Association of Driver Oncogene Variations With Outcomes in Patients With Locally Advanced NSCLC Treated With Chemoradiation and Consolidative Durvalumab

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BACKGROUND

- PACIFIC trial 1 year of consolidative therapy with durvalumab, after chemoradiation led to significantly improved PFS and OS in Stage 3 NSCLC

- Benefit of this regimen for patients with variations in driver oncogenes such as EGFR or KRAS is uncertain

MD Anderson database

- Retrospective cohort analysis (June 2017 – May 2020)

Adult patients with locally advanced, unresectable, stage III NSCLC without progression following platinum-based chemotherapy concurrent with radiation therapy
N=104

→ **Durvalumab** 10 mg/kg IV Q2W for up to 12 mo (At least one dose) →

Until disease progression or unacceptable toxicity

- Grouped according to the presence or absence of driver variations
- KRAS Vs non–KRAS variations

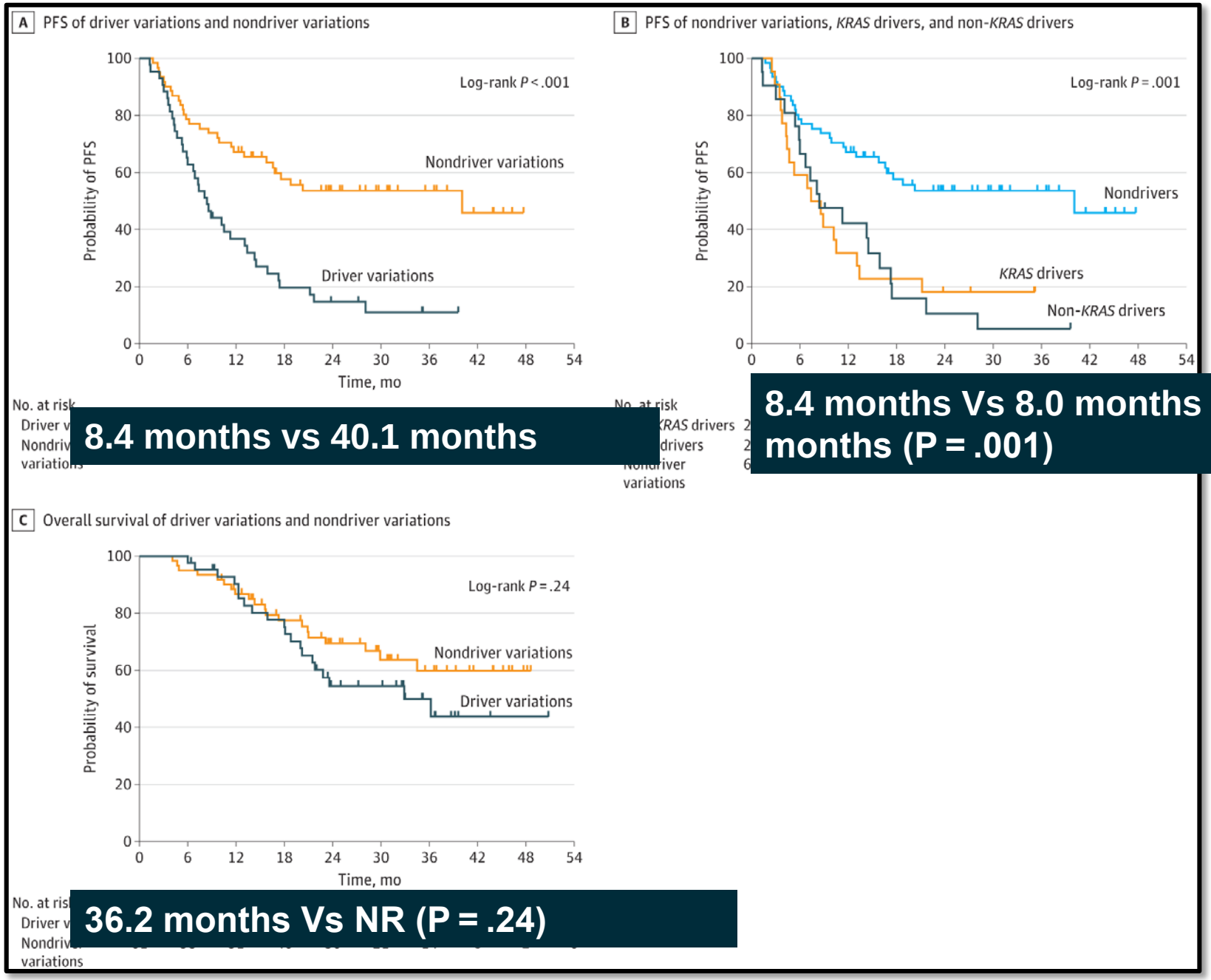
Study outcomes

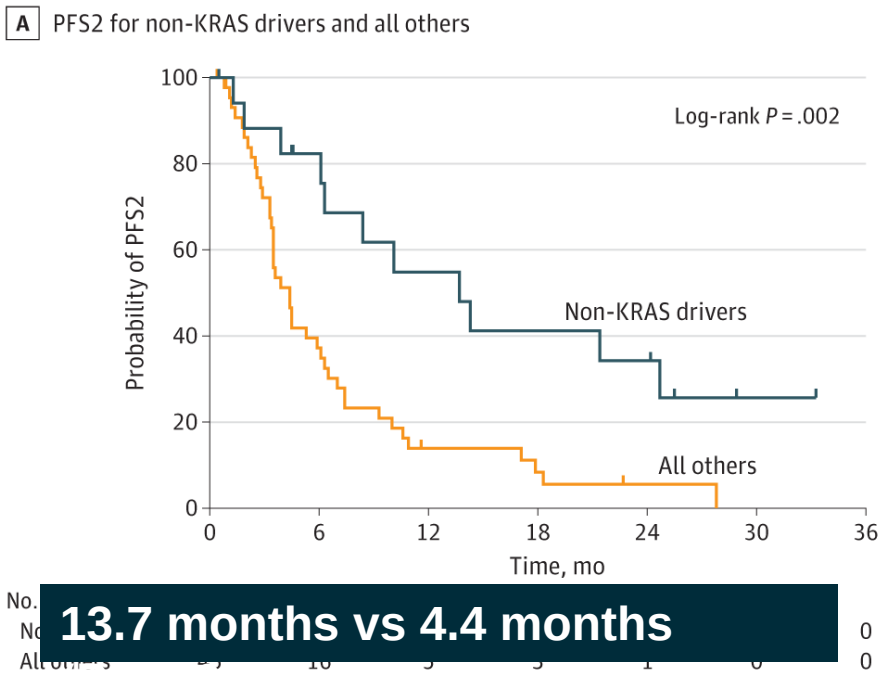
- PFS : date of CRT completion to the date of disease recurrence, death from any cause, or last follow-up
- OS
- PFS 2

Results

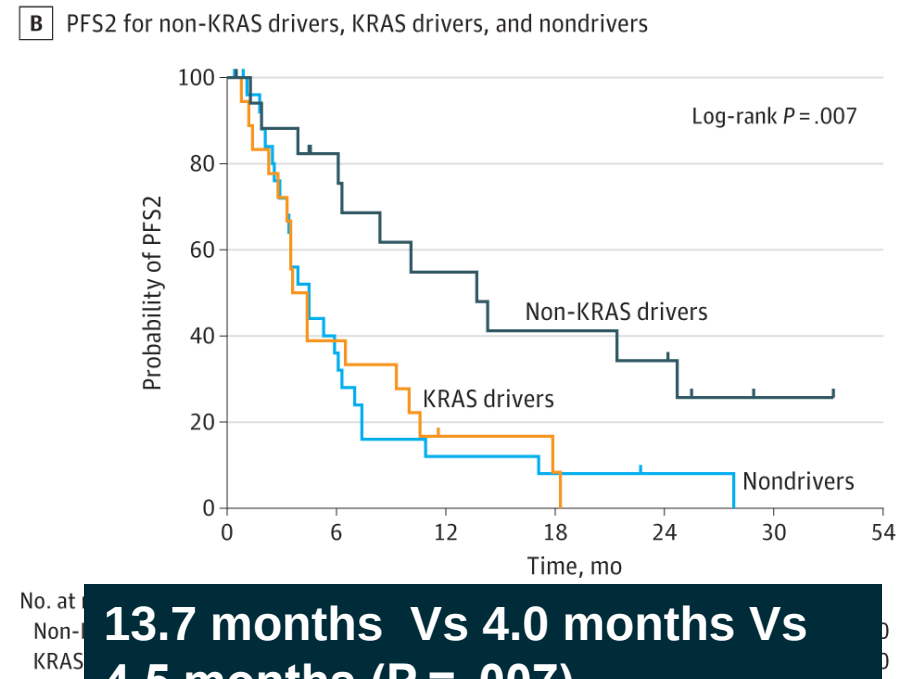
Table 1. Patient Characteristics Stratified by Variation Status

Characteristic	No. (%) All patients (n = 104)	Non-*KRAS* driver variations (n = 21)	*KRAS* driver variations (n = 22)	Nondriver variations (n = 61)	*P* value
Age at completion of CRT, mean (SD), y	65.1 (9.8)	63.8 (11.0)	66.8 (9.1)	65.0 (9.7)	.59
Sex					
Male	49 (47)	6 (29)	6 (27)	37 (61)	.004
Female	55 (53)	15 (71)	16 (73)	24 (39)	
Race					.013
Asian	4 (4)	4 (19)	0	0	
Black	8 (8)	1 (5)	3 (14)	4 (7)	
Hispanic	2 (2)	1 (5)	0	1 (2)	
Middle Eastern	2 (2)	0	1 (4)	1 (2)	
White	88 (85)	15 (71)	18 (82)	55 (90)	
Smoking status					<.001
Current	14 (13)	0	3 (14)	11 (18)	
Former	78 (75)	11 (52)	19 (86)	48 (79)	
Never	12 (12)	10 (48)	0	2 (3)	


A PFS of driver variations and nondriver variations
Probability of PFS
Log-rank P < .001
Nondriver variations
Driver variations
Time, mo
No. at risk
Driver v
Nondriv
variations
8.4 months vs 40.1 months
B PFS of nondriver variations, KRAS drivers, and non-KRAS drivers
Probability of PFS
Log-rank P = .001
Nondrivers
KRAS drivers
Non-KRAS drivers
No. at risk
KRAS drivers 2
drivers 2
Nondriver 6
variations
8.4 months Vs 8.0 months vs 40.1 months (P = .001)
C Overall survival of driver variations and nondriver variations
Probability of survival
Log-rank P = .24
Nondriver variations
Driver variations
Time, mo
No. at ris
Driver v
Nondriv
variations
36.2 months Vs NR (P = .24)



13.7 months vs 4.4 months



13.7 months Vs 4.0 months Vs 4.5 months (P = .007).

Table 3. Treatment Toxic Effects by Variation Status

Toxic Effects	No. (%) All patients (n = 104)	Non-*KRAS* driver variations (n = 21)	*KRAS* driver variations (n = 22)	Nondriver variations (n = 61)	*P* value
All toxicities					
Grade 2 or higher	78 (75.0)	17 (81.0)	17 (77.3)	44 (72.1)	.78
Grade 3 or higher	24 (23.1)	6 (28.6)	5 (22.7)	13 (21.3)	.77
Pneumonitis					
Grade 2 or higher	44 (42.3)	13 (61.9)	10 (45.5)	21 (34.4)	.09
Grade 3 or higher	17 (16.3)	4 (19.0)	3 (13.6)	10 (16.4)	.87
Dysphagia					
Grade 2 or higher	30 (28.8)	4 (19.0)	6 (27.3)	20 (32.8)	.53
Grade 3 or higher	0	0	0	0	> .99
Esophagitis					
Grade 2 or higher	48 (46.2)	9 (42.9)	9 (40.9)	30 (49.2)	.80
Grade 3 or higher	2 (1.9)	0	0	2 (3.3)	> .99
Pain					
Grade 2 or higher	25 (24.0)	4 (19.0)	3 (13.6)	18 (29.5)	.30
Grade 3 or higher	3 (2.9)	0	0	3 (4.9)	.57
Dermatitis					
Grade 2 or higher	12 (11.5)	2 (9.5)	2 (9.1)	8 (13.1)	> .99
Grade 3 or higher	2 (1.9)	1 (4.8)	0	1 (1.6)	.41
Arthritis					
Grade 2 or higher	1 (1.0)	1 (4.8)	0	0	.202
Grade 3 or higher	0	0	0	0	> .99
Diarrhea					
Grade 2 or higher	2 (1.9)	1 (4.8)	1 (4.5)	0	.169
Grade 3 or higher	2 (1.9)	1 (4.8)	1 (4.5)	0	.17
Anorexia					
Grade 2 or higher	6 (5.8)	0	1 (4.5)	5 (8.2)	.62
Grade 3 or higher	1 (1.0)	0	0	1 (1.6)	> .99
Dehydration					
Grade 2 or higher	3 (2.9)	0	0	3 (4.9)	.57
Grade 3 or higher	1 (1.0)	0	0	1 (1.6)	> .99
Fatigue					
Grade 2 or higher	9 (8.7)	0	2 (9.1)	7 (11.5)	.38
Grade 3 or higher	0	0	0	0	> .99

The rates of both grade 2/3 toxicity did not differ by driver

Why do driver mutation do badly with IO?

- oncogene-driven NSCLC may have a smaller tumor mutation burden (TMB)
- *EGFR*-variant NSCLC has markedly lower TMB compared with *EGFR*-wildtype NSCLC
- Lower TMB has been shown in multiple studies to predict worse outcomes on immune checkpoint inhibitors

Discussion

- Retrospective study reported significantly improved PFS among patients with *EGFR*-mutated stage III NSCLC who were given induction or consolidative *EGFR* TKI in conjunction with CRT compared with the PACIFIC regimen (26.1 months vs 10.3 months)*
- ADAURA – PFS benefit with Osimertinib
- LAURA – phase 3 , consolidative osimertinib for patients with unresectable stage III NSCLC after CRT

*Aredo JV et al. J Thorac Oncol

Limitations

- Small sample size
- Single institution
- Short follow-up time and immature OS data

Conclusions

- Prognostic importance of assessing gene variation status in unresectable Stage 3NSCLC patients in guiding treatment decisions
- Future clinical trials>> replacing/ combining durvalumab with TKI therapy for patients with driver variations

My take

- Stage 3 driver mutations positive patients will have to be treated differently
- PFS in FLAURA 18.9mths Vs PACIFIC 16.9mths
- PFS in ALEX 34.8mths Vs PACIFIC 16.9mths

- In ALK and ROS, would definitely prefer TKI
- For EGFR , mostly TKI

Thank you