OXFORD

JNCI J Natl Cancer Inst (2022) 114(5): djac015

https://doi.org/10.1093/jnci/djac015
First published online January 30, 2022
Article

Randomized Trial of First-Line Tyrosine Kinase Inhibitor With or Without Radiotherapy for Synchronous Oligometastatic *EGFR*-Mutated Non-Small Cell Lung Cancer

Xiao-Shan Wang, MD,[1,‡] Yi-Feng Bai, MD,[1,‡] Vivek Verma, MD,[2] Rui-Lian Yu, MD,[1] Wei Tian, MS,[1] Rui Ao, MD,[1] Ying Deng, MD,[1] Jian-Ling Xia, MD,[1] Xue-Qiang Zhu, MD,[1] Hao Liu, MD,[1] Hai-Xia Pan, MD,[1] Lan Yang, MD,[1] Yang-Ke He, MD,[1] Han-Song Bai, MD,[3] Xing Luo, MD,[3] Yan Guo, MS,[3] Ming-Xiu Zhou, MD,[3] Yue-Mei Sun, MD,[4] Zi-Can Zhang, MD,[4] Si-Min Li, MD,[3,5] Xue Cheng, MD,[3] Bang-Xian Tan, MD,[3] Liang-Fu Han, MD,[6] Ying-Yi Liu, MD,[7] Kai Zhang, MD,[8] Fan-Xin Zeng, PD,[9] Lin Jia, MD,[10] Xin-Bao Hao, MD,[11] You-Yu Wang, MD,[1] Gang Feng, MD,[1] Ke Xie, MD,[1] You Lu, MD,[12] Ming Zeng, MD, PhD[1,*]

Review by – Dr Rakesh Pinninti
Consultant medical oncology
Basavatarakam Indo-American cancer hospital, Hyderabad

10 slides
8 minutes

Introduction

- Trials of aggressive local therapy to all existing areas of disease **(two randomized trials in NSCLC as well as a randomized basket trial)** have illustrated improvements in PFS and OS.

- Underrepresentation of NSCLC cases harboring mutations in the EGFR.

- The phase III **SINDAS trial (NCT02893332**) tries to address this knowledge gap, to examine outcomes of TKI therapy with or without upfront RT to all areas of disease for EGFRm synchronous oligometastatic (< 5 metastases) NSCLC.

Trial design

- Open-label, parallel-group, phase III clinical trial

Inclusion criteria for this randomized trial were

1) patients aged 18 years and older and 75 years or younger
2) performance status of 0-2,
3) Estimated life expectancy of at least 6 months,
4) biopsy-proven EGFRm adenocarcinoma
5) synchronous (newly diagnosed, treatment-naive) oligometastatic disease.

Exclusion criteria were the presence of brain metastases and prior radiotherapy

Definitions

- Oligometastatic disease was defined as

a) 5 or less discrete distant metastases

b) no more than 2 discrete areas of metastatic disease in any one organ

c) confirmed by multidisciplinary review.

d) The involved regional lymph nodes (regardless of nodal number) were not counted in the definition of metastatic disease and were grouped with the primary tumor.

e) Involved nonregional lymph nodes were categorized as metastatic disease

Study interventions

- Osimertinib was not allowed on this study, as randomized data supporting Osimertinib were published toward the end of study accrual
- RT was directed to all metastases plus the primary tumor/involved regional nodes on imaging; it was performed in 5 fractions using well-recognized principles
- Because the total prescribed dose is highly dependent on tumor location and/or size, trial allowed for a dose of 25-40 Gy.
- RT was delivered to all areas concurrently, and all RT was to be completed within 2 weeks.
- No radiotherapy was allowed in the TKI-only arm unless symptomatology dictated a need for palliative radiation
- In both arms, standard-of-care chemotherapy (specific agents as per oncologist judgment) was recommended upon disease progression; neither second- or third-generation TKIs nor immune checkpoint inhibitors were allowed

Endpoints

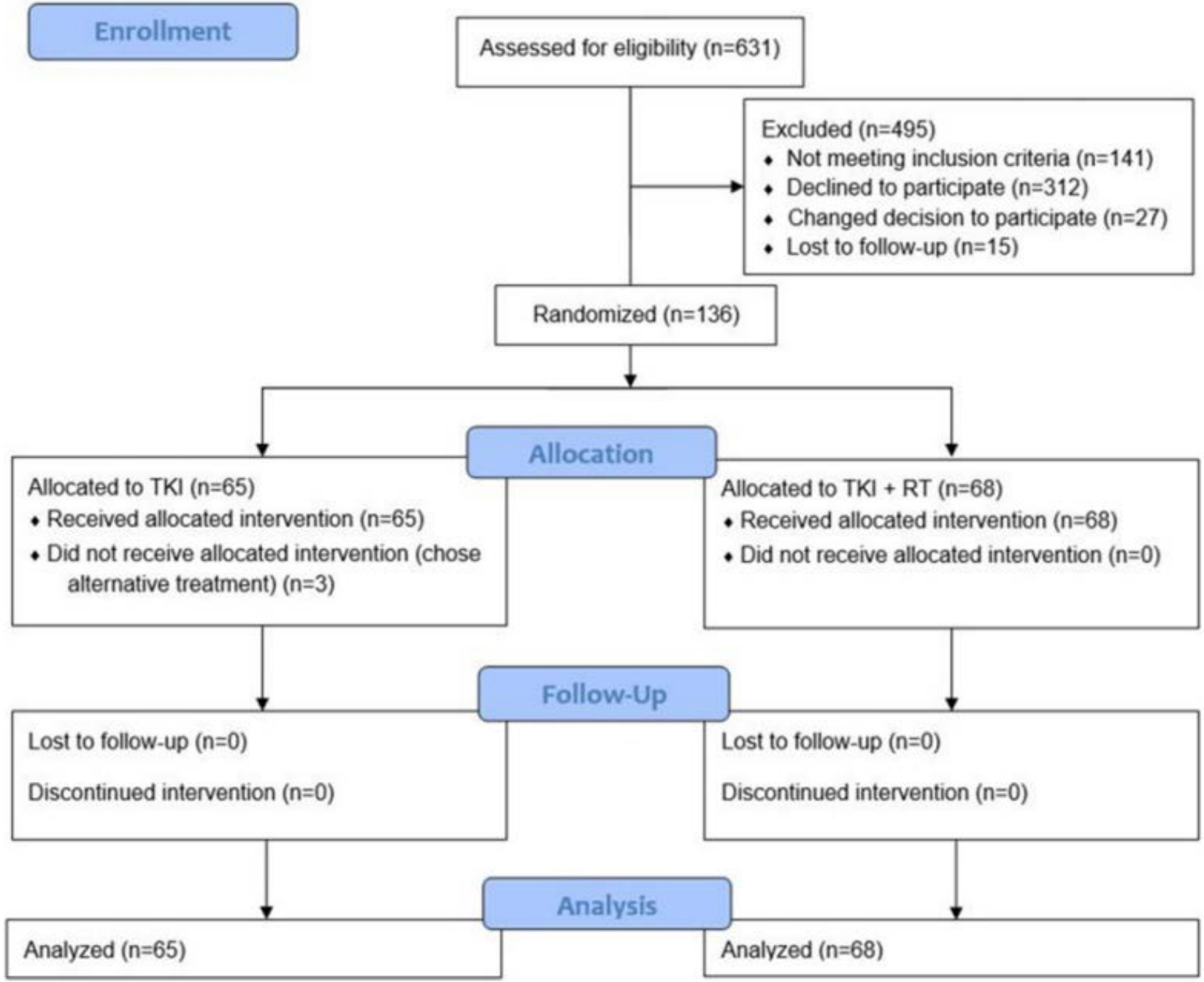
- The primary endpoint was PFS, defined from the time of randomization to the time of disease progression or death;
- Secondary endpoints were OS (from randomization to death from any cause) and safety.

Hypothesis

- It was hypothesized that the addition of RT would increase the 6-month PFS from 75% with TKI only to 90%.
- As a result, the trial would require 200 patients to achieve a power of 80% with a 2-sided alpha of .05
- The protocol prespecified an interim analysis when 68% of accrual was reached

CONSORT diagram for the trial

From January 15, 2016, to June 28, 2019, a total of 631 patients from 5 centers were screened for enrollment, of whom 136 participants met criteria and were randomly assigned



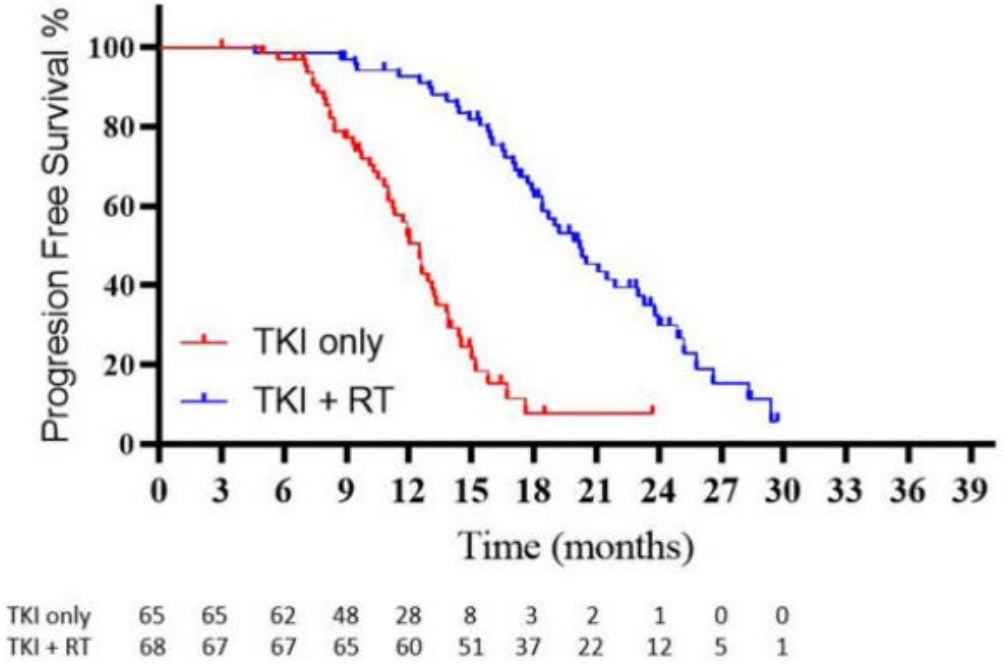
Results

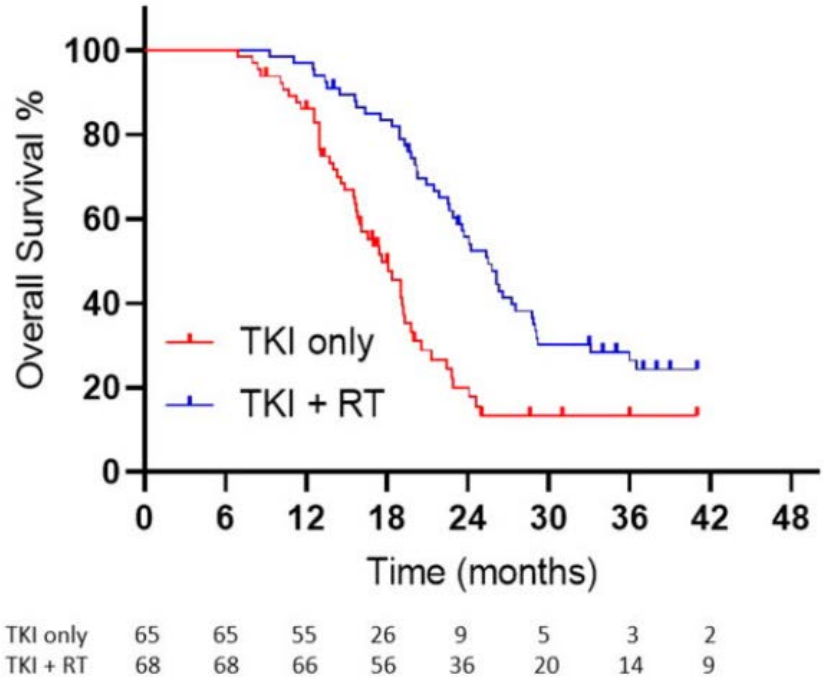
Table 1. Clinicopathologic characteristics of the study population[a]

Parameter	TKI only (n = 65)	TKI + RT (n = 68)
Age, y		
Mean (SD)	63 (11)	67 (10)
Sex, No. (%)		
Male	26 (40.0)	25 (36.8)
Female	39 (60.0)	43 (63.2)
Zubrod performance status, No. (%)		
0	31 (47.7)	36 (52.9)
1	33 (50.8)	32 (47.1)
2	1 (1.5)	0 (0.0)
Clinical T classification, No. (%)		
1	9 (13.8)	5 (7.4)
2	16 (24.6)	17 (25.0)
3	22 (33.8)	20 (29.4)
4	17 (26.2)	23 (33.8)
Unknown	1 (1.5)	3 (4.4)
Clinical N classification, No. (%)		
0	8 (12.3)	8 (11.8)
1	23 (35.4)	19 (27.9)
2	24 (36.9)	27 (39.7)
3	10 (15.4)	13 (19.1)
Unknown	0 (0.0)	1 (1.5)
EGFR mutation, No. (%)		
Exon 19	47 (72.3)	45 (66.2)
Exon 21	18 (28.7)	23 (33.8)
Number of metastases, No. (%)		
1-2	38 (58.5)	32 (47.1)
3-4	23 (35.4)	30 (44.1)
5	4 (6.2)	6 (8.8)
TKI, No. (%)		
Gefitinib	38 (58.5)	32 (47.1)
Erlotinib	23 (35.4)	30 (44.1)
Icotinib	4 (6.2)	6 (8.8)

- The distribution of oligometastatic lesions was comparable in both arms; the majority of all lesions were bone metastases
- The most common EGFR abnormality was in exon 19 (92 of 133 [69.2%]).
- Gefitinib (70 of 133 [52.6%]) and erlotinib (53 of 133 [39.8%]) were used more often than icotinib.
- The most common RT doses were 30 Gy (121 of 226 fields [53.5%]) and 25 Gy (70 of 226 fields [31.0%]).

Results





- At the time of last follow-up, local control of both the primary tumor and metastases was maintained in **36 of 65 (55.4%) patients in the TKI-only arm, compared with 62 of 68 (91.2%)** patients in the TKI with RT arm (P < .001).
- The median PFS in the TKIonly and TKI with RT arms was **12.5 months vs 20.2 months** P < .001, **HR 0.22**.
- The respective median OS times were **17.6 months vs 25.5 months** P < .001, **HR 0.44.**
- Independent predictors of PFS included performance status (P <0.02) and the number of metastases (P <0.004), along with RT (P <0.005).
- Independent predictors of OS were performance status (P <0.02), T stage (P <0.02), number of metastases (P <0.004), mutation type (P <0.001), and RT (P <0.004).

Conclusions

- The results of this trial corroborate the utility of local therapy for limited metastatic NSCLC in a population with markedly distinct tumor biology, treatment approaches, and prognosis

- Radiotherapy in this trial was not standardized and allowed for a wide variety of radiotherapy doses, PTV margins, and planning techniques.

- Although local control in the RT arm of this study was quite satisfactory, this study was not designed to evaluate whether higher RT doses would impact PFS as compared with the doses used.

- This study was not designed to evaluate upfront RT vs RT at the time of oligo-progression, nor was it powered for a stratified analysis based on the particular type of EGFR mutation.

- *Thank you*