Pattern of Rash, Diarrhea, and Hepatic Toxicities Secondary to Lapatinib and Their Association With Age and Response to Neoadjuvant Therapy: Analysis From the NeoALTTO Trial

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ABSTRACT

Purpose

We investigated the pattern of rash, diarrhea, and hepatic adverse events (AEs) secondary to lapatinib and their association with age and pathologic complete response (pCR) in the Neoadjuvant Lapatinib and/or Trastuzumab Treatment Optimisation (NeoALTTO) phase III trial.

Patients and Methods

Patients with HER2-positive early breast cancer were randomly assigned to receive lapatinib (Arm A), trastuzumab (Arm B), or their combination (Arm C) for 6 weeks followed by the addition of paclitaxel for 12 weeks before surgery. We investigated the frequency and time to developing each AE according to age (≤ 50 v > 50 years) and their association with pCR in a logistic regression model adjusted for age, hormone receptors, tumor size, nodal status, planned breast surgery, completion of lapatinib administration, and treatment arm.

Results

Only patients randomly assigned to arms A and C were eligible ($n = 306$). Younger patients (≤ 50 years) experienced significantly more rash compared with older patients (74.4% v 47.9%; $P < .0001$). Diarrhea and hepatic AEs were observed in 78.8% and 41.2% of patients, respectively, with no differences in rate or severity or time of onset according to age. Early rash (ie, before starting paclitaxel) was independently associated with a higher chance of pCR, mainly in patients older than 50 years (odds ratio [OR] = 3.76; 95% CI, 1.69 to 8.34) but not in those ≤ 50 years (OR = 0.92; 95% CI, 0.45 to 1.88; P for interaction = .01). No significant association was observed between pCR and diarrhea or hepatic AEs.

Conclusion

Our results indicate that the frequency and clinical relevance of lapatinib-related rash is largely dependent on patient age.

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INTRODUCTION

Lapatinib is a tyrosine kinase inhibitor (TKI) targeting the epidermal growth factor receptor (EGFR; HER1) and HER2.¹ It is considered one of the key agents in managing metastatic HER2-positive breast cancer, particularly after failure of trastuzumab. Its combination with capecitabine or trastuzumab in the trastuzumab-refractory setting has been shown to significantly improve progression-free survival.^{2,3} In addition, it showed interesting activity in patients with brain metastasis.⁴⁻⁷

Skin rash, diarrhea, and hepatic toxicities are adverse events (AEs) that have been linked with not only lapatinib,⁸⁻¹¹ but also other EGFR TKIs.^{12,13}

These AEs seem to affect a considerable portion of patients and could result in dose modification and treatment discontinuation. In breast cancer, two previous reports evaluated lapatinib toxicities on the basis of a combined analysis of several studies.^{9,11} However, these analyses were performed on heavily pretreated patients in the metastatic setting and had little emphasis on the pattern of diarrhea and hepatic AEs. In addition, they did not address whether certain age groups are more susceptible to any of these AEs.

For EGFR TKIs, skin rash was proposed as a potential early sign of activity in non-small-cell lung cancer (NSCLC) and also head and neck cancer.¹⁴⁻¹⁶ Patients developing rash secondary to erlotinib or

gefitinib had better response rate and better progression-free and overall survival. Although rash was consistently reported in all the lapatinib clinical trials, none of them have addressed whether it predicts benefit to lapatinib.

Here, we reported on lapatinib-specific AEs, namely rash, diarrhea, and hepatic AEs, in patients enrolled on the Neoadjuvant Lapatinib and/or Trastuzumab Treatment Optimisation (NeoALTO) trial,¹⁷ which investigated the role of lapatinib as **neoadjuvant therapy**. We also examined their association with patients' age and pathologic complete response (pCR).

PATIENTS AND METHODS

The NeoALTO trial is a neoadjuvant, multicenter, randomized phase III trial in which patients with HER2-positive early breast cancer were randomly assigned to receive lapatinib 1,500 mg/day (Arm A), trastuzumab (Arm B), or the combination of lapatinib 1,000 mg/day and trastuzumab (Arm C) for 6 weeks followed by the addition of paclitaxel (80 mg/m²) for 12 weeks before surgery.¹⁷ After surgery, all patients received three cycles of fluorouracil, epirubicin, and cyclophosphamide (FEC) and then continued the same anti-HER2-targeted therapy as administered in the neoadjuvant setting to complete a total duration of 1 year.

The detailed description of the NeoALTO trial and key eligibility criteria is provided in the original publication.¹⁷ In brief, eligible patients had to have a HER2-positive primary breast cancer with a minimum tumor size of 2 cm and adequate cardiac function. Informed consent was obtained from all patients at study entry. The study was approved by the ethics committee of all the participating sites. This sub-study was approved by the NeoALTO Executive Committee, and was not preplanned as a part of the NeoALTO trial initial analysis.

The primary end point of NeoALTO was pCR, defined as the absence of invasive tumor cells in the breast at the time of surgery.¹⁸ The main analysis indicated the combined arm (ie, Arm C) had nearly double the rate of pCR (51.3%) compared with arm A (24.7%) and arm B (29.5%). In addition, patients randomly assigned to the lapatinib-containing arms had significantly more rash, diarrhea, and hepatic AEs compared with those randomly assigned to the trastuzumab-alone arm, which is not known to be associated with any of these AEs.

In the current analysis, only patients randomly assigned to the lapatinib-alone arm (ie, Arm A) or the combination arm (ie, Arm C) were included (Fig 1). Lapatinib-specific AEs were defined as skin rash, diarrhea, and hepatic

toxicities. Skin rash was defined as per the Medical Dictionary for Regulatory Activities (MedDRA; Data Supplement). Diarrhea was defined as AEs reported as diarrhea or frequent bowel movements. Hepatic AEs were defined as elevated liver enzymes (ie, AST, ALT, gamma-glutamyl transferase [GGT]), alkaline phosphatase (ALP), and/or elevated total bilirubin. Grading of all AEs was made using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 3.0.

According to the NeoALTO protocol, strict criteria were applied for treatment discontinuation and AE reporting secondary to lapatinib-related AEs. These criteria did not apply for patients randomly assigned to Arm B (ie, trastuzumab-only arm). For hepatic AEs, patients receiving lapatinib had to discontinue lapatinib permanently in case of developing grade 3 or 4 abnormal bilirubin and/or ALT, or grade 2 abnormal bilirubin and ALT, or if either was grade 2 with signs and symptoms of liver injury per the investigator assessment. For skin rash, patients had to discontinue lapatinib in case of developing grade 4 rash. Finally, patients had to discontinue lapatinib in cases of persistent grade 3 or 4 diarrhea, or grade 2 diarrhea compromising patients' quality of life. In all instances, patients were allowed to continue other assigned anticancer treatment if deemed acceptable by the investigator.

In the current analysis, we investigated the frequency of each of the three AEs by NCI CTCAE grade according to patient age (≤ 50 v > 50 years) in patients randomly assigned to Arm A (ie, lapatinib alone) and Arm C (ie, lapatinib plus trastuzumab), and in patients in both arms combined. The priori hypothesis was that tolerance to lapatinib might be worse in older patients. We evaluated the rate of treatment discontinuation and dose reduction in each group. We also examined the median time to developing each AE and their onset in relation to the initiation of paclitaxel. Finally, we investigated the association between each of the AEs (ie, rash, diarrhea, hepatic toxicities) and pCR in a logistic regression model adjusted for the trial's stratification factors: hormone receptor (HR) status (negative v positive), clinical tumor size (≤ 5 v > 5 cm), clinical nodal status ($N_{2/3}$ v $N_{0/1}$), and type of planned breast surgery at the time of random assignment (conservative v not conservative), in addition to two other factors: completion of lapatinib administration (yes v no) and treatment arm (Arm C v Arm A). For each AE, we constructed two models: 1) AE (present v absent); and 2) AE early onset (ie, before initiation of paclitaxel) versus AE no early onset (ie, no AE or AE developed after the initiation of paclitaxel). Analyses were done using SAS (version 9.1.2). All statistical analyses were performed by Frontier Science Scotland (FSS; Kington, United Kingdom).

RESULTS

A total of 306 patients were included in the current analysis; 154 in the lapatinib-alone arm (ie, Arm A) and 152 in the combination arm (ie, Arm C; Fig 1).

Table 1 shows the distribution of the lapatinib-specific AEs in the two treatment arms and in all patients according to age. We found significantly higher incidence of rash in younger (ie, ≤ 50 years) compared with older patients. This was observed in both Arm A and Arm C. On considering patients in both arms, the incidence of rash in young versus older patients was 74.4% and 47.9%, respectively ($P < .0001$). The severity of skin rash was similar according to age; approximately 90% of the AEs were of grade 1 or 2 intensity (Data Supplement). Overall the rate of treatment discontinuation and dose reduction secondary to rash did not differ according to age and was generally low: 1.3% and 5.8%, respectively.

We did not find significant differences according to age regarding the frequency of diarrhea and hepatic AEs or their severity (Table 1). Diarrhea occurred in 78.8% of patients ($n = 241$), of whom 68 (28%) experienced grade 3 or 4 diarrhea (ie, 22.2% of all patients). Slightly more than 25% of patients required dose reduction secondary to diarrhea, but only 5% discontinued therapy for this reason. This was

Fig 1. Diagram summarizing patients eligible for the study. pCR, pathologic complete response.

Table 1. Lapatinib-Specific AEs According to Age and Randomly Assigned Treatment Arm

AE	Age				Total		P	
	≤ 50 Years*		> 50 Years*					
	No.	%	No.	%	No.	%		
Arm A (n = 154)†								
Rash								
All grades	63	77.8	33	45.2	96	62.3	< .0001	
Grade I/II	57	70.3	30	41	87	56.4		
Grade III/IV	5	6.1	2	2.7	7	4.5		
Missing grade	1	1.4	1	1.5	2	1.4		
Discontinuation	2	2.4	0		2	1.3		.176
Dose reduction	7	8.6	3	4.1	10	6.4		.254
Diarrhea								
All grades	66	81.4	56	76.7	122	79.2	.466	
Grade I/II	43	53	42	57.5	85	55.1		
Grade III/IV	23	28.4	13	17.8	36	23.3		
Missing grade	0		1	1.4	1	0.8		
Discontinuation	0		2	2.7	2	1.2		.133
Dose reduction	26	32.1	20	27.4	46	29.9		.524
Hepatic AEs								
All grades	32	39.5	32	43.8	64	41.6	.586	
Grade I/II	17	20.9	19	26	36	23.3		
Grade III/IV	15	18.6	13	17.8	28	18.3		
Missing grade	0		0		0			
Discontinuation	8	9.88	11	15.1	19	12.3		.327
Dose reduction	9	11.1	9	12.3	18	11.7		.814
Arm C (n = 152)‡								
Rash								
All grades	56	70.9	37	50.7	93	61.2	.0107	
Grade I/II	54	68.3	32	43.8	86	56.5		
Grade III/IV	1	1.25	5	6.9	6	3.9		
Missing grade	1	1.25	0		1	0.8		
Discontinuation	0		2	2.74	2	1.32		.138
Dose reduction	2	2.5	6	8.22	8	5.26		.116
Diarrhea								
All grades	62	78.5	57	78.1	119	78.3	.952	
Grade I/II	45	56.9	41	56.1	86	56.5		
Grade III/IV	16	20.2	16	22	32	21		
Missing grade	1	1.8	0		1	0.8		
Discontinuation	7	8.86	7	9.59	14	9.21		.876
Dose reduction	15	19	25	34.2	40	26.3		.032
Hepatic AEs								
All grades	32	40.5	30	41.1	62	40.8	.941	
Grade I/II	24	30.3	21	28.8	45	29.6		
Grade III/IV	7	8.8	9	12.3	16	10.5		
Missing grade	1	1.4	0		1	0.7		
Discontinuation	6	7.59	8	11	14	9.21		.473
Dose reduction	7	8.86	6	8.22	13	8.55		.887
Arm A and Arm C combined (n = 306)§								
Rash								
All grades	119	74.43	70	47.9	189	61.8	< .0001	
Grade I/II	111	69.3	62	42.4	173	56.5		
Grade III/IV	6	3.7	7	4.8	13	4.2		
Missing grade	2	1.3	1	0.7	3	1.1		
Discontinuation	2	1.3	2	1.4	4	1.3		.926
Dose reduction	9	5.63	9	6.1	18	5.8		.841
Diarrhea								
All grades	128	80	113	77.4	241	78.8	.578	
- Grade I/II	88	55	83	56.8	171	55.8		
- Grade III/IV	39	24.3	29	19.8	68	22.2		
- Missing grade	1	0.7	1	0.8	2	0.8		

(continued on following page)

Table 1. Lapatinib-Specific AEs According to Age and Randomly Assigned Treatment Arm (continued)

Table 1. Adverse Events Associated With the Use of the Study Drug, by Age Group (n = 100)							
AE	Age				Total		P
	≤ 50 Years*		> 50 Years*				
	No.	%	No.	%	No.	%	
Discontinuation	7	4.3	9	6.1	16	5.2	.482
Dose reduction	41	25.6	45	30.8	86	28.1	.312
Hepatic AEs							
All grades	64	40	62	42.5	126	41.2	.661
Grade I/II	41	25.6	40	27.3	81	26.4	
Grade III/IV	22	13.7	22	15.2	44	14.3	
Missing grade	1	0.7	0		1	0.5	
Discontinuation	14	8.75	19	13	33	10.8	.229
Dose reduction	16	10	15	10.3	31	10.1	.936

NOTE. Arm A, lapatinib only; Arm C, lapatinib plus trastuzumab.

Abbreviation: AE, adverse event.

*Number used as denominator to calculate percentage.

†Age ≤ 50 years, n = 81; age > 50 years, n = 73.

‡Age ≤ 50 years, n = 79; age > 50 years, n = 73.

§Age ≤ 50 years, n = 160; age > 50 years, n = 146.

the same irrespective of age. Hepatic AEs occurred in 41.2% of patients (n = 126), of whom 44 (36%) had grade 3 or 4 AEs (ie, 14.3% of all patients; Data Supplement). Discontinuation rate and dose reduction secondary to hepatic AE were around 10% irrespective of age.

Table 2 summarizes the onset of the different AEs in relation to starting paclitaxel in the different treatment arms. Considering all patients who received lapatinib (n = 306), the median time to developing rash, diarrhea, and hepatic toxicities was 2 weeks (interquartile range [IQR], 1.1 to 4.2 weeks), 2.1 weeks (IQR, 0.4 to 7.7 weeks), and 6.8 weeks (IQR, 4.1 to 10.3 weeks), respectively. Given the higher prevalence of rash in younger patients, we investigated whether the time to developing rash differed by age, but there were no obvious differences; median time was 1.7 weeks (IQR, 1 to 4 weeks) and 2.2 (IQR, 1.1 to 6.3 weeks) for patients age ≤ 50 and > 50 years, respectively. Diarrhea seemed to occur relatively earlier in patients randomly assigned to the combination

arm (median, 1.7 weeks; IQR, 0.4 to 6.3 weeks) compared with those randomly assigned to the lapatinib-alone arm (median, 3.1; IQR, 0.4 to 8.1 weeks). Overall, rash and diarrhea tended to occur earlier before the initiation of paclitaxel, unlike hepatic AEs in which 60% developed after the start of paclitaxel.

Table 3 shows a descriptive analysis on the association between pCR, lapatinib dose reduction, and completion of lapatinib administration. pCR rates were comparable between patients who were or were not subjected to lapatinib dose reduction (33.8% v 39.2%). However, those who did not complete lapatinib as planned seemed to have a lower rate of pCR compared with those who completed lapatinib (28.3% v 43.5%).

Finally, we evaluated the association between pCR and the different AEs and their onset time in a logistic regression model adjusted for age, clinical tumor size, clinical nodal status, HR status, the type of planned surgery at diagnosis, completion of lapatinib administration

Table 2. Time to Developing the Different Lapatinib-Specific AEs

AE (all grades)	Time to Developing AE (weeks)		Early Onset (pre-paclitaxel)*		Late Onset (during paclitaxel)*	
	Median	IQR	No.	%	No.	%
Arm A (n = 154)						
Rash (n = 96)	2.0	1.1-4.1	78	81.2	18	18.8
Diarrhea (n = 122)	3.1	0.4-8.1	71	58.1	51	41.9
Hepatic AEs (n = 64)	6.3	4.1-10.2	25	39	39	61
Arm C (n = 152)						
Rash (n = 93)	2.0	1.1-5.1	71	76.3	22	23.7
Diarrhea (n = 119)	1.7	0.4-6.3	87	73.1	32	26.9
Hepatic AEs (n = 62)	8.0	4.1-11.9	25	40.3	37	59.7
Arm A and Arm C combined (n = 306)						
Rash (n = 189)	2.0	1.1-4.3	149	78.8	40	21.2
Diarrhea (n = 241)	2.1	0.4-7.7	158	65.5	83	34.5
Hepatic AEs (n = 126)	6.8	4.1-10.3	50	39.6	76	60.4

NOTE. Arm A, lapatinib only; Arm C, lapatinib plus trastuzumab.

Abbreviations: AE, adverse event; IQR, interquartile range.

*The percentage uses the denominator of patients who actually developed the toxicity and not patients randomly assigned to the given arm.

Table 3. Descriptive Analysis Showing the Association Between pCR, Lapatinib Dose Reduction, and Completion of Lapatinib Administration

	No		Yes	
	No.	%	No.	%
Dose reduction	232		74	
No pCR	141	60.8	49	66.2
pCR	91	39.2	25	33.8
Completion as planned	113		193	
No pCR	81	71.7	109	56.5
pCR	32	28.3	84	43.5

Abbreviation: pCR, pathologic complete response.

and treatment arm. As expected, treatment arm, HR status, and lapatinib completion were significantly associated with pCR in the different models (Figs 2 and 3).

Figure 2 shows the association between the development of rash and pCR. No significant association was observed when analyzing the association between the development of rash at any time and pCR. However, when restricting the analysis to patients who developed rash before starting paclitaxel, the early development of rash was significantly associated with a higher chance of pCR ($P = .039$). However, this seemed to be more obvious in patients older than 50 years (odds

ratio [OR] = 3.76; 95% CI, 1.69 to 8.34) and not those ≤ 50 years (OR = 0.92; 95% CI, 0.45 to 1.88; P for interaction = .01). Patients who developed early rash had a pCR rate of 44.3% (66 of 149 patients) compared with 31.8% (50 of 157 patients) in those who did not develop an early rash. When restricting to patients older than 50 years, the pCR rate was 50% (26 of 52 patients) with early rash compared with 26.6% (25 of 94 patients) with no early rash. Yet no obvious differences in pCR rate were observed in younger patients on the basis of developing early rash (41.2% v 39.6%). No other interactions with pCR were observed (HR status $P = .955$; treatment arm $P = .883$).

Figure 3 shows the association between hepatic AEs, diarrhea, and pCR. We did not find a significant association between developing any of the later toxicities or their time of onset and pCR.

DISCUSSION

This is the first analysis from a randomized phase III trial that evaluates the pattern of lapatinib-specific AEs and their association with age and response to treatment. The unique design of the NeoALLTO trial, in which targeted therapies were administered alone during the first six weeks, allowed us to examine the effect of lapatinib on developing these toxicities independent of chemotherapy. The prospective nature of the study and the careful documentation of the different AEs and their NCI CTCAE grade enabled us

Fig 2. Logistic regression model showing the association between rash and pathologic complete response (pCR). Dotted line represents an odds ratio of 1.0, and error bars represent 95% CIs. (A) Effect of development of rash at any time point on pCR. (B) Effect of development of early rash (ie, before initiating paclitaxel) on pCR. BCS, breast cancer surgery; HR, hormone receptor; Lap., lapatinib.

Fig 3. Logistic regression model showing the association between diarrhea, hepatic adverse effect (AE) and pathologic complete response (pCR). Dotted line represents an odds ratio of 1.0, and error bars represent 95% CIs. (A) Effect of development of diarrhea at any time point on pCR. (B) Effect of development of early diarrhea (ie, before initiating paclitaxel) on pCR. (C) Effect of development of hepatic AE at any time point on pCR. (D) Effect of development of early hepatic AE (ie, before initiating paclitaxel) on pCR. BCS, breast cancer surgery; HR, hormone receptor; Lap., lapatinib.

to provide an important overview on the pattern of these AEs and their possible clinical implications.

In the current analysis, 61.8% of patients who received lapatinib developed skin rash, in which 6.8% were grade 3 or 4 in severity. In a previous combined analysis of the dermatologic AEs secondary to lapatinib, Lacouture et al⁹ reported a 55% rate of skin AEs (almost all were skin rash)—only 3% of those were grade 3 or 4 in severity, which is rather in line with our results. In our study, 78.8% of patients developed diarrhea, which is also consistent with the rate of developing diarrhea in other studies, which ranged between 70% and 90%.^{19,20}

On the other hand, although studies with other EGFR TKIs have shown elevated liver enzymes secondary to these agents,^{12,21} earlier studies with lapatinib in the metastatic setting did not highlight this association. However, recent trials with lapatinib in the early breast cancer setting have underscored this risk.^{17,22} Guarneri et al reported grade 1 or greater hepatic AEs in patients with breast cancer who received chemotherapy in combination with lapatinib (with or without trastuzumab) in a phase II neoadjuvant study.²² In this study, a total of 85 patients received lapatinib and the rates of grade 2 and 3/4 hepatic AEs were approximately 16% and 10%, respectively. In our analysis, which includes more than triple the number of patients, we observed grade 1/2 hepatic AEs in 26.4% of patients, with slightly more grade 3/4 toxicities (14.3%). On the other hand, the TEACH study,²³ which investigated the role of lapatinib ($n = 1,571$) after the completion of adjuvant chemotherapy, reported only 2% grade 3/4 hepatic AEs. The differences in the incidence of hepatic AEs between the later study and ours (grade 3/4 2% v 14.3%) could be related to the concomitant administration of paclitaxel in our study, which is also known to be associated with hepatic toxicities.

We hypothesized that older patients might have poorer tolerance to lapatinib. Yet, we did not find an association between patient age

and developing either diarrhea or hepatic toxicities. However, we observed a significant association between the development of rash and patient age in which younger patients seemed to develop skin rash at a significantly higher rate. This was observed in patients receiving either lapatinib alone or in combination with trastuzumab. Rash and diarrhea mainly developed during the first 2 to 3 weeks of lapatinib administration. Previous analysis of skin rash secondary to lapatinib has also shown that the majority of patients tend to develop these AEs within the first 2 weeks.⁹ However, this was not the case for hepatic toxicities, which seemed to develop later—around 6 to 8 weeks after starting lapatinib. This underscores that hepatic AEs secondary to lapatinib are partly aggravated by the addition of chemotherapy, in this case paclitaxel. The relatively late onset of hepatic AEs could partly explain the reason that hepatic toxicities secondary to lapatinib were not highlighted in earlier metastatic studies, possibly owing to some patients' discontinuing therapy early because of underlying disease progression or the presence of liver metastases, which could be a reason for elevation of liver enzymes and hence could mask a possible lapatinib-related toxicity.

No association was found between diarrhea or hepatic AEs and pCR. This is not unexpected, considering that none have been suggested to predict benefit of EGFR TKIs in other diseases. However, we found a significant association between early development of rash and pCR. To the best of our knowledge, this is the first and only study to evaluate the association between rash and response to lapatinib. Given the association between age and the development of skin rash, we evaluated the interaction between the development of early rash and patient age on pCR and found that although rash was more common in younger patients, it seemed to predict pCR only in older patients. We do not have clear explanation for this observation. Further investigation on the relationship between patient age and lapatinib-related rash is warranted. In this regard, interrogation of pharmacogenomic

parameters from blood samples collected in NeoALTTO and in the sister adjuvant trial, ALTTO, could potentially elucidate our findings.

Although our results are in line with data associating the development of skin rash to benefit for other EGFR TKIs in NSCLC and head and neck cancers, our findings remains rather intriguing given that skin rash is secondary to the effects of lapatinib on EGFR, a biomarker in which data supporting its role as a potential target in breast cancer have been difficult to reconcile. EGFR expression by immunohistochemistry has not been shown to predict benefit from lapatinib on the basis of data from a large randomized phase III trial in the metastatic setting.²⁴ On the contrary, recent data from a small study in patients with HER2-positive metastatic breast cancer showed a significant association between high EGFR gene copy number (> 3.36) and clinical response to lapatinib.²⁵ Whether the association between early rash and pCR reflects an adequate blocking of lapatinib to the EGFR tyrosine kinase domain resulting in improved treatment efficacy, this remains to be determined. Nevertheless, these results may call for revisiting the role of EGFR as a relevant target in breast cancer treated with lapatinib. We endeavored to evaluate whether the severity of rash could be associated with pCR; however, given that a minority of patients developed grade 3/4 AEs, we were not able to perform such analysis.

It is important to note that the current analysis was not initially planned as a part of the NeoALTTO trial, and hence it should serve as hypothesis generating, requiring further confirmation. Another limitation is relying on the NCI CTCAE in reporting rash, rather than a more specific skin toxicity–related questionnaire. However, it is worth noting that the later was also seldom used in previous analyses looking into skin toxicities secondary to EGFR TKIs.

In conclusion, our results indicate that the rate and clinical relevance of lapatinib-related rash is largely dependent on patient age. We found that patients older than 50 years who developed early lapatinib-related rash had a significantly higher chance of achieving a pCR. These findings, if further confirmed, would help identifying patients likely to derive the maximum benefit of primary lapatinib-based therapy.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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GLOSSARY TERMS

Lapatinib: A dual tyrosine kinase inhibitor, lapatinib has been developed as an inhibitor of the tyrosine kinase activities of ErbB1 (EGFR) and ErbB2. Like other tyrosine kinase inhibitors, it competes with ATP binding to the intracellular regions of the receptors that are activated following tyrosine phosphorylation.

Neoadjuvant therapy: The administration of chemotherapy prior to surgery. Induction chemotherapy is generally designed to decrease the size of the tumor prior to resection and to increase the rate of complete (R0) resections.

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