Best of WCLC 2020

Locally Advanced NSCLC

Chemotherapy / Targeted Therapy / Immunotherapy

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Disclosures

- Consulting: Janssen, Calithera
- Research (funding to institution): Merck, Janssen, Pharmacyclics, Taiho, Incyte

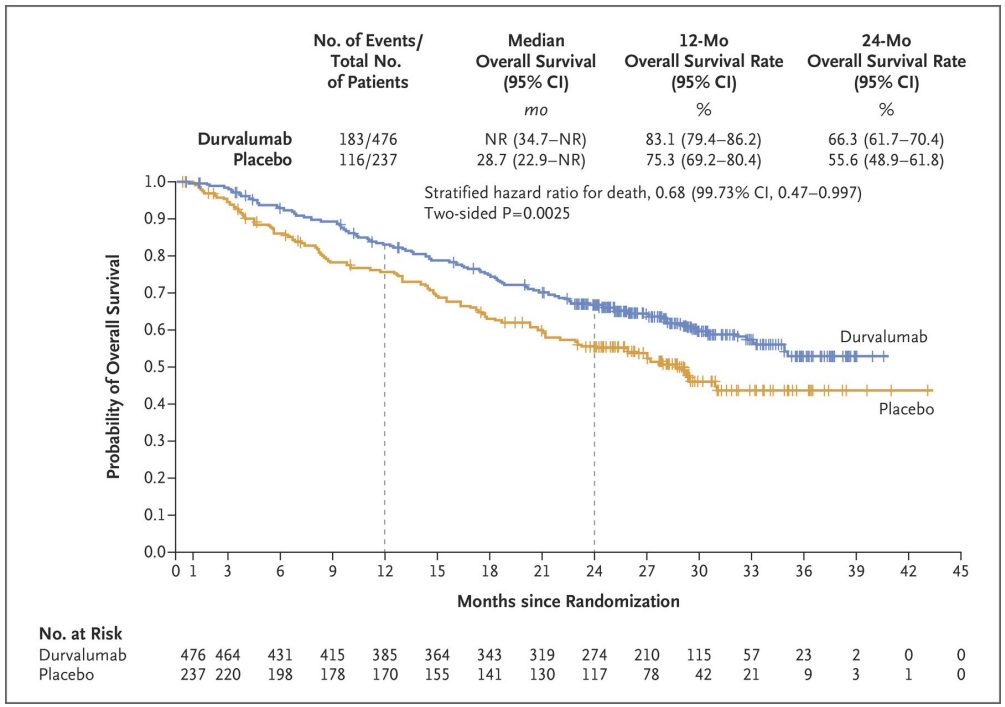
Highlights from WCLC 2020
Locally Advanced NSCLC

- Reck, et al. (OA-02.03) KN-799: Pembrolizumab + Platinum Chemo + Radiotherapy in Unresectable Locally Advanced NSCLC

- Jazieh, et al (OA.05.03) Real-World Global Data on Targeting Epidermal Growth Factor Receptor in Stage III Non-Small Cell Lung Cancer: The Results of the KINDLE Study

Locally advanced, unresectable NSCLC

- Highly heterogeneous cohort
- Requires a multidisciplinary approach
- Fit patients with unresectable T-disease, clinically evident multi-station N2, and those with N3 status are best treated with definitive concurrent chemoRT
- Examples of chemoRT regimens:
  - cisplatin/etoposide/RT 60Gy
  - carbo/paclitaxel/RT 60 Gy
  - platinum/pemetrexed/RT (non-squamous)
- Eligible patients who do not have PD after chemoRT receive consolidation durvalumab (PACIFIC trial)



Antonia, et al NEJM 2018

Pembrolizumab Plus Platinum Chemotherapy and Radiotherapy in Unresectable, Locally Advanced, Stage III NSCLC: KEYNOTE-799

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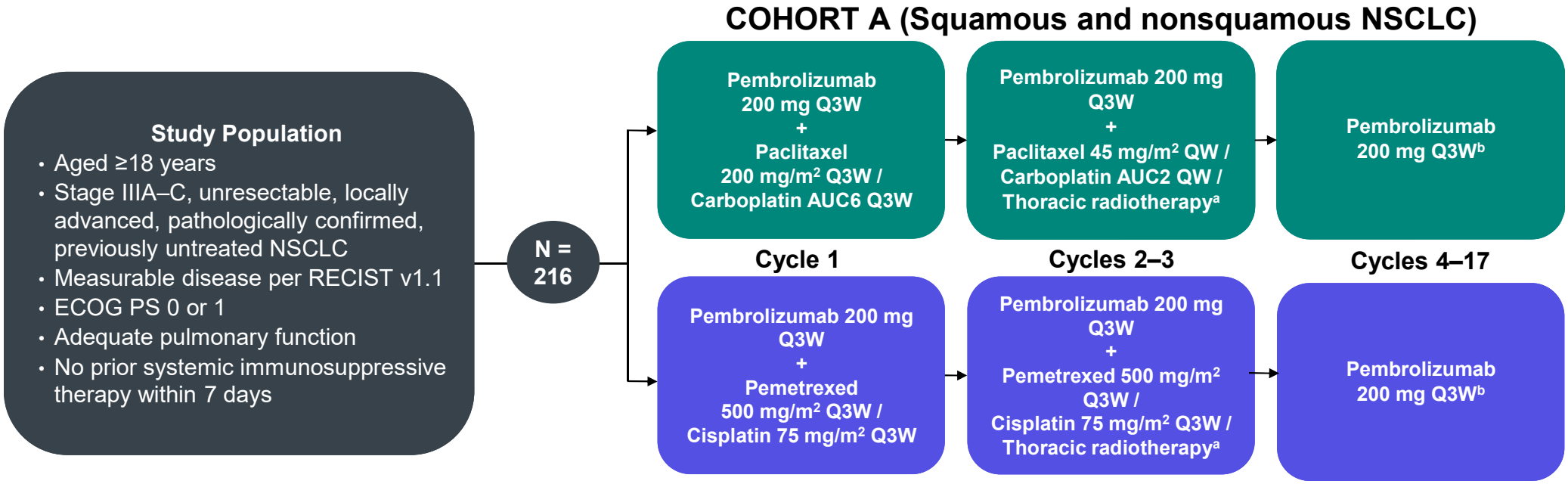
Background

- Standard of care for patients with stage III unresectable NSCLC includes cCRT and durvalumab as consolidation therapy in patients who have not progressed after ≥2 cycles of cCRT[1]
  - However, a subset of patients (22%–30%) might not be eligible for consolidation therapy with durvalumab[2,3] representing a significant unmet medical need
- Pembrolizumab, as monotherapy[4] and in combination with chemotherapy,[5,6] has shown durable clinical benefit in patients with advanced/metastatic squamous and nonsquamous NSCLC
- KEYNOTE-799, a nonrandomized phase 2 study of pembrolizumab plus cCRT in stage III NCSLC reported after ≥15 weeks of follow-up[7]:
  - ORR of 67.0% in cohort A (squamous/nonsquamous) and 56.6% in cohort B (nonsquamous)
  - Grade ≥3 pneumonitis in 8.0% in cohort A and 5.5% in cohort B
  - **Here we present results with 6 additional calendar months of follow-up**

cCRT, concurrent chemoradiation therapy; NSCLC, non–small-cell lung cancer.

1. National Comprehensive Cancer Network. Non-Small Cell Lung Cancer (Version 1.2021). https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. 2. Agulnik et al. *Curr Oncol*. 2020;27:e459-e466. 3. Horinouchi et al. *Cancer Med*. 2020;9:6597-6608. 4. Mok et al. *Lancet*. 2019;393:1819-1830. 5. Gandhi et al. *N Engl J Med.* 2018; 378:2078-2092. 6. Paz-Ares et al. *N Engl J Med*. 2018;379:2040-2051. 7. Jabbour et al. *J Clin Oncol*. 2020;38(15 suppl):9008.

KEYNOTE-799 (NCT03631784)



Primary Objectives

- ORR per RECIST version 1.1 by BICR
- Percentage of patients who develop grade ≥3 pneumonitis

Secondary Objectives

- PFS, OS, safety

Statistical Analysis Details

- Efficacy assessed in all patients with first study dose before or on October 31, 2019 (PE population)
- Safety assessed in all patients in the as-treated population

BICR, blinded, independent central review; PE, primary efficacy.

[a]60 Gy in 30 daily 2-Gy fractions. [b]Treatment will continue until cycle 17 is completed or until documented disease progression, unacceptable AEs, intercurrent illness that prevents further administration of treatment, or study withdrawal. Pembrolizumab therapy will be discontinued permanently in patients who develop grade ≥3 or recurrent grade 2 pneumonitis.

Study Disposition
(All Patients As-Treated)

Cohort A[a]: 112 patients enrolled

Status for Study Treatment

- 43 (38.4%) completed
- 2 (1.8%) ongoing
- 67 (59.8%) discontinued
  - 41 (36.6%) AE
  - 14 (12.5%) progressive disease[c]
  - 5 (4.5%) physician decision[d]
  - 6 (5.4%) unable to provide therapy per protocol[e]
  - 1 (0.9%) withdrawal by patient

Cohort B[b]: 101 patients enrolled

Status for Study Treatment

- 24 (23.8%) completed
- 41 (40.6%) ongoing
- 36 (35.6%) discontinued
  - 17 (16.8%) AE[d]
  - 11 (10.9%) progressive disease[c]
  - 3 (3.0%) unable to provide therapy per protocol[e]
  - 2 (2.0%) protocol violation
  - 2 (2.0%) withdrawal by patient
  - 1 (1.0%) noncompliance with study drug

Median (range) time from first dose to database cutoff[f]:

Cohort A: 15.5 (10.6–20.8) months

Cohort B: 13.6 (9.1–20.6) months

[a]Squamous and nonsquamous. [b]Nonsquamous only. [c]Includes progressive disease and clinical progression. [d]Includes 1 incidence associated with COVID-19.
[e]Patients discontinued due to inability to meet protocol-defined thoracic radiation requirements. [f]Primary efficacy population.
Data cutoff: July 30, 2020.

Baseline Characteristics

Characteristics	Cohort A[a] n = 112[b]	Cohort B[c] As-treated population n = 101	Cohort B[c] Primary efficacy population n = 61
Age, median (range), y	66.0 (46–90)	64.0 (35–81)	64.0 (45–78)
Men	76 (67.9)	62 (61.4)	36 (59.0)
ECOG PS 1	61 (54.5)	44 (43.6)	29 (47.5)
Histology			
Squamous	73 (65.2)	0	0
Nonsquamous	39 (34.8)	101 (100)	61 (100)
Former/current smoker	106 (94.6)	96 (95.0)	59 (96.7)
PD-L1 TPS			
≥1%	66 (58.9)	40 (39.6)	26 (42.6)
<1%	21 (18.8)	28 (27.7)	17 (27.9)
Unknown/not evaluable	25 (22.3)	33 (32.7)	18 (29.5)

TPS, tumor proportion score. Data listed as n (%) unless otherwise noted.
[a]Squamous and nonsquamous. [b]As-treated and primary efficacy populations were the same for cohort A. [c]Nonsquamous only.
Data cutoff: July 30, 2020.

ORR and Duration of Response
By BICR per RECIST v1.1 (Primary Efficacy Population)

	Cohort A[a] n = 112		Cohort B[b] n = 61	
PE Population	**n = 112**		**n = 61**	
ORR, n (%) [95% CI]	78 (69.6) [60.2−78.0]		43 (70.5) [57.4−81.5]	
CR	4 (3.6)		3 (4.9)	
PR	74 (66.1)		40 (65.6)	
SD, n (%)	21 (18.8)		12 (19.7)	
PD, n (%)	1 (0.9)		0	
Not evaluable, n (%)	2 (1.8)		0	
No assessment, n (%)	10 (8.9)		6 (9.8)	
DOR, median (range),[c] mo	NR (1.4+ to 16.1+)		NR (2.0+ to 15.9+)	
DOR ≥12 mo,[c] n (%)	31 (82.2)		5 (72.1)	
PD-L1 Status	**TPS <1% (n = 21)**	**TPS ≥1% (n = 66)**	**TPS <1% (n = 17)**	**TPS ≥1% (n = 26)**
ORR, n (%)	14 (66.7)	49 (74.2)	11 (64.7)	18 (69.2)
	Nonsquamous	**Squamous**	**Nonsquamous**	**Squamous**

CI, confidence interval; DOR, duration of response; NR, not reached.
[a]Squamous and nonsquamous. [b]Nonsquamous only. [c]Kaplan-Meier estimate. "+" indicates there is no progressive disease by the time of last disease assessment.
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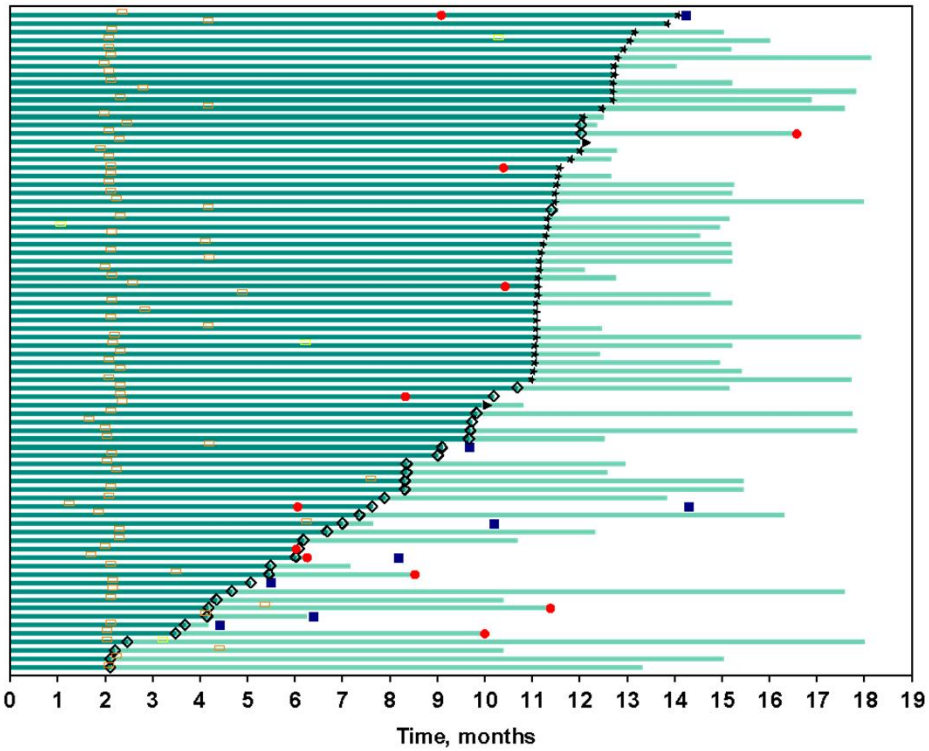
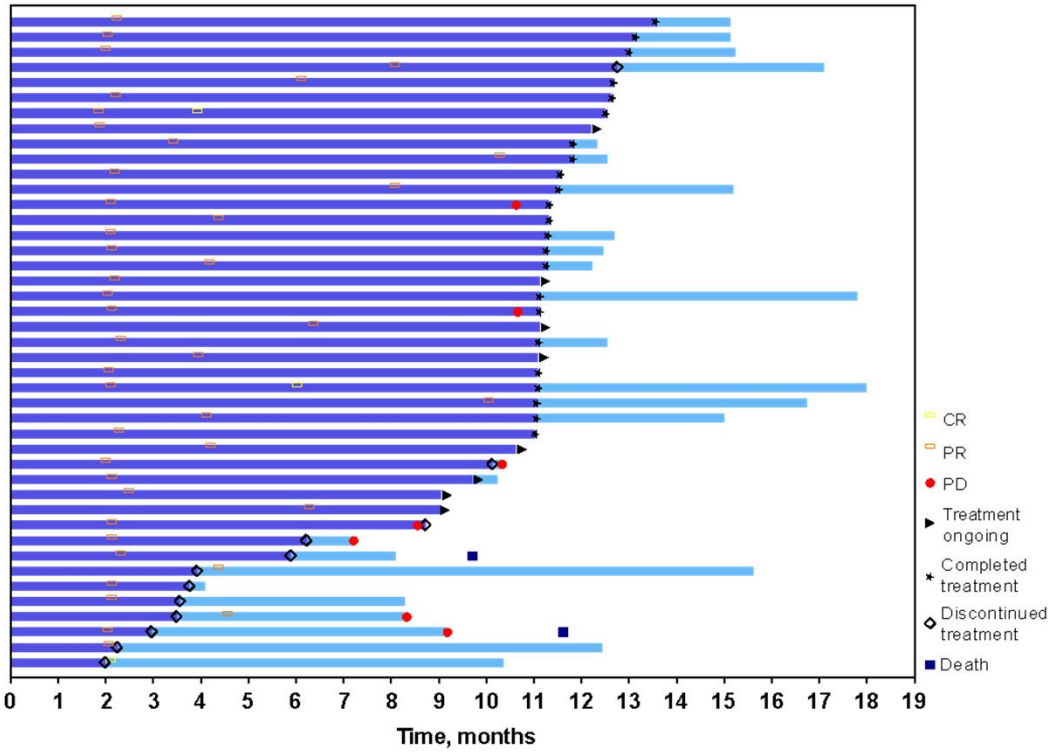
Treatment Duration and Time to Response

By BICR per RECIST v1.1 (Primary Efficacy Population)

Cohort A[a] (2 patients ongoing)



Cohort B[b] (8 patients ongoing)



Median (range) time to response:

Cohort A: 2.1 (1.1–7.6) months

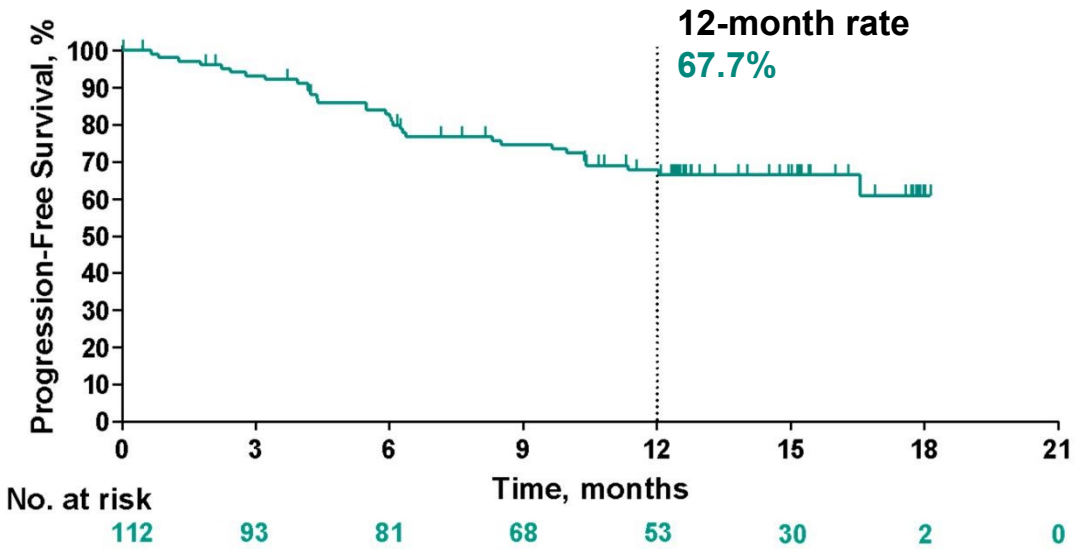
Cohort B: 2.2 (1.8–10.3) months

[a]Squamous and nonsquamous. [b]Nonsquamous only. Dark bars indicate treatment duration and light bars indicate follow-up duration. Data cutoff date: July 30, 2020.

Progression-Free Survival
By BICR per RECIST v1.1 (Primary Efficacy Population)

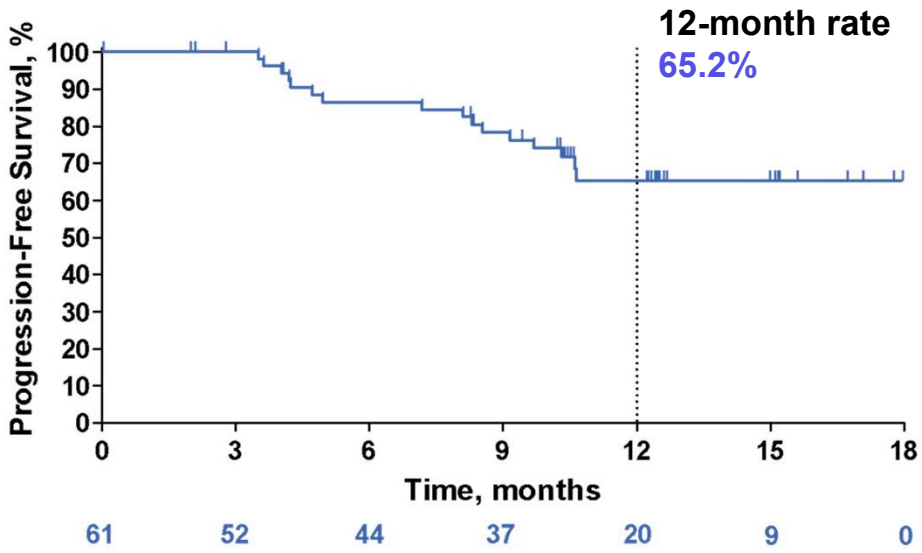
Cohort A[a]

n	Median (95% CI)
112	NR (16.6–NR)



Cohort B[b]

n	Median (95% CI)
61	NR (10.6–NR)

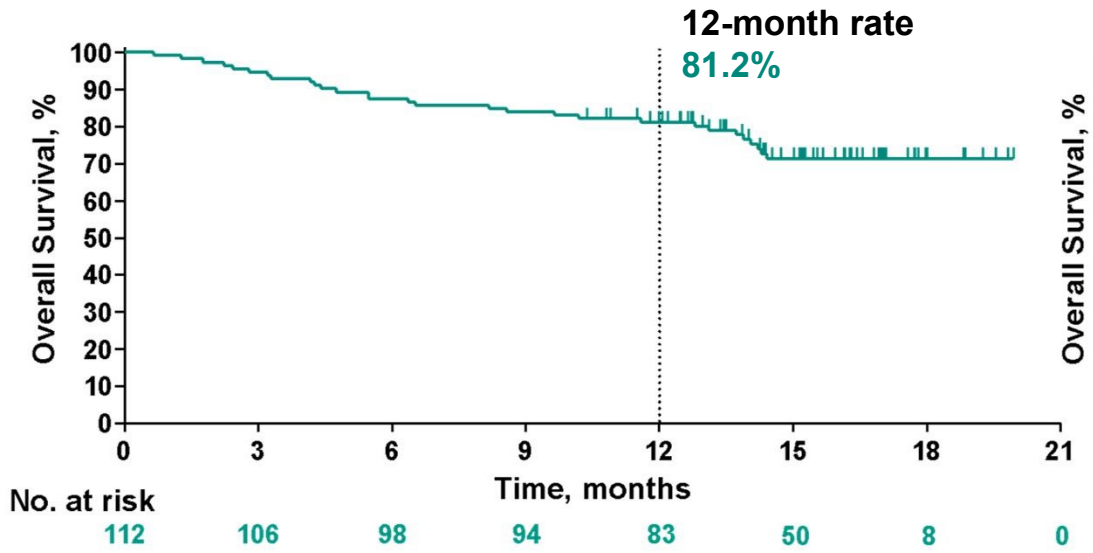


[a]Squamous and nonsquamous. [b]Nonsquamous only.
Data cutoff date: July 30, 2020.

Overall Survival
(Primary Efficacy Population)

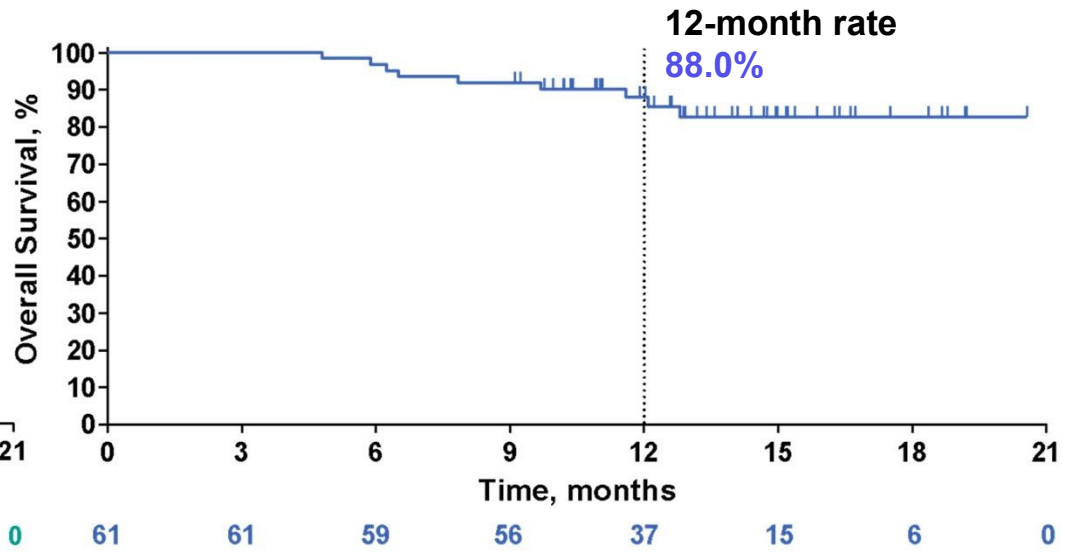
Cohort A[a]

n	Median (95% CI)
112	NR (NR–NR)



Cohort B[b]

n	Median (95% CI)
61	NR (NR–NR)



[a]Squamous and nonsquamous. [b]Nonsquamous only.
Data cutoff date: July 30, 2020.

Incidence of Grade ≥3 Pneumonitis/Safety

Per NCI-CTCAE Version 4.0 (All-Treated Patients)

	Cohort A[a] (n = 112)	Cohort B[b] (n = 101)
Grade ≥3 pneumonitis (all cause),[c,d] n (%) [95% CI]	**9 (8.0) [3.7−14.7]**	**8 (7.9) [3.5−15.0]**
Treatment-related AEs, n (%)	105 (93.8)	96 (95.0)
Grades 3−5	72 (64.3)	47 (46.5)
Led to death	4[c] (3.6)	1 (1.0)
Led to discontinuation of any treatment component	38 (33.9)	16 (15.8)
Discontinued pembrolizumab	27 (24.1)	15 (14.9)
Discontinued radiotherapy	2 (1.8)	0
Discontinued any chemotherapy	18 (16.1)	3 (3.0)
Immune-mediated AEs and infusion reactions, n (%)	59 (52.7)	36 (35.6)
Grades 3−5	18 (16.1)	10 (9.9)
Led to death[d]	4 (3.6)	1 (1.0)

[a]Squamous and nonsquamous. [b]Nonsquamous only. [c]Includes immune-mediated AE of "pneumonitis" and the MedDRA preferred term of "radiation pneumonitis". [d]Includes 4 patients (3.6%) with grade 5 pneumonitis in cohort A and 1 patient (1.0%) with grade 5 interstitial lung disease in cohort B. These events were classified as both treatment-related events and under immune-mediated AEs and infusion reactions.

Data cutoff date: July 30, 2020.

Key Points: Keynote 799

- In locally advanced stage III NSCLC, definitive chemoRT plus pembrolizumab results in:
  - ORR of 70%, regardless of PD-L1 status and tumor histology
  - Response duration ≥12 months in most patients
  - 1-year OS rate >80%
  - Acceptable adverse event profile within expected range of toxicities

- A randomized comparison of concurrent versus sequential (consolidation) immunotherapy approaches is warranted

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CONQUERING THORACIC CANCERS WORLDWIDE

Real-World Global Data on Targeting Epidermal Growth Factor Receptor in Stage III Non-Small Cell Lung Cancer: The Results of the KINDLE Study

Abdul Rahman Jazieh[1], Huseyin Cem Onal[2], Daniel Shao Weng Tan[3], Ross Soo[4], Kumar Prabhash[5], Amit Kumar[6], Reto Huggenberger[7], Stephen Robb[7], Byoung Chul Cho[8]

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KINDLE real world evidence study

- Retrospective, non-interventional study
- Patients with stage III NSCLC diagnosed between 1st January, 2013 and 31st December, 2017, with ≥9 months of documented follow-up
  - Covers the period prior to inclusion of PACIFIC Regimen into stage III clinical management
- **3151** patients enrolled
  - From 19 countries and 100 sites outside of N. America and Europe
- Data abstraction from existing medical records
- Data captured on patient demographics, disease characteristics, treatments and outcomes

In this presentation, we will focus on testing practices and EGFRm NSCLC

EGFRm, epidermal growth factor receptor mutation positive

Baseline characteristics of the KINDLE study population

Characteristics (n=3151)	
Age (years), median (range)	**63.0 (21–92)**
Gender, male, n(%)	**2411 (76.5)**
Smoking Status, n(%)	
- Current smoker	**976 (31.2)**
- Ex-smoker	**1187 (38.0)**
- Never smoker	**712 (22.8)**
AJCC stage (7th edition), n (%)	
- Stage IIIA	**1568 (55.9)**
- Stage IIIB	**1239 (44.1)**

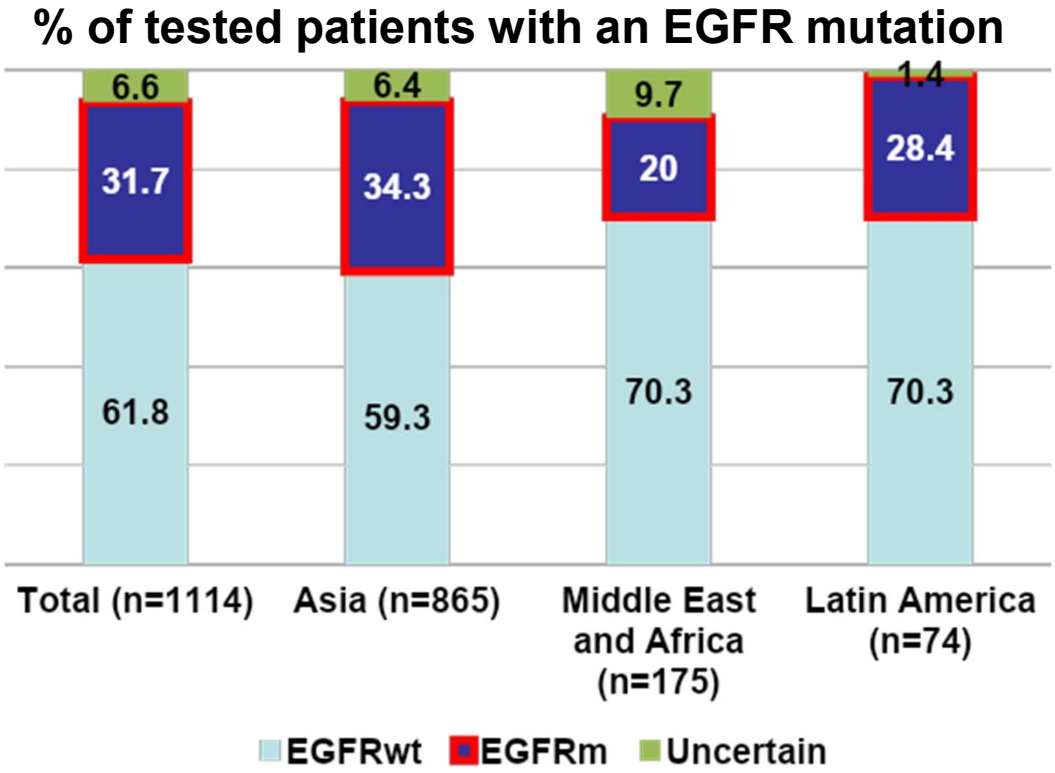
Histology type, n (%)	
- Adenocarcinoma	**1665 (53.7)**
- Epidermoid or squamous cell carcinoma	**1134 (36.6)**
- Other	**96 (3.1)**
- Large cell carcinoma	**61 (2.0)**
- Mixed	**34 (1.1)**
- Bronchiole-alveolar	**14 (0.5)**
ECOG, n (%)	
- 0	**663 (30.3)**
- 1	**1278 (58.4)**
- ≥2	**246 (11.3)**

T stage, n (%)	
- T1	**37 (1.2)**
- T1a	**75 (2.4)**
- T1b	**111 (3.6)**
- T1c	**26 (0.8)**
- T2	**831 (27)**
- T3	**1007 (32.5)**
- T4	**951 (30.6)**
- TX	**41 (1.3)**
- NA	**24 (0.8)**
N stage, n (%)	
- N0	**272 (7.8)**
- N1	**338 (10.9)**
- N2	**1745 (56.2)**
- N3	**715 (23.0)**
- NX	**64 (2.1)**

AJCC, American Joint Committee on Cancer; ECOG, Eastern Cooperative Oncology Group

More than a third of stage III NSCLC patients were tested for presence of EGFR mutation

	Number of patients (%)	EGFRm test performed, n (%)
Total	**3151**	**1114 (35)**
Asia	1874 (59)	865 (46)
Middle East and Africa	1046 (33)	175 (17)
Latin America	231 (7)	74 (32)



EGFRwt, epidermal growth factor receptor wild type

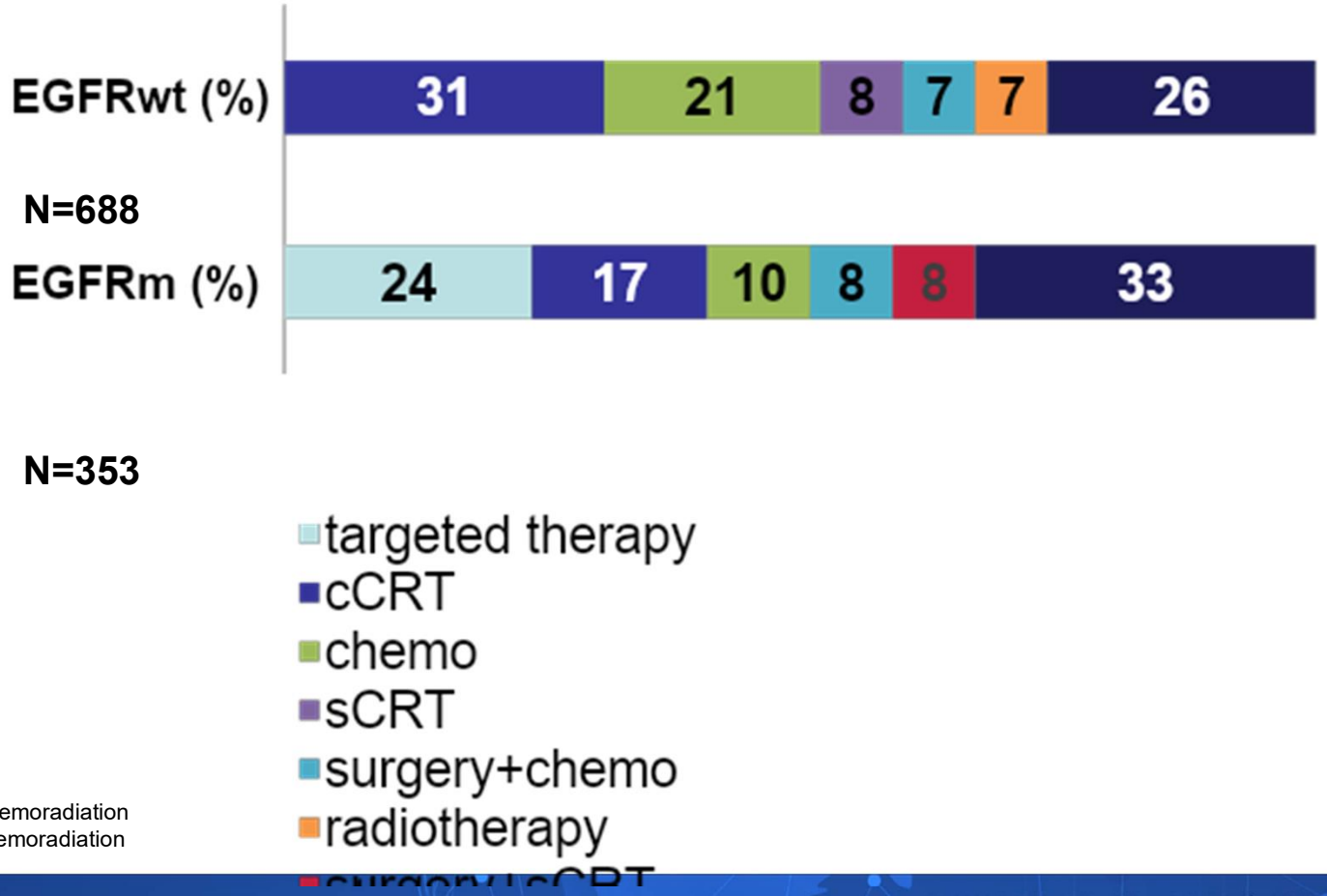
Characteristics of all, the tested, EGFRm, EGFRwt and untested patients

	All patients (n=3151)	Tested (n=1114)	Untested (n=2037)	p-vlaue	EGFRm (n=353)	EGFRwt (n=688)	p-value
Median Age, years (range)	63 (21–92) (n=3084)	63 (24-92) (n=1107)	62 (21–89) (n=2038)	NS	64 (25–90) (n=352)	63 (24–92) (n=682)	NS
Gender, n (%)				***			***
- Female	740 (24%)	373 (34%)	367 (18%)		181 (51%)	172 (25%)	
- Male	2411 (77%)	741 (67%)	1670 (82%)		172 (49%)	516 (75%)	
Tobacco Smoking, n (%)				***			***
- Current / ex-smoker	2163 (69%)	655 (59%)	1508 (75%)		112 (32%)	491 (71%)	
- Never-smoker	712 (23%)	375 (34%)	337 (17%)		204 (58%)	154 (22%)	
- Unknown/missing	276 (9%)	84 (8%)	192 (9%)		37 (11%)	43 (6%)	
Stage, AJCC 7th edition, n (%)				NS			NS
- Stage IIIA	1568 (56%)	601 (57%)	967 (55%)		208 (61%)	357 (55%)	
- Stage IIIB	1239 (44%)	451 (43%)	788 (45%)		131 (39%)	291 (45%)	
Histology, n (%)				***			***
- Adenocarcinoma	1665 (54%)	880 (79%)	785 (39%)		325 (92%)	503 (73%)	
- Epidermoid or Squamous Cell Carcinoma	1134 (37%)	155 (14%)	979 (48%)		17 (5%)	131 (19%)	
- Other / unknown	352 (11%)	79 (7%)	273 (13%)		11 (3%)	53 (8%)	
ECOG PS, n (%)				***			NS
-0-1	1941 (62%)	667 (60%)	1274 (63%)		209 (59%)	409 (59%)	
- ≥2	246 (8%)	61 (5%)	185 (9%)		16 (5%)	42 (6%)	
- Missing	964 (31%)	386 (35%)	578 (28%)		128 (36%)	237 (34%)	
Resectability, n (%)[1)]				***			***
- Resectable	667 (30%)	337 (39%)	330 (24%)		133 (48%)	193 (35%)	
- Unresectable	1545 (70%)	521 (61%)	1024 (76%)		142 (52%)	358 (65%)	

*** <0.001; NS p > 0.05; 1) Information was missing for 939 (all patients), 256 (tested), 78 (EGFRm), 137 (EGFRwt), and 683 (untested) patients, respectively.

PS, performance status

Most common initial treatments of patients with EGFRwt vs. EGFRm stage III NSCLC



cCRT = concurrent chemoradiation
sCRT = sequential chemoradiation

Outcomes following concurrent CRT in unresectable stage III NSCLC: EGFRm and EGFRwt

Unresectable Stage III	EGFRm (n=37)	EGFRwt (n=151)	P-value
Median PFS, months (95% CI)	**10.5 (5.1–16.2)**	**10.8 (8.7–12.7)**	**0.651**
Median OS, months (95% CI)	**48.0 (47.2–NC)**	**36.5 (27.1–51.2)**	**0.065**

- The EGFRm patients were older (66y vs. 62y); more likely to be female (70% vs. 24%); to have adenocarcinoma (87% vs. 67%) and to be never-smokers (78% vs. 20%)
- EGFRm patients have similar PFS after cCRT compared to EGFRwt
- Subsequent treatment (EGFR-TKI) might have influenced the trend for improved OS in EGFRm (73% received a TKI-based treatment post any line of progression)

EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor; OS, overall survival; PFS, progression-free survival; y, years

Unresectable EGFRm patients: initial treatment with cCRT associated with longer OS than TKI monotherapy without any irradiation

Unresectable EGFRm	cCRT (n=37)	TKI mono (n=35)[1)]	**P-value**
mPFS, months (95% CI)	10.5 (5.1–16.2)	14.6 (8.0–18.5)	0.825
mOS, months (95% CI)	48.0 (47.2–NC)	24.0 (14.6–30.5)	<0.001

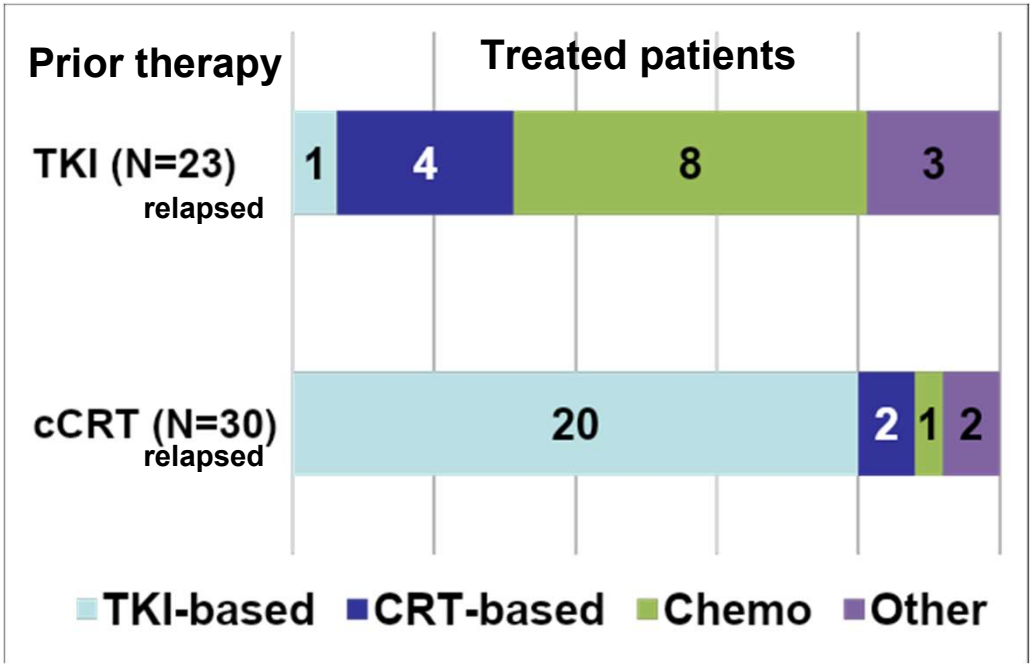
The patients with unresectable EGFRm disease treated with cCRT were younger (66y vs. 74y) and fitter (ECOG 0/1 73% vs. 37%) than those treated with TKI monotherapy

1) Gefitinib was used in 23, erlotinib in 10, afatinib in five, and osimertinib in one patient(s); three patients had to change their TKI, one patient changed twice

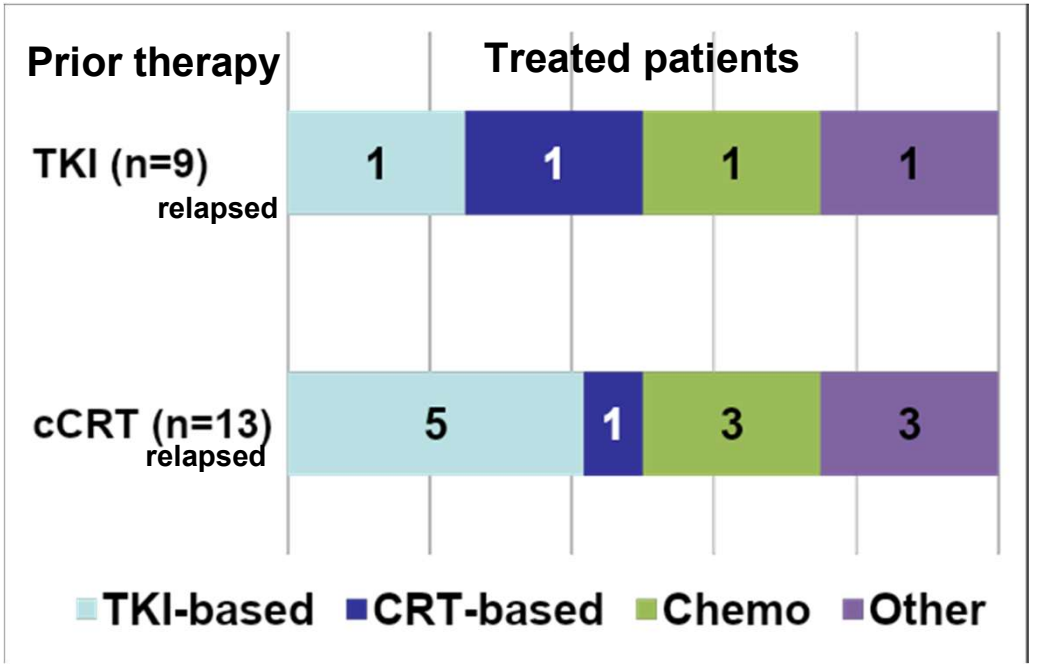
mOS, median overall survival; mPFS, median progression-free survival

Post progression therapy for unresectable EGFRm patients initially treated with cCRT (n=37) or TKI monotherapy (n=35)

1st therapy post progression



2nd therapy post progression



Key Points: KINDLE Study

- Molecular phenotyping of stage III NSCLC is performed in only 35% of patients
- Patients with EGFR mutated and EGFR wt tumors have comparable PFS following chemoRT
- Patients with EGFR mutated tumors appear to have longer OS compared to EGFR wt
  - Likely due to subsequent EGFR TKI therapy
- A subset of patients with EGFR mutated tumors treated with TKI alone (without RT) as initial treatment had a worse OS than those treated with upfront chemoRT
- The LAURA study of osimertinib + chemoRT in EGFR mutated unresectable stage III NSCLC will provide additional insights