Dr. Khalid Hirmiz

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CANCER EDUCATION DAY

The Decision Between Surgery, Chemotherapy and Radiation

Dr. Khalid Hirmiz

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Stage III Non Small Lung Cancer

- T4:Primary tumor size >7cm,invasion of the trachea or carina,2 separate tumors in an ipsilateral different lobes. Invasion of the mediastinal or surrounding structures.
- N2 Mediastinal nodal disease.
- N3:Contralateral hilar or mediastinal nodal disease, or supraclavicular nodal disease.
- Absence of distant metastases(M0)
- Any T+N2 or N3,M0.
- T4+any N,M0
- T3N1M0

T/M	Label	N0	N1	N2		N3
9th				N2a	N2b	
TX	Primary tumor cannot be assessed					
T0	No evidence of primary tumor					
Tis	Carcinoma in situ, Tis(AIS): adenocarcinoma, Tis(SCIS): squamous cell carcinoma					
T1	T1a ≦ 1 cm	IA1	IIA	IIB	IIIA	IIIB
	T1b > 1 to ≦2 cm	IA2	IIA	IIB	IIIA	IIIB
	T1c > 2 to≦3 cm	IA3	IIA	IIB	IIIA	IIIB
T2	T2a	IB	IIB	IIIA	IIIB	IIIB
	T2a > 3 to ≦ 4 cm	IB	IIB	IIIA	IIIB	IIIB
	T2b > 4 to ≦ 5 cm	IIA	IIB	IIIA	IIIB	IIIB
T3	T3 > 5 to ≦ 7 cm	IIB	IIIA	IIIA	IIIB	IIIC
	T3 Invasion	IIB	IIIA	IIIA	IIIB	IIIC
	T3 Satellite nodules	IIB	IIIA	IIIA	IIIB	IIIC
T4	T4 > 7 cm	IIIA	IIIA	IIIB	IIIB	IIIC
	T4 Invasion	IIIA	IIIA	IIIB	IIIB	IIIC
	T4 Ipsilateral nodules	IIIA	IIIA	IIIB	IIIB	IIIC
M1	M1a Contralateral nodules	IVA	IVA	IVA	IVA	IVA
	M1a Pleural, pericardial effusion	IVA	IVA	IVA	IVA	IVA
	M1b Single Extrathoracic Lesion	IVA	IVA	IVA	IVA	IVA
	M1c1 Mult. Lesions, Single Organ system	IVB	IVB	IVB	IVB	IVB
	M1c2 Mult. Lesions, Mult. Organ system	IVB	IVB	IVB	IVB	IVB

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Treatment Challenges in Stage III NSCLC

- Tumor heterogeneity within stage III NSCLC.
- Requirement to simultaneously control the disease locoregionally and systemically.
- Treatment related toxicity.
- Patient related factors(weight loss,PS,age,comorbidities).

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Treatment Decision Making

- Tumor Factors:

  -Thorough staging is required

  -PET imaging, Brain imaging.

  -Invasive mediastinal staging(EBUS, Mediastinoscopy).
- Patient factors:

  -Performance status

  -Comorbidities

  -Pulmonary reserve.
- Multidisciplinary team treatment coordination on decision on treatment.

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How to decide on Resectable vs Unresectable disease?

- Resectable:

  -Primary tumor is separate from the mediastinum so it can be removed with lobectomy.

  -Discrete and easily distinguishable nodes not invading mediastinal structures, preferably small non bulky and single or few stations.

- Unresectable:

  -Primary is invading mediastinum or surrounding structures.

  -Multiple station or bulky or non discrete nodes with involvement of the mediastinal or surrounding structures.

- Medically Inoperable:

  -Poor pulmonary reserve, active comorbid illness, poor performance status.

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Resectable Disease
Neoadjuvant systemic therapy

- Enhanced immune response(T cells).
- Early elimination of micrometastases.
- No treatment interruption or delays and more likely to get the full dose(better compliance).
- Achieve better pathological response prior to surgery, which results in improvement in surgical feasibility and completion, locol-regional control and survival.

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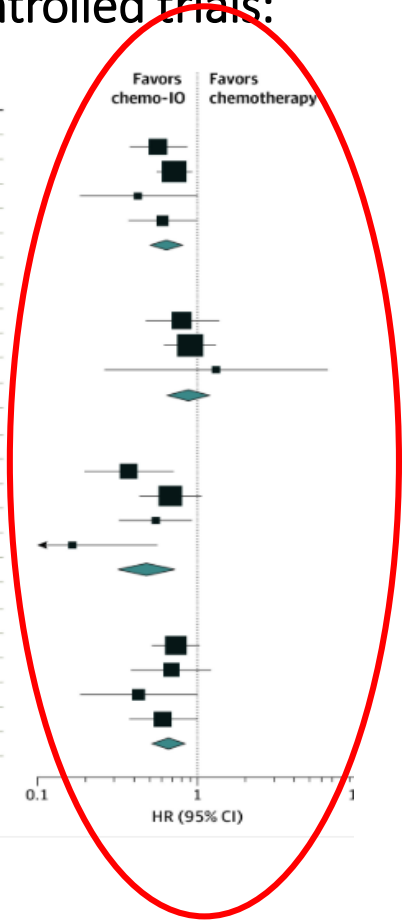
Resectable Disease

Neoadjuvant chemoimmunotherapy for NSCLC
Systematic Review and Meta-Analysis,Sorin et al JAMA ONC 2024

Pooled hazard ratio for overall survival across randomized controlled trials:

Study	Patients, No. Chemo-IO	Chemotherapy	HR (95% CI)
All patients			
Forde et al,[8] 2022; Forde et al,[64] 2023; Provencio Pulla et al,[65] 2023; Provencio Pulla et al,[66] 2023	179	179	0.57 (0.38-0.87)
Wakelee et al,[10] 2023; Spicer et al,[11] 2023; Spicer et al,[67] 2023	397	400	0.72 (0.56-0.93)
Provencio et al,[21] 2023	57	29	0.43 (0.19-0.98)
Lu et al,[63] 2023; Lu et al,[68] 2023	202	202	0.62 (0.38-1.00)
Random-effects model	835	810	0.65 (0.54-0.79)
Heterogeneity: $I^2 = 0\%$; $\tau^2 \leq 0.1$; $P = .57$			
PD-L1 <1%			
Forde et al,[8] 2022; Forde et al,[64] 2023; Provencio Pulla et al,[65] 2023; Provencio Pulla et al,[66] 2023	78	77	0.81 (0.48-1.36)
Wakelee et al,[10] 2023; Spicer et al,[11] 2023; Spicer et al,[67] 2023	138	151	0.91 (0.63-1.32)
Provencio et al,[21] 2023	20	8	1.31 (0.27-6.41)
Random-effects model	236	236	0.89 (0.66-1.19)
Heterogeneity: $I^2 = 0\%$; $\tau^2 \leq 0.1$; $P = .83$			
PD-L1 ≥1%			
Forde et al,[8] 2022; Forde et al,[64] 2023; Provencio Pulla et al,[65] 2023; Provencio Pulla et al,[66] 2023	89	89	0.38 (0.20-0.71)
Wakelee et al,[10] 2023; Spicer et al,[11] 2023; Spicer et al,[67] 2023[a]	127	115	0.69 (0.44-1.07)
Wakelee et al,[10] 2023; Spicer et al,[11] 2023; Spicer et al,[67] 2023[b]	132	134	0.55 (0.33-0.57)
Provencio et al,[21] 2023	30	15	0.17 (0.05-0.57)
Random-effects model	378	353	0.49 (0.33-0.73)
Heterogeneity: $I^2 = 48.5\%$; $\tau^2 \leq 0.1$; $P = .12$			
Stage III			
Wakelee et al,[10] 2023; Spicer et al,[11] 2023; Spicer et al,[67] 2023[c]	217	224	0.74 (0.53-1.03)
Wakelee et al,[10] 2023; Spicer et al,[11] 2023; Spicer et al,[67] 2023[d]	62	55	0.69 (0.39-1.22)
Provencio et al,[21] 2023	57	29	0.43 (0.19-0.98)
Lu et al,[63] 2023; Lu et al,[68] 2023	202	202	0.62 (0.38-1.00)
Random-effects model	538	510	0.67 (0.53-0.85)
Heterogeneity: $I^2 = 0\%$; $\tau^2 \leq 0.1$; $P = .67$			



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Unresectable Disease

- Concurrent Chemotherapy and radical thoracic irradiation,6000cGy in 30 fractions over 6 weeks.
- Restaging and if good response and no distant progression, maintenance Durvalumab for 1 year.
- PACIFIC study: Robust and sustainable OS and durable PFS benefit at 5years with adding durvalumab after chemoradiation compared to chemoradiation alone.

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PACIFIC Trial

Spigel et al, JCO,2022

- Patients with WHO performance status 0 or 1 (any PDL-1 status) after completion of chemoradiation and no progression,were randomly assigned (2:1) to durvalumab (10 mg/kg intravenously; administered once every 2 weeks for 12 months) or placebo, stratified by age, sex, and smoking history.
- 713 patients enrolled,13 randomly assigned patients received durvalumab (473 of 476) or placebo (236 of 237).

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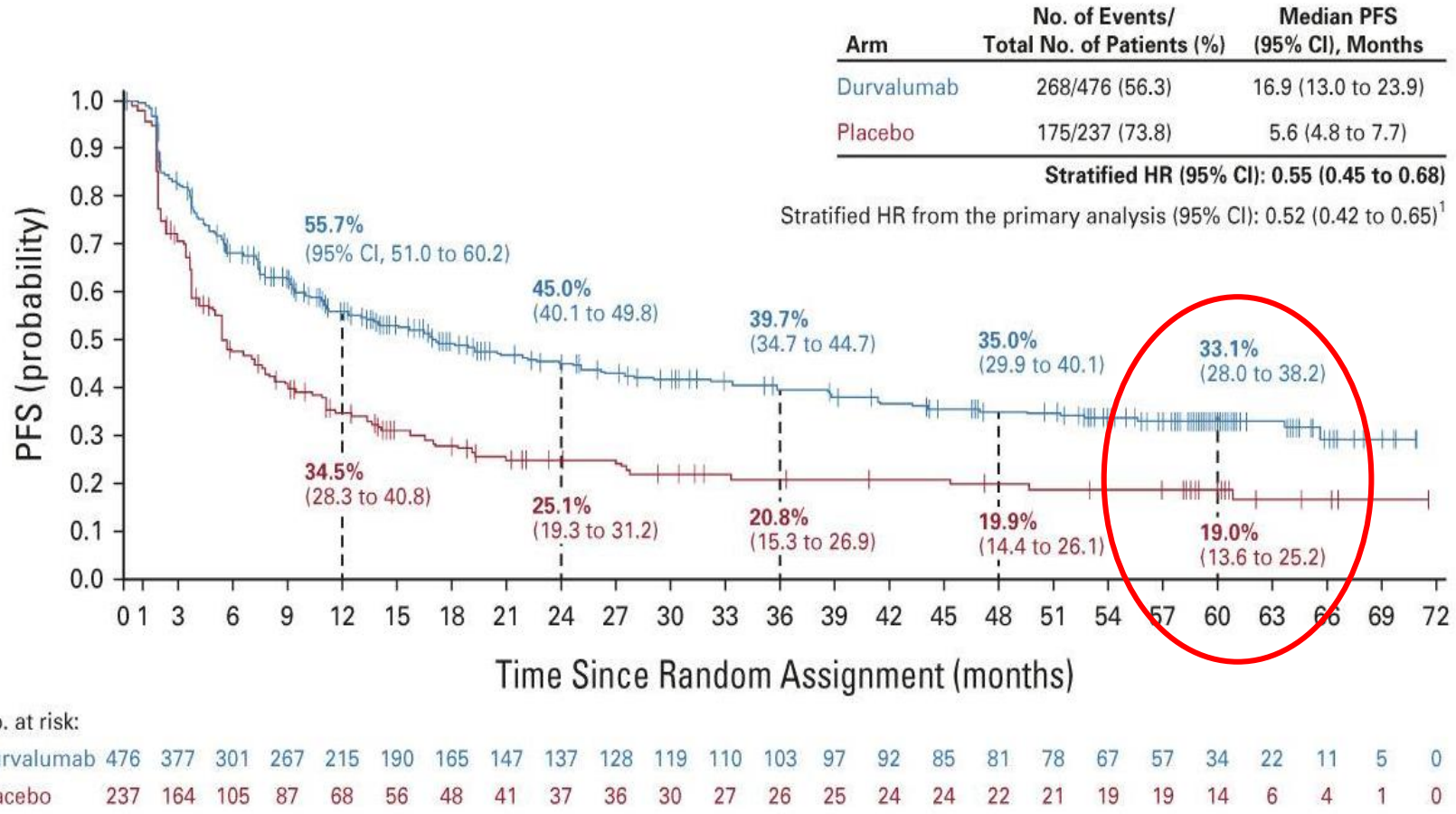
PACIFIC Trial

Spigel et al, JCO,2022



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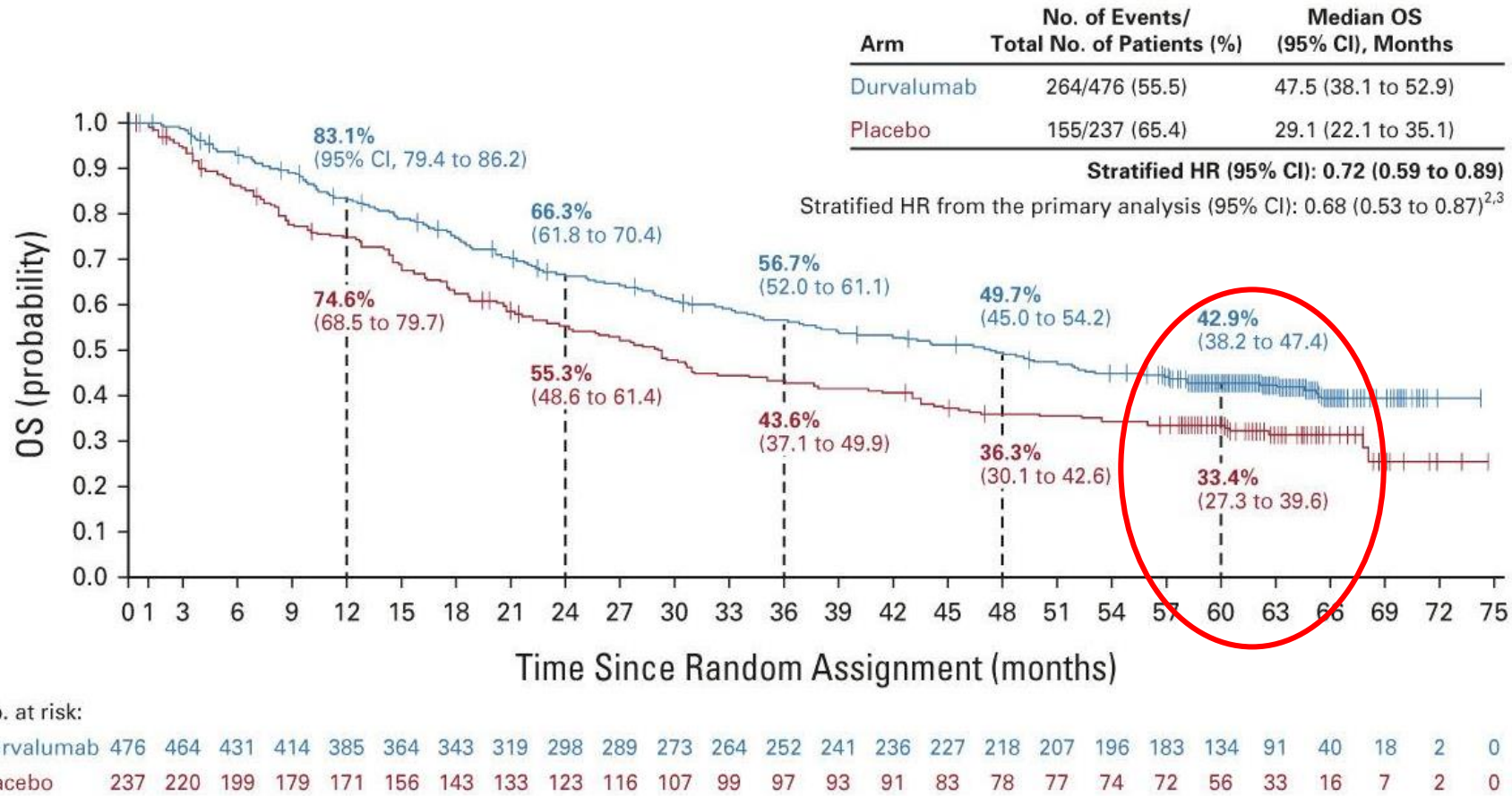
PACIFIC Trial

Spigel et al, JCO,2022



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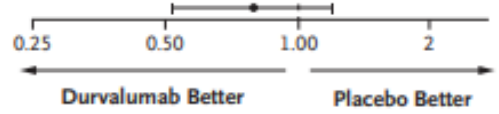
PACIFIC Trial

Spigel et al, JCO,2022

Subgroup	Durvalumab	Placebo	Unstratified Hazard Ratio for Disease Progression or Death (95% CI)
	no. of patients		
All patients	476	237	0.55 (0.45–0.68)
Sex			
Male	334	166	0.56 (0.44–0.71)
Female	142	71	0.54 (0.37–0.79)
Age at randomization			
<65 yr	261	130	0.43 (0.32–0.57)
≥65 yr	215	107	0.74 (0.54–1.01)
Smoking status			
Smoker	433	216	0.59 (0.47–0.73)
Nonsmoker	43	21	0.29 (0.15–0.57)
NSCLC disease stage			
IIIA	252	125	0.53 (0.40–0.71)
IIIB	212	107	0.59 (0.44–0.80)
Tumor histologic type			
Squamous	224	102	0.68 (0.50–0.92)
Nonsquamous	252	135	0.45 (0.33–0.59)
Best response			
Complete response	9	7	—
Partial response	232	111	0.55 (0.41–0.75)
Stable disease	222	114	0.55 (0.41–0.74)
PD-L1 status			
≥25%	115	44	0.41 (0.26–0.65)
<25%	187	105	0.59 (0.43–0.82)
Unknown	174	88	0.59 (0.42–0.83)
EGFR mutation			
Positive	29	14	0.76 (0.35–1.64)
Negative	315	165	0.47 (0.36–0.60)
Unknown	132	58	0.79 (0.52–1.20)



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PACIFIC Trial

Spigel et al, JCO,2022

Adverse Events:

Event	Durvalumab (N = 475)		Placebo (N = 234)	
	Any Grade*	Grade 3 or 4	Any Grade*	Grade 3 or 4
	number of patients with event (percent)			
Any event	460 (96.8)	142 (29.9)	222 (94.9)	61 (26.1)
Cough	168 (35.4)	2 (0.4)	59 (25.2)	1 (0.4)
Pneumonitis or radiation pneumonitis†	161 (33.9)	16 (3.4)	58 (24.8)	6 (2.6)
Fatigue	113 (23.8)	1 (0.2)	48 (20.5)	3 (1.3)
Dyspnea	106 (22.3)	7 (1.5)	56 (23.9)	6 (2.6)
Diarrhea	87 (18.3)	3 (0.6)	44 (18.8)	3 (1.3)
Pyrexia	70 (14.7)	1 (0.2)	21 (9.0)	0
Decreased appetite	68 (14.3)	1 (0.2)	30 (12.8)	2 (0.9)
Nausea	66 (13.9)	0	31 (13.2)	0
Pneumonia	62 (13.1)	21 (4.4)	18 (7.7)	9 (3.8)
Arthralgia	59 (12.4)	0	26 (11.1)	0
Pruritus	58 (12.2)	0	11 (4.7)	0
Rash	58 (12.2)	1 (0.2)	17 (7.3)	0
Upper respiratory tract infection	58 (12.2)	1 (0.2)	23 (9.8)	0
Constipation	56 (11.8)	1 (0.2)	20 (8.5)	0
Hypothyroidism	55 (11.6)	1 (0.2)	4 (1.7)	0
Headache	52 (10.9)	1 (0.2)	21 (9.0)	2 (0.9)
Asthenia	51 (10.7)	3 (0.6)	31 (13.2)	1 (0.4)
Back pain	50 (10.5)	1 (0.2)	27 (11.5)	1 (0.4)
Musculoskeletal pain	39 (8.2)	3 (0.6)	24 (10.3)	1 (0.4)
Anemia	36 (7.6)	14 (2.9)	25 (10.7)	8 (3.4)

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Conclusion

- All stage III NSCLC should be staged thoroughly and reviewed at Multidisciplinary Rounds to determine best treatment plan.
- Resectable cases should undergo neoadjuvant systemic therapy followed by surgery.
- Unresectable cases should be treated with concurrent chemoradiation followed by maintenance durvalumab.

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Question & Answer