Pre-treatment ctDNA Levels Significantly Predicts of OS and PFS in NADIM II Trial

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NADIM II: Background

- ~20% of patients with NSCLC are diagnosed with stage IIIA(N2) disease, and historical 5-yr OS for these patients is ~36%[1,2]
  - Preoperative CT is shown to improve survival in resectable NSCLC (HR for OS: 0.87; 95% CI: 0.78-0.96; *P* = .007), but absolute 5-yr OS improvement is only 5%[3]

- Results from various clinical trials suggest benefit for addition of nivolumab to neoadjuvant CT for patients with resectable NSCLC[4,5]
  - Phase II NADIM trial reported high OS rate and promising rate of pCR vs historical data[4]
  - Phase III CheckMate 816 trial reported improved EFS and pCR rate with addition of nivolumab to CT vs CT alone[5]

1. Siegel. CA Cancer J Clin. 2020;70:7. 2. Ramnath. Chest. 2013;143:e314s. 3. NSCLC Meta-analyses Collaborative Group. Lancet 2014;383:1561.
4. Provencio. JCO. 2022[Epub]. 5. Forde. NEJM. 2022;386:1973. 6. Provencio-Pulla. ASCO 2022. Abstr 8501. 7. Provencio. WCLC 2022. Abstr PL03.12.

NADIM II: Contd

- In additional follow-up of NADIM II trial, PFS and OS results with addition of neoadjuvant nivolumab to CT vs CT alone in patients with resectable stage IIIA-B NSCLC reflected improved pCR rate previously reported[1,2]
  - PFS rate: 12 mo, 89.3% vs 60.7%; 24 mo, 66.6% vs 42.3%
  - OS rate: 12 mo, 98.2% vs 82.1%; 24 mo, 84.7% vs 63.4%

- Investigators concluded that NADIM II is first clinical trial with neoadjuvant immunotherapy-based combination to show improved OS

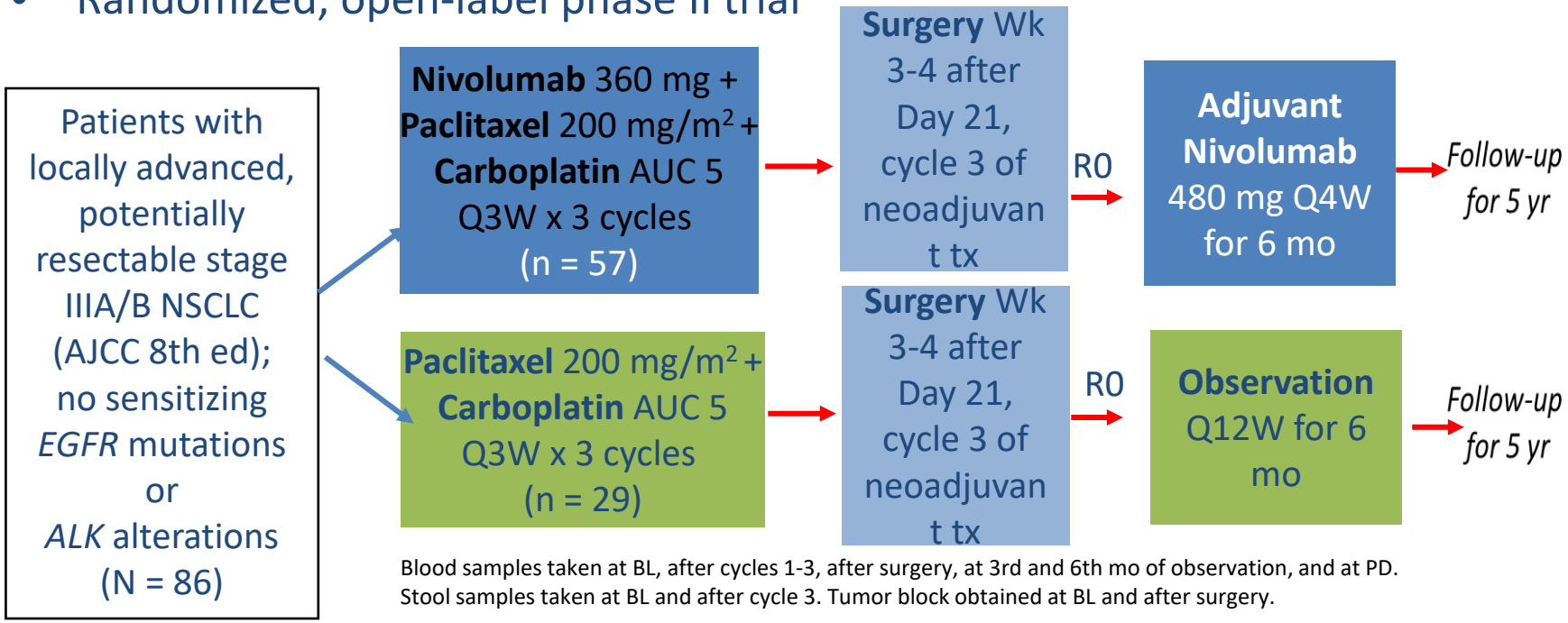
- Prognostic factors capable to discriminate between patients at high- or low-risk of progression and death can be useful to tailor subsequent treatment

1. Provencio. WCLC 2022. Abstr PL03.12. 2. Provencio-Pulla. ASCO 2022. Abstr 8501.

- Currently there are no biomarkers available to identify patients who exhibit long term benefit from chemo-imunotherapy treatment
- In NADIM trial pre treatment ctDNA analysis identified patients at high risk of progression and outperformed radiologic response assessed acc to RECIST criteria v 1.1 in the prediction of survival

NADIM II: Study Design

- Randomized, open-label phase II trial



Blood samples taken at BL, after cycles 1-3, after surgery, at 3rd and 6th mo of observation, and at PD.
Stool samples taken at BL and after cycle 3. Tumor block obtained at BL and after surgery.

- The circulating tumor DNA (ctDNA), from the pretreatment plasma sample, was analyzed with the TruSight Oncology ctDNA next-generation sequencing (NGS) assay

Provencio. WCLC 2022. Abstr PL03.12.

NADIM II: Baseline Characteristics (ITT)

Characteristic, n (%)	Nivo + CT (n = 57)	CT (n = 29)
Median age, yr (range)	63 (58-70)	62 (57-66)
Female	21 (36.8)	13 (44.8)
History of tobacco use		
▪ Never	5 (8.7)	0
▪ Former	23 (40.4)	10 (34.5)
▪ Current	29 (50.9)	19 (65.5)
ECOG PS		
▪ 0	31 (54.4)	16 (55.2)
▪ 1	26 (45.6)	13 (44.8)
Histology		
▪ Adenocarcinoma	25 (43.9)	11 (37.9)
▪ Adenosquamous	1 (1.8)	0
▪ Squamous	21 (36.8)	14 (48.3)
▪ Large cell carcinoma	2 (3.5)	1 (3.5)
▪ NOS/undifferentiated	7 (12.3)	2 (6.9)
▪ Other	1 (1.8)	1 (3.5)

Characteristic, n (%)	Nivo + CT (n = 57)	CT (n = 29)
TNM classification (AJCC 8th ed)		
▪ T1N2M0	12 (21.1)	4 (13.8)
▪ T2N2M0	16 (28.1)	7 (24.1)
▪ T3N1M0	2 (3.5)	1 (3.5)
▪ T3N2M0	13 (22.8)	5 (19.3)
▪ T4N0M0	6 (10.5)	9 (31.0)
▪ T4N1M0	8 (14.0)	3 (10.3)
Median tumor size, mm (range)	43 (29-54)	52 (39-75)
Nodal stage		
▪ N0	6 (10.5)	9 (31.0)
▪ N1	10 (17.5)	4 (13.8)
▪ N2	41 (71.9)	16 (55.2)
N2 multiple station	21 (36.8)	10 (34.5)

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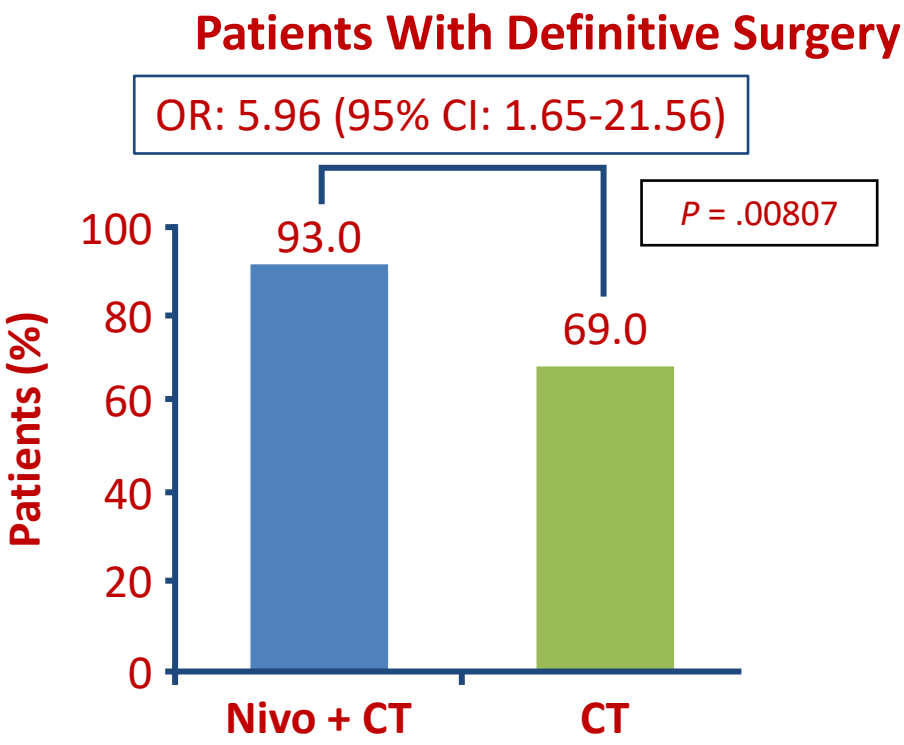
NADIM II: Surgery Summary

Type of Surgery, n (%)[1]	Nivo + CT (n = 53)	CT (n = 20)	Total (n = 73)
Pneumonectomy	6 (11.3)	2 (10.0)	8 (11.0)
Lobectomy	40 (75.5)	17 (85.0)	57 (78.1)
Bilobectomy	4 (7.5)	1 (5.0)	5 (6.8)
Segmentectomy	2 (3.8)	0 (0.0)	2 (2.7)
Right lower lobectomy + segmentectomy	1 (1.9)	0 (0.0)	1 (1.4)

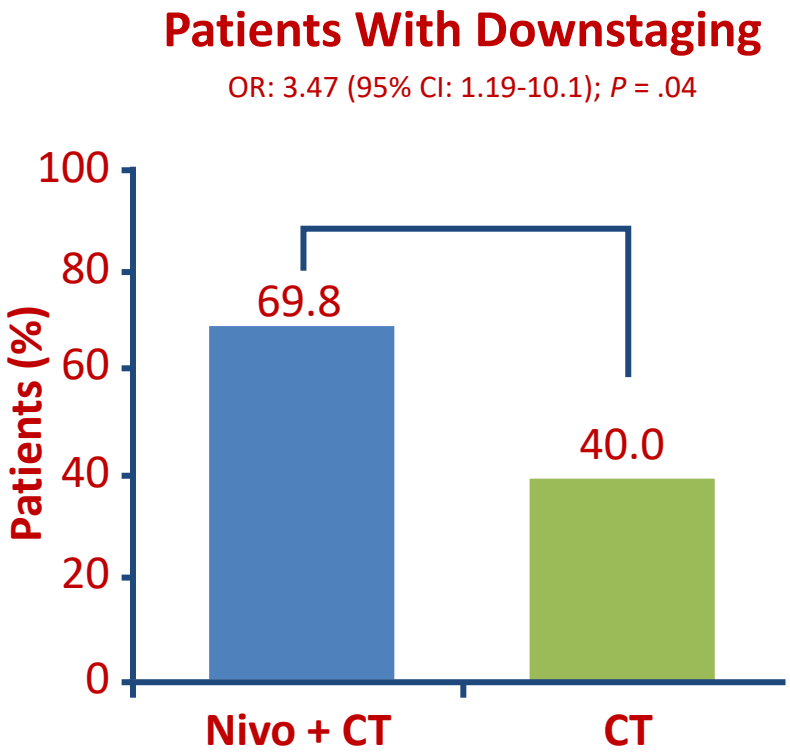
Resection Degree, n (%)[1]	Nivo + CT (n = 57)	CT (n = 29)
RO	49 (92.5)	13 (65.0)

Odds ratio: 6.60 (95% CI: 1.67-26.02); *P* = .007



NADIM II: Downstaging (Secondary Endpoint)

Downstaging, n (%)	Nivo + CT (n = 53)	CT (n = 20)	Total (n = 73)
Yes	37 (69.8)	8 (40.0)	45 (61.6)
No	16 (30.2)	12 (60.0)	28 (38.4)



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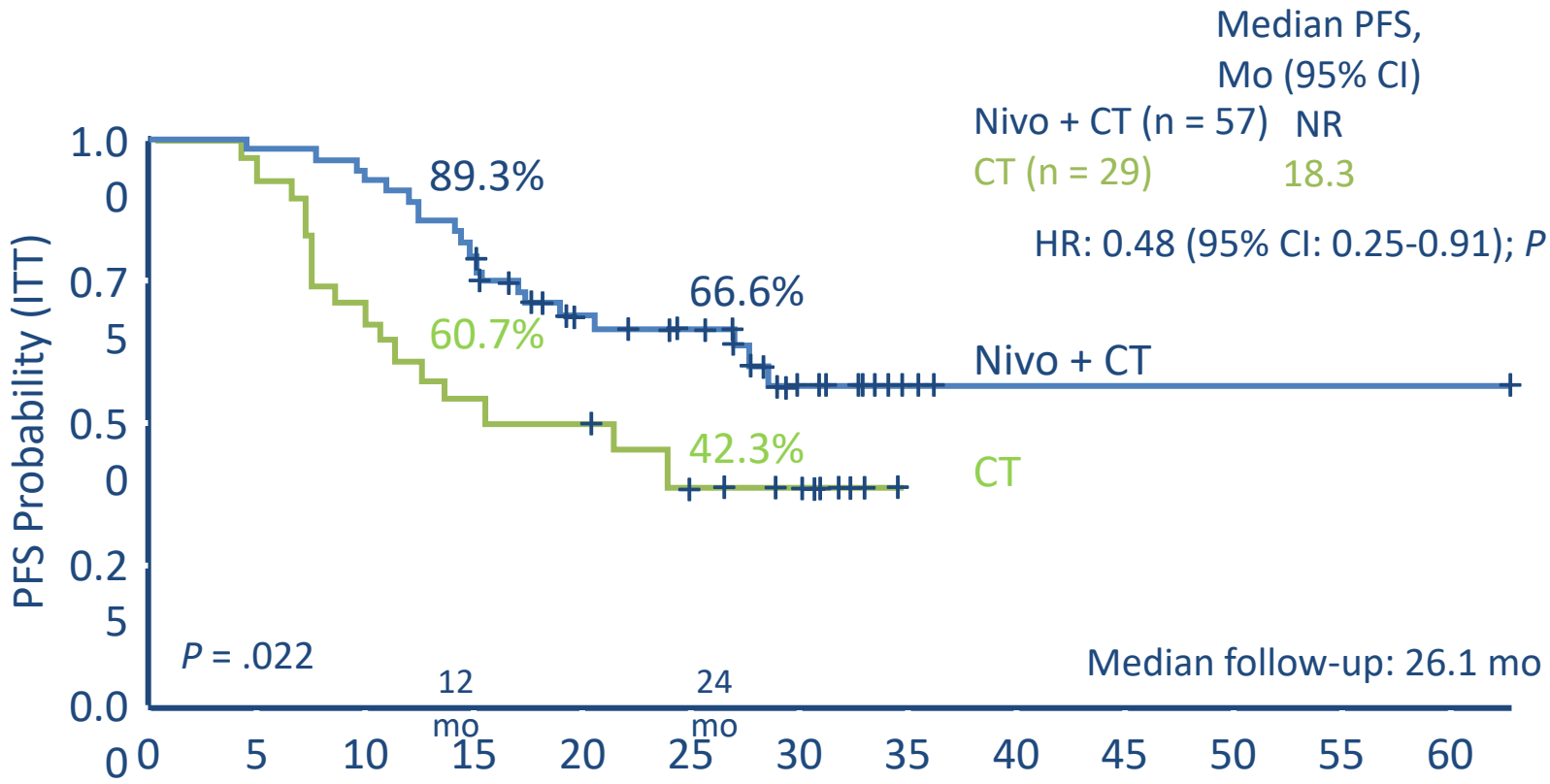
NADIM II: PFS (Secondary Endpoint)



Patients at Risk, n

Nivo + CT	56	55	52	44	30	24	11	4	1	1	1	1	1
CT	28	26	20	15	14	9	7	0	0	0	0	0	0

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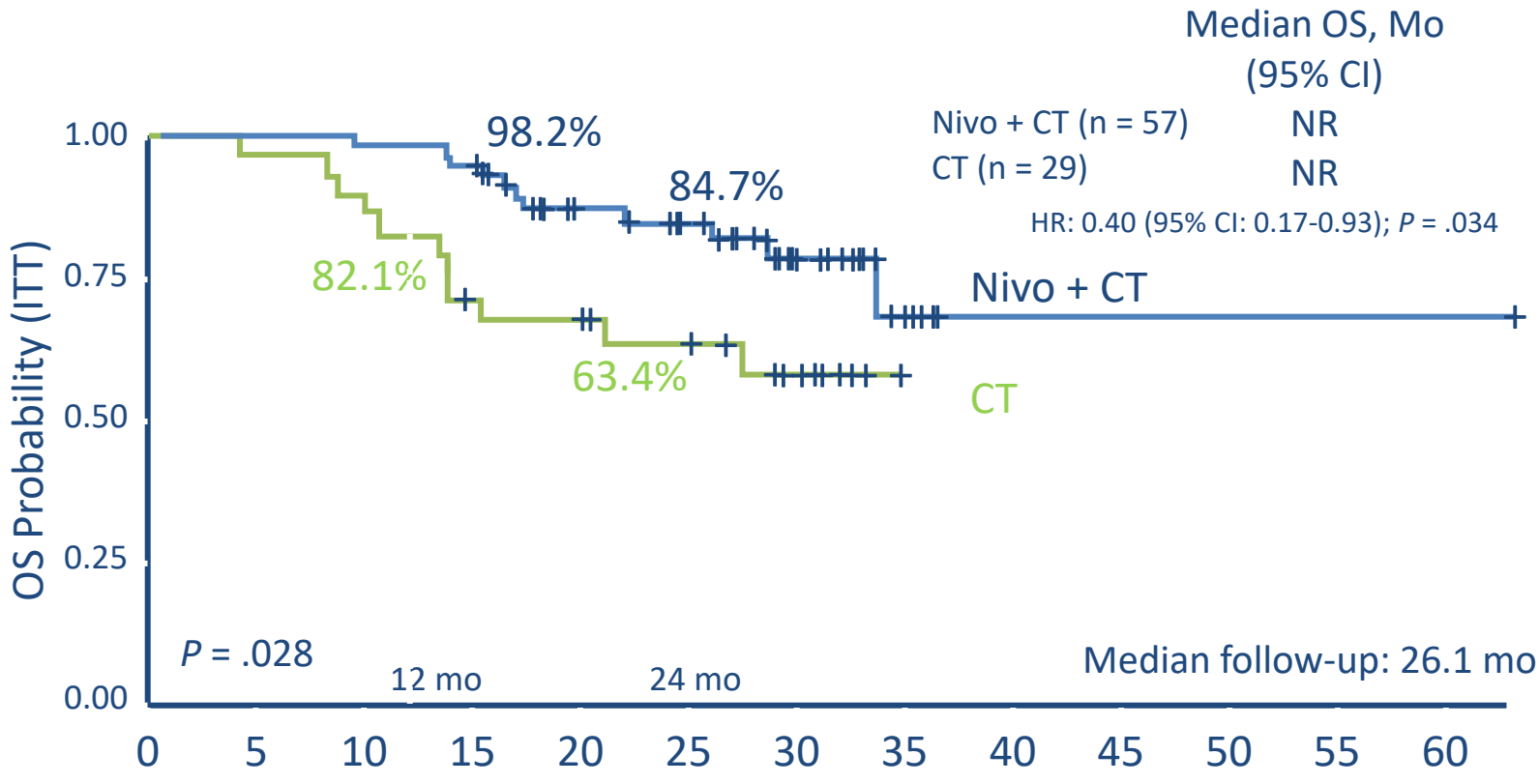
NADIM II: OS (Secondary Endpoint)



Patients at Risk, n

Nivo + CT	56	56	55	53	37	31	15	5	1	1	1	1	1
CT	28	27	25	19	17	13	9	0	0	0	0	0	0

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- Median follow up time was 21.2 (15.1-25.6) months.
- Baseline ctDNA was detected in 52 of 54 (91.4%) of the pre-treatment plasma samples and were significantly associated with tumor size (maximum diameter 70mm) (P=0.006).

- Pre-treatment ctDNA levels were significantly associated with progression free survival (PFS) and overall survival (OS) and regardless of the cutoff used .

- Using a cutoff of <5% mutant allele frequency (MAF)
  - Patients with low ctDNA levels), at baseline, had significantly improved PFS and OS than patients with high ctDNA levels
  - HR: 0.19; 95%CI: 0.07-0.52; P=0.013 for PFS
  - HR: 0.13; 95%CI:0.04-0.45; P=0.001, for OS,

Table 1. Hazard ratio and 95% CI for PFS and OS according to ctDNA levels at baseline

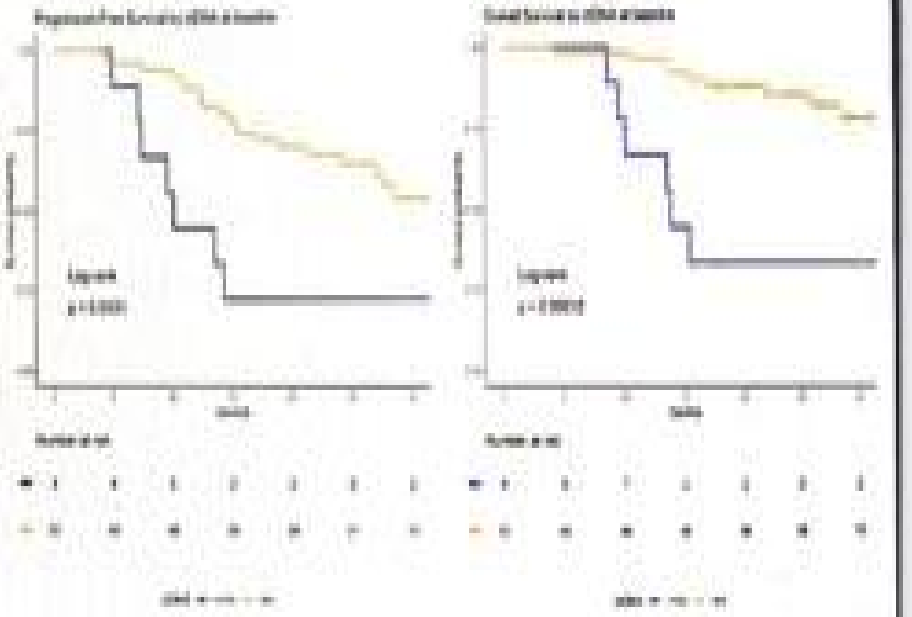
Cutoff	PFS		OS	
	HR (95% CI)	p.value	HR (95% CI)	p.value
MAF4	0.24 (0.089-0.67)	0.006	0.15 (0.042-0.53)	0.0032
MAF4.5	0.19 (0.068-0.52)	0.0013	0.13 (0.036-0.45)	0.0014
MAF5	0.19 (0.068-0.52)	0.0013	0.13 (0.036-0.45)	0.0014
MAF5.5	0.29 (0.094-0.9)	0.033	0.26 (0.067-1)	0.055
MAF6	0.24 (0.067-0.84)	0.025	0.31 (0.064-1.5)	0.14
MAF6.5	0.24 (0.067-0.84)	0.025	0.31 (0.064-1.5)	0.14
MAF7	0.24 (0.067-0.84)	0.025	0.31 (0.064-1.5)	0.14
MAF7.5	0.24 (0.067-0.84)	0.025	0.31 (0.064-1.5)	0.14
MAF8	0.24 (0.067-0.84)	0.025	0.31 (0.064-1.5)	0.14
MAF8.5	0.24 (0.067-0.84)	0.025	0.31 (0.064-1.5)	0.14
MAF9	0.24 (0.067-0.84)	0.025	0.31 (0.064-1.5)	0.14
MAF9.5	0.24 (0.067-0.84)	0.025	0.31 (0.064-1.5)	0.14
MAF10	0.24 (0.067-0.84)	0.025	0.31 (0.064-1.5)	0.14
MAF15	0.18 (0.023-1.5)	0.11	0.15 (0.019-1.2)	0.08

RESULTS

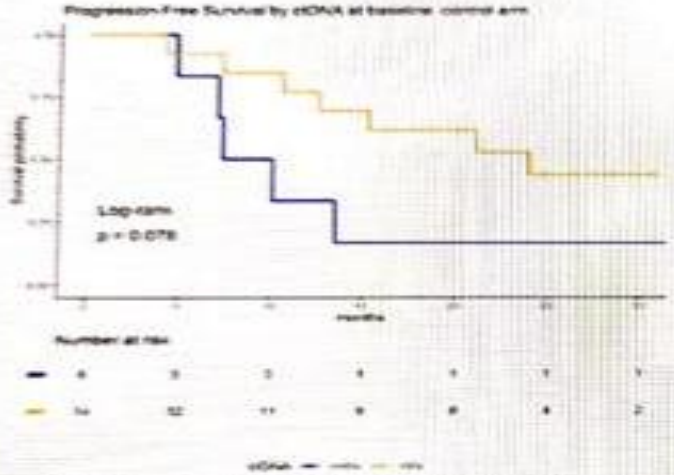
Pre-treatment ctDNA levels were significantly associated with progression free survival (PFS) and overall survival (OS) and regardless of the cutoff used (Table 1).

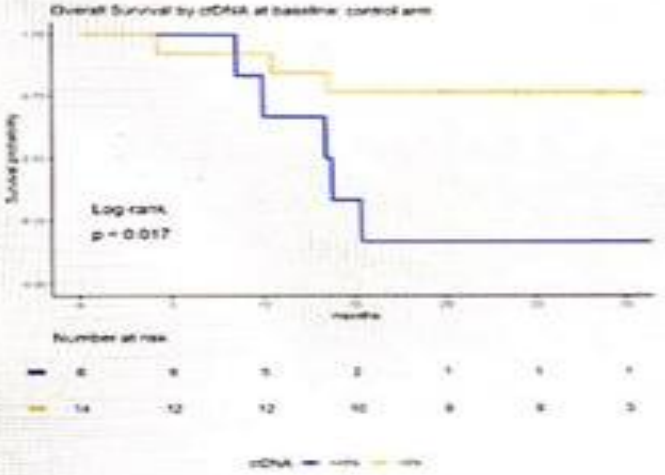
PFS				OS			
Cut-off	HR (95% CI for HR)	P-value	P-value (Log-Rank)	Cut-off	HR (95% CI for HR)	P-value	P-value (Log-Rank)
MAF 5%	0.43 (0.26-0.70)	0.001	0.000	MAF 5%	0.30 (0.15-0.61)	0.001	0.000
MAF 10%	0.44 (0.26-0.75)	0.002	0.000	MAF 10%	0.33 (0.16-0.66)	0.002	0.000
MAF 15%	0.39 (0.22-0.68)	0.001	0.000	MAF 15%	0.29 (0.13-0.63)	0.002	0.000
MAF 20%	0.37 (0.20-0.68)	0.001	0.000	MAF 20%	0.24 (0.09-0.62)	0.003	0.000
MAF 25%	0.35 (0.18-0.69)	0.002	0.000	MAF 25%	0.19 (0.06-0.62)	0.004	0.000
MAF 30%	0.33 (0.16-0.67)	0.002	0.000	MAF 30%	0.17 (0.05-0.62)	0.005	0.000
MAF 35%	0.31 (0.14-0.70)	0.003	0.000	MAF 35%	0.15 (0.04-0.62)	0.006	0.000
MAF 40%	0.30 (0.13-0.70)	0.003	0.000	MAF 40%	0.13 (0.03-0.62)	0.008	0.000
MAF 45%	0.30 (0.13-0.70)	0.003	0.000	MAF 45%	0.13 (0.03-0.62)	0.008	0.000
MAF 50%	0.30 (0.13-0.70)	0.003	0.000	MAF 50%	0.13 (0.03-0.62)	0.008	0.000
MAF 55%	0.30 (0.13-0.70)	0.003	0.000	MAF 55%	0.13 (0.03-0.62)	0.008	0.000
MAF 60%	0.30 (0.13-0.70)	0.003	0.000	MAF 60%	0.13 (0.03-0.62)	0.008	0.000

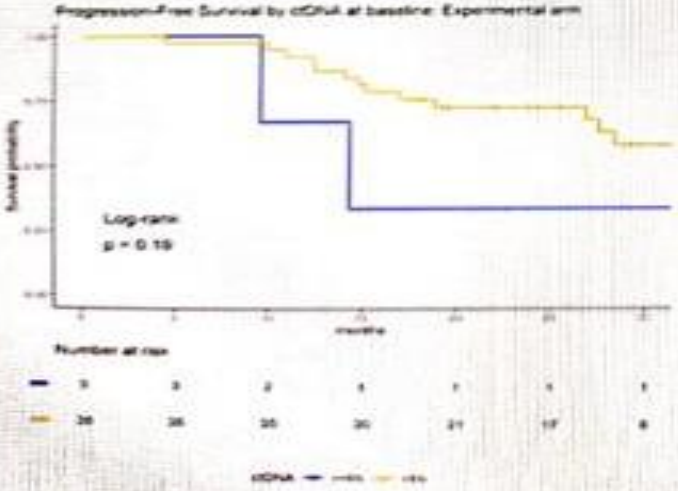
Table 1. Hazard ratio (HR), 95% confidence interval (95%CI), and P-values for PFS and OS according to ctDNA levels at baseline. Abbreviations: MAF, mutant allele fraction; OS, overall survival; PFS, progression-free survival.

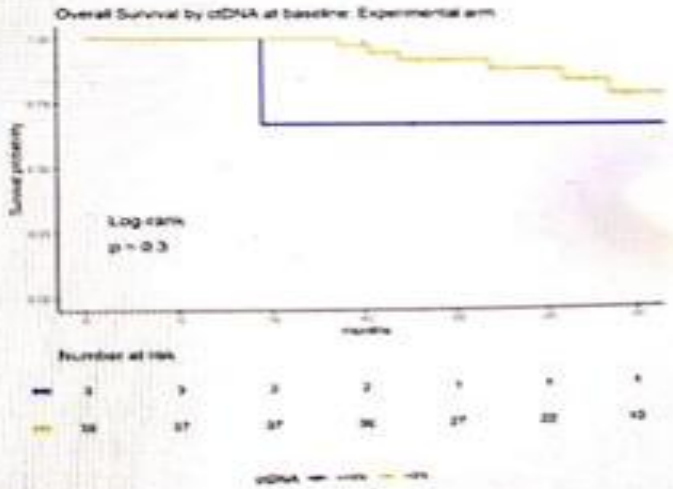


RESULTS

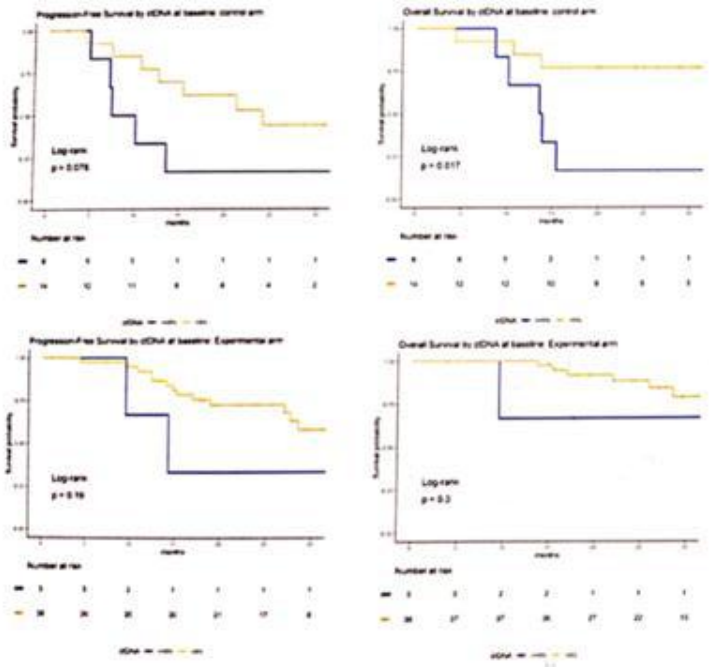

Log-rank
p = 0.079
months
Number at risk


Log-rank
p = 0.017
months
Number at risk


Log-rank
p = 0.19
months
Number at risk

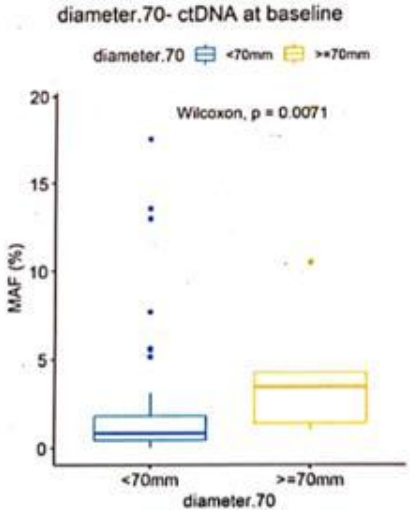

Log-rank
p = 0.3
months
Number at risk

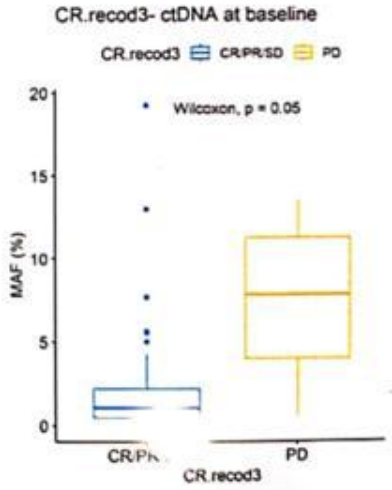
RESULTS

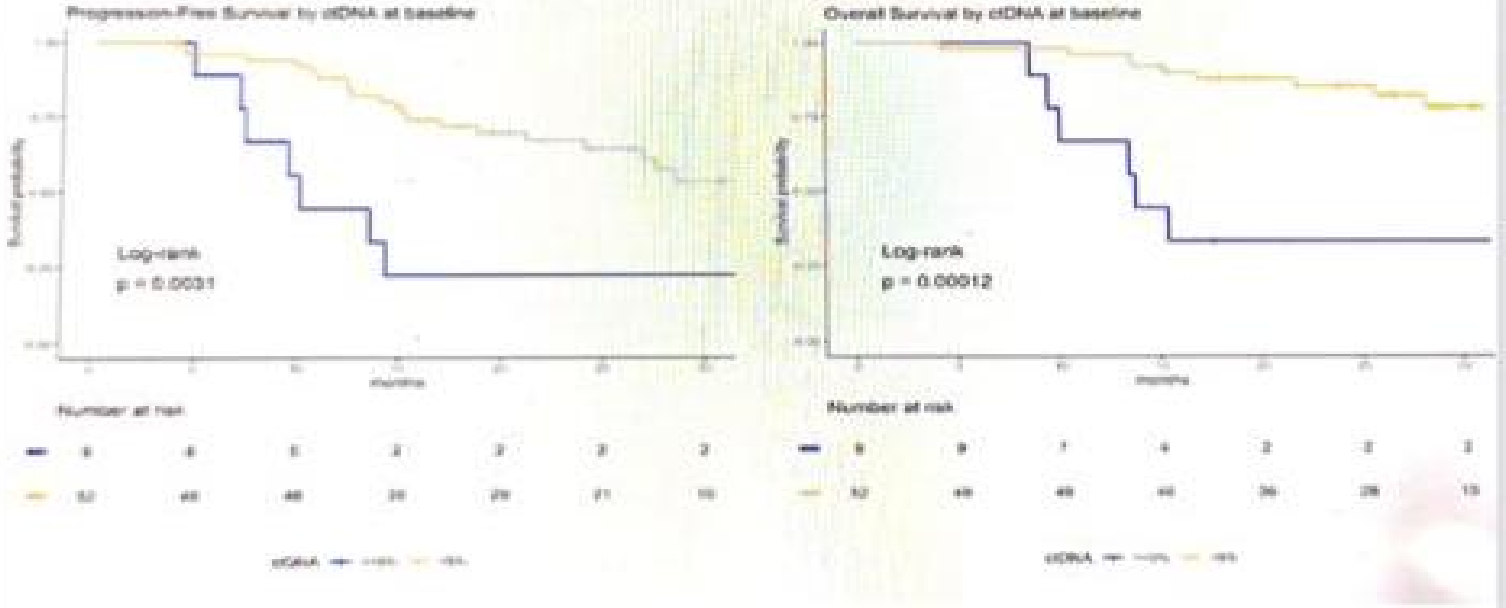


Pre-treatment ctDNA levels were significantly associated with tumor size (maximum diameter ≥ 70mm)

Pre-treatment ctDNA levels were significantly higher in patients diagnosed as having disease progression during neoadjuvant treatment (N=4; control arm)






Progression-Free Survival by ctDNA at baseline
Log-rank
p = 0.0031
Number at risk
Overall Survival by ctDNA at baseline
Log-rank
p = 0.00012
Number at risk

Authors Conclusion

- Baseline ctDNA clearly identified patients at high risk of progression and death and may be used to tailor subsequent treatments accordingly.

Conclusion

- The prognostic information provided by the clinical stage can improve by adding ctDNA information
- ctDNA added a significant degree of prognostic information in the clinical stage in terms of OS and PFS
- Pre-treatment ctDNA levels significantly corelated with tumor size

Thank you