitude of Clinical Benefit Scale (MCBS) table for new therapies/indications in neuroendocrine tumours (bronchial, thymic and gastro-entero-pancreatic)**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Disease setting</th>
<th>Trial</th>
<th>Control</th>
<th>Absolute survival gain</th>
<th>HR (95% CI)</th>
<th>G0/1 toxicity</th>
<th>MCBS score††</th>
</tr>
</thead>
<tbody>
<tr>
<td>Everolimus, an mTOR inhibitor</td>
<td>Unresectable or metastatic, well-differentiated (Grade 1 or Grade 2) non-functional neuroendocrine tumours of gastrointestinal or lung origin in adult with progressive disease</td>
<td>Placebo: Median PFS: 3.8 months</td>
<td>PFS gain: 7.1 months</td>
<td>PFS: HR: 0.46 (0.30–0.67)</td>
<td>Deteriorated toxicity profile.</td>
<td>3 (Form 2b; mature data on OS not available, data on G0/1 assessment not available)</td>
<td></td>
</tr>
</tbody>
</table>

NCT01924783
POCKET GUIDELINES 2016

- The following titles are in preparation:
  - Lung & Chest Tumours
  - Gynaecological Malignancies
  - Breast cancer
  - Upper GI Cancer
  - Lower GI Cancer
  - Urogenital Cancer
  - Lymphomas
  - Leukaemias & Myeloma **NEW**
  - Supportive Care
Interactive Guidelines App

- Existing sections (to be updated):
  - Lung & Chest tumours
  - Urogenital Cancers
  - Upper GI
  - Lower GI

- New sections (to be added):
  - Lymphoma
  - Supportive care