PACIFIC 4 / RTOG 3515

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NRG Summer 2022 Lung Committee

@SBRT_CR
Increasing Use of SBRT for Early NSCLC

Corso, et al Am J Clin Oncol 2017
Jang, et al ASTRO 2019
SBRT Failures Increase With Size

Kaplan-Meier survival estimates

<table>
<thead>
<tr>
<th>Number at risk</th>
<th>C = 3</th>
<th>C = 2</th>
<th>C = 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>365</td>
<td>258</td>
<td>198</td>
<td></td>
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<tr>
<td>292</td>
<td>204</td>
<td>152</td>
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<td>246</td>
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<td>212</td>
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<td>174</td>
<td>97</td>
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<td>142</td>
<td>73</td>
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<tr>
<td>108</td>
<td>62</td>
<td>29</td>
<td></td>
</tr>
</tbody>
</table>

Freedom from First Failure (Death Competing Risk)

<table>
<thead>
<tr>
<th></th>
<th>1y</th>
<th>2y</th>
<th>3y</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;=2 cm</td>
<td>80.3</td>
<td>69.1</td>
<td>62.8</td>
</tr>
<tr>
<td>&gt;2-3 cm</td>
<td>74.1</td>
<td>65.1</td>
<td>60.2</td>
</tr>
<tr>
<td>&gt;3-7 cm</td>
<td>67.2</td>
<td>56.9</td>
<td>51.1</td>
</tr>
</tbody>
</table>

n=821

Washington University - Unpublished
Stage IA:
- Peripheral T1abc, N0

(-) mediastinal nodes

Operable
- Surgical Resection
- Definitive RT (SBRT)

Inoperable

Stage IB, Stage II
- (-) mediastinal nodes

Operable
- Surgical Resection
- Definitive RT (SBRT)

N0
- Consider Adjuvant Chemo (Category 2B)
  - High Risk Ib-IIb

Inoperable
- Definitive Chemoradiation

IB: Peripheral T2a, N0
I: Central T1-2a, N0
II: T1-2ab, N1; T2b, N0
IIB: T3, N0
Adjuvant therapy after SBRT?

Pignon et al, JCO 2008
N=4,584

- Cytotoxic chemo NCCN Category 2B rec for “high risk” based on surgical data
- Challenging in frail SBRT population.

5y OS improvement 5.2%, no clear benefit for IA/IB
PACIFIC – CRT +/- durva for stage III

- 713 pts, 2:1 randomized
- **Durva** q2wk 10 mg/kg or placebo up to 12 mo
- PFS 17.2 mo vs. 5.6 mo
- OS NR vs. 28.7 mo
- Well tolerated
  - G3/4 AEs – 30.5% vs. 26.1%
  - Pulmonary – 4.8% vs. 2.6%

mPFS 16.8 mo vs. 5.6 mo

mOS NR vs. 28.7 mo

Antonia et al, NEJM 2018
Increasing evidence of synergy between RT + IO

Potentiation
- More immunogenic cell death
  - Larger fx size (SBRT) may increase antigen release and uptake
- Increased tumor infiltrating lymphocytes
- Upregulation of PD-L1 expression

Cytoreduction
- Relieve immunosuppression
# Early Clinical Data Shows Safety Signal

**iSABR (MDACC)**  
*Chang et al, ASCO 2020*

- rPh2
- SBRT +/- nivo
- SBRT w/nivo => nivo (4-7 total)

- N=>100/145 *(current)*
- 2xG2 RP, 1xG3 dyspnea
- No pt discontinue therapy from AE

**iSABR (UCLA)**  
*Lee et al (personal comm, recently closed)*

- Ph1/rRh2
- SBRT +/- durva
- Durva x 1 => SBRT => durva (4 mo)

- Ph1 (N=15)
- No SAEs, DSM rec go to rPh2

**UC Davis**  
*Kelly et al, ASCO 2020*

- Ph1/Ph2 expansion
- SBRT + atezo
- Atezo x 2 => SBRT w atezo => atezo x 3 (6 total)

- 3+3 (3mg/kg, 10mg/kg 1200 mg flat)
- Ph1 (N=15)
- 1xG3 rash DLT @ 10mg/kg
- RP2D 1200 mg, N=5
- No other SAEs to date
**Inclusion Criteria**

- Clinical Stage I/II node negative (T1 – T3 N0)
- Medically inoperable or refuse surgery
- ECOG PS 0-2
- All comers for histology and PDL-1 status
- Sync/Metach allowed

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**SBRT Dose Reflects Int’l Variability**

50-60 Gy/8, 50-55 Gy/5
42-48 Gy/4, 54 Gy/3

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**Primary Endpoint:**

PFS (BICR) In T1c – T3N0M0

**Key Secondary Endpoint:**

OS (powered)

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Total n for primary analysis population = 530 (T1c-T3), Total n for ITT = 630
Primary Endpoint: PFS (BICR)

Key Secondary Endpoints: OS, Lung Cancer Mortality

SBRT + Durvalumab 1500mg q 4 wks x 24 mos

1:1

SBRT + Placebo q 4 wks x 24 mos

Main Cohort Key Eligibility Criteria:
- Stage I/II (T1–T3N0M0)
- Medically inoperable or refuses surgery
- ECOG 0-2
- All comers for histology and PD-L1 status

Stratifications:
- T1 vs. T2/3
- Central vs. peripheral

Osimertinib Cohort Key Eligibility Criteria
- Known EGFR TKI sensitizing mutation by local testing
- Stage I/II (T1–T3N0M0)
- Medically inoperable or refuses surgery
- ECOG 0-2

Patient Screening (up to 42 days)
Submit Tumor Samples (if available)
Collect baseline ctDNA
Baseline RECIST Scan (within 28 days of randomization)

SBRT (SOC)
Osimertinib 80mg orally QD for 36 months N=60

Osimertinib treatment to start within 7 days & no more than 14 days after SBRT completion

Total n for primary analysis population = 530 (T1c-T3), for ITT = 630
>200 sites, 16 countries

07/12/22:
Screened – 605
Randomized – 408/630