Dacomitinib (PF-00299804), an Irreversible pan-HER Tyrosine Kinase Inhibitor, for First-Line Treatment of *EGFR*-Mutant or *HER2*-Mutant or -Amplified Lung Cancers

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Disclosures

- Z. Goldberg is compensated as an employee by Pfizer Inc. (Medical Director) and holds stock in Pfizer Inc.
- P. Jänne has received compensation for consultant / advisory roles with Boehringer Ingelheim, Roche, Genentech, Abbott, Astra-Zeneca, Pfizer Inc., Sanofi and Teva, and has received other compensation from LabCorp
- D-W. Kim has received compensation for an advisory role with Pfizer Inc. and has received honoraria from Pfizer Inc.
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- I. Taylor is compensated as an employee of Pfizer Inc. (Senior Director) and holds stock in Pfizer Inc.
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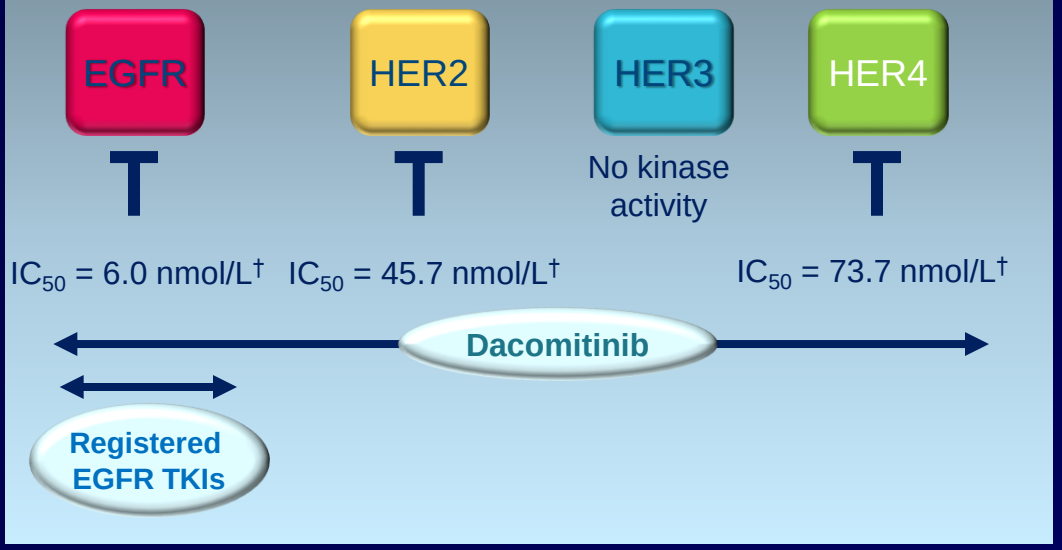
Dacomitinib

Pan–HER inhibition



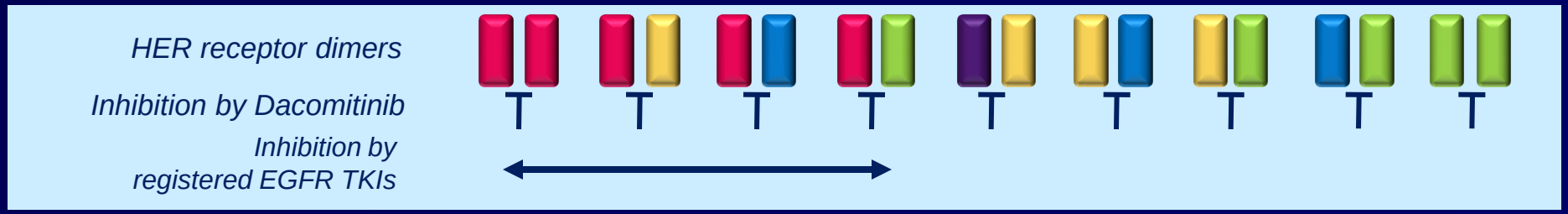
Irreversible inhibition‡

- Permanent blockade of catalytic activity
- Non-competitive inhibition
- Higher specificity and selectivity
- Low intracellular levels capable of inhibiting TK activity

†*In vitro* kinase assay against WT receptor ;↑[ATP] = high concentrations of ATP (e.g. intracellular concentrations)

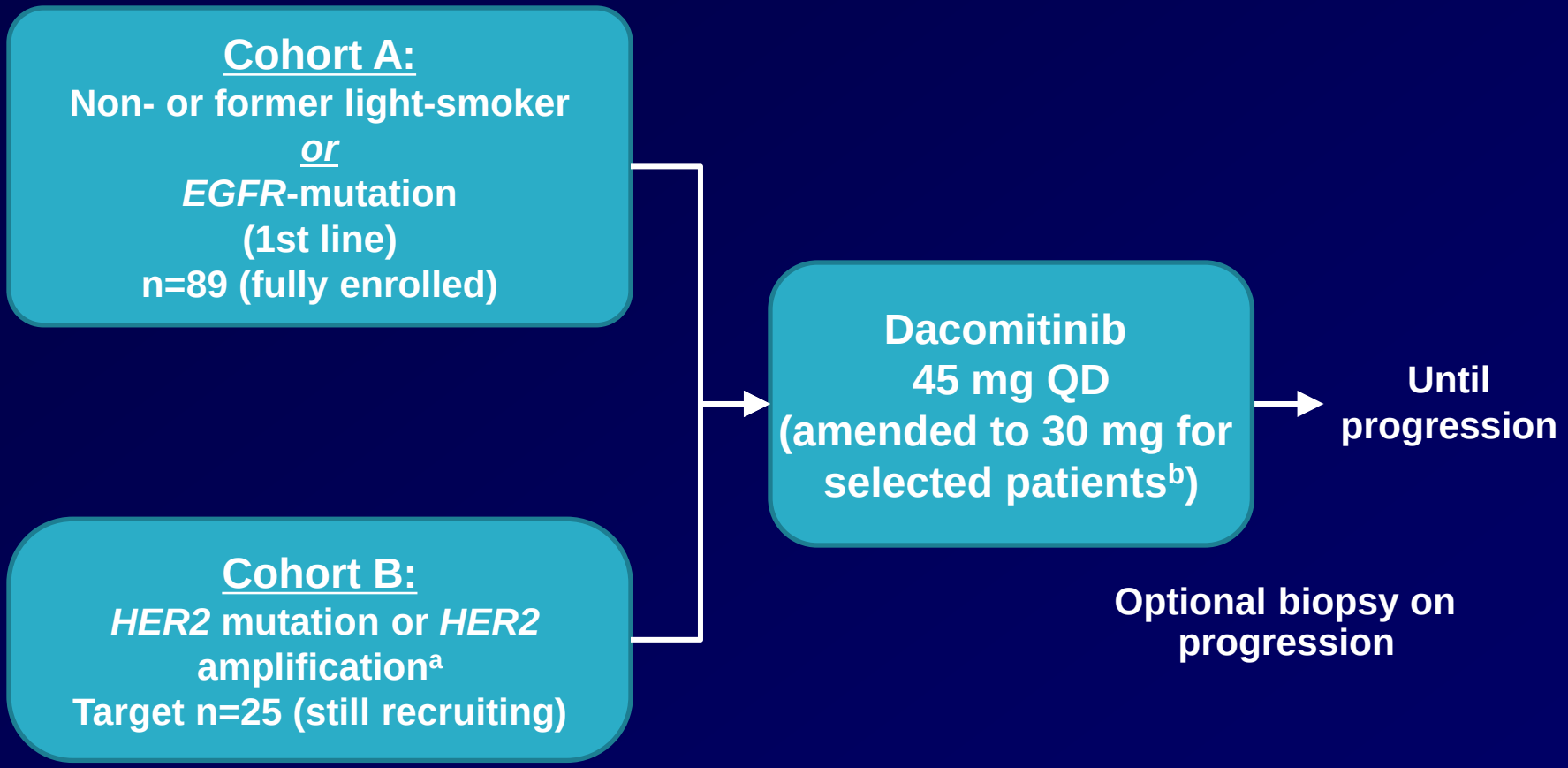
‡ Potential benefits – based on preclinical data

Inhibition of all kinase-active HER receptors offers potential for a more complete inhibition of HER signaling: receptor dimerization is key to HER-family signaling



Engleman JA, *et al.* Cancer Res 2008;67:11924–32

Study 1017: Clinical Activity of Dacomitinib (PF-00299804) in First-Line Advanced NSCLC with an *EGFR*-activating Mutation



[a][gene]/[centromere of chromosome 17] ratio >2

[b]Starting dose changed to 30 mg QD with dose escalation to 45 mg QD after 8 weeks of treatment in absence of grade >1 toxicity for ≥1 month for 30 patients in Cohort A , and patients in Cohort B who had no prior lines of therapy

Mok T, *et al*. LBA18 presentation at the 35th ESMO, 2010

Eligibility of *EGFR*-mutant Cohort Dacomitinib Dose and Schedule

- **Eligibility**
  - **Stage IIIB/IV lung adenocarcinoma**
  - **No prior systemic treatment for advanced disease**
  - ***EGFR* mutation**
- **Dose and schedule**
  - **Patients started treatment with dacomitinib 45 mg, or 30 mg with escalation to 45 mg, by mouth (po) daily if toxicity <grade 2 at 8 weeks**

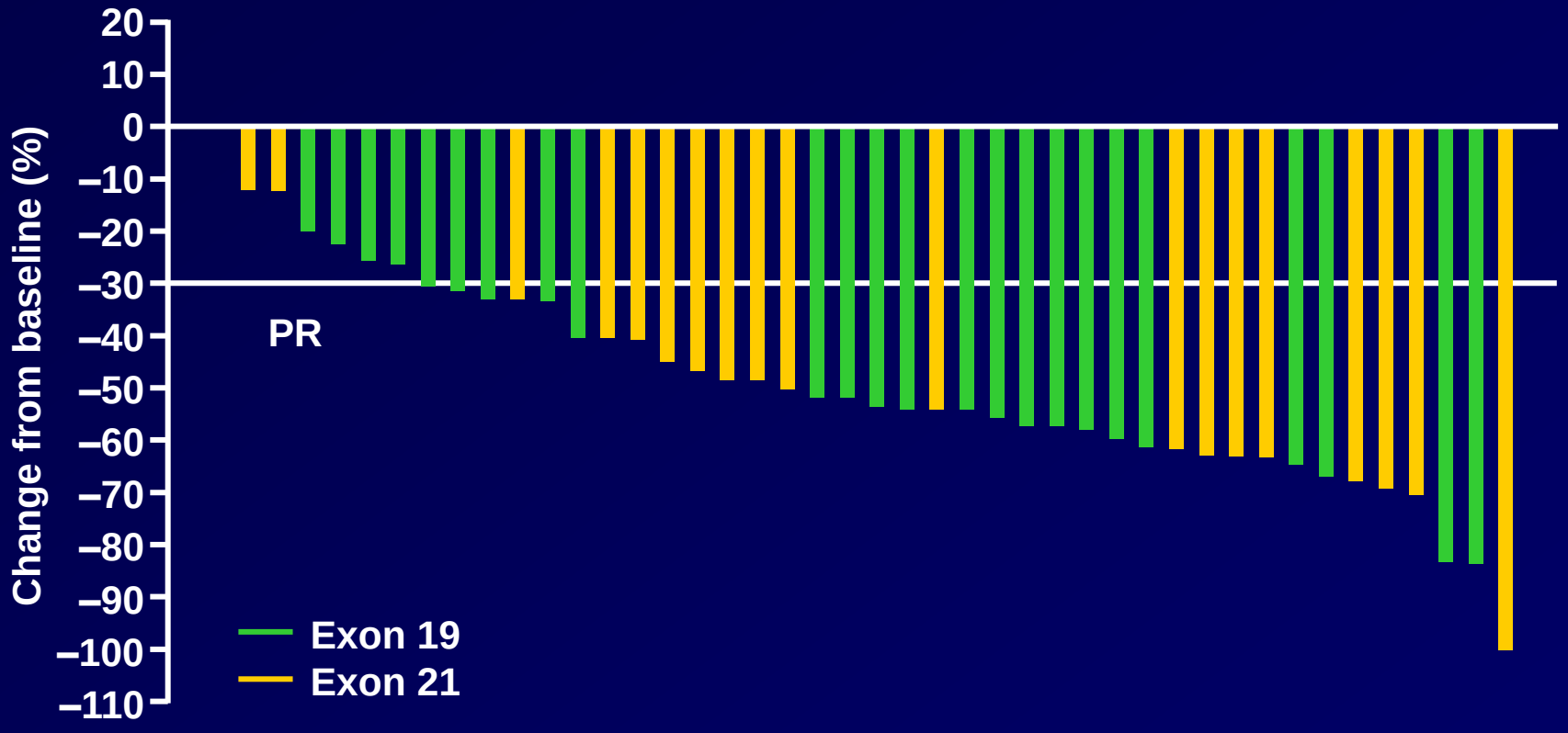
Patients with *EGFR*-mutant Lung Cancers: Baseline Characteristics

Clinical characteristic	*EGFR* exons 19 and 21 (n=45)	Other *EGFR* mutations (n=8)
Median age, years (range)	62 (39–84)	63.5 (54–83)
Gender, n (%)		
Female	31 (69)	5 (63)
Male	14 (71)	3 (38)
Race, n (%)		
Asian	25 (56)	3 (38)
Caucasian	18 (40)	5 (63)
Black	1 (2)	0
Other	1 (2)	0
Smoking history, n (%)		
Never	36 (80)	5 (63)
Current/former	9 (20)	3 (38)
Mutations, n (%)		
Exon 19 deletion	25 (56)	
L858R	20 (44)	

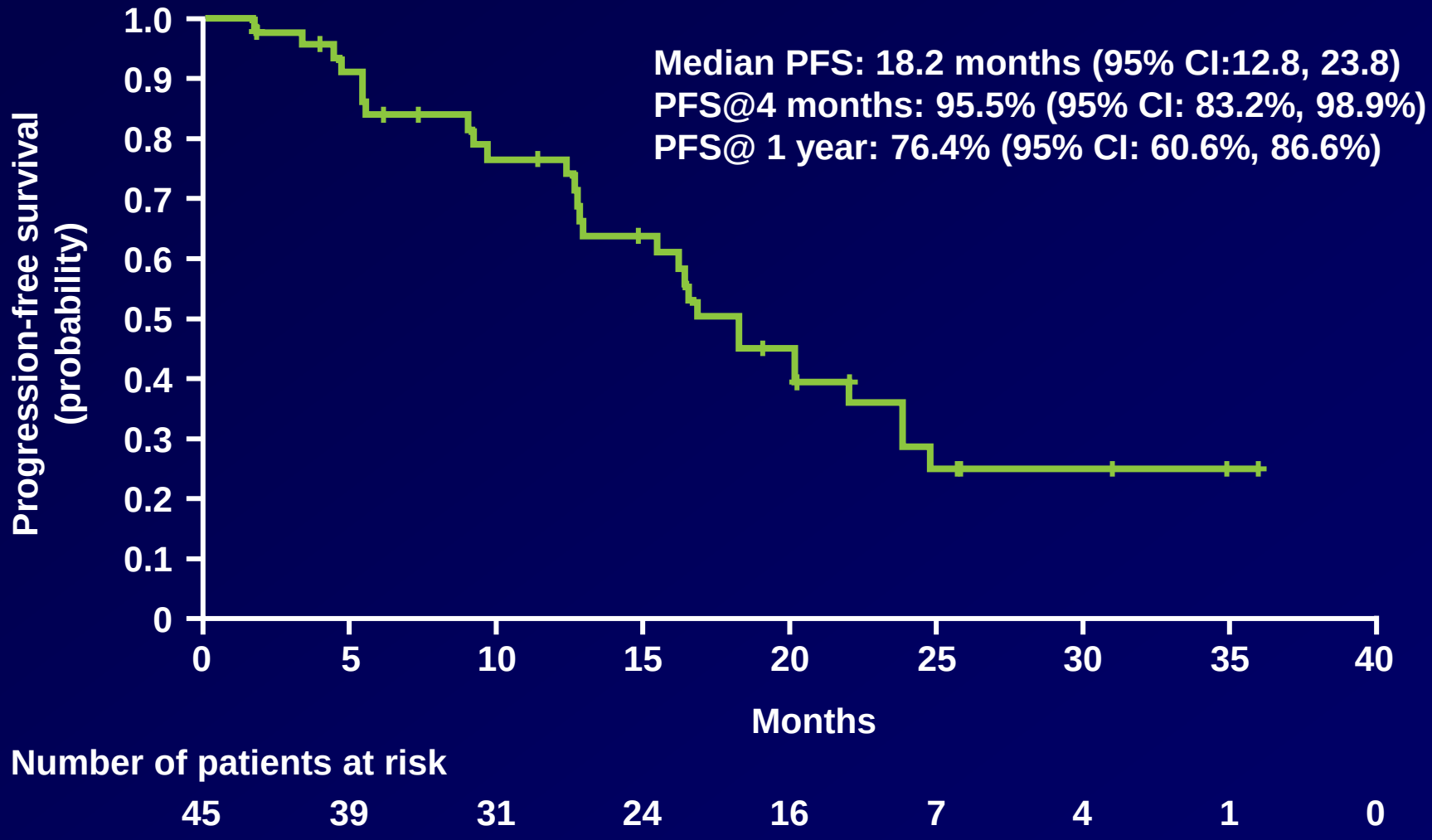
Best Overall Response

Best response to dacomitinib	*EGFR* exon 19 and 21 mutations (n=45)	Other *EGFR* mutations (n=8)
Complete response, n (%)	0	0
Partial response, n (%)	34 (76)	3 (38)
Stable disease, n (%)	10	3
Progression, n (%)	1	1
Indeterminate, n (%)	0	1
Exon 19 partial responses, n (%) [n=25]	19 (76)	–
Exon 21 partial responses, n (%), [n=20]	15 (75)	–

Waterfall Plot for Patients with *EGFR*-mutant Lung Cancers with Exon 19 and Exon 21 Mutations (N=45)



PFS for Patients with *EGFR*-mutant Lung Cancers with Exon 19 and Exon 21 Mutations



EGFR-mutant Subgroup: Conclusions

- For patients with *EGFR*-mutant lung cancers with exon 19 and *L858R* mutations
  - 76% experienced partial responses
  - 76% remained progression free at one year
  - Median PFS was 18 months
- Partial response rates and progression-free survival are similar for patients with exon 19 and *L858R* mutations
- Common side-effects were diarrhea and skin and nail changes

Patients with *HER2*-Mutant or -Amplified Lung Cancers: Baseline Characteristics

Clinical characteristic	30mg* (n=4)	45mg* (n=18)	Total (n=22)
Median age, years (range)	65 (62–73)	59 (42–72)	62 (42–73)
Gender, n (%)			
Female,	2 (50)	7 (39)	9 (41)
Male	2 (50)	11 (61)	13 (59)
Smoking history, n (%)			
Never	4 (100)	9 (50)	13 (59)
Current/former	0	8 (44)	8 (36)
Not Reported	0	1 (6)	1 (5)
HER2 Status, n (%)			
Amplification	0	4 (22)	4 (18)
Mutation	4 (100)	14 (78)	18 (82)
Exon 20 insertion			
Point Mutation			
Prior systemic therapies			
1	0	6 (33)	6 (27)
2	0	2 (11)	2 (9)
≥3	0	10 (56)	10 (45)

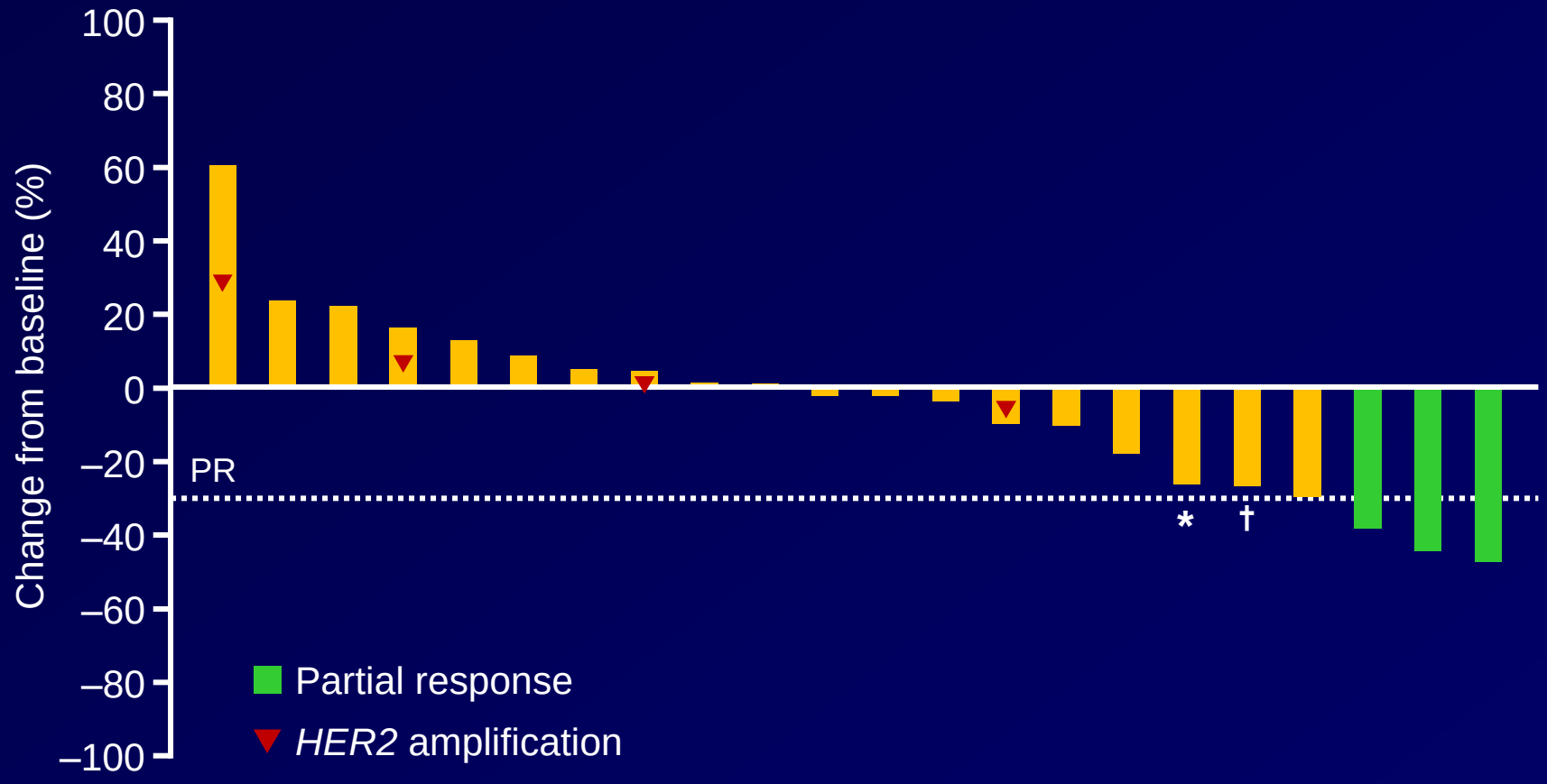
*Starting dose level

Best Overall Response: *HER2* Cohort

Best response to dacomitinib	30mg* (n=4)	45mg* (n=18)	Total (n=22)
Complete response, n (%)	0	0	0
Partial response, n (%)	2 (50)	1 (6)	3 (14)
Stable disease, n (%)	1 (25)	5 (28)	6 (27)
Progression, n (%)	0	10 (56)	10 (45)
Indeterminate, n (%)	1 (25)	2 (11)	3 (14)
HER2 amplification, n=4: partial response, n (%) [95% CI]	0	0	0
HER2 mutation, n=18: partial response, n (%) [95% CI]	2 (50) [6.8, 93.2]	1 (7) [0.2, 33.9]	3 (17) [3.6, 41.4]

*Starting dose level

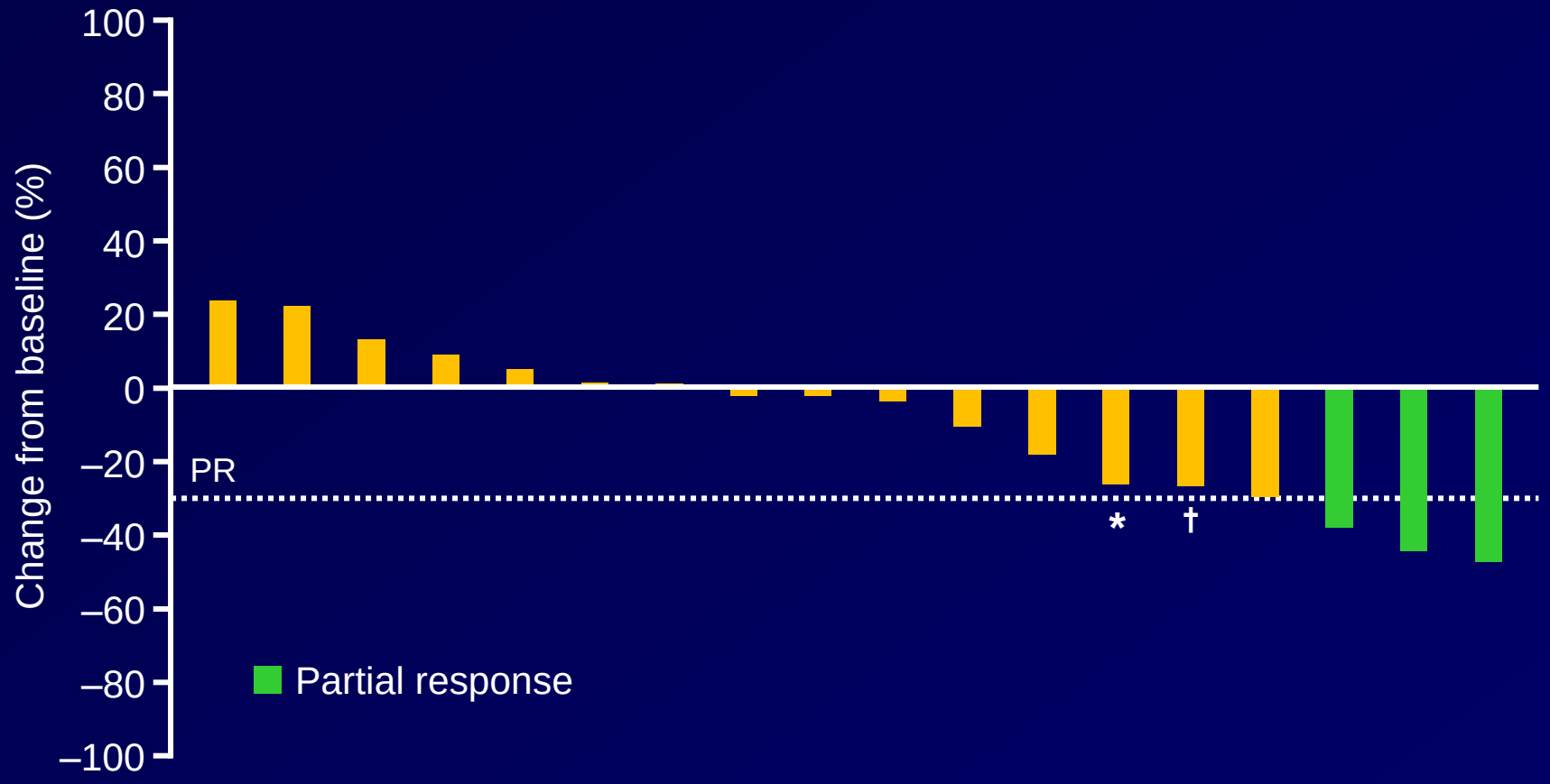
Waterfall Plot: *HER2* Cohort (n=22)



***Patient was treated for 55 days but was removed from treatment due to an edge recurrence of a previously treated brain metastasis**

†Patient was treated for 28 days but discontinued due to an AE

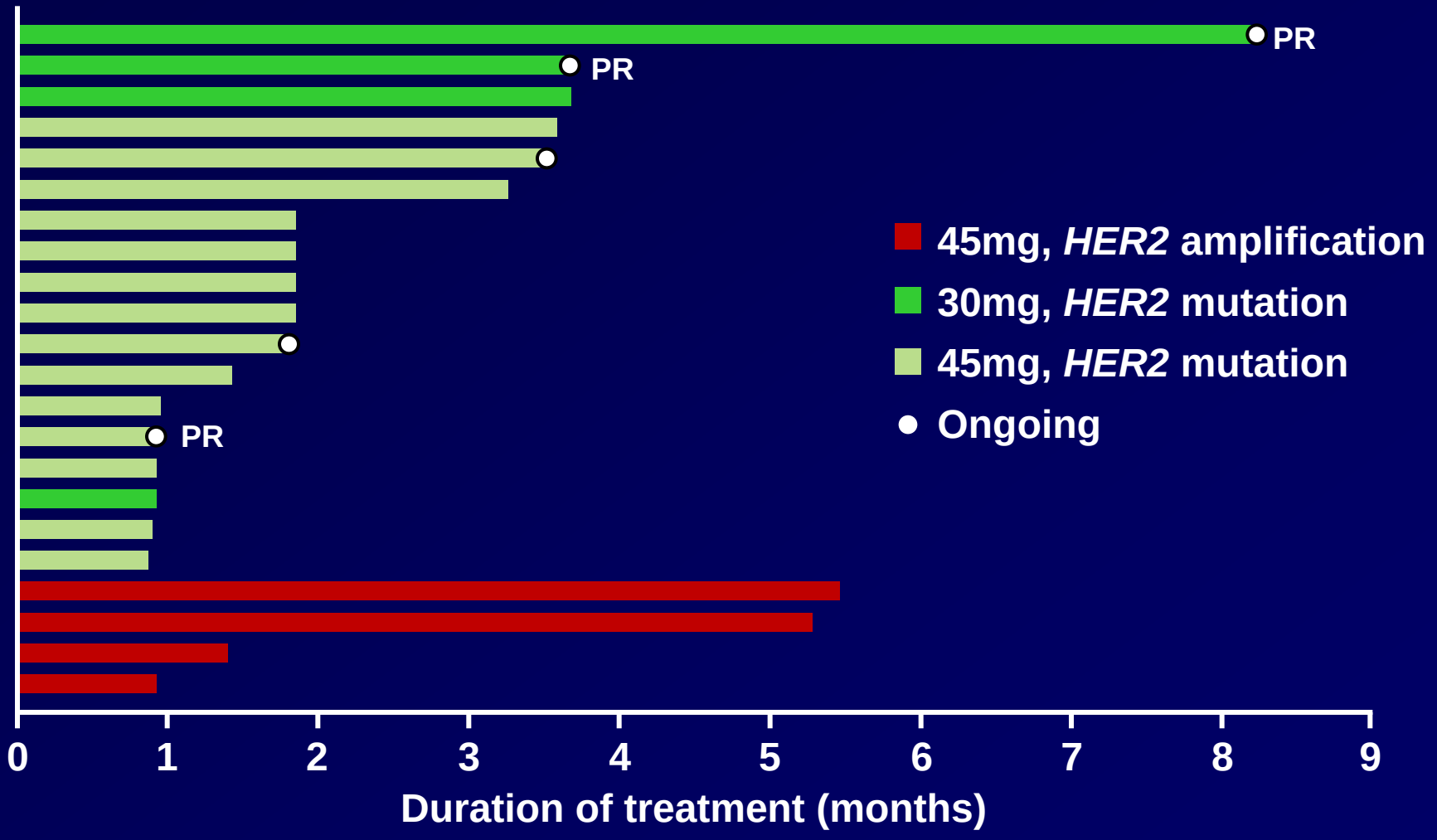
Waterfall Plot for Patients with *HER2*-Mutant Lung Cancers (n=18)



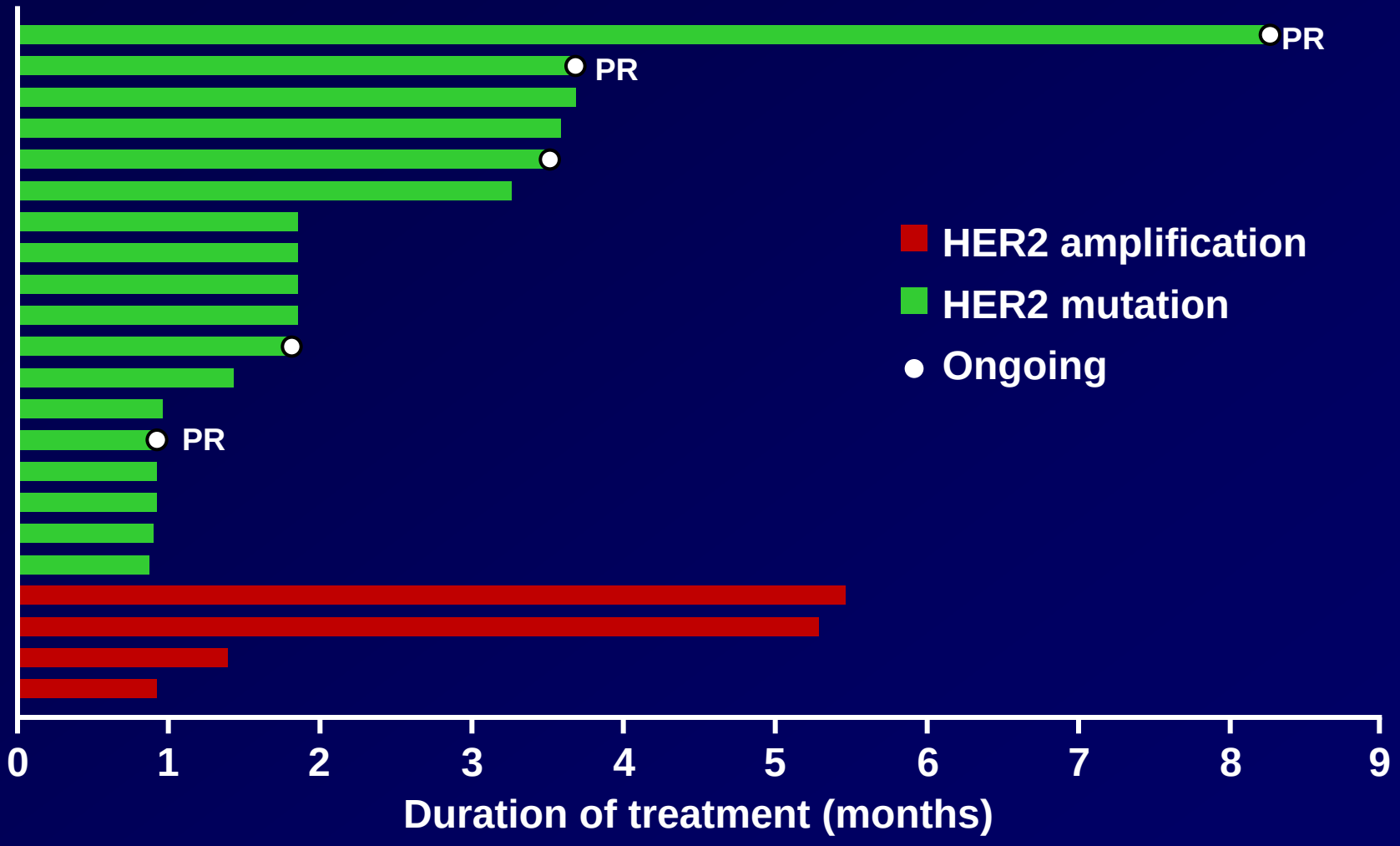
***Patient was treated for 55 days but was removed from treatment due to an edge recurrence of a previously treated brain metastasis**

†Patient was treated for 28 days but discontinued due to an AE

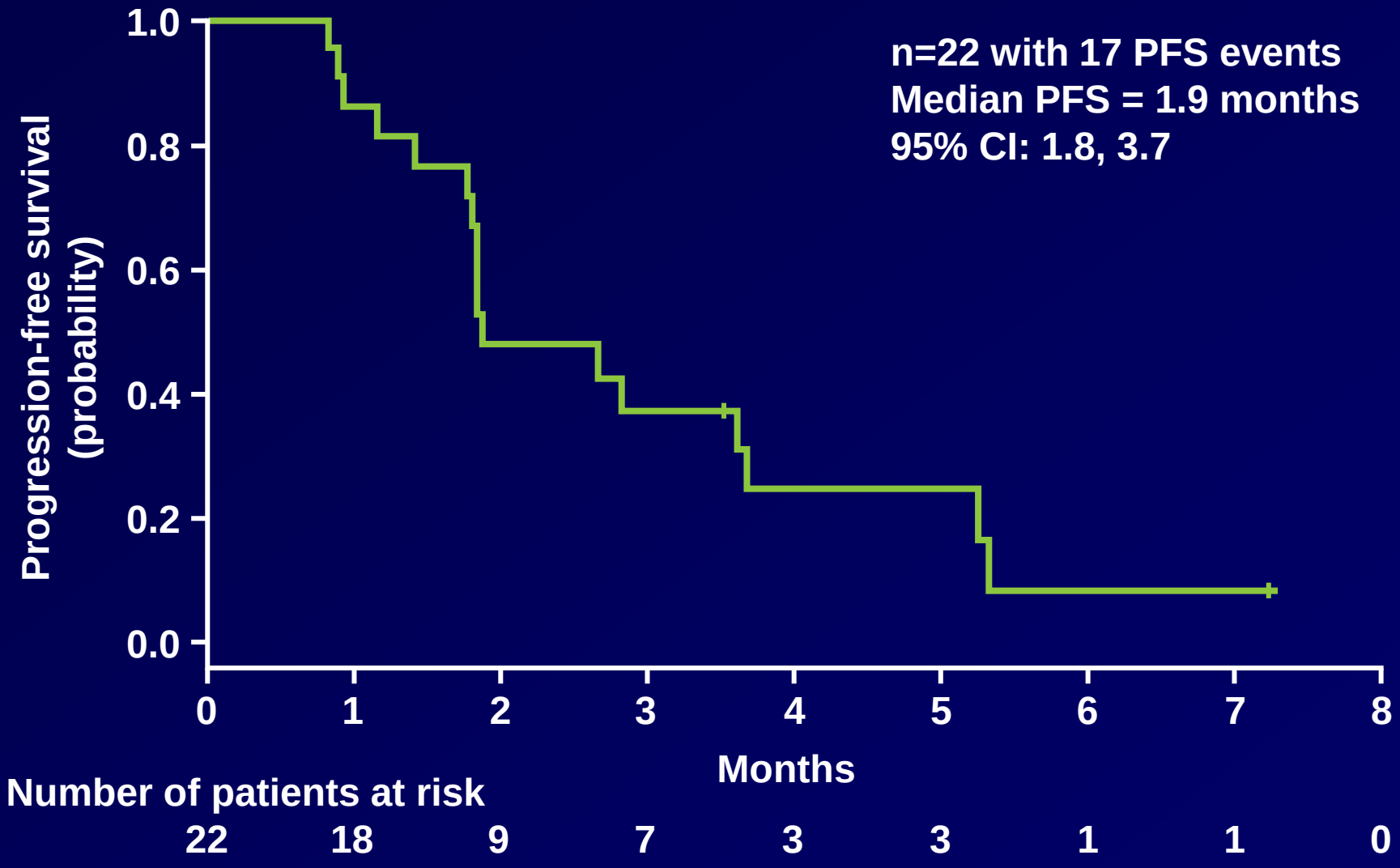
Duration of Treatment: *HER2* Cohort



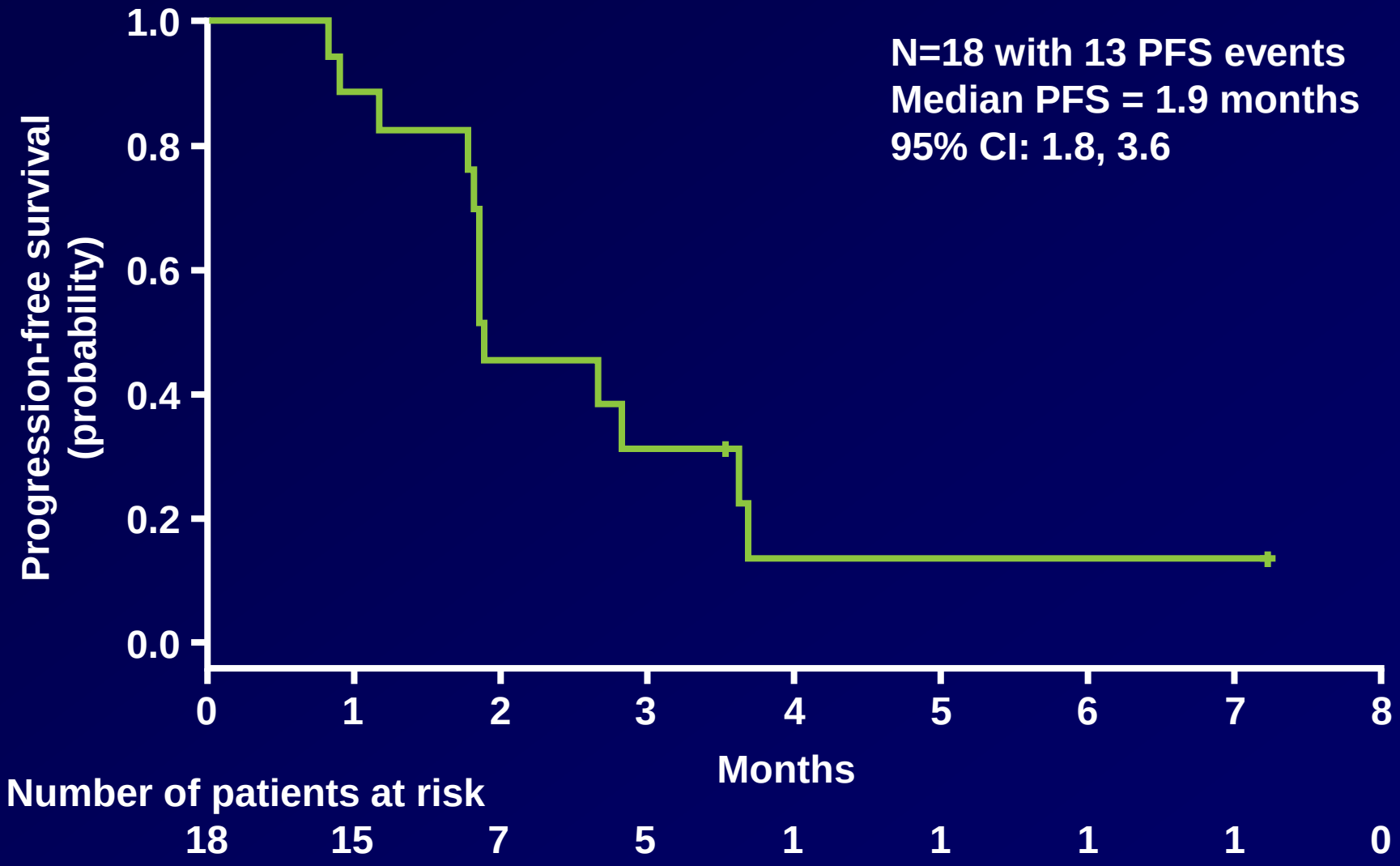
Duration of Treatment by *HER2* Status



PFS: *HER2* Cohort



PFS: Patients with *HER2*-Mutant Lung Cancers



HER2 Cohort: Treatment-related Adverse Events in ≥15% of Patients

Adverse event, n (%)	Total (N=22)
Diarrhea	19 (86.4)
Dermatitis acneiform	16 (72.7)
Fatigue	11 (50.0)
Dry skin	9 (40.9)
Nausea	8 (36.4)
Paronychia	7 (31.8)
Vomiting	7 (31.8)
Decreased appetite	6 (27.3)
Pruritus	6 (27.3)
Skin fissures	6 (27.3)
Mucosal inflammation	5 (22.7)
Dehydration	4 (18.2)
Epistaxis	4 (18.2)
Rash erythematous	4 (18.2)
Stomatitis	4 (18.2)

HER2 Cohort: Toxicities

- Three (13.6%) out of 22 patients experienced treatment related serious AEs
- Three (13.6%) patients stopped dacomitinib due to treatment-related side effects
- One grade 5 hepatic failure was observed in one patient starting from 30 mg (drug-drug interaction with a concurrent medication)
- No grade 4–5 treatment-related AEs were observed in patients starting from 45 mg

Conclusions

- Dacomitinib has demonstrated high activity in *EGFR*-mutant lung cancer. This activity signal supports further development in a phase 3 study, which is currently planned
- The toxicity profile of dacomitinib is consistent with the mode of action and class effects. AEs are predominantly grades 1 and 2 and manageable.
- While dacomitinib targets HER2, the clinical activity is mixed, with 3 PRs and 9 SD in 22 enrolled patients as BOR to date. Enrollment is ongoing
- Further data analysis is ongoing to identify predictive markers of response

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