Multi-disciplinary lung tumour board
Management of stage III NSCLC- Case presentation

• 64 year old married man, retired painter.
• Smoker 50 pack years
• Chronic cough 3/12 unresponsive to multiple courses of AB
• CXR- left lung mass
• CT thorax: left upper lobe mass 7 x 5 cm with collapse of left upper lobe.
• Bronchoscopy and bx: lesion in left main 3-4 cm from carina
• Histology: moderately differentiated squamous cell carcinoma
• PET CT: FDG avid left UL mass SUVmax 30.6 with complete left upper lobe collapse extending into the left mediastinum and closely abutting the aortic arch and left atrial appendage. Intensely FDG-avid left anterior mediastinal lymph node.
• No distant metastasis
• MRI brain: nil mets
• Lung function: FEV1 1.01
• Creatinine clearance 45mL/min
• Other end organ function: WNL
• T4N2M0 (Stage IIIb)

• Management from
  • Radiotherapist’s point of view
  • Medical oncologist’s point of view
  • Surgeon’s point of view
Outcome

• Received carboplatin/ paclitaxel weekly x 6 + RT 60Gy/30#, completed 13/5/2015
• Treatment complicated by 5% weight loss, grade 2 odynophagia requiring morphine and fentanyl patch
• Last seen 4/10/18 with no radiological evidence of progression
Medical oncologist’s point of view

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DISCLOSURE OF INTEREST

Personal financial interests
None

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- Institutional financial interests
  BMS: Sponsoring of SCAN-LEAF, an epidemiological study of non-small cell lung cancer.

- Non-financial interests
  Principal Investigator for SCAN-LEAF, an epidemiological study sponsored by BMS.
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Systemic treatment stage III NSCLC

Non-resectable
• In combination with radiotherapy
  - concomitant
  - sequential
  - consolidation

Resectable
• In combination with surgery +/- radiotherapy
  - adjuvant
  - neoadjuvant
Radiotherapy vs Combined Radiotherapy+Chemotherapy

Figure 1. Odds ratio (OR) at 1 year (combined treatment: radiotherapy alone) — | — = Trial results and 95% confidence intervals. Solid vertical line represents OR of unity.

Figure 2. Odds ratio (OR) at 2 years (combined treatment: radiotherapy alone) — | — = Trial results and 95% confidence intervals. Solid vertical line represents OR of unity.

Sequential versus concomitant chemoradiotherapy

PACIFIC: Study Design
Phase 3, Randomized, Double-blind, Placebo-controlled, Multicenter, International Study

- 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

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

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

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

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

1–42 days post-cCRT

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

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*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

Overall Survival* (ITT)

**Probability of Overall Survival**

- **Time from Randomization (months)**
- **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

**No. of events / No. of patients (%)**

- **Durvalumab**
  - 183/476 (38.4)
- **Placebo**
  - 116/237 (48.9)

**Median OS (95% CI) months**

- **Durvalumab**: NR (34.7–NR)
- **Placebo**: 28.7 (22.9–NR)

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

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

NR, not reached
**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
Which chemotherapy combination is best in chemoradiotherapy?

Cisplatin/etoposide vs carboplatin/paclitaxel

3-year OS rate: 41.1% EP arm vs 26.0% PC arm (p=0.024)


Cisplatin/etoposide vs cisplatin/pemetrexed (PROCLAIM)

Less haematological toxicity with cis/pem


ESMO Guidelines (2017):

- In the absence of contraindications, the **optimal ChT** to be combined with radiation in **stage III NSCLC** should be based on **cisplatin**. There are no firm conclusions supporting single-agent carboplatin as a radiation sensitiser [I, A]
- In the stage III disease **CRT** strategy, **two to four cycles of concomitant ChT** should be delivered [I, A]. There is no evidence for further induction or consolidation ChT. In the **perioperative setting**, **three to four cycles of cisplatin-based ChT** are recommended [I, A], aiming at a total cumulative dose of at least 300mg/m2 of cisplatin [II, B].
Resectable locally advanced NSCLC - systemic treatment within multimodality treatment including surgery

ESMO Guidelines (2017):

- **Concurrent radiochemotherapy** in the neoadjuvant phase of the resection arm showed a **better overall survival** than the other trials using induction chemotherapy alone before surgery.
- Overall survival was not significantly different between surgical and definitive radiotherapy arms (HR=0.92 [95%CI 0.82-1.04], p=0.19).
- **Broad heterogeneity** of patient groups in these stages - further research on predictive factors supporting individual therapy selection is necessary.

Definitive radiochemotherapy **versus** surgery within multimodality treatment in stage III non-small cell lung cancer (NSCLC) - a cumulative meta-analysis of the randomized evidence

Christoph Pöttgen¹, Wilfried Eberhardt², Georgios Stamatis³ and Martin Stuschke¹

- If single station N2 disease can be demonstrated by preoperative pathological nodal analysis, resection followed by **adjuvant ChT**, induction **ChT** followed by surgery or induction **CRT** followed by surgery are options. If induction ChT alone is given preoperatively, PORT is not standard treatment, but may be an option based on critical evaluation of locoregional relapse risks [IV, C]. In **multistation N2 or N3**, **concurrent definitive CRT** is preferred [I, A].
- An experienced **multidisciplinary team** is of paramount importance in any complex multimodality treatment strategy decision, including the role of surgery in these cases [IV, C].
What can we expect from the future?

**PACIFIC2**: A phase III placebo controlled study of Durvalumab + RCT followed by Durvalumab maintenance for unresectable stage III NSCLC

- **Key patient inclusion criteria**
  - Unresectable stage III NSCLC
  - ECOG 0-1
  - No progression after chemoradiotherapy (≥2 cycles of platinum based and ≥50 Gy)
  - (n=300)

Primary endpoint
- PFS, ORR

Other clinical trials with IO in stage III NSCLC:
- **LUN 14-179 consolidation pembrolizumab** (Durm ASCO 2018): estimates 1-yr and 2-yr OS 80.5% and 68.7%, respectively. mPFS 15.4 months (95% CI 10.4-NR). G≥2 pneumonitis: 16 (17.2%) pts, 5 (5.4%) G3-4 pneumonitis. 1 pneumonitis-related death.
- **ETOP NICOLAS phase II trial with nivolumab** - interim safety analysis showed that the addition of nivolumab to concurrent chemo-RT is safe and tolerable (Peters ASCO 2018)
- **ALLIANCE phase II induction/adjuvant atezolizumab**

Stage III and TKIs – so far a failure. ESMO Guidelines: there is currently no role for targeted agents in stage III NSCLC outside clinical trials [I, A]
Take home messages

• Management of stage III NSCLC should include a multidisciplinary approach

• From a Medical Oncologist’s perspective future research and development will focus on optimal patient selection using clinical and molecular biomarkers and optimal integration of systemic treatments (immunotherapy, targeted therapies) with CRT/surgery

• Patient case: chemoradiotherapy, if patient eligible and drug accessible followed by durvalumab (check PD-L1, cut-off 1%)
Multi-disciplinary lung tumour board

Management of stage III - Surgeon’s point of view

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Discussable issues

- One N2 node (#5) was a solitary metastasis?
  - In this case, the primary tumor directly involved the #5 LN?
  - Need to consecutive CT images

- No clear definition for “resectable N2”
  - Inclusion criteria of Chemo. with atezo. in neoadjuvant set. : Deemed surgically resectable by a thoracic surgeon
  - Eligibility of chemo. with nivo. in neoadjuvant set. : surgically resectable NSCLC
  - In the INT0139 study; “potentially technically resectable”: Patients were assessed by a thoracic surgeon, radiation oncologist, and medical oncologist
  - Depend on surgeon’s experiences (successful cases)
Various formations for mediastinal lymph node metastases

N1-Stage II

Discrete N2

Infiltrative N2

Single station N2

Multi-station N2

Resectable

Unresectable

Stage IV

Courtesy by Dr. Yamaguchi
SOC for N2-stage IIIA/B NSCLC

ⅢA期 T1-2N2 ⅢB期 T3-4N2

N2: ipsilateral and/or Subcarinal LN

Resectable
Induction Tx → Surgery

Unresectable
Chemoradiotherapy followed by Durvalumab

Discrete N2 without perinodal invasion (The number does not matter)

Infiltrative N2 (with perinodal invasion)

Courtesy by Dr. Hamada
Discussable issues

- T4 was true??....The possibility of the tumor invasion to aortic arch, left atrial appendage and the proximal site of lt. main pulmonary artery
  - The limitation of image series such as CT and 3D images for vascular phase
  - One thinkable option: By using techniques for artificial pneumothorax
  - If the space between the tumor and T4 organs are found out, the complete resection may be carried out without artificial cardiopulmonary system.

Anyway, in this case, the resectability will be discussed after definitive CRT.
Expected surgical procedures, if technically resectable in curative intent

- Left pneumonectomy
- Left double sleeve upper lobectomy with the interposition of pericardium roll
- Left sleeve upper lobectomy/apex segmentectomy of lower lobe (by using the lung transplantation techniques?)
71 y.o. Male

- Chief complaints: cough and bloody sputum
- Onset and Course:
  - Cough since April in 2018
  - Bloody sputum and slight fever since May in 2018
  - Home doctor pointed out the abnormal shadow at the right hilar.
- TBB: squamous cell carcinoma
- Clinical diagnosis: cT4N2(#4, solitary)M0, IIIA
Surgical procedures

- Hemi-clamshell incision
- Right upper/middle bi-lobectomies and partial resection of lower lobe with wedge resection and reconstruction of lower trachea and tracheal carina by using the auto-lung transplantation techniques
  - Operative period: 6 hours and 58 minutes
  - Bleeding amount: 662g

- Patho.: Sq. cc, M/D, pT4N2(#4R)M0, IIIB
“Oxygen tanks”
Postoperative BF findings (14POD)
**SOC for N2-stage IIIA/B NSCLC**

**Surgeon’s point of view**

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<th>Stage IIIA</th>
<th>T1-2N2</th>
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<td>Stage IIIB</td>
<td>T3-4N2</td>
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N2: ipsilateral and/or Subcarinal LN

**Multidisciplinary team discussions are essential.**

**Resectable**

- Induction Tx
- Surgery

**Unresectable**

- Chemoradiotherapy followed by Durvalumab

**discrete N2**

without perinodal invasion
(The number dose not matter)

**infiltrative N2**
(with perinodal invasion)

Courtesy by Dr. Hamada