IGF-1R Expression has More Potential Proliferation Effect in Invasive Breast Carcinoma Of No Special Type Compared to HER-2 Expression

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Abstract. About 75% of breast carcinoma is invasive carcinoma of no special type (NST) and between 20%-30% of breast carcinoma is HER-2 positive. HER-2 overexpression now is a predictive factor for targeted therapy with anti-HER-2 agent like trastuzumab (*herceptin*). However, primary (*de novo*) resistance with trastuzumab occured in 65% patients and secondary resistance occured in 70% patients who have had good initial response. IGF-1R expression have been reported high in many malignancies including breast carcinoma. Researches have showed that IGF-1R signaling pathway have a cross-talk with HER-2 signaling pathway and was thought to become one of resistance mechanism in anti-HER-2 targeted therapy. This research was a retrospective observational cross-sectional study with a total 55 samples. Expression of IGF-1R and HER-2 was evaluated immunohistochemically. A strong positive IGF-1R cytoplasm and membranous expression was found in 18,2% and 34,5% cases, respectively. HER-2 expression was positive in 23,6% cases. IGF-1R cytoplasm expression was correlated significantly with mitosis count (p=0.049). There was no correlation between IGF-1R membranous expression with mitosis count (p=0,641). There was no correlation between IGF-1R membranous and cytoplasm expression with histological grade (p=1,000) and there was no correlation between HER-2 expression with mitosis count (p=0,495) and histological grade (p=1,000). IGF-1R expression has more potential effect in mitosis compared with HER-2 expression. Inhibition it's signaling pathway may have therapeutic value in breast carcinoma. Combination therapy of anti-HER-2 with anti-IGF-1R could overcome resistancy of trastuzumab in HER-2 positive breast carcinoma.

Keywords : Invasive breast carcinoma of NST, IGF-1R and HER-2 expression.

1 Introduction

Approximately 75% breast carcinoma is invasive carcinoma of no special type (NST) (1). Breast carcinoma is heterogenous disease. Tumor with similar histologic subtype can have different clinical outcome and response to systemic therapy (2). Invasive carcinoma of NST have been reported to show highest heterogeneity among other subtype of breast carcinoma (3).

Breast carcinoma is the most common malignancy in woman all over the world (4). According to data from GLOBOCAN 2012, new cases of breast carcinoma was approximately 1,67 million (43 cases per 100,000 people) (5). A total of 48,998 breast carcinoma cases (40,3

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cases per 100,000 people) was reported in Indonesia. It was the third rank in the Ocean Pasific region after China and Japan (6). Data from Indonesian Association of Pathologist 2013 reported that a total 6,324 cases of breast carcinoma was diagnosed in all Center of Diagnostic of the Anatomic Pathology in Indonesia, and it was the most common diagnosed primary malignant lesion including in West Sumatera (7).

The mortality rates of breast carcinoma have been reported still high eventhough significant improvements in survival rates was reported. Breast carcinoma is the fifth cause of mortality in malignancy in the world (522,000 cases or 13 cases per 100,000 people) (5) (8). Resistance of targeted therapy is known as one of the cause of the high mortality rate in breast carcinoma. Based on expression of *Estrogen Receptor* (ER), *Progesterone Receptor* (PR), *Human Epidermal Growth Factor Receptor-2* (HER-2) dan proliferation index of Ki-67, breast carcinoma is classified into 5 molecular subtype. Approximately 20%-30% of breast carcinoma is HER-2 positive (9) (10). *HER-2* gene is located at chromosome 17q and have function to encode HER-2 protein, a transmembrane receptor family tyrosine kinase (11) (12) (13). Overexpression of HER-2 in breast carcinoma is correlated with aggressive behaviour, rapid progression, high grade tumor and higher number of recurrence and mortality rate. Overexpression of HER-2 is known as a predictive factor for targeted therapy with anti-HER-2 agents like trastuzumab (*herceptin*).

Many researches have reported that *insulin-like growth factor type-1 receptor* (IGF-1R) may have role in anti-HER-2 resistancy. IGF-1R expression have been reported high in many malignancies including breast carcinoma (17). IGF-1 ligand binds IGF-1R to initiate downstream signaling pathway of *phosphatidylinositol 3-kinase (PI3K)-Akt* which have role in cell survival and *mitogen-activated protein kinase (MAPK)* which have role in cell proliferation (18). These signaling pathway are also known initiated by HER-2 signaling pathway and was thought to become one of resistance mechanism in anti-HER-2 targeted therapy. There was no study about IGF-1R and HER-2 expression in breast carcinoma in Indonesia, especially in West Sumatera. Different ethnic and race is thought to have different role in pathogenesis of breast carcinoma in Indonesia. Study reported that not all breast carcinoma risk factors in the West are found in Minangese breast carcinoma (19). Therefore, this study was aimed to analyze expression of IGF-1R and HER-2 with histopathological factor of invasive carcinoma of no special type.

2 Methods

This research was a retrospective observational cross-sectional study. Samples were taken from Central Diagnostic of Pathology Anatomic of Andalas University Medicine Faculty and a total 55 samples fulfilled inclusion criterias from period 2014-2015. Samples were chosen using a simple random sampling method. IGF-1R and HER-2 expression was evaluated immunohistochemically from embedded paraffin blocks of invasive breast carcinoma of NST. IGF-1R expression was interpreted according to *h-score* system for cytoplasm staining and HER-2 scoring system for membranous staining. *H-score* calculated based on multiplying the products of the percentage of cells stained at a given staining intensity (0-100) by the staining intensity score (0, none; 1, weak; 2, moderate; and 3, intense): 0-10 points were considered to be negative, 11-100 points as weak, 101-200 points as moderate, and 201–300 points as strong positive. HER-2 expression interpreted based on American Society of Clinical Oncology/College of American Pathologists 2013 guideline as positif/3+, equivocal/2+ and negative (1+/0). HER-2 strong positive/3+ defined as complete and circumferential membrane staining that is intense and within >10% of the invasive tumor cells, HER-2 equivocal/2+ based

on circumferential membrane staining that is incomplete and/or weak/moderate and within >10% of the invasive tumor cells; or complete and circumferential membrane staining that is intense and within ≤10% of the invasive tumor cells, and HER-2 negative defined as weak or pale staining, incomplete >10% of tumor cells (1+) or no staining (0). Samples were stained histologically with Hematoxyllin & Eosin (H&E) to determine mitosis count and histological grade. The correlation between IGF-1R and HER-2 expression with histopathological factors (mitosis count and histological grade) was analyzed using t-Test, Oneway Anova or Chi Square test. Only p-values <0,05 were considered as significant. All statistical analyses were performed using the SPSS statistical software version 17.0 (SPSS Inc., Chicago, USA)

3 Results

During period 2014-2015, there was 217 cases which have been diagnosed as invasive breast carcinoma of NST but only 55 cases fulfilled the criterias with mean age 48,89±11,25 year (range 28-69 year). The group of age between 50-59 year was the most frequently found invasive breast carcinoma of NST. Mitosis count in 10 HPF had median of 22 (range 4-51) (figure 1). High grade invasive breast carcinoma of NST was the most frequently found histological grade (figure 2). IGF-1R expression positive membranous staining was found in 19 cases (34,5%) whereas positive cytoplasm staining 10 cases (18,2%) (figure 3). HER-2 expression positive was found in 13 cases (23,6%) (figure 4). Characteristics of patient is showed in table 1.

Statistical analysis found that there was no correlation between IGF-1R membranous staining with mitosis count (p=0,641) (Table 2) but there was a correlation between IGF-1R cytoplasm staining with mitosis count (p=0,049) with Post hoc tests p=0,049 (Table 2, 3a and 3b). There was no correlation between IGFR-1R expression both of membranous and cytoplasm staining with histological grade, p=0,587 and p=1,000 respectively (Table 4 and 5). Also, there was no correlation between HER-2 expression with mitosis count and histological grade, p=0,495 and p=1,000 respectively (Table 6 and 7).

Table 1. Characteristics of patient (55 samples).

Characteristics		n (%)
Age (year)		
- Mean	48,89 (Median 50, SD 11,249)	
- Range	(28-69)	
Age of group (year)		
- <30		3 (5,5)
- 30-39		9 (16,4)
- 40-49		15 (27,3)
- 50-59		17 (30,9)
- >59		11 (20,0)
Mitosis count per 10 HPF		
- Mean	22,85 (*Median* 22, SD 10,952)	
- Range	(4-51)	
Histological grade		
- Low grade		23 (41,8)
- High grade		32 (58,2)
IGF-1R membranous		
- Positive		19 (34,5)

- Negative	36 (65,5)
IGF-1R cytoplasm	
- Strong positive	10 (18,2)
- Moderate	9 (16,4)
- Negative	36 (65,5)
HER-2 expression	
- Positive	13 (23,6)
- Equivocal	8 (14,5)
- Negative	34 (61,8)

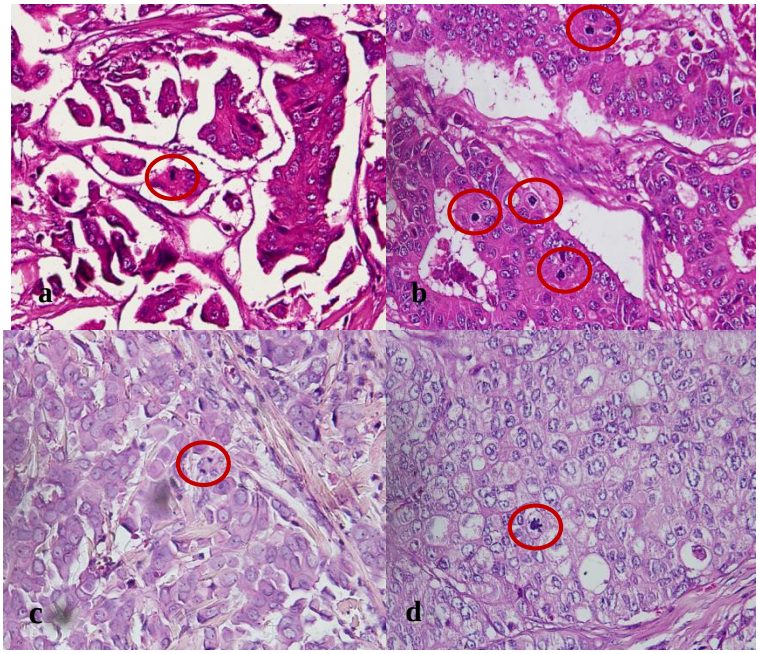

Figure 1 Mitosis images (a) at metaphase, (b) anaphase, (c) telophase, (d) atypical mitosis with multipolar nuclei chromatin (objective 40x).

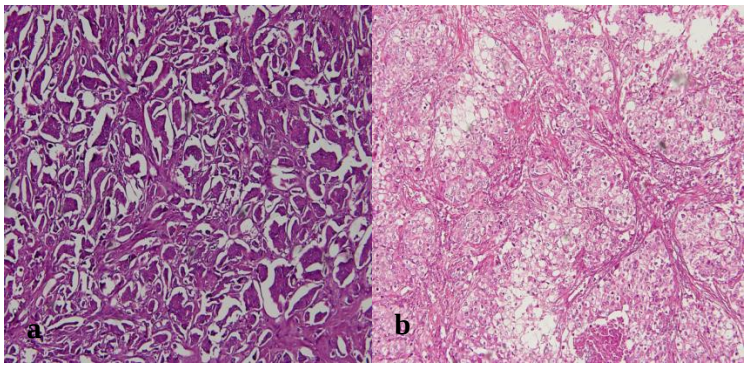

Figure 2 Histological grade invasive breast carcinoma of NST, (a) *low grade* (b) *high grade* (objective 20x).

Table 2 Correlation between IGF-1R membranous staining with mitosis count

IGF-1R membranous	**Mitosis count (*mean* ± *standard deviation*)**	**p *value***
Negative	23,36 ± 10,680	0,641
Positive	21,89 ± 11,685	

Table 3.a Correlation between IGF-1R cytoplasm staining with mitosis count

IGF-1R cytoplasm	**Mitosis count (*mean* ± *standard deviation*)**	**p *value***
Negative	23,36 ± 10,680	0,049
Moderate	28,22 ± 10,733	
Strong positive	16,20 ± 9,727	

Table 3.b Post hoc test IGF-1R cytoplasm staining with mitosis count

IGF-1R cytoplasm	**Negative**	**Moderate**	**Strong positive**
Negative	-	0,663	0,188
Moderate	0,663	-	**0,049**
Strong positive	0,188	**0,049**	-

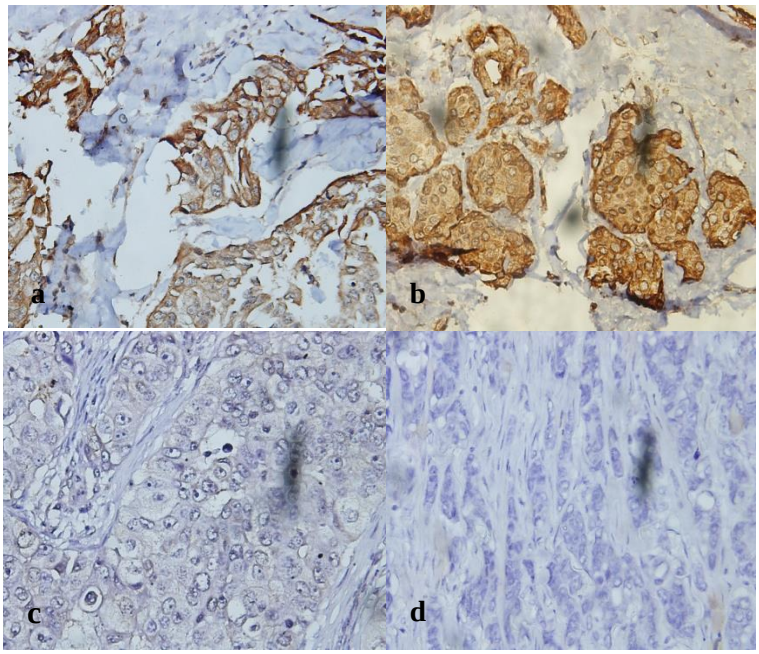

Figure 3 IGF-1R expression, (a) membranous staining moderate incomplete ≤10% of tumor cells (+2/positif), (b) cytoplasm staining strong positive (*h-score* 201-300) (c) pale staining, incomplete >10% of tumor cells (+1/negative) (d) no staining (negative/0) (objective 40x).

Table 4 Correlation between IGF-1R membranous staining with histological grade

IGF-1R membranous	**Histological grade**				**Total**		***p value***
	Low grade		***High grade***				
	F	%	F	%	F	%	
Negative	16	44,4	20	55,6	36	100	
Positive	7	36,8	12	63,2	19	100	0,587

Table 5 Correlation between IGF-1R cytoplasm staining with histological grade

IGF-1R cytoplasm	**Histological grade**				**Total**		***p value***
	Low grade		***High grade***				
	F	%	F	%	F	%	
Negative	16	44,4	20	55,6	36	100	
Moderate	2	22,2	7	77,8	9	100	1,000
Strong positive	5	50,0	5	50,0	10	100	

Table 6 Correlation between HER-2 expression with mitosis count

HER-2 expression	**Mitosis count (*mean ± standard deviation*)**	**p *value***
Negative	24,18 ± 12,197	0,495
Equivocal	21,88 ± 10,829	
Positive	20,00 ± 6,916	

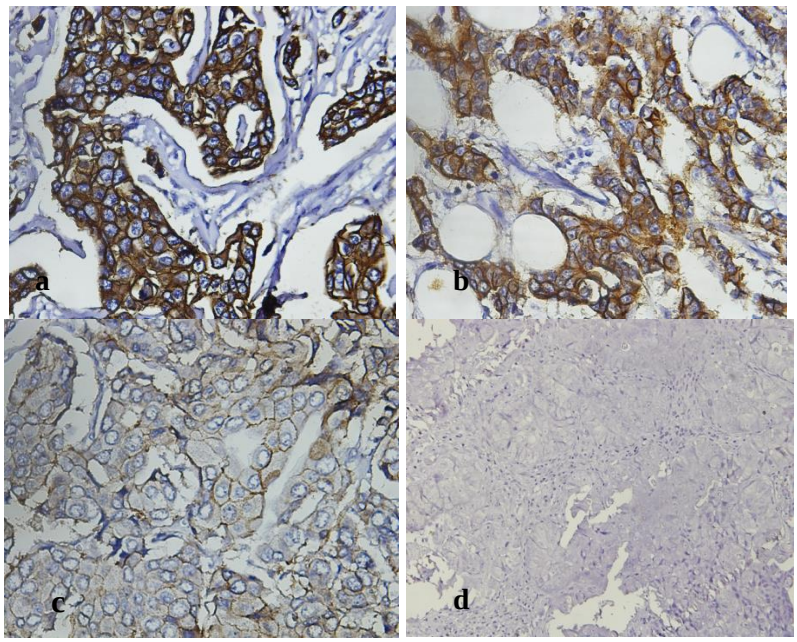

Figure 4 HER-2 expression, (a) strong staining, complete/*circumferential* >10% of tumor cells (+3/positive), (b) moderate staining, incomplete >10% of tumor cells (+2/*equivocal*) (c) pale

staining, incomplete >10% of tumor cells (+1/negative) (d) no staining (negative/0) (objective 40x).

Table 7 Correlation between HER-2 expression with histological grade

HER-2 expression	**Histological grade**				**Total**		**p *value***
	Low grade		***High grade***				
	F	%	F	%	F	%	
Negative	15	44,1	19	55,9	34	100	
Equivocal	2	25,0	6	75,0	8	100	1,000
Positive	6	46,2	7	53,8	13	100	

4 Discussions

Mean age of invasive breast carcinoma of NST in this study was similar to other studies in Indonesia. Khambri (2015) reported that mean age of breast carcinoma patients in West Sumatera was 48,59, Tinambunan *et al* (2013) found it was 47,9 in Palembang, Kosasih and Artha (2011) found it was 47,57 in Denpasar (20) (21) (22). Meanwhile, Ng *et al* (2011) study which compared clinicopathological characterictics between Indonesian and Malaysian breast carcinoma reported that mean age of patients was 47 in Indonesia (23). From literatures we have already known that mean age of breast carcinoma in Asian countries including Indonesia is lower than in the Western countries. This circumstance can be explained by the structure of the population pyramid which mainly consist of young population. Other, it can also be explained by the difference of age-spesific incidence pattern between Asian and Western. In Asian, there was a flat age–incidence curve after menopause (4) (23).

In this study, invasive breast carcinoma of NST was frequently found between age 50-59 year (30,9%). It was different from many studies that have been reported in Indonesia and Asia. According to Hutagalung *et al* (2014), Kosasih and Artha (2011) in Denpasar, breast carcinomas was frequently found between 41-50 year (22) (24). The similar found was reported by Tinambunan *et al* (2013) in Palembang and also Khambri (2015) in West Sumatera (21) (20). In Asia, Mousavi *et al* (2006) in Tehran and Yip *et al* (2006) in Malaysia found that it was between age of 40-49 (25) (26). However, a study from Kamarlis (2017) in Medan Indonesia reported that basal-like subtype breast carcinoma was frequently found between age 50-59 year (27). Also, Devi *et al* (2012) in Malaysia have reported that breast carcinoma in Chinese ethnic of Southeast Asia was frequently found between age 50-59 year (28). From all those studies we concluded that different molecular subtype, also ethic/race was related with age of group of breast carcinoma.

More than half of invasive breast carcinoma of NST was high grade (58,2%). Result from this study similar with other studies that have been reported in Indonesia. Aryondono *et al* (2006), Tinambunan *et al* (2013), Hutagalung *et al* (2014), Jatiluhur *et al* (2014), Kadi and Hoesin (2014) also Nelson *et al* (2014) reported that high grade breast carcinoma was more frequently found than low grade (21) (24) (29) (30) (31) (32). However, widodo *et al* (2014) in Yogyakarta and Aini *et al* (2015) in Semarang reported that invasive breast carcinoma of NST grade 2 (low grade) was the most frequently found histological grade (33) (34).

The high number of high grade breast carcinoma was found in Indonesia probably due to late-stage diagnoses. Reason for the late stage diagnoses was patient's delay to search medical help. Factors have known to contribute for the delay including culture and belief in most of

Asian and Indonesian which seek for traditional medication first to treat their disease, reluctance or refusal to have one's breasts examined by a male doctor, woman should ask family or husband's permission for every decision she made and lack access to health care facilities particularly in suburban district due to lower income (8) (23). In Indonesia, many reports found that most of breast carcinoma patients came to the hospital at late stage of clinical desease. Data from Division of Oncology Surgery Department of Dr. M. Djamil National Hospital registry in Padang, West Sumatera showed that in 2013 a total 77,2% breast carcinoma patients came to the hospital at late stage (IIIB and IV) (19) (20). Widodo *et al* (2014) also reported that 54,8% breast carcinoma patients who came to Sardjito National Hospital in Yogyakarta was at stage III (33). Jatiluhur *et al* (2014) reported 50% breast carcinoma patients who came to National Hospital of Dr. Hasan Sadikin Bandung was at late stage (30).

IGF-1R expression in other researches have a wide range of value. Shin *et al* (2014) reported only IGF-1R positive membranous expression which they found as much as 65,4% (17). Yerushalmi *et al* (2012) also reported IGF-1R positive membranous expression in total 46% cases (35). Both of them didn't report any cytoplasm expression. In this study, IGF-1R expression was reported as membranous and cytoplasm staining. A total 19 cases (34,5%) invasive breast carcinoma of NST have IGF-1R expression moderate positive membranous staining. In this study, we didn't find a strong positive membranous staining of IGF-1R expression according to HER-2 scoring system that most of studies adopted. Meanwhile, IGF-1R cytoplasm expression was found moderate in 9 cases (16,4%) and strong positive in 10 cases (18,2%) according to *h-score* system. This study was similar to Fu *et al* (2011) who also reported IGF-1R membranous and cytoplasm expression. They found a strong positive membranous and cytoplasm of IGF-1R expression in 3% and 9% cases respectively (36). Before that, Köstler *et al* (2006) reported similar found of IGF-1R expression. They reported a strong positive membranous and cytoplasm of IGF-1R expression in 14% and 8% cases respectively (37).

Although IGF-1R expression is frequently found in breast carcinoma, there is no a valid immunohistochemically guidelines universally with respect to both intensity and pattern of the IGF-1R staining. Most of studies referred to HER-2 scoring guidelines system from DAKO but in this study we can't only use HER-2 scoring system as we found cytoplasm expression was more visible than membranous expression. According to Fu *et al* (2011) and Köstler *et al* (2006), as IGF-1R is a transmembrane tyrosine kinase, it is reasonable to find a membranous staining. For the cytoplasm expression, there was two explanations that should be taken into consideration. First, the antibody that is used in this study detected the β subunit of IGF-1R which is located on the internal side of the membranous. Second, although IGF-1R represents as membrane-bound tyrosine kinase receptor, the IGF-1R is translocated from the cell membranous to the cytosol with cytoplasmic IGF-1R representing a bound, internalized and thus a potentially activated receptor. Alternately, predominant cytoplasm staining may represent a failure to translocate IGF-1R to the surface (36) (37).

HER-2 positive expression was found in 13 cases (23,6%). This finding was concordant with other findings that had established. Studies found that HER-2 overexpression is reported between 20%-30% breast carcinoma (9) (10). Some studies reported that it is between 15%-20% breast carcinoma (13) (38).

We found that there was a significant correlation between IGF-1R cytoplasm expression with mitosis count (p=0,049) but there was no correlation between IGF-1R membranous expression with mitosis count (p=0,641). As we have explained before, IGF-1R cytoplasm expression was more visible than membranous and thought have more potential effect. From literatures, IGF-1R signaling pathway was mainly iniatiated PI3K/Akt signaling pathway. Activated this molecular signaling pathway increased mitogenesis, cell cycle progression and

apoptosis inhibition (39). There was no correlation between IGF-1R expression both cytoplasm and membranous with histological grade and also we didn't find correlation between HER-2 expression with mitosis count and histological grade. We assumed that there is another molecular pathway that involve in pathogenesis of invasive breast carcinoma of NST in this recent study. In this study, we found that more than a half of invasive breast carcinoma of NST was high grade. From literatures, group of high grade breast carcinoma are HER-2 positive and basal-like subtype. Basal-like subtype is a group of breast carcinoma which have ER, PR and HER-2 negative expression also known as triple negative breast carcinoma (TNBC) (40). We suspect that in this study there was a chance that high grade breast carcinoma was basal-like subtype. The similar finding was reported by Köstler *et al* (2006) who also found that there was no correlation between IGF-1R and HER-2 with histopathological factors in breast carcinoma that was assumed as a group of basal-like subtype (37).

5 Conclusions

We concluded that IGF-1R expression has more potential effect in mitosis. Inhibition it's signaling pathway may have therapeutic value in breast carcinoma. Combination therapy of anti-HER-2 with anti-IGF-1R may overcome resistancy of anti-HER-2 agent in breast carcinoma HER-2 positive.

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