Post ESMO/WCLC 2017:

Radiotherapy

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Dept. Radiation Oncology (Maastro clinic)
GROW School
Conflict of Interest

• None to declare
Overall survival $\text{BED}_{10} < 100$ vs. $\text{BED}_{10} \geq 100$

- Overall survival in all patients
  - $\text{BED}_{10} \geq 100$ Gy (n=211)
  - $\text{BED}_{10} < 100$ Gy (n=70)
  - $P < 0.01$

- Overall survival in operable patients
  - $\text{BED}_{10} \geq 100$ Gy (n=80)
  - $\text{BED}_{10} < 100$ Gy (n=23)
  - $P < 0.05$

Onishi H et al. Cancer 2004
SPACE study

**Randomized phase II trial**

- **NSCLC T_{1-2} N0-M0**
  - < 6 cm
  - PS 0-2

A) SBRT 22 Gy x 3 to 66 Gy in one week
B) 3DCRT 2 Gy x 35 to 70 Gy in 7 weeks

**Primair eindpunt:** PFS

3\times15 \text{ Gy on the PTV edge} = 103 \text{ Gy EQD}_{2,T} (a/b=8 \text{ Gy})

= 58 \text{ Gy EQD}_{2,T} (a/b=8 \text{ Gy})
CHISEL: A randomized phase III trial of SABR vs conventional radiotherapy for inoperable stage I non-small cell lung cancer
TROG 09.02, ALTG 09.05
Trial Registration NCT01014130

David Ball, Tao Mai, Shalini Vinod, Scott Babington, Jeremy Ruben, Tomas Kron, Brent Chesson, Alan Herschtal, Marijana Vanevski, Angela Rezo, Christine Elder, Marketa Skala, Andrew Wirth, Greg Wheeler, Adeline Lim, Mark Shaw
On behalf of the CHISEL investigators
CHISEL Aims

Hypothesis:
SABR with a hypofractionated dose of 54 Gy in 3 fractions or 48 Gy in 4 fractions results in superior local control of peripherally located inoperable T1–T2a N0 non-small cell lung cancer compared with more fractionated conventional radiotherapy (66 Gy in 33 fractions or 50 Gy in 20 fractions)

Endpoints:
• Primary: - Time to local failure
• Secondary: - Overall and lung cancer specific survival
• - Toxicities (CTCAE v 4.0)
• - Quality of life (QLQ C30 and LC 13, State-Trait Anxiety Inventory)
Study design

Stratify:
- T1 vs T2a
- Medically inoperable vs medically operable
- Randomize 2:1

54 Gy 3 fx in 2 weeks
or
48 Gy 4 fx in 2 weeks

66 Gy 33 fx in 6.5 weeks
or
50 Gy 20 fx in 4 weeks

96 Gy EQD$_{2T}$
140 Gy EQD$_{2T}$

56 Gy EQD$_{2T}$
53 Gy EQD$_{2T}$

66 Gy/24 fractions = 67 Gy EQD$_{2T}$
## Patient characteristics (n =101)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>SABR (n=66)</th>
<th>CRT (n= 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>55%</td>
<td>57%</td>
</tr>
<tr>
<td>Median age (years)</td>
<td>73</td>
<td>77</td>
</tr>
<tr>
<td>Ever smoker</td>
<td>97%</td>
<td>100%</td>
</tr>
<tr>
<td>T1 stage</td>
<td>71%</td>
<td>69%</td>
</tr>
<tr>
<td>Comorbidity (median, range)</td>
<td>9 (6-19)</td>
<td>9 (0-17)</td>
</tr>
<tr>
<td>Maximum diameter (mm) (median, IQR)</td>
<td>22.5 19-31</td>
<td>27 20.5-32</td>
</tr>
<tr>
<td>Prior cancer</td>
<td>43%</td>
<td>31%</td>
</tr>
</tbody>
</table>
Freedom from local failure and overall survival

HR 0.29, 95% CI 0.13, 0.66, P = 0.002

HR 0.51, 95% CI 0.29, 0.91, P = 0.020
## Grade 3+ toxicities by arm

<table>
<thead>
<tr>
<th></th>
<th>SABR</th>
<th>Conventional</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnoea</td>
<td>2 (1 grade 4)</td>
<td>0</td>
</tr>
<tr>
<td>Cough</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Chest wall pain/pain</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Lung infection</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Weight loss</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>
Conclusies voor ons

Niets veranderen
Long term follow-up on NRG Oncology RTOG 0915 (NCCTG N0927): A randomized phase II study comparing 2 stereotactic body radiation therapy schedules for medically inoperable patients with stage I peripheral non-small cell lung cancer

Gregory M M Videtic, MD, Rebecca Paulus, BS, Anurag K Singh, MD, Joe Y Chang, MD, William Parker, MSc, Kenneth R Olivier, MD, Robert D Timmerman, MD, Ritsuko R Komaki, MD, James J Urbanic, MD, Kevin L Stephens, MD, Sue S Yom, MD, Clifford G Robinson, MD, Chandra P Belani, MD, Puneeth Iyengar, MD, Munther I Ajlouni, MD, Darinda D Gopaul, MD, Shashikant B Lele, MD, Ronald C McGarry, MD, Hak Choy, MD, Jeffrey D Bradley, MD

Primary Endpoint:
Rates of ≥ grade 3 pre-specified toxicities (CTC 4.0, Respiratory, Soft tissue/chest wall, Skin)

Secondary Endpoints:
- LC/OS/DFS
- PET response
- PFTs
- Biomarkers

Stratify

Zubrod
- 0
- 1
- 2

T-Stage
- T1
- T2

Randomize

Arm 1:
1 x 34 Gy
143 Gy EQD2T

Arm 2:
4 x 12 Gy over 4 consecutive days
96 Gy EQD2T

N=94
<table>
<thead>
<tr>
<th></th>
<th>34 Gy/ 1 fr</th>
<th>48 Gy/ 4 fr</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>41</td>
<td>45</td>
</tr>
<tr>
<td>LR</td>
<td>7.9 %</td>
<td>6.8 %</td>
</tr>
<tr>
<td>psAEs</td>
<td>10.3 %</td>
<td>13.3 %</td>
</tr>
<tr>
<td>PFS</td>
<td>19.1 Mo</td>
<td>31.8 Mo</td>
</tr>
<tr>
<td>Sec. prim.</td>
<td>15.5 %</td>
<td>13.3 %</td>
</tr>
<tr>
<td>5 y OS</td>
<td>28.8 %</td>
<td>40.2 %</td>
</tr>
</tbody>
</table>
Conclusies voor ons

• Nog preliminair
• Grotere studies nodig
• 1 fractie: evolutie om te volgen
Toxicity and second primary lung cancers in late survivors following lung SBRT. Giuliani et al.

Second primaries:
2-4 %/year up to 18 years following treatment
• 1192 patients
• 5 y OS: 14 % (182 patients)
• **Toxicity**
  – G2 fatigue: 5/182 (2.7 %)
  – G2 rib fracture: 1/182
  – G2 chronic myositis: 8/182 (4.4 %)
• **Failures**
  – LR: 3/182; regional failure: 2/182; DM: 5/182
• **Second primary lung cancers**
  – 22 (12 %)
Conclusies voor ons

• Levenslang jaarlijks low-dose CT thorax?
Toxicity results from the randomized phase III NVALT-11/ DLCRG02 study of prophylactic cranial irradiation vs. observation in stage III NSCLC

De Ruysscher DKM (1), Dingemans A (1), Praag J (2), Belderbos J (3), C. Tissing-Tan C (4), Herder G (5), Haitjema T (6); Ubbels F (7); Lagerwaard J (8); Stigt J (9); Smit E (10); van Tinteren H (10), van der Noort V (10), Groen HJM (7)

1 University Medical Center Maastricht and Maastro Clinic, Maastricht; 2 Erasmus Medical Center, Rotterdam; 3 Anthonie van Leeuwenhoek hospital, Amsterdam; 4 Radiotherapeutic Institute Arnhem; 5 Antonius hospital Nieuwegein; 6 Medical Center Alkmaar; 7 University Medical Center Groningen; 8 Free University Medical Center, Amsterdam; 9 Isala hospital, Zwolle; 10 Netherlands Cancer Institute, Amsterdam; All in The Netherlands
Primary endpoint: Incidence of symptomatic brain metastases

<table>
<thead>
<tr>
<th></th>
<th>PCI (n=86)</th>
<th>Observation (n=88)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>BM + neuro symptoms</td>
<td>6 (7.0%)</td>
<td>24 (27.2%)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>
All neurological adverse events: Physician rated

<table>
<thead>
<tr>
<th></th>
<th>All grades</th>
<th>Grade 3, 4, 5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PCI</td>
<td>Observation</td>
</tr>
<tr>
<td>Memory impairment</td>
<td>26</td>
<td>7</td>
</tr>
<tr>
<td>Cognitive disturbance</td>
<td>18</td>
<td>3</td>
</tr>
</tbody>
</table>

After Holms-Bonferoni correction: significant differences between arms considering all grades: Memory impairment and cognitive disturbance.

Grade 3-5: number of AE too small to see significant differences.
All non-neurological adverse events Physician rated

<table>
<thead>
<tr>
<th></th>
<th>All grades</th>
<th>Grade 3, 4, 5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PCI</td>
<td>Observation</td>
</tr>
<tr>
<td>Alopecia</td>
<td>86</td>
<td>88</td>
</tr>
<tr>
<td>Fatigue</td>
<td>36</td>
<td>5</td>
</tr>
<tr>
<td>Headache</td>
<td>55</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>1</td>
</tr>
</tbody>
</table>

After Holms-Bonferoni correction: significant differences between arms considering all grades: **Alopecia, fatigue, headache**

Grade 3-5: number of AE too small to see significant differences.
## Patient reported adverse events

<table>
<thead>
<tr>
<th></th>
<th>All grades</th>
<th></th>
<th>Grade 3, 4</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PCI</td>
<td>Observation</td>
<td>PCI</td>
<td>Obs</td>
</tr>
<tr>
<td>Dizziness</td>
<td>50</td>
<td>36</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>Headache</strong></td>
<td>55</td>
<td>36</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>69</td>
<td>70</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Memory impairment</td>
<td>50</td>
<td>47</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>16</td>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

After Holms-Bonferoni correction: significant differences between arms considering all grades: **headache**

Grade 3-5: number of AE too small to see significant differences.
Conclusions/ Take home messages

- PCI reduces *symptomatic* brain metastases (7 % vs. 27 %), but at the expense of increased side effects
- When rated by physicians, G1-2 cognitive disturbance (3.4 % vs. 20.9 %) and G1-2 memory impairment (7.9 % vs. 30.2 %) are significantly increased
- Rated by patients, only headache G1-2 (40.9 % vs. 63.2 %) is significantly increased

➡ Detailed analysis of QoL is ongoing
➡ Strategies to reduces the toxicity of PCI (an efficient treatment) is needed (hippocampus sparing?)