CANCER RESEARCH AND STATISTIC FOUNDATION

6th Annual Year End Review in **Lung Cancer**

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original reports

Randomized Phase III Study of Gefitinib Versus Cisplatin Plus Vinorelbine for Patients With Resected Stage II-IIIA Non–Small-Cell Lung Cancer With *EGFR* Mutation (IMPACT)

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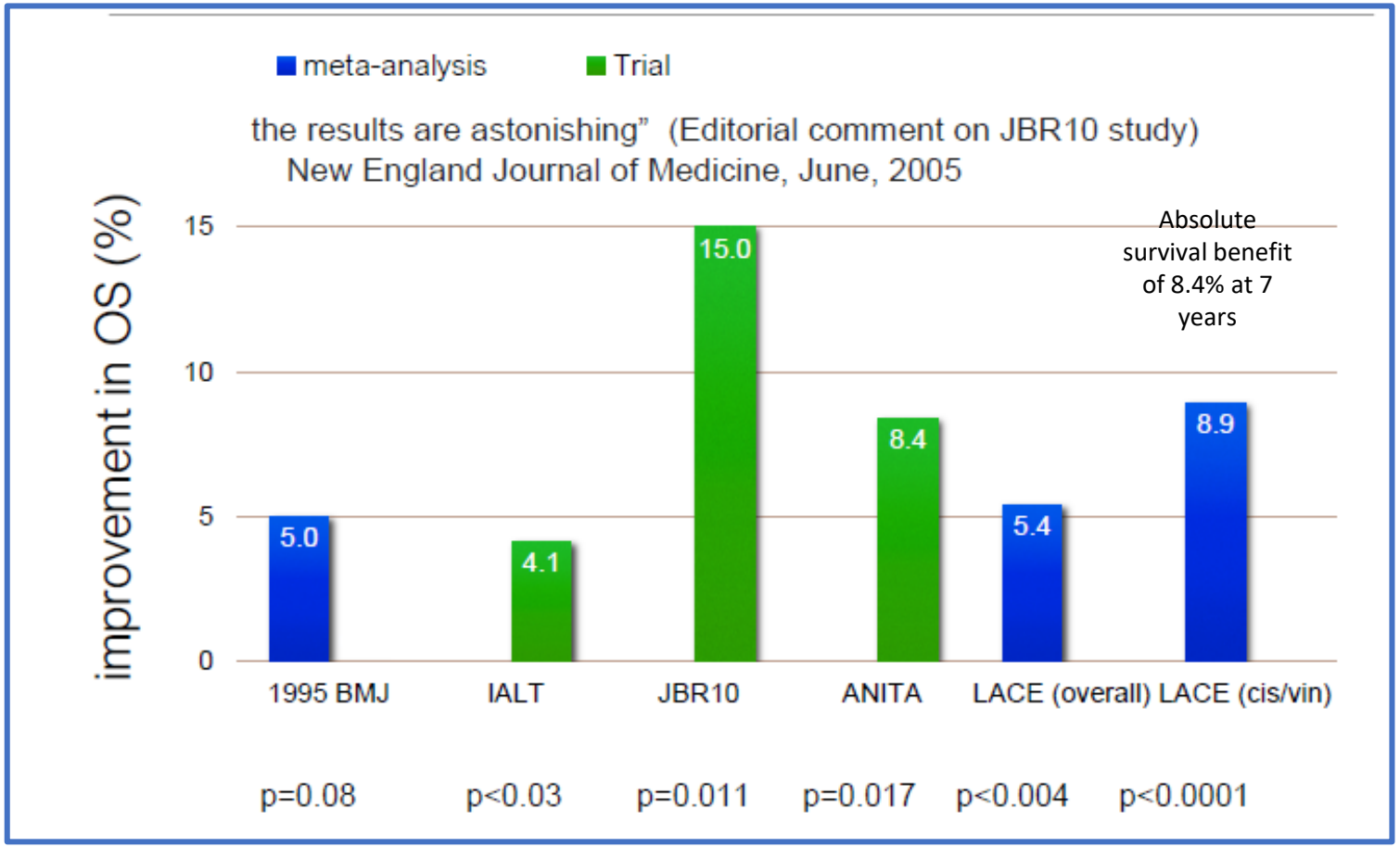
Adjuvant Chemotherapy in NSCLC: cisplatin doublet standard of care



Approximately 30% of patients with NSCLC present with resectable disease at diagnosis(1–3)

surgery is the primary treatment(4,5)

Adjuvant cisplatin-based chemotherapy is recommended for patients with resected stage II–IIIA NSCLC and select patients with stage IB disease (6)
associated with only a 16% DFS risk reduction and 5% OS benefit at 5 years (7)

Disease recurrence or death remain high across disease stages, regardless of postoperative chemotherapy use(7)

Scope to improve outcomes in resectable EGFR mutated NSCLC ???

1. Datta et al. Chest 2003;123: 2096–2123; 2. Le Chevalier Ann Oncol. 2010;21 Suppl7:vii196–8; 3. Cagle et al. Arch Pathol Lab Med. 2013;137:1191–1198; 4. Chansky et al. J Thorac Oncol 2017;12:1109–1121; 5. Al-Shahrabani et al. World J Clin Oncol 2014; 10;5:595–603 6. Kris et al. J Clin Oncol 2017;35:2960–2974; 7. Pignon et al. J Clin Oncol 2008;26:3552–3559;

Multicenter, open-label, randomized phase III trial in Japan: September 2011 till December 2015

- 20-75 years
- pathologic stage II-III NSCLC (AJCC 7)
- ECOG PS 0/1
- Tumours with exon 19 deletion (Del 19) or L858R EGFR gene mutation
- detected using a commercially available method approved in Japan

Randomisation 1:1 ratio

complete surgical resections via either lobectomy or pneumonectomy with mediastinal lymph node dissection within 3-8 weeks

Post operative Radiotherapy not permitted

Gefitinib
250 mg once daily for 24 months

Cisplatin (80 mg/m2 on day 1) plus **vinorelbine** (25 mg/m2 on days 1 and 8 once every 3 weeks for four cycles

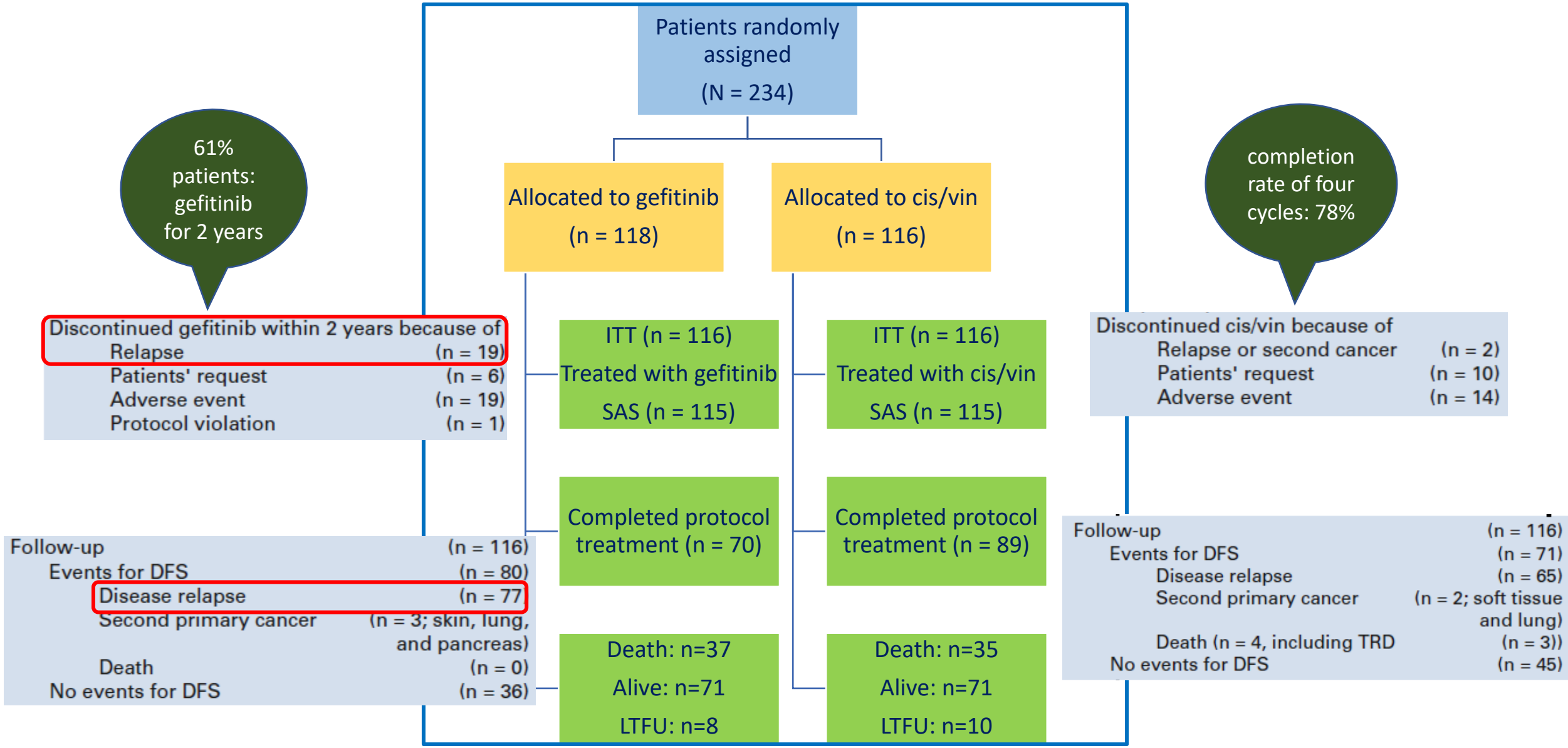
Follow up:
Chest radiographs and physical examination every 8 weeks
CE chest and abdominal CT every 6 months
Brain MRI and whole-body PET-CT every 1 year until trial discontinuation

Some Exclusion criteria

Synchronous and metachronous cancer
previous treatment with anticancer agents or radiotherapy
severe postoperative complications, interstitial pneumonitis

Primary End point
Disease free survival (DFS)

Secondary end points
OS, safety profile, recurrence types (local v distant), and adverse events


Patients randomly assigned
(N = 234)
Allocated to gefitinib
(n = 118)
Allocated to cis/vin
(n = 116)
61% patients: gefitinib for 2 years
completion rate of four cycles: 78%
Discontinued gefitinib within 2 years because of
Relapse (n = 19)
Patients' request (n = 6)
Adverse event (n = 19)
Protocol violation (n = 1)
ITT (n = 116)
Treated with gefitinib
SAS (n = 115)
ITT (n = 116)
Treated with cis/vin
SAS (n = 115)
Discontinued cis/vin because of
Relapse or second cancer (n = 2)
Patients' request (n = 10)
Adverse event (n = 14)
Completed protocol treatment (n = 70)
Completed protocol treatment (n = 89)
Follow-up (n = 116)
Events for DFS (n = 80)
Disease relapse (n = 77)
Second primary cancer (n = 3; skin, lung, and pancreas)
Death (n = 0)
No events for DFS (n = 36)
Death: n=37
Alive: n=71
LTFU: n=8
Death: n=35
Alive: n=71
LTFU: n=10
Follow-up (n = 116)
Events for DFS (n = 71)
Disease relapse (n = 65)
Second primary cancer (n = 2; soft tissue and lung)
Death (n = 4, including TRD (n = 3))
No events for DFS (n = 45)

Characteristic	Gefitinib (n = 116), No. (%)	cis/vin (n = 116), No. (%)
Sex		
Male	44 (37.9)	45 (38.8)
Female	72 (62.1)	71 (61.2)
Age, years		
Median (range)	64 (34-74)	64 (34-74)
< 65	61 (52.6)	61 (52.6)
≥ 65	55 (47.4)	55 (47.4)
ECOG PS		
0	94 (81.0)	91 (78.4)
1	22 (19.0)	25 (21.6)
EGFR mutation		
Exon 19 deletion	64 (55.2)	59 (50.9)
Exon 21 L858R	52 (44.8)	56 (48.3)
Both	0 (0.0)	1 (0.9)
Smoking history		
Never smoker	68 (58.6)	74 (63.8)
Former smoker	48 (41.4)	42 (36.2)
Current smoker	0 (0.0)	0 (0.0)
Surgery		
Pneumonectomy	0 (0.0)	1 (0.9)
Lobectomy	115 (99.1)	115 (99.1)
Others	1 (0.9)	0 (0.0)

Characteristic	Gefitinib (n = 116), No. (%)	cis/vin (n = 116), No. (%)
Residual tumor classification		
R0	116 (100.0)	116 (100.0)
pT factor (seventh TNM classification)		
T1a	13 (11.2)	10 (8.6)
T1b	17 (14.7)	26 (22.4)
T2a	62 (53.4)	53 (45.7)
T2b	8 (6.9)	10 (8.6)
T3	14 (12.1)	14 (12.1)
T4	2 (1.7)	3 (2.6)
pN (seventh TNM classification)		
N0	7 (6.0)	9 (7.8)
N1	41 (35.3)	35 (30.2)
N2	67 (57.8)	72 (62.1)
N3	1 (0.9)	0 (0.0)
Pathologic stage (seventh TNM classification)		
IIA	36 (31.0)	38 (32.8)
IIB	6 (5.2)	3 (2.6)
IIIA	71 (61.2)	73 (62.9)
IIIB	3 (2.6)	2 (1.7)

65% patients: pathologic stage III disease

Patient Characteristics: well balanced between the 2 groups

Data cutoff: December 24, 2020

Median follow-up 70

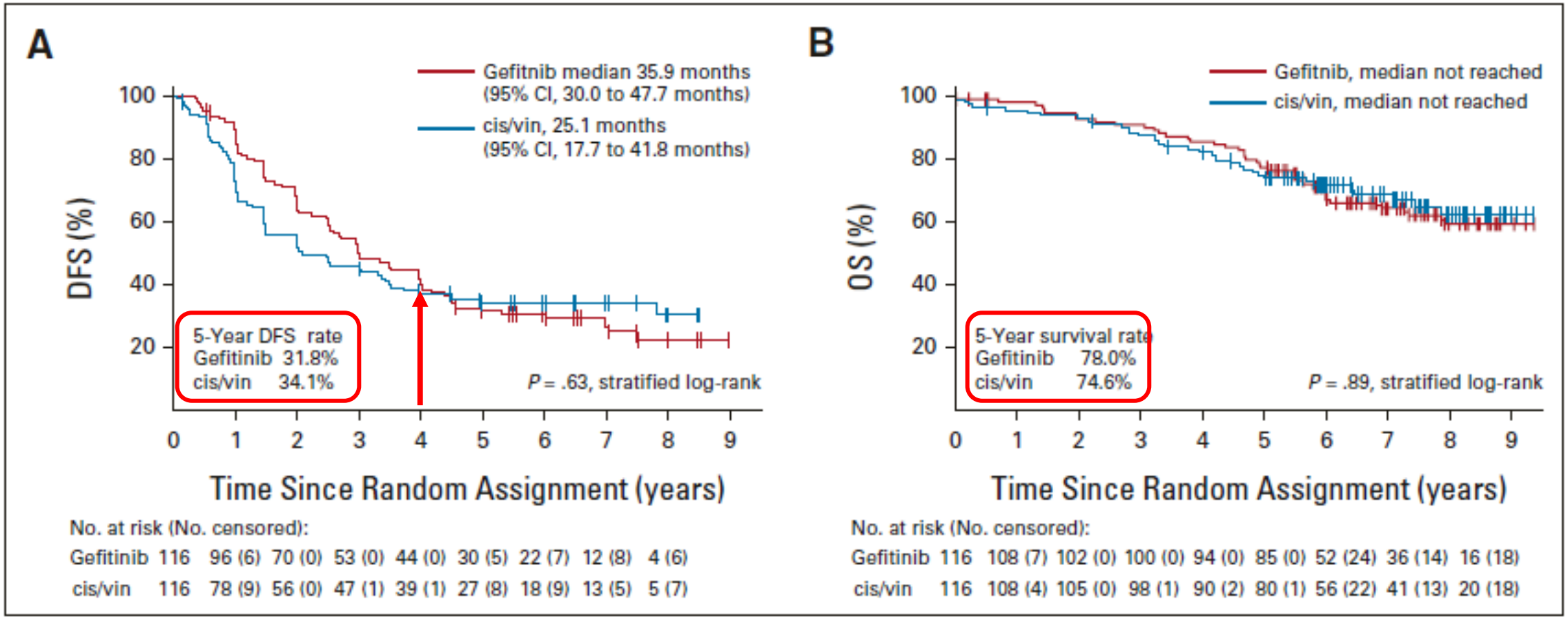
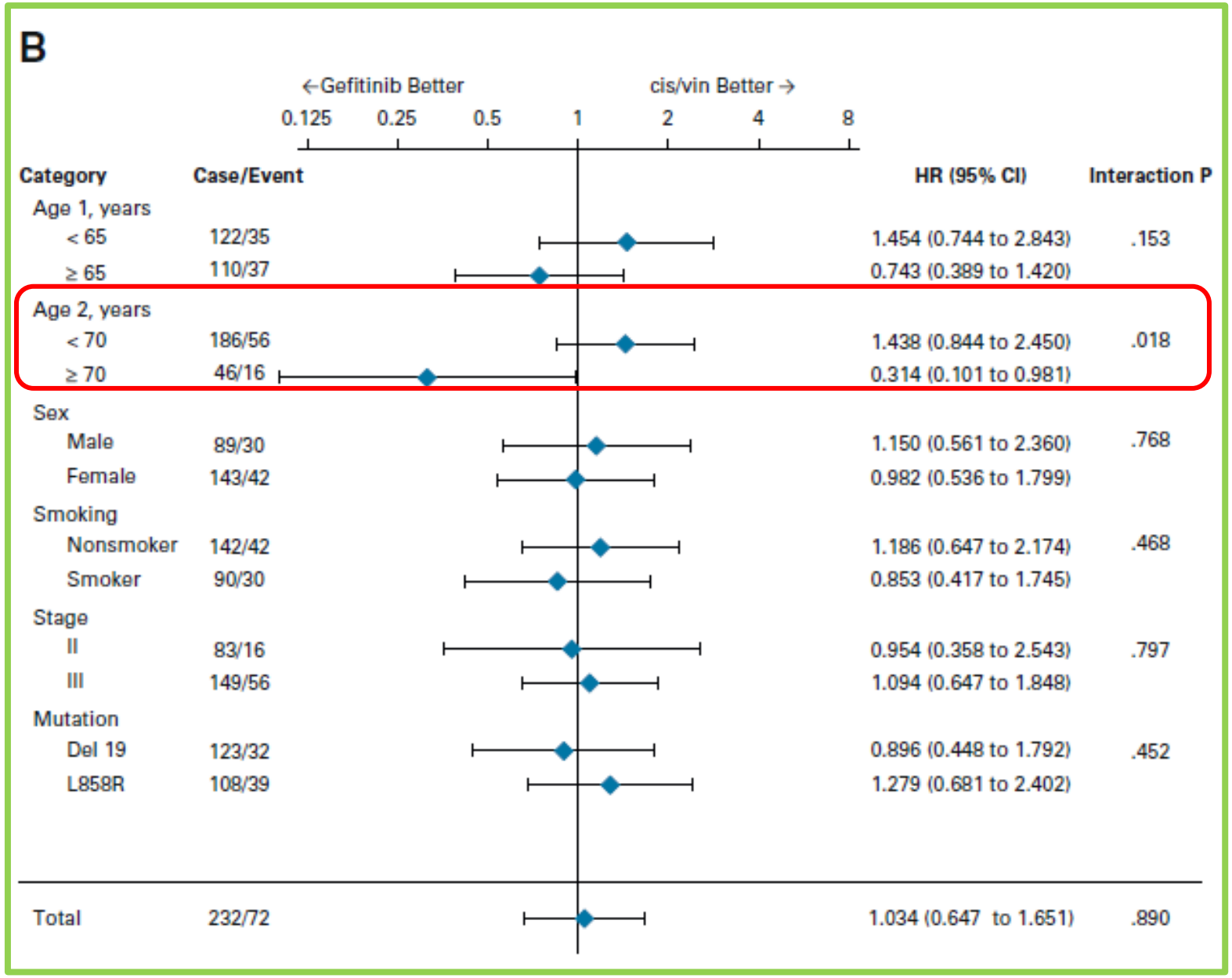


FIG 2. Kaplan-Meier curves for (A) DFS and (B) OS in the ITT population. cis/vin, cisplatin plus vinorelbine; DFS, disease-free survival; ITT, intention-to-treat; OS, overall survival.

mDFS after completion of gefitinib:
29.8 m



Subgroup analyses of OS with respect to baseline characteristics:
No apparent difference in the treatment efficacy between the 2 groups

Safety

Chemo: more neutropenia, febrile neutropenia

Gefitinib : more diarrhoea, rashes , mucositis : less Grade ¾

ALT increase 25% Grade ¾

No ILD

	Gefitinib (n = 115), No. (%)			cis/vin (n = 115), No. (%)			
Adverse Event	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4	Grade 5
Any adverse events	112 (97.4)	43 (37.4)	5 (4.3)	115 (100)	35 (30.4)	68 (59.1)	3 (2.6)
Hematologic							
Neutropenia	2 (1.7)	1 (0.9)		110 (95.7)	30 (26.1)	70 (60.9)	
Leukopenia	3 (2.6)			104 (90.4)	54 (47.0)	12 (10.4)	
Anemia	3 (2.6)			75 (65.2)	11 (9.6)		
Neural							
Neuropathy	1 (0.9)			15 (13.0)	1 (0.9)		
Dysgeusia	14 (12.2)			38 (33.0)			
Cerebral infarction				1 (0.9)			1 (0.9)
GI							
Nausea	8 (7.0)			104 (90.4)	7 (6.1)		
Vomiting	6 (5.2)			32 (27.8)			
Constipation	7 (6.1)			88 (76.5)			
Anorexia	22 (19.1)	1 (0.9)		96 (83.5)	16 (13.9)		
Diarrhea	75 (65.2)	2 (1.7)		18 (15.7)	3 (2.6)		
Mucositis	47 (40.9)	1 (0.9)		34 (29.6)			
General							
Fatigue	3 (2.6)			16 (13.9)	2 (1.7)		
Fever	1 (0.9)			7 (6.1)			
Suicide				1 (0.9)			1 (0.9)
Serum chemistry							
ALT increased	79 (68.7)	26 (22.6)	5 (4.3)	29 (25.2)	4 (3.5)		
AST increased	75 (65.2)	17 (14.8)	1 (0.9)	11 (9.6)	1 (0.9)		
BUN increased	2 (1.7)			19 (16.5)			
Creatinine increased	5 (4.3)			22 (19.1)			
K decreased				8 (7.0)	2 (1.7)		
Na decreased				25 (21.7)	11 (9.6)		
Dermatologic							
Alopecia	14 (12.2)			53 (46.1)			
Rash	44 (38.3)	5 (4.3)		5 (4.3)			
Dermatitis acneiform	67 (58.3)	5 (4.3)		3 (2.6)			
Infectious							
Febrile neutropenia				10 (8.7)	9 (7.8)	1 (0.9)	
Paronychia	53 (46.1)	4 (3.5)					
Pneumonia	1 (0.9)			1 (0.9)			1 (0.9)

Grade ¾ AE
42% vs 90%

Grade 4 or greater adverse events:
five patients (4%) in the gefitinib group
71 patients (62%) in the cis/vin group

3 treatment related deaths in chemo gp

TABLE 3. First Relapse Sites by Treatment Group

Site of Relapse	Treatment Group	
	Gefitinib, No.	cis/vin, No.
Local relapse	26	24
Resection margin or others	5	2
Regional lymph node	15	17
Pleural effusion or pleural metastases	6	5
Distant metastasis	60	52
Brain	26	14
Lung	14	13
Bone	10	10
Extrathoracic lymph node	5	6
Contralateral pleura	2	3
Liver	1	2
Adrenal gland	1	2
Scapular muscle	1	0
Kidney	0	1
Pancreas	0	1

CNS recurrence rate

26 of 86 [30%] in the gefitinib group

14 of 76 [18%] in the cis/vin group

Subsequent Therapy

Gefitinib Arm

Received subsequent treatments	(n = 76)
No drug therapy	(n = 11)
Surgery alone	(n = 3)
Radiation alone	(n = 7)
Surgery plus radiation	(n = 1)
Drug therapy	(n = 66)
Initial drug therapy	
Cytotoxic chemotherapy	(n = 23)
EGFR-TKI	(n = 43)

Cis/Vin Arm

Received subsequent treatments	(n = 71)
No drug therapy	(n = 7)
Surgery alone	(n = 2)
Radiation alone	(n = 3)
Surgery plus radiation	(n = 2)
Drug therapy	(n = 64)
Initial drug therapy	
Cytotoxic chemotherapy	(n = 4)
EGFR-TKI	(n = 59)
Others	(n = 1)

Crossover to cis/vin to EGFR-TKI (59 of 71, 83%)
Crossover from gefitinib to chemotherapy (23 of 66, 35%)

When the second and third subsequent regimens were included, 34 of 66 (52%) patients in the gefitinib group received chemotherapy

How many received 3rd generation EGFR TKI in each arm???

Author conclusions

- Gefitinib as postoperative adjuvant therapy for patients with resected stage II-III NSCLC harboring EGFR mutations was not beneficial in prolonging DFS and OS
- Platinum-doublet therapy should remain the standard of care followed by adjuvant osimertinib when available
- For select patient subsets with contraindications to this approach, adjuvant gefitinib could be considered as an alternative
- This was not a noninferiority trial

Postoperative adjuvant therapy with first-generation EGFR-TKIs

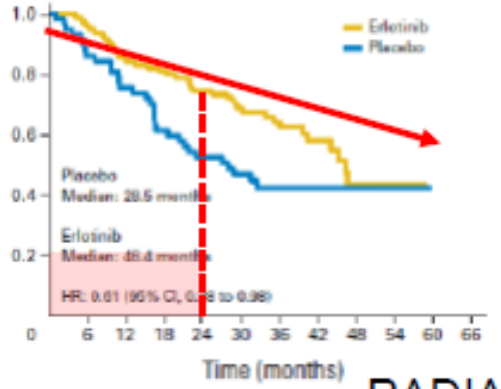
	Stage	regimen	N	mDFS (month)	HR	mOS (month)	HR
RADIANT (Phase 3)	IB-IIIA	Erlotinib	102	46.4	0.61 p=0.039	-	1.09
		placebo	59	28.5		-	
BR19 (Phase 3)	IIIA-N2	Gefitinib	7	-	1.84 p=0.40	-	3.16 p=0.15
		placebo	8	-		-	
EVAN (Phase 2)	IIIA	Erlotinib	51	42.4	0.27 p<0.001	84.2	0.32 p=0.0015
		CDDP+VNR	51	21.0		61.1	
ADJUVANT (Phase 3)	II-IIIA (N1-N2)	Gefitinib	111	28.7	0.60 p=0.0054	75.5	0.92 p=0.674
		CDDP+VNR	111	18.0		62.8	
IMPACT (Phase 3)	II-III	Gefitinib	116	35.9	0.92 p=0.63	78.0% (5YS)	1.03 p=0.89
		CDDP+VNR	116	25.0		74.6% (5YS)	

Postoperative adjuvant therapy with 1st generation EGFR-TKIs tends not to contribute to OS compared with DFS

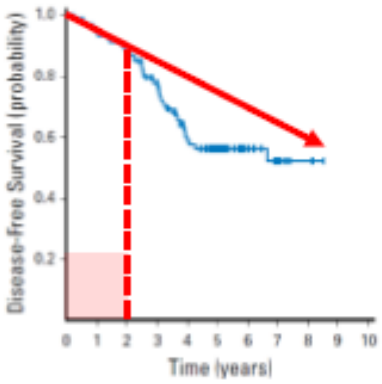
EVIDENCE Trial: m FU approx. 25 months
3-year disease-free survival 63·9% in the icotinib group and 32·5% in the chemotherapy group. Overall survival data are immature

Waning treatment effect of TKIs after discontinuation

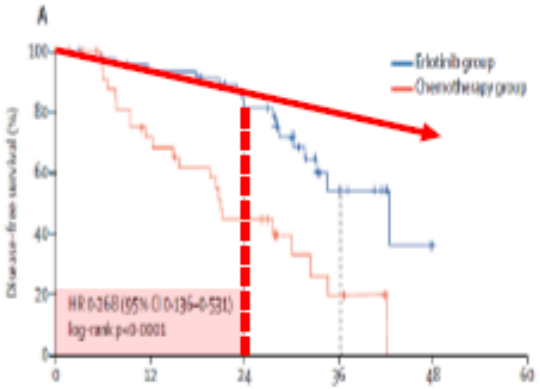
Identified in other adjuvant EGFR TKI trials



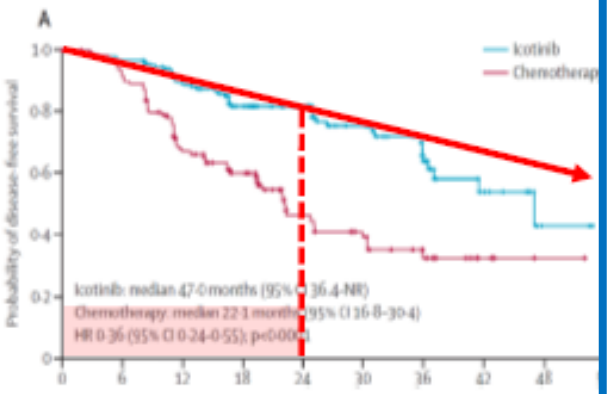
RADIANT[1]
erlotinib



SELECT[2]
erlotinib

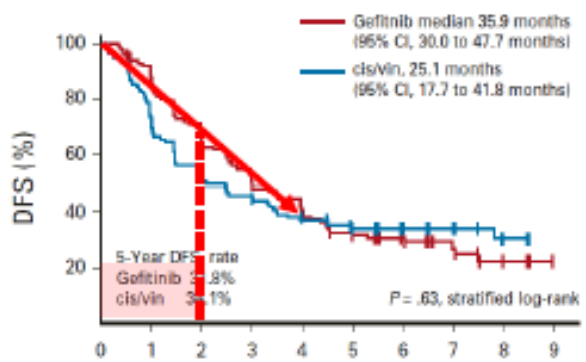


EVAN[3]
erlotinib

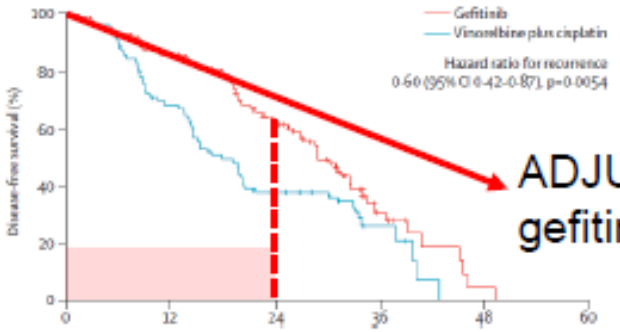


EVIDENCE[4]
icotinib

Treatment Duration



IMPACT[5]
gefitinib



ADJUVANT[6]
gefitinib

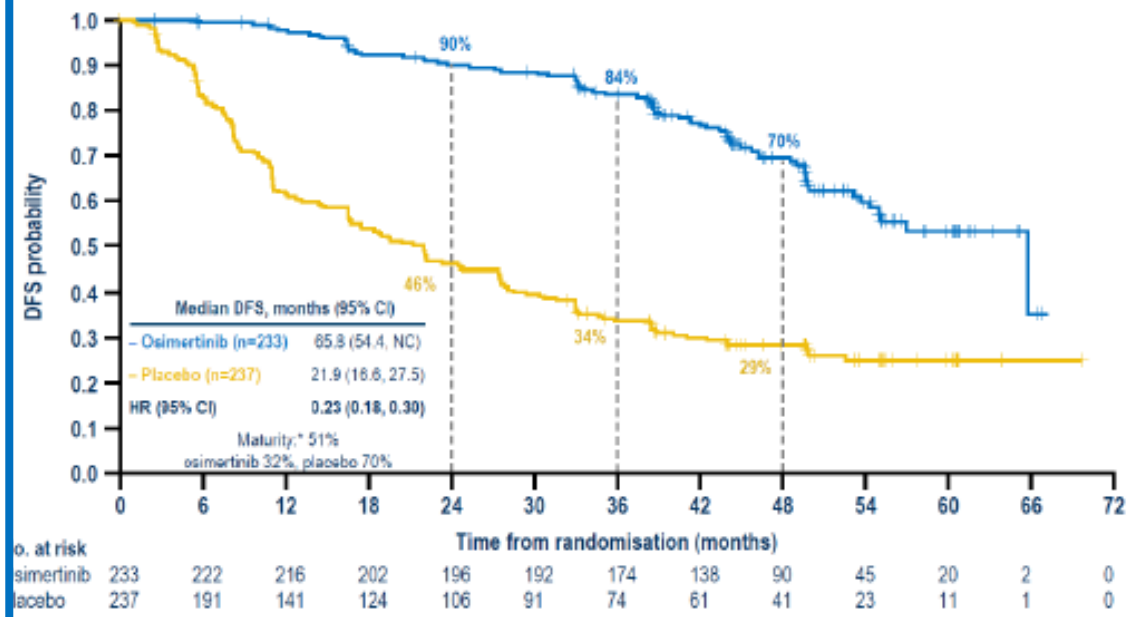
PARIS 2022 ESMO congress

Kelly et al. JCO (2015); 2, Pennell et al. JCO (2018);3, Yue et al. Lancet Rep Med (2018); 4, He et al. Lancet Resp Med (2021); 5, Tada et al. JCO (2021); 6; Zhong et la. Lancet Oncol (2017)

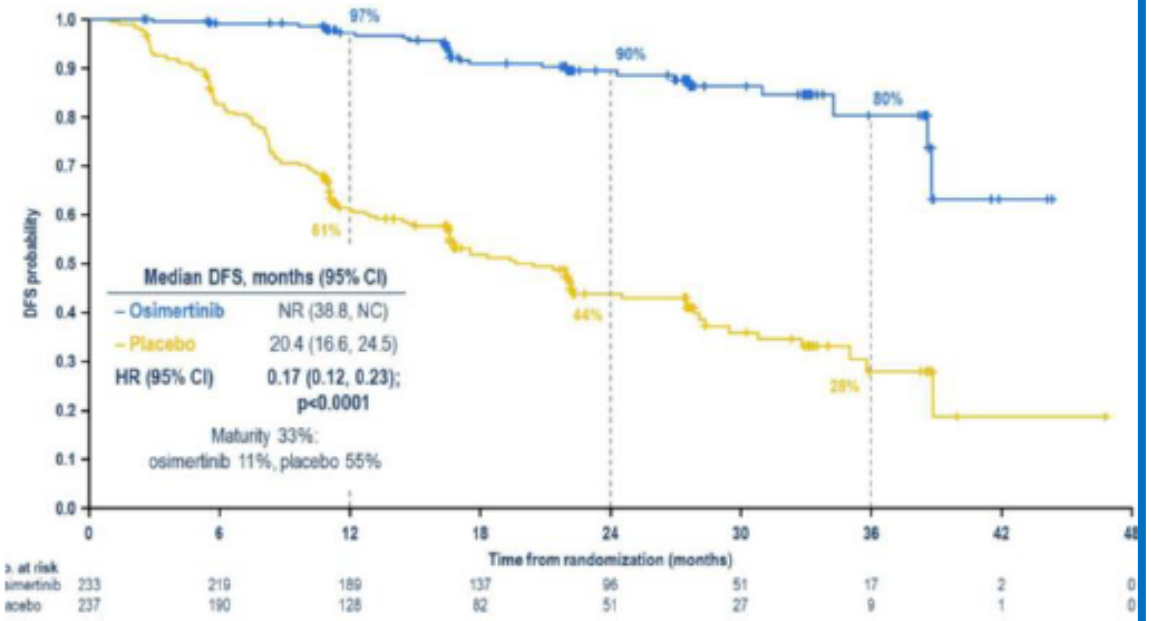
Updated primary endpoint: DFS II/IIIA ADAURA

A consistent and meaningful HR DFS improvement: 0.23 (0.18, 0.30) from 0.17 (0.12, 0.23)

ESMO 2022



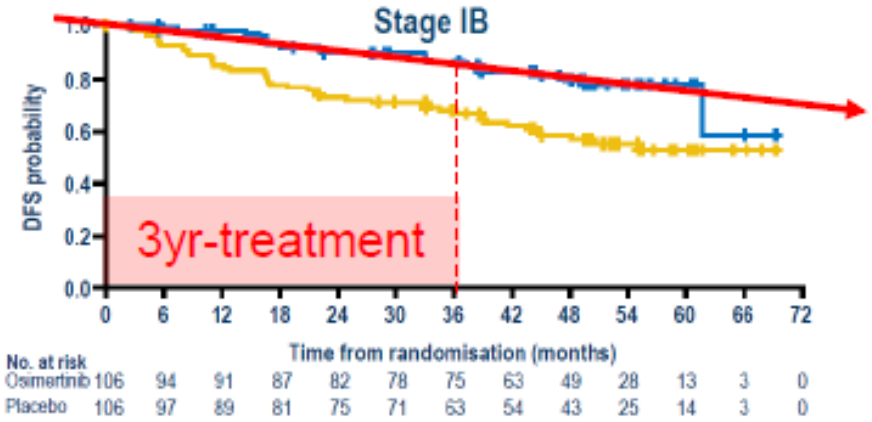
ASCO 2020

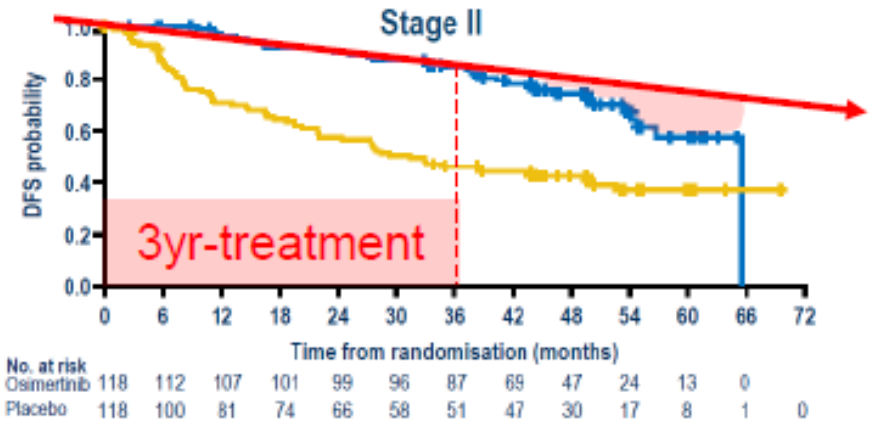


PARIS 2022 ESMO congress

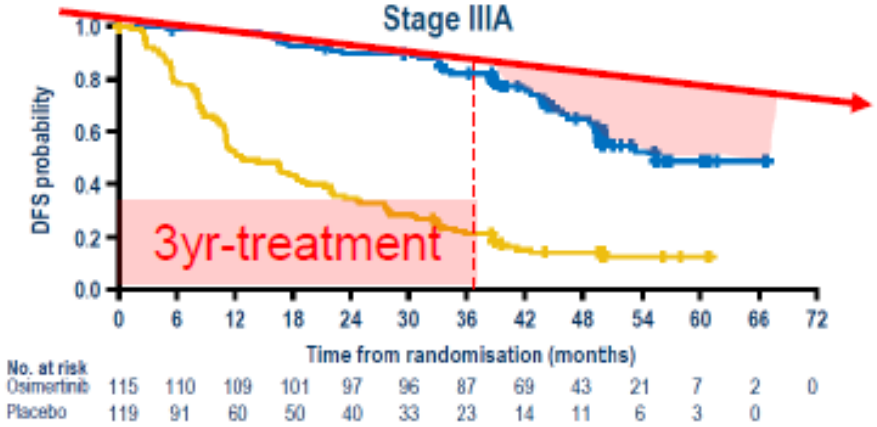
Tsuboi et al. ESMO (2022); Herbst et al. ASCO (2020)

A potential excess of DFS events for stage II and IIIA post month 36

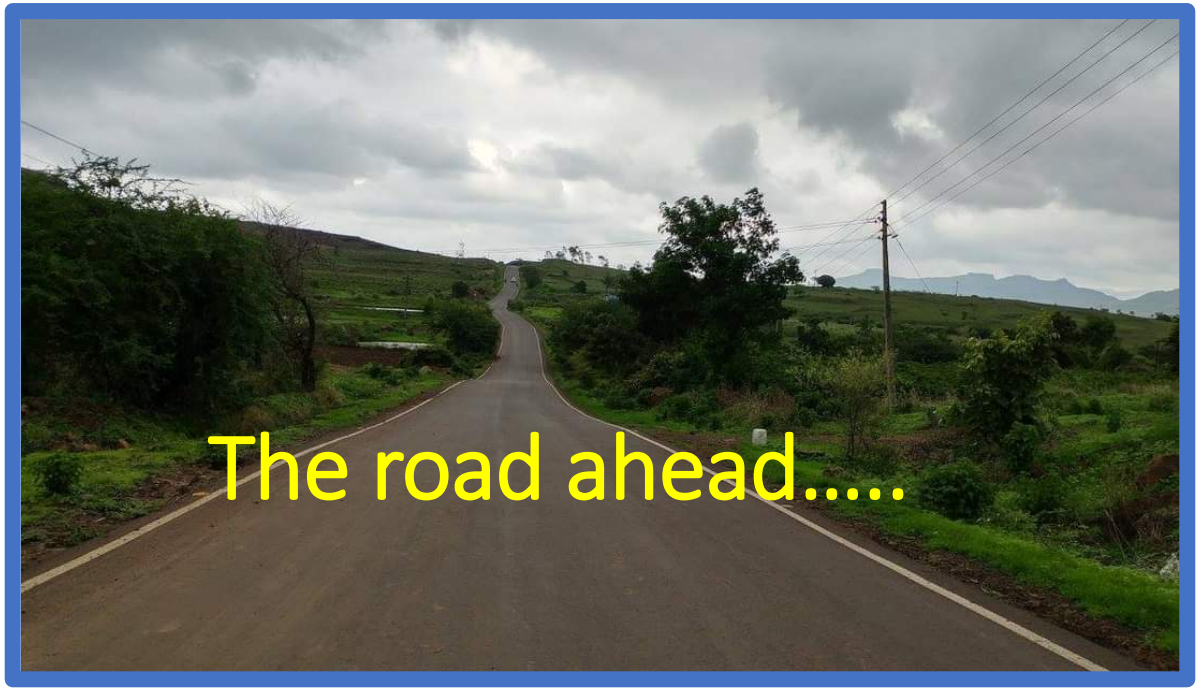




ADAURA ESMO 2022 update



congress



- OS data for ADAURA awaited
- To define which subpopulation will benefit
- Biomarker?
- Duration of TKIs


#SCIENCE
givesHOPE


THANK YOU!