S 1933

A Pilot Study of Hypofractionated Radiotherapy Followed by Atezolizumab Consolidation in Stage II or III NSCLC Patients with Borderline Performance Status

Background

- Lack of evidence-based data to guide treatment decision in patients with stage III NSCLC with PS 2 and stage II patients who are not candidates for surgical resection.
- Basic science and clinical data support the synergistic activity of radiotherapy and immune checkpoint inhibitors.
- Hypofractionated radiotherapy was better tolerated than standard fractionation in this patient population with similar outcomes based on UTSW trial by Iyengar et al.
- Immune checkpoint inhibitors were better tolerated than chemotherapy with less TRAEs in clinical trials.

Background

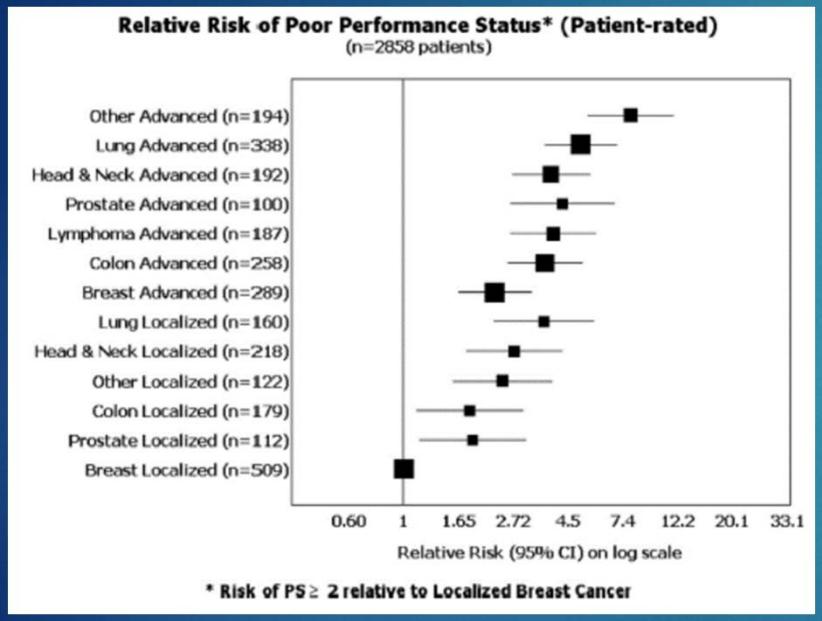


TABLE 2. Patient-Rated and Provider-Rated ECOG PS, Lung Cancer Patients (n = 503)[a]

Patient-Reported ECOG PS	Provider-Reported ECOG PS 0	1	2	3	4	Total	
0	59	38	6	4	0	107	(22.0)
1	43	77	21	2	0	146	(30.0)
2	16	69	53	20	2	163	(33.5)
3	2	19	25	22	1	70	(14.4)
4	0	3	1	7	3	15	(3.1)
Total	121	207	106	55	6		
	(24.4)	(41.8)	(21.4)	(11.1)	(1.2)		

All values inside parentheses indicate percentages.
[a] Eight patients were missing patient-rated PS, two patients were missing provider rated PS.
ECOG PS, Eastern Cooperative Oncology Group Performance Status.

Lilenbaum et al, J Thorac Oncol 2008;3:125

Hypothesis

- Hypofractionated radiotherapy followed by atezolizumab consolidation in patients with stage III NSCLC with PS 2 or stage II patients who are not candidates for surgical resection will be well tolerated and will lead to better outcomes compared to historic controls in this patient population.

Objectives

- Primary Objective:

To evaluate the rate of Grade 3-5 Treatment-Related Adverse Events (TRAEs) in patients who are not candidates for surgery or concurrent chemoradiation and who have either performance status 0-2 and Stage II or performance status 2 and Stage III non-small cell lung cancer (NSCLC), treated with hypofractionated thoracic radiotherapy followed by atezolizumab.

- Secondary Objectives:

1. To evaluate response rate.
2. To evaluate PFS.
3. To evaluate OS.
4. To evaluate TRAEs (all grades).

Key Inclusion and Exclusion Criteria

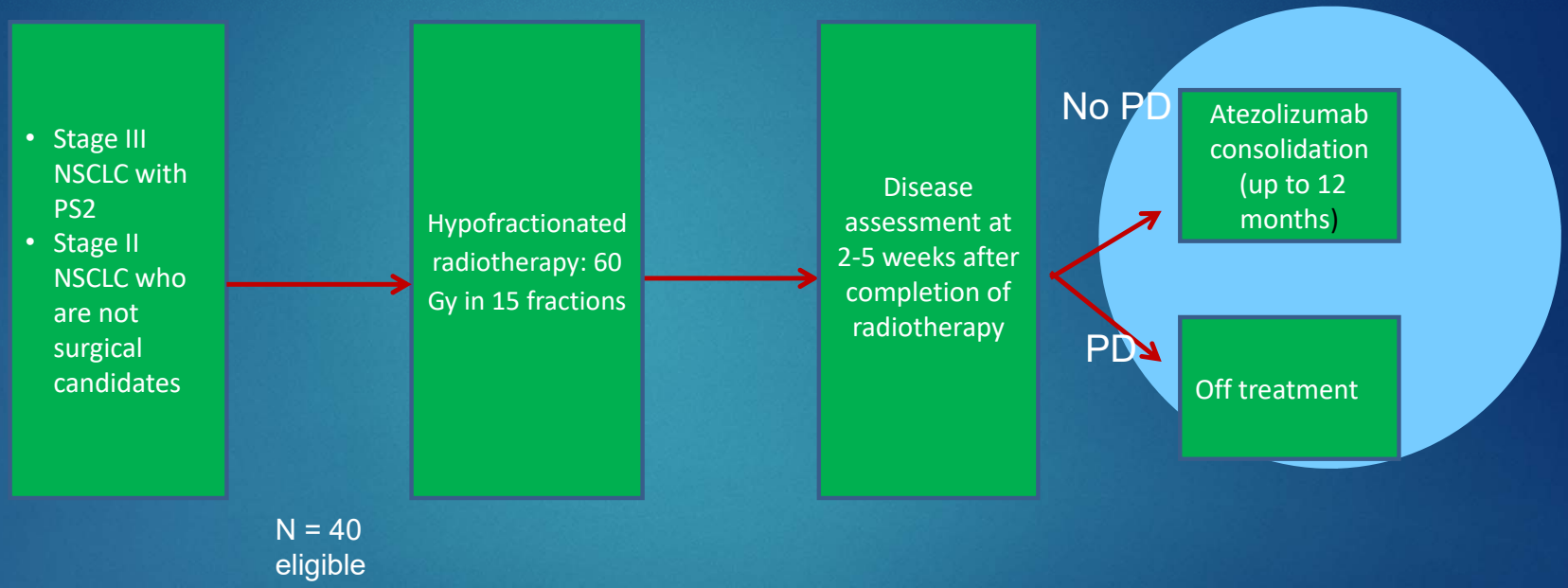
- **Key Inclusion Criteria:**

Step 1: Before radiotherapy: Patients with stage III NSCLC with PS 2 or stage II NSCLC with PS 0-2 and are not surgical candidates.

Step 2: After radiotherapy & before atezolizumab: Patients must have received at least 45 Gy of radiation with no disease progression.

- **Key Exclusion Criteria:**

1. Patients with active autoimmune disease.
2. Patients with a history of interstitial lung disease or ≥ G3 pneumonitis.


• Stage III NSCLC with PS2
• Stage II NSCLC who are not surgical candidates
N = 40 eligible
Hypofractionated radiotherapy: 60 Gy in 15 fractions
Disease assessment at 2-5 weeks after completion of radiotherapy
No PD
Atezolizumab consolidation (up to 12 months)
PD
Off treatment

Statistical Consideration

- Sample size needed for this study is 40 patients in the safety analysis population.
- Observation of 8 or fewer patients with toxicity (20%) would be considered evidence to rule out 34% or greater toxicity rate calculated from historic controls.
- Estimating that 10% of patients registered to Step 1 will not register to Step 2 and 5% registered to Step 2 will either not meet eligibility criteria or receive at least one dose of atezolizumab, the total target accrual is 47 patients.

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Patterns of care for non-operable T1-4 N+ M0 NSCLC in the US: NCDB Analysis 2004-2013

- N+ M0 NSCLC in NCDB, 2004-2013
  - 74,867 patients
    - Chemoradiation therapy (10,915, 15%)
    - Chemotherapy alone (34,978, 47%)
    - Radiation Therapy alone (2,396, 3%)
    - No aggressive treatment (26,578, 36%)

Study	1 year	2 years	3 years	4 years	5 years	Median
Chemotherapy (CTmono)	57%	31%	20%	15%	12%	14.5 months
Radiation (RTmono)	51%	25%	15%	11%	8%	12.3 months
Roswit 1968	18%					7.6 months
Perez 1980		<25%				
Sause 1995						11.4 months
Dillman 1996	40%	13%	10%	7%	6%	
Sigel 2013						9 months

Ellen Kim, et al., Unpublished

UTSW: A Phase III Randomized Study of Image Guided Conventional (60 Gy/30 fx) Versus Accelerated, Hypofractionated (60 Gy/15 fx) Radiation for Poor Performance Status Stage II and III NSCLC Patients

- 60 patients:
  - Stage II NSCLC not candidates for surgery or Stage III NSCLC not candidates for chemoradiation due to diminished PS (Zubrod PS 2 or greater)
- Outcomes:
  - median OS for the evaluable 48 patients was 11.5 months, with no statistical difference between conventional vs hypofractionated radiation treatment arms
  - PFS was 14 months with no statistical difference between treatment arms
  - No grade 4 toxicities were attributed to radiation
  - Grade 3 toxicities: 10 (36%) in 60/30 arm and 6 (19%) in 60/15 arm

Iyengar et al., IJROBP 2016, Volume 96 (2S): Abstract 3110

Radiation Therapy Details

- RT must begin within 28 days after registration.
- Simulation can take place before registration
- Treatment must begin within 3 weeks after simulation
- Digital submission of treatment plans: 4DCT, planning CT, RT plan, RT dose and structure set.
- IROC will perform a rapid review of each treatment plan. Institutions should allow 5 business days for each case to be received, processed, and reviewed. If the plan must be resubmitted it will be given a rapid review (within 3 business days).

- Allowed modes: photons (6-10 MV) with IMRT/VMAT
- 4-D treatment planning is required
- One of the motion control techniques is mandatory if the tumor motion is > 1 cm during 4D CT sim:
  - Abdominal compression
  - Gating
  - Tumor tracking
  - Active breath-holding
- Daily CBCTs

Target Volumes

- OARs=spinal cord + 10 mm; esophagus + 5 mm, trachea + 3 mm, heart + 3 mm, brachial plexus + 5 mm, great vessels + 3 mm, rib + 3 mm, skin + 3 mm
- GTV = primary tumor and clinically and/or pathologically involved lymph nodes
- CTV = GTV + 5-10 mm with trimming expansions into normal structures
- ITV = CTV + motion quantified from 4D-scan (using MIP)
- PTV = ITV + 5 mm
  - PTV60: PTV as created MINUS organs at risk with expansion margins
  - PTV45: PTV as created without subtraction of OARs

Treatment Planning Protocol Requirements

Target/OAR	Metric	Per Protocol	Variation Acceptable	Deviation Unacceptable
PTV60	D95%[%]	≥100% of protocol dose	≥97% of protocol dose	<97% of protocol dose
	D99%[%]	≥90% of protocol dose	≥87% of protocol dose	<87% of protocol dose
	D2cc[%]	≤110% of protocol dose	>110% of protocol dose	>115% of protocol dose
PTV45	D95%[%]	≥100% of protocol dose	≥97% of protocol dose	<97% of protocol dose
	D99%[%]	≥90% of protocol dose	≥87% of protocol dose	<87% of protocol dose
SpinalCord	D5cc[Gy]	<39 Gy		>39 Gy
	D0.03cc[Gy]*	<42.3 Gy		>42.3 Gy
BrachialPlexus	D3cc[Gy]	<44.5 Gy	≤49.0 Gy	>49.0 Gy
	D0.03cc[Gy]*	<50.6 Gy	≤55.7 Gy	>55.7 Gy
Lungs (Right and Left minus GTV)	D1500cc[Gy]	<15.5 Gy	≤17.1 Gy	>17.1 Gy
	D1000cc[Gy]	<16.3 Gy	≤17.9 Gy	>17.9 Gy
	Mean Dose	<18 Gy	≤19.8 Gy	>19.8 Gy
	V18 Gy	<37%	≤40.7%	>40.7%
Heart	D15cc[Gy]	<39.5 Gy	≤43.5 Gy	>43.5 Gy
	D0.03cc[Gy]*	<60.0 Gy	≤66.0 Gy	>66.0 Gy
Esophagus	D15cc[Gy]	<51.3 Gy	≤56.4 Gy	>56.4 Gy
	D0.03cc[Gy]*	<55.3 Gy	≤60.8 Gy	>60.8 Gy
Great Vessels	D15cc[Gy]	<48.9 Gy	≤53.8 Gy	>53.8 Gy
	D0.03cc[Gy]*	<60.0 Gy	≤66.0 Gy	>66.0 Gy
Trachea	D15cc[Gy]	<39.5 Gy	≤43.5 Gy	>43.5 Gy
	D0.03cc[Gy]*	<60.0 Gy	≤66.0 Gy	>66.0 Gy
Rib	D15cc[Gy]	<48.9 Gy	≤53.8 Gy	>53.8 Gy
	D0.03cc[Gy]*	<60.0 Gy	≤66.0 Gy	>66.0 Gy
Skin	D15cc[Gy]	<49 Gy	≤53.9 Gy	>53.9 Gy
	D0.03cc[Gy]*	<55.4 Gy	≤60.9 Gy	>60.9 Gy

Questions:

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