

Outcomes with neoadjuvant nivolumab plus chemotherapy by metabolic response status in CheckMate 816

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Introduction

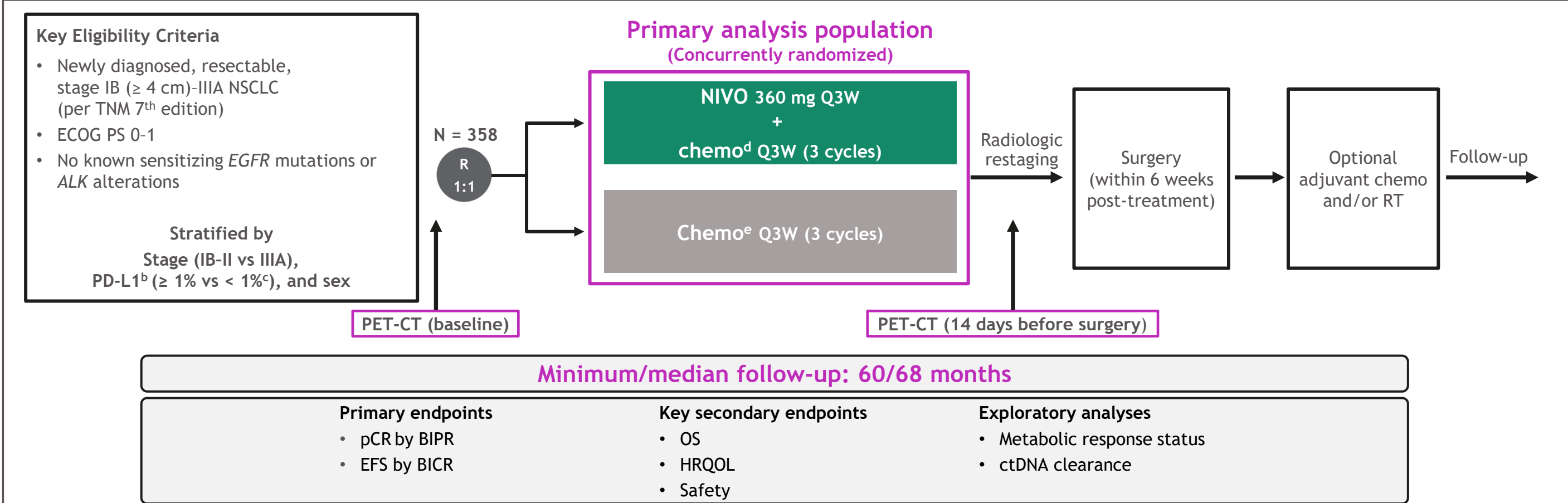
- In CheckMate 816, a phase 3 study, neoadjuvant nivolumab (NIVO) + chemotherapy (chemo) significantly improved event-free survival (EFS; hazard ratio [HR], 0.63; 97.38% CI, 0.43-0.91; $P = 0.005$), pathologic complete response (pCR; odds ratio, 13.94; 99% CI, 3.49-55.75; $P < 0.001$),¹ and overall survival (OS; HR, 0.72; 95% CI, 0.523-0.998; $P = 0.048$),² versus chemo in patients with resectable non-small cell lung cancer (NSCLC)
 - Five-year follow-up demonstrated consistent EFS benefit²
 - Based on the primary EFS and pCR results, NIVO + chemo was approved for neoadjuvant treatment of resectable NSCLC³
- There is an unmet need for noninvasive biomarkers that can facilitate patient selection and predict pathologic response or long-term outcomes prior to surgery for NSCLC
- The use of ¹⁸F-fluorodeoxyglucose positron emission tomography-computed tomography (¹⁸F-FDG PET-CT) imaging to measure changes in tumor size and metabolic activity represents an emerging noninvasive biomarker for predicting cancer treatment outcomes⁴⁻⁶
- Here we report exploratory outcomes from CheckMate 816 by metabolic and radiologic response parameters

Methods

- In CheckMate 816 (NCT02998528), newly diagnosed adults with stage IB-IIIA (per American Joint Committee on Cancer Staging Manual, 7th Edition [AJCC v7]) resectable NSCLC, Eastern Cooperative Oncology Group performance status (ECOG PS) ≤ 1 , and no known *EGFR/ALK* alterations were eligible (Figure 1)
- Patients were randomized 1:1 to receive NIVO 360 mg + chemo every 3 weeks (Q3W) or chemo Q3W for 3 cycles, followed by surgery within 6 weeks after treatment

- Endpoints**
- Primary endpoints (EFS and pCR both per blinded independent review) and OS (a key prespecified, statistically powered, hierarchically tested secondary endpoint) in the overall population were previously reported^{1,2}
 - Exploratory analyses of metabolic and radiologic response were conducted through blinded independent review of available baseline and presurgical ¹⁸F-FDG PET-CT scans (14 days presurgery) and quantified using Positron Emission Tomography Response Criteria in Solid Tumors version 1.0 (PERCIST) and Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST) criteria^{7,8}
 - Per PERCIST, PET lesions were defined as positive when the tumor to background ratio (TBR) was > 1.5 times greater than the liver background
 - One target lesion (most positive) and up to 4 non-target lesions were assessed
 - Complete metabolic response (CMR) was defined as complete resolution of ¹⁸F-FDG uptake compared with liver and blood-pool levels
 - Partial metabolic response (PMR) was defined as a reduction of a minimum of 30% in target lesion ¹⁸F-FDG SUL_{peak} (peak standardized uptake value adjusted for lean body mass [SUL] in a spherical 1-cm³ volume of interest), with an absolute drop in SUL of at least 0.8 SUL units
 - Progressive metabolic disease (PMD) was defined as a $> 30\%$ increase in ¹⁸F-FDG SUL_{peak}, with a > 0.8 SUL unit increase in tumor SUL_{peak} from the baseline scan OR new ¹⁸F-FDG-avid lesion
 - Stable metabolic disease (SMD) was defined as a response other than CMR, PMR, or PMD
 - Exploratory analyses were also conducted on circulating tumor DNA (ctDNA) clearance

Figure 1. CheckMate 816 study design^a



Database lock: January 23, 2025. From *The New England Journal of Medicine*, Forde PM, et al. Neoadjuvant nivolumab plus chemotherapy in resectable lung cancer. 2022;386:1973-1985. Copyright © 2022 Massachusetts Medical Society. Adapted with permission from Massachusetts Medical Society. ^aNCT02998528. ^bDetermined by the PD-L1 IHC 28-8 pharmDx assay (Dako). ^cIncluded patients with PD-L1 expression status not evaluable and indeterminate. ^dNoninvasive: pembrexed + cisplatin or paxitaxel + carboplatin; squamous: gemcitabine + cisplatin or paxitaxel + carboplatin. ^eVinorelbine + cisplatin, docetaxel + cisplatin, gemcitabine + cisplatin (squamous only), pembrexed + cisplatin (noninvasive only), or paxitaxel + carboplatin. BICR, blinded independent central review; BIPR, blinded independent pathologic review; chemo, chemotherapy; ctDNA, circulating tumor deoxyribonucleic acid; ECOG PS, Eastern Cooperative Oncology Group performance status; EFS, event-free survival; HRQOL, health-related quality of life; IHC, immunohistochemistry; NIVO, nivolumab; NSCLC, non-small cell lung cancer; OS, overall survival; pCR, pathologic complete response; PD-L1, programmed death-ligand 1; PET-CT, positron emission tomography-computed tomography; Q3W, once every 3 weeks; R, randomized; RT, radiotherapy; TNM, tumor, node, metastasis.

Results

- Of 179 patients randomized to each arm, metabolic response was evaluable in 135 (75%) patients receiving neoadjuvant NIVO + chemo and 124 (69%) patients receiving chemo; baseline characteristics were generally consistent between the all-randomized and PERCIST-evaluable populations (Table 1)
- In the PERCIST evaluable population, 100 (74%) and 79 (64%) patients in the NIVO + chemo and chemo arms, respectively, were responders
- Metabolic response rates in the NIVO + chemo arm were similar irrespective of histology
 - Among patients with squamous histology, 50/87 (57%) in the NIVO + chemo arm and 48/95 (51%) in the chemo arm were metabolic responders
 - Among patients with nonsquamous histology, 50/92 (54%) in the NIVO + chemo arm and 31/84 (37%) in the chemo arm were metabolic responders
- At a minimum follow-up of 60 months (median, 68 months), improved survival outcomes were observed in patients with metabolic response versus patients without metabolic response (Figures 2 and 3)

Table 1. Baseline demographics of FDG PET available population^a

	All concurrently randomized patients		PERCIST evaluable population	
	NIVO + chemo (n = 179)	Chemo (n = 179)	NIVO + chemo (n = 135)	Chemo (n = 124)
Age, median (range), years	64.09 (41-82)	63.63 (34-84)	64.24 (47-82)	63.03 (35-84)
Male, n (%)	128 (72)	127 (71)	97 (72)	91 (73)
ECOG PS, n (%)				
0	124 (69)	117 (65)	95 (70)	87 (70)
I	55 (31)	62 (35)	40 (30)	37 (30)
Stage, ^b n (%)				
IB	10 (6)	8 (4)	9 (7)	3 (2)
IIA	30 (17)	32 (18)	24 (18)	25 (20)
IIIB	25 (14)	21 (12)	23 (17)	16 (13)
IIIA	113 (63)	116 (65)	79 (59)	80 (65)
IV	1 (1)	1 (1)	0	0
IA	0	1 (1)	0	0
Histology, n (%)				
Squamous	92 (51)	84 (47)	70 (52)	56 (45)
Nonsquamous	87 (49)	95 (53)	65 (48)	68 (55)
Smoking status, n (%)				
Current/former	160 (89)	158 (88)	123 (91)	109 (88)
Never	19 (11)	20 (11)	12 (9)	15 (12)
Unknown	0	1 (1)	0	0
Tumor PD-L1, ^c mean (range)	22 (0-100)	23 (0-100)	23 (0-100)	24 (0-100)

^aPercentages may not total 100 due to rounding. ^bDisease stage (per AJCC TNM 7th edition) as reported in case report forms. Among patients without definitive surgery, 1 patient in the chemo arm had stage IA disease, and 1 patient in each treatment arm had stage IV disease. ^cDetermined using the PD-L1 IHC 28-8 pharmDx assay (Dako); patients with tumor tissue that could not be assessed for PD-L1 (< 10% of concurrently randomized patients) were stratified to the PD-L1 expression < 1% subgroup at randomization. AJCC, American Joint Committee on Cancer; chemo, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; NIVO, nivolumab; PD-L1, programmed death-ligand 1; PERCIST, PET Response Criteria in Solid Tumors; PET, positron emission tomography; TNM, tumor, node, metastasis.

Figure 2. EFS by metabolic response status

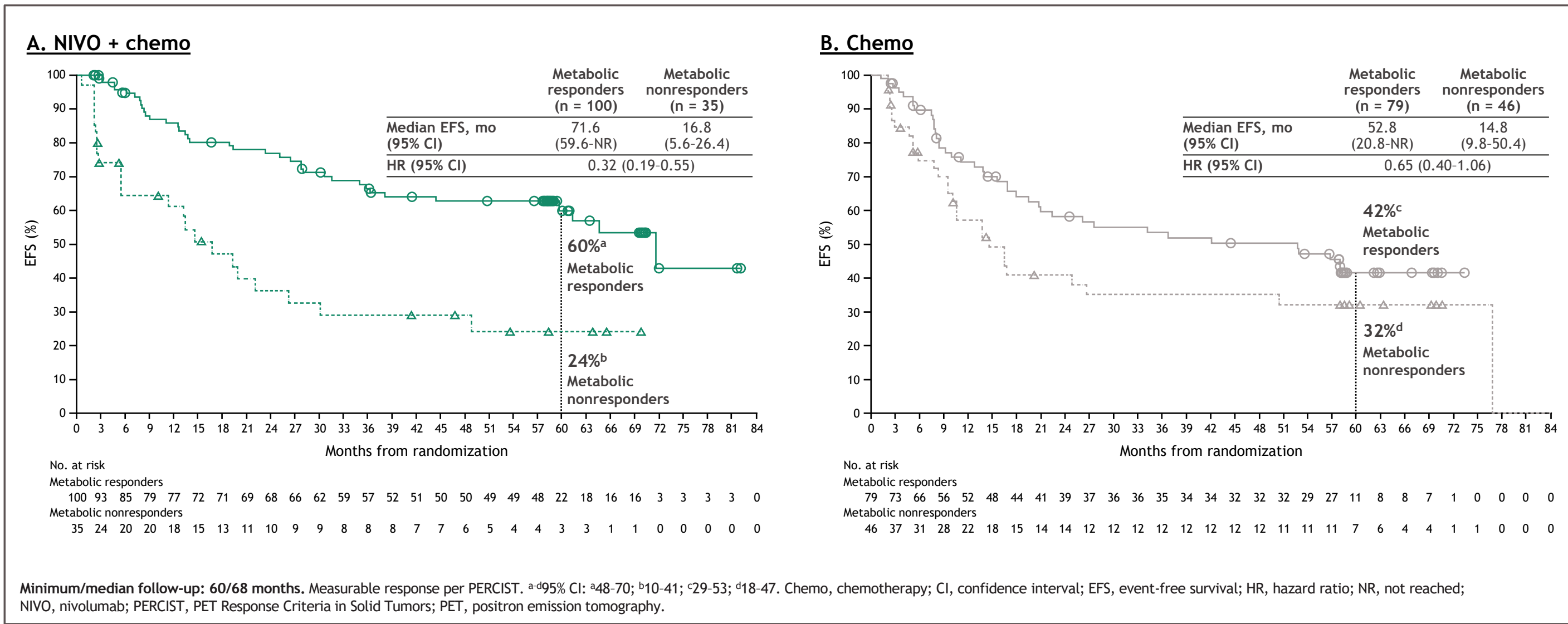
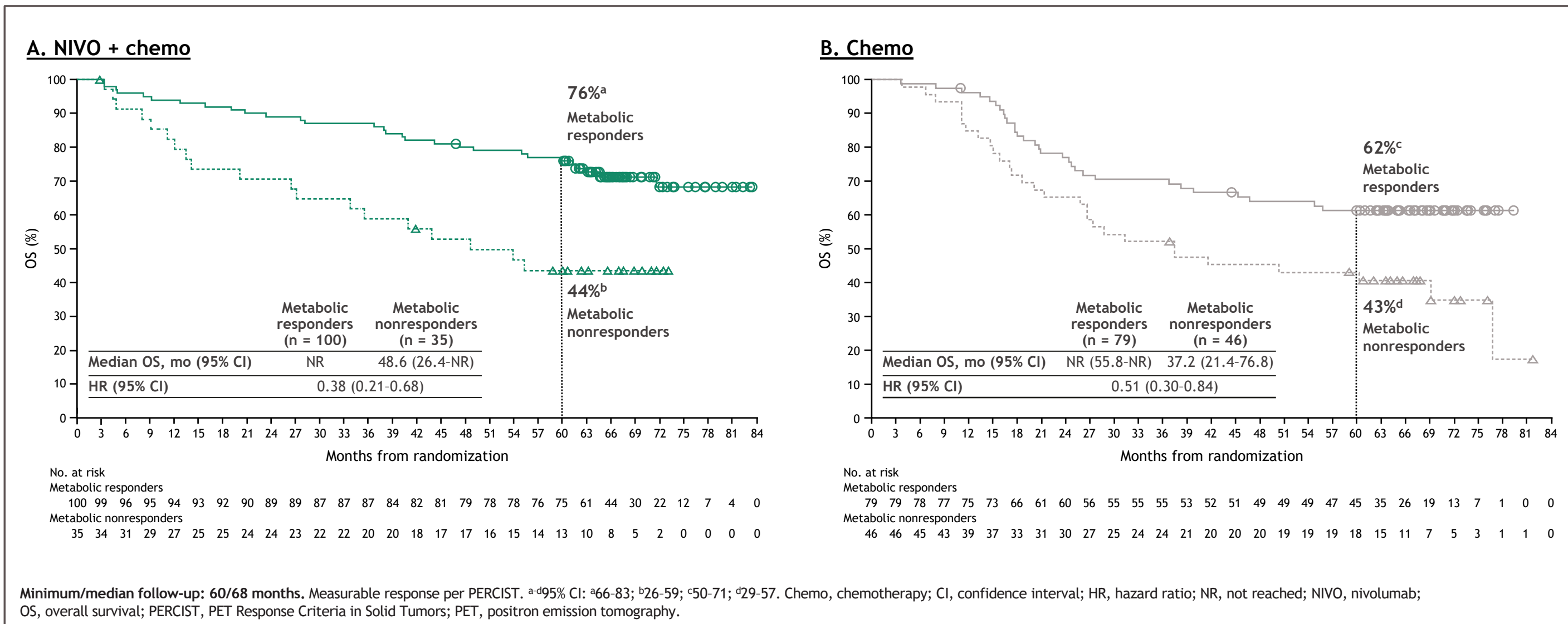


Figure 3. OS by metabolic response status



- 33% of metabolic responders receiving NIVO + chemo had pCR (Table 2)
- Among PERCIST or RECIST evaluable patients, the combination of both metabolic response per PERCIST and radiologic response per RECIST resulted in higher 5-year EFS (72%) and OS (86%) rates in patients receiving NIVO + chemo vs patients with response to only one set of response criteria (Figure 4A and B)
 - Moreover, patients receiving NIVO + chemo who obtained CMR and radiologic response prior to surgery demonstrated higher 5-year EFS (82%) and OS (96%) rates (Figure 4C and D)
 - These rates were similar to those obtained by patients with pCR (all randomized patients, n = 43; EFS, 88%; OS, 95%)²
- Among patients with CMR and radiologic response, 62% experienced pCR, an additional 15% experienced MPR, 19% did not have pathologic status reported, and only 4% (n = 1) did not achieve MPR (Table 3)
- Sensitivity and specificity analyses for predicting pCR in the NIVO + chemo patient group showed mixed results (Table 4)
 - The more stringent definition (CMR and CR/PR) demonstrated high specificity (93%) and a low false-positive rate (7%) but identified only 37% of patients who achieved pCR
 - In contrast, the broader definition (CMR/PMR and CR/PR) substantially improved sensitivity (67%), capturing approximately two-thirds of pCR patients, but at the cost of a higher false-positive rate (29%)
- In PERCIST-assessed patients, ctDNA clearance was evaluable in 33 patients (24%) receiving NIVO + chemo and 32 patients (26%) receiving chemo
 - ctDNA clearance rates were higher in metabolic responders than nonresponders in both arms
 - NIVO + chemo: 68% (17/25) vs 25% (2/8)
 - Chemo: 60% (12/20) vs 8% (1/12)
 - The small subset of patients treated with NIVO + chemo with metabolic response and ctDNA clearance (n = 17) experienced good 5-year rates for EFS (45%) and OS (77%)

Table 2. pCR by metabolic response status

Patients, n (%)	NIVO + chemo		Chemo	
	Metabolic responders (n = 100)	Metabolic nonresponders (n = 35)	Metabolic responders (n = 79)	Metabolic nonresponders (n = 46)
pCR	33 (33)	2 (6)	2 (3)	0
Non-pCR	67 (67)	33 (94)	77 (98)	46 (100)

Minimum/median follow-up: 60/68 months. Measurable response per PERCIST. Chemo, chemotherapy; NIVO, nivolumab; pCR, pathologic complete response; PERCIST, PET Response Criteria in Solid Tumors; PET, positron emission tomography.

Table 3. Metabolic and radiologic response status by pCR and %RVT among patients receiving NIVO + chemo

%RVT	CMR and radiologic response (CR or PR) ^a (n = 26)		Metabolic (CMR or PMR) and radiologic (CR or PR) response (n = 69)	
	Non-pCR	pCR	Non-pCR	pCR
Total, n (%)	10 (38)	16 (62)	40 (58)	29 (42)
0% RVT	0	16 (62)	0	29 (42)
> 0-5% RVT	4 (15)	-	11 (16)	-
> 5-10% RVT	0	-	4 (6)	-
> 10-30% RVT	1 (4)	-	8 (12)	-
> 30-100% RVT	0	-	7 (10)	-
Not reported	5 (19) ^b	-	10 (14) ^c	-

Measurable response per PERCIST and RECIST. ^aThere were no CRs in this population. ^bTwo patients had pathologic response status of "not evaluable" and three had a status of "no sample available". ^cFour patients had pathologic response status of "not evaluable" and six had a status of "no sample available". Chemo, chemotherapy; CMR, complete metabolic response; CR, complete response; NIVO, nivolumab; MPR, major pathologic response; pCR, pathologic complete response; PERCIST, PET Response Criteria in Solid Tumors; PET, positron emission tomography; PMR, partial metabolic response; PR, partial response; RVT, residual viable tumor; RECIST, Response Evaluation Criteria in Solid Tumors.

Figure 4. EFS and OS by metabolic and/or radiologic response for patients receiving NIVO + chemo

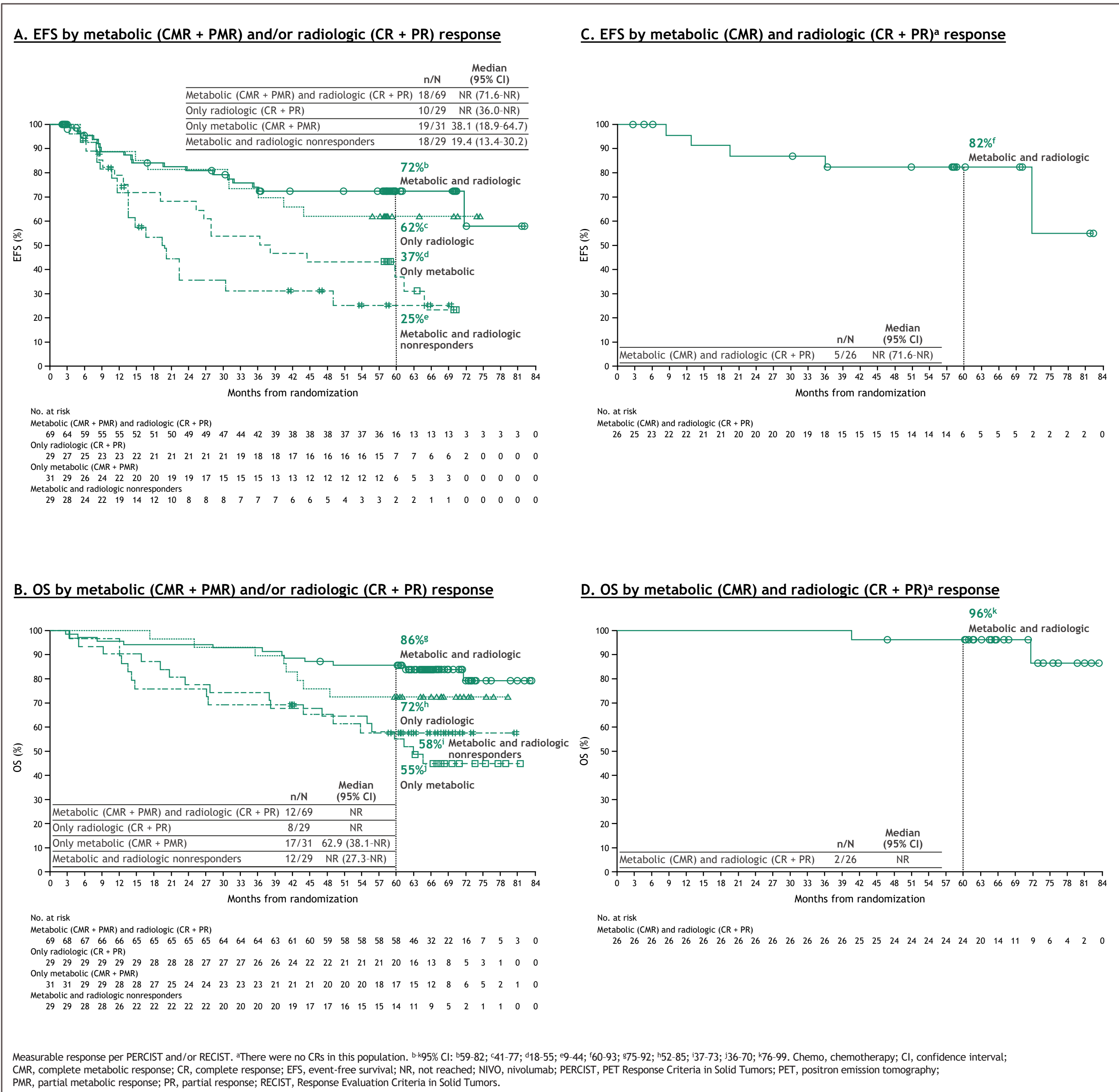


Table 4. Sensitivity and specificity metrics for predicting pCR among patients receiving NIVO + chemo

Predictor definition	True positive	False positive	False negative	True negative	Sensitivity	Specificity	False positive rate
CMR and CR/PR, ^a n	16	10	27	126	37%	93%	7%
CMR/PMR and CR/PR, n	29	40	14	96	67%	71%	29%

Measurable response per PERCIST and RECIST. ^aThere were no CRs in this population. Chemo, chemotherapy; CMR, complete metabolic response; CR, complete response; NIVO, nivolumab; pCR, pathologic complete response; PERCIST, PET Response Criteria in Solid Tumors; PET, positron emission tomography; PMR, partial metabolic response; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors.

Conclusion

- In patients with resectable NSCLC in CheckMate 816 across both treatment groups, metabolic response was associated with prolonged survival
- Among patients receiving NIVO + chemo:
 - Nearly one third of metabolic responders receiving NIVO + chemo had pCR, demonstrating that metabolic response alone is not sufficient to noninvasively predict pCR
 - Metabolic response combined with radiologic response was associated with higher EFS (72%) and OS (86%) rates
 - Among patients with CMR and radiologic response, 62% had pCR (pCR was not reported in 19%) and the 5-year OS rate (96%) was similar to that among patients with pCR (95%)²
- These results support the potential of ¹⁸F-FDG PET-CT as a practical, noninvasive biomarker for assessing benefit from neoadjuvant therapy, that could guide future neo-adjuvant dose escalation trial designs for patients with suboptimal early response and potentially limit exposure to ineffective surgical procedures

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