

Advances in Brief

Predictive Value of the EphA2 Receptor Tyrosine Kinase in Lung Cancer Recurrence and Survival

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Abstract

Purpose: Underestimation of disease severity is a major problem confronting the successful clinical management of non-small cell lung cancer. Recent advances in molecular biological substaging may provide an opportunity to identify those patients with the most aggressive forms of the disease, but there is a continuing need for accurate markers of disease relapse and survival.

Experimental Design: In our present study, immunohistochemical analyses of a retrospective database of pathologic specimens were used to demonstrate that the EphA2 receptor kinase is frequently overexpressed in NSCLC.

Results: Initial presentation with high levels of EphA2 predicts subsequent survival, overall relapse, and site of relapse. Specifically, high levels of EphA2 in the primary tumor predict brain metastases, whereas low levels of EphA2 relate to disease-free survival or contralateral lung metastasis.

Conclusions: These data suggest that EphA2 may provide a molecular marker to identify and predict patients who have isolated brain metastases. Moreover, the high levels of EphA2 in lung cancer may provide an opportunity for therapeutic targeting.

Introduction

NSCLC² is the leading cause of cancer mortality in the United States (1). Approximately 177,000 cases of new lung cancer will be diagnosed this year and 160,000 people will die of the disease. The current standard of care for clinical stage I (pathologic stage I, II, and IIIA) NSCLC is surgical resection of the primary tumor followed by observation (2). However, patients with clinical stage I NSCLC who have undergone a resection have an estimated 50% recurrence and death rate within 5 years, representing one of the poorest outcomes for stage I disease among all tumor types (3–5).

One of the main contributing factors to such a poor survival rate is that a significant number of patients are understaged at the time of resection (4, 6). There is an urgent need for a detection method that is more sensitive and reliable than current approaches (4, 7). In particular, many of the most dangerous forms of lung cancer arise when a population of tumor cells gains the ability to colonize the brain (8, 9). Brain metastases comprise greater than one-quarter of all recurrences in patients with resected NSCLC and are a major source of lung cancer morbidity and mortality. When symptomatic, the median survival of patients with brain lesions is <4 months (5, 6, 10). Thus, it is critical to identify and treat those patients who are at risk for brain metastases before the onset of symptoms.

Recent investigation has sought to identify factors that predict poor prognosis. Unfortunately, the use of conventional histopathological variables (performance status, subtype, size, differentiation, and mitotic rate) to construct a risk model has been limited by low prevalence and the discontinuous nature of individual variables (4, 11, 12). These limitations have underscored recent efforts to ask if molecular markers might improve risk stratification (4). A series of genetic and epigenetic changes facilitate the transition from normal bronchial epithelium to carcinoma and examples include mutation or overexpression of Ras oncogenes (K-Ras, H-Ras, and N-Ras), receptor tyrosine kinases (epidermal growth factor receptor and HER2) and cell cycle proteins (retinoblastoma and p53; Ref. 4). However, none of these markers has been linked with the recurrence of brain metastases.

Our laboratories have sought to identify the causes of metastatic cell behavior, with emphasis upon the identification of markers that predict metastatic recurrence in the clinical setting. Our most recent studies have focused upon the EphA2 receptor tyrosine kinase, which is overexpressed and functionally altered in a variety of different solid tumor types (13–18). EphA2 has been linked to the regulation of cellular behaviors that promote a metastatic phenotype and appears to provide an exciting new opportunity for therapeutic targeting (13, 15). In this study, we demonstrate that EphA2 provides a new and independent marker of lung cancer recurrence and survival. Importantly, high levels of EphA2 identify those patients that are at risk of lung cancer metastasis to the brain. Thus, EphA2 provides a new and independent marker of aggressive behavior with potential clinical utility in cancer diagnosis and treatment.

Materials and Methods

Database and Staining Procedures. Formalin-fixed, paraffin-embedded blocks of pathologic specimens were used from a retrospective database consisting of patients who had undergone a complete resection for NSCLC as detailed previously (4).

Histological examination of the specimens was performed by board-certified pathologists at the Duke University Medical Center at the time of resection. Clinical grading of the patients

Received 7/15/02; revised 10/7/02; accepted 10/11/02.

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² The abbreviation used is: NSCLC, non-small cell lung cancer.

Table 1 Retrospective database of NSCLC specimens

Shown is an overview of the retrospective database that was used to evaluate EphA2 immunoreactivity in NSCLC. Note that clinical stage refers to data obtained at the time of initial diagnosis.

Average age (yr):	63.6	(±0.6)
Gender distribution		
Male	174	(65.9%)
Female	90	(34.1%)
Carcinoma type		
Adeno	127	(43.4%)
Squamous	112	(38.3%)
Large	31	(10.6%)
Unknown	11	(8.1%)
Clinical stage		
I	194	(66.4%)
II	41	(14.0%)
III	20	(6.8%)
IV	4	(1.4%)
Unknown	33	(11.3%)

was performed by Dr. Harpole, a board certified thoracic surgeon. Sections (4–6 μM) sections were obtained from each tissue block by microtome sectioning and deparaffinized as detailed previously (4). The samples were then stained with EphA2-specific polyclonal (catalogue no. SC-924; 1:100; Santa Cruz Biotechnology, Santa Cruz CA) or monoclonal antibodies (catalogue no. 05-480; 1:500; Upstate Biotechnology, Inc., Lake Placid, NY) as detailed previously (16). Powerblock Universal Blocking Reagent (catalogue no. HK085-5K; BioGenex Laboratories, San Ramon, CA) was used to block nonspecific binding. The slides were developed using diaminobenzidine as the chromogen and counterstained with hematoxylin. Known positive tumors and normal lung tissue were used as positive and negative controls, respectively.

Data Interpretation and Analysis. All slides were read independently by two experienced observers who were blinded as to the tissue source. Differences in immunohistochemical scores were rare and resolved by consensus. There were no instances of one-third discordance (2 point differences). Each sample was scored using a 0–3 scale, with 0 denoting no staining. In general, the tumor cells were found to stain uniformly across the sample, thus the scoring system did not consider the fraction of tumor cells with positive staining. All statistical analyses were performed using statistical software (Microsoft Excel). A two-tailed, homoscedastic Student's *t* test was used for comparisons among primary tumor samples. A two-tailed, paired analysis was used to compare EphA2 immunoreactivity in matched pairs of primary tumor and brain metastases. All analyses defined $P < 0.05$ as significant.

Results

EphA2 Immunoreactivity in Lung Cancer. The goal of this study was to ask if EphA2 could serve as a tissue tumor marker in patients with NSCLC to predict cancer survival or early recurrence. Formalin-fixed, paraffin-embedded specimens were obtained from a retrospective cohort of 270 NSCLC patients to evaluate EphA2 levels using immunohistochemical analyses (Table 1). The samples were then analyzed in a blinded manner by at least two independent readers, with the levels of

Table 2 Overview of EphA2 staining of NSCLC database

EphA2 staining intensity was evaluated using a 0–3 scale as detailed in the “Materials and Methods.” Note that EphA2 staining intensity did not relate to histological type or differentiation. NS, not significant.

Staining intensity		Score	SE	Significance
0	Negative	12	(4.1%)	
1	Low	70	(23.9%)	
2	Moderate	127	(43.4%)	
3	High	82	(28.0%)	
Histologic type				
Overall		2.0	0.1	
Adeno		1.9	0.1	NS
Squamous		2.0	0.1	NS
Large		1.9	0.1	NS
Histologic differentiation				
Overall		2.0	0.1	
Well		2.0	0.2	NS
Moderate		2.0	0.1	NS
Poorly		1.9	0.1	NS
Undifferentiated		2.0	0.2	NS

EphA2 scored using a 0–3 scale (negative, low, moderate, and high). Comparable results were obtained from the different investigators (data not shown).

Elevated levels of EphA2 immunoreactivity applied to many lung cancer specimens, with 71.4% of the specimens receiving a score of moderate or high (staining intensities of 2+ or 3+, respectively; Table 2). In general, the staining pattern of the specimens was uniform, with prominent membrane and cytoplasmic staining (Fig. 1). The staining was specific for the carcinoma component of the tumor, with minimal staining of surrounding connective tissues.

EphA2 levels did not appear to relate to histological type or differentiation but did relate to clinical stage. Detailed analysis of EphA2 immunoreactivity revealed comparable results with adenocarcinomas, squamous cell carcinomas, and large cell carcinomas that did not significantly differ from one another or from the overall levels of EphA2 in NSCLC (Table 2). Similarly, EphA2 levels did not vary relative to the histopathological differentiation state of the tumor cells. However, EphA2 levels did relate to clinical stage, with the highest levels of EphA2 consistently found in the more advanced stages of the disease (Fig. 2). In particular, stage I NSCLC displayed significantly lower levels of EphA2 than stage II ($P = 0.003$), stage III ($P = 0.007$), or stage IV ($P = 0.003$) diseases. Notably, all stage IV tumors had high levels of EphA2 (score of 3+) and the fraction of tumors with high EphA2 decreased with decreasing stage. Altogether, consistent findings suggest that high levels of EphA2 are associated with most advanced forms of the disease.

EphA2 Immunoreactivity Predicts Survival and Recurrence. On the basis of the apparent relationship between EphA2 and clinical stage, we then asked if EphA2 levels could predict clinical outcome. Patients with high levels of EphA2 upon initial clinical presentation had a significantly worse prognosis as compared with the overall data set ($P = 0.02$) and with patients, who did not express EphA2 ($P = 0.02$; Fig. 2 and Table 3). It is important to note that noncancer deaths were excluded from this

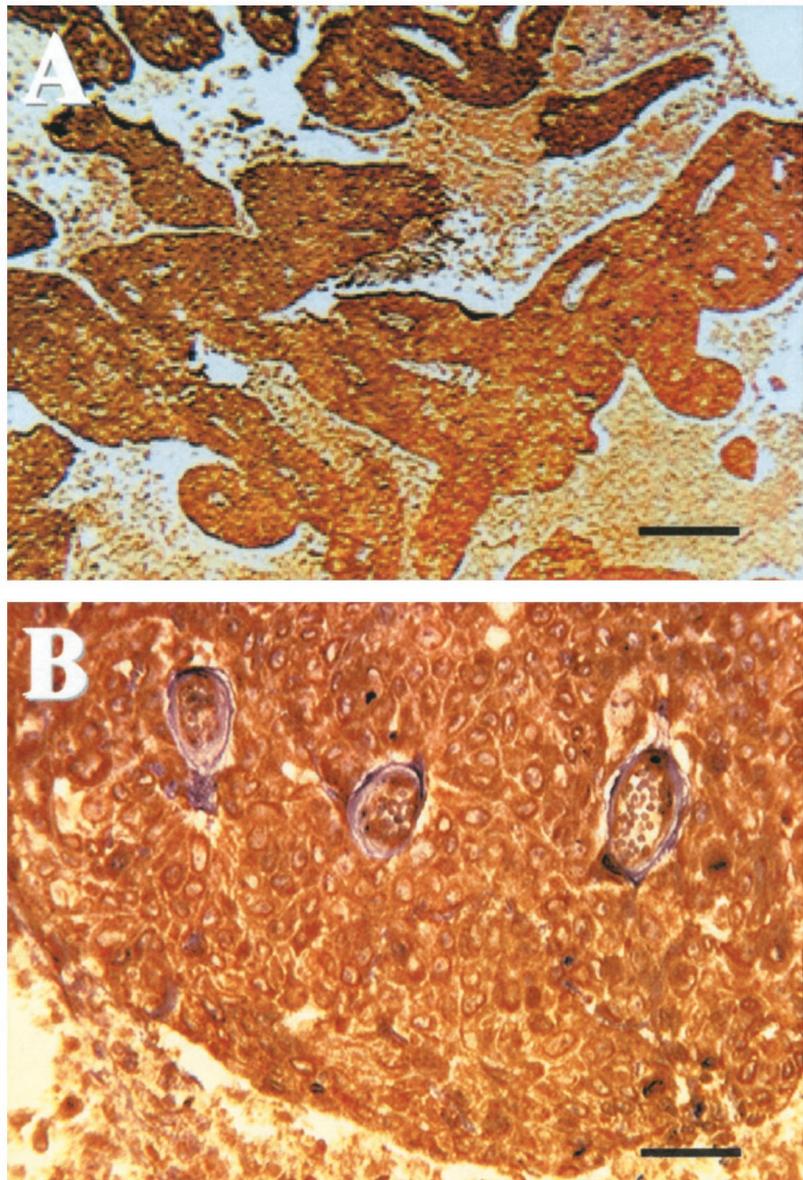


Fig. 1 Overexpression of EphA2 in NSCLC specimens. The expression of EphA2 was evaluated using immunohistochemical staining of formalin-fixed, paraffin-embedded tissue specimens. Shown are representative examples of high (score = 3) staining of EphA2 using low- (A) and high- (B) powered objectives. Bar = 160 and 40 μm in A and B, respectively.

analysis. As an additional means of relating EphA2 levels to survival, the levels of EphA2 were compared in patients who had achieved more or less than 5 years of survival Fig. 3B. Significantly higher levels of EphA2 immunoreactivity were observed in those patients who subsequently survived <5 years (average staining intensity of 2.1) as compared with ≥ 5 -year survival (average staining intensity of 1.8; $P = 0.02$). However, EphA2 immunoreactivity was not significant in predicting of one year survival ($P = 0.099$), although this likely resulted from the relatively small sample size with 1-year follow-up ($N =$).

EphA2 immunoreactivity also predicted disease-free survival and disease recurrence (Table 3). Initially, the intensity of EphA2 immunoreactivity was related to disease-free survival using the cutoffs as detailed above. These analyses identified a significant difference between the levels of EphA2 in patients

who experience more (average score of 1.9) or less (average score of 2.1) than 5 years of disease-free survival ($P = 0.04$), whereas EphA2 levels did not differ in patient with more or less than 1 year of disease-free survival ($P = 0.60$). The analyses were then broadened to consider current status (as of the most recent updates), which revealed differences between the levels of EphA2 on those patients who have remained disease free (average score of 2.0) as compared with those who eventually suffered a recurrence or who succumbed to lung cancer (average score of 2.2). These differences approached, but did not quite obtain, statistical significance ($P = 0.07$), which will become important below. Similarly, the levels of EphA2 immunoreactivity were almost significantly different in patients with or without disease recurrence (average scores of 1.9 and 2.2, respectively; $P = 0.05$).

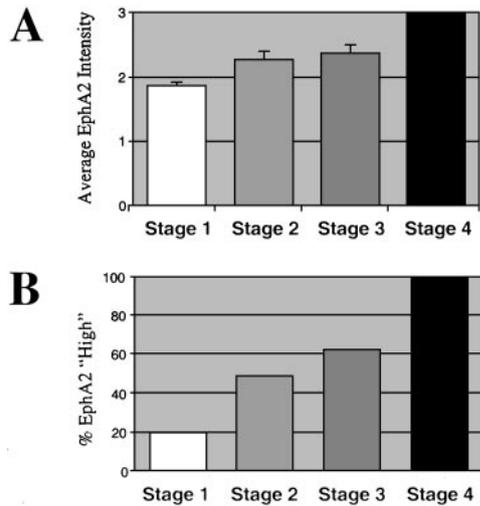


Fig. 2 EphA2 levels increased in advanced stages of the disease. **A**, the average staining intensity of EphA2 (using a 0–3 scale) was related to clinical stage. Note that stage I disease had significantly less EphA2 than stage 2 ($P = 0.003$), stage 3 ($P = 0.007$), or stage 4 ($P = 0.003$) disease. **B**, the fraction of samples that were scored as high was evaluated in each clinical stage. Note the prevalence of EphA2 expression in high-grade disease (stage 4).

Table 3 EphA2 predicts disease recurrence and site of metastasis

EphA2 staining was evaluated in NSCLC samples that varied with regards to disease-free survival, recurrence, and site of metastasis. Note that differential EphA2 immunoreactivity distinguished patients who subsequently developed brain metastases from those who developed contralateral (CL) lung cancer.

	EphA2 intensity (SE)	Significance
Disease-free survival		
<5 years	2.1 (0.06)	$P = 0.04$
>5 years	1.9 (0.09)	
<1 year	2.0 (0.11)	$P = 0.60$
>1 year	2.0 (0.06)	
Current status		
Disease free	2.0 (0.08)	$P = 0.07$
Recurrence or death	2.2 (0.12)	
(Remove CL)	2.3 (0.13)	$P = 0.02$
Overall recurrence		
None	1.9 (0.07)	$P = 0.05$
All recurrence	2.2 (0.12)	
(Remove CL)	2.3 (0.13)	$P = 0.01$
Site of recurrence		
None	2.0 (0.07)	$P = 0.01$
Brain	2.3 (0.14)	
CL lung	1.6 (0.26)	$P = 0.14$

EphA2 Levels in Brain and Contralateral Lung Metastases. The site of disease recurrence was available for a subset of the clinical specimens ($N = 60$). An analysis of EphA2 suggested an interesting implication for interpreting the results of EphA2 expression in overall disease recurrence. The average intensity of EphA2 staining was highest in those patients who subsequently developed brain metastases (Table 3). In contrast, EphA2 levels were lowest in patients whose metastases were restricted to the contralateral lung. The differences between

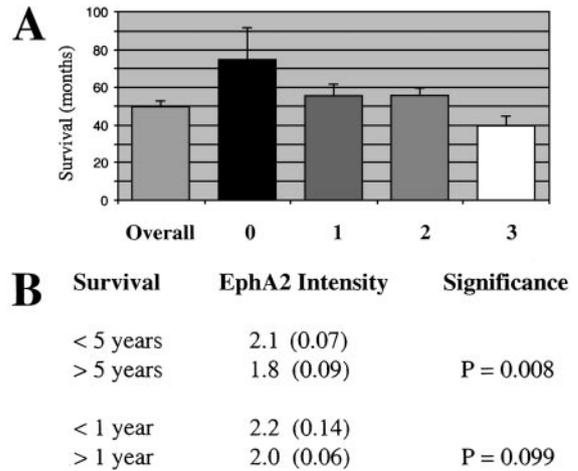


Fig. 3 EphA2 immunoreactivity at time of resection predicts subsequent survival. **A**, the average survival after initial diagnosis (in months) was calculated relative to EphA2 immunoreactivity. The subsequent survival of patients who presented with high levels of EphA2 in the primary tumor was significantly lower than overall survival of the patient population ($P = 0.02$) or patients with no EphA2 ($P = 0.02$). **B**, as a second measure to relate EphA2 with survival, the average intensity of EphA2 staining was calculated in patients who survived >1 or 5 years. Differential EphA2 immunoreactivity predicted 5-year survival rates ($P = 0.008$) but did not predict 1-year survival ($P = 0.10$). Note that the analyses of survival information excluded information from patients who expired because of causes unrelated to lung cancer.

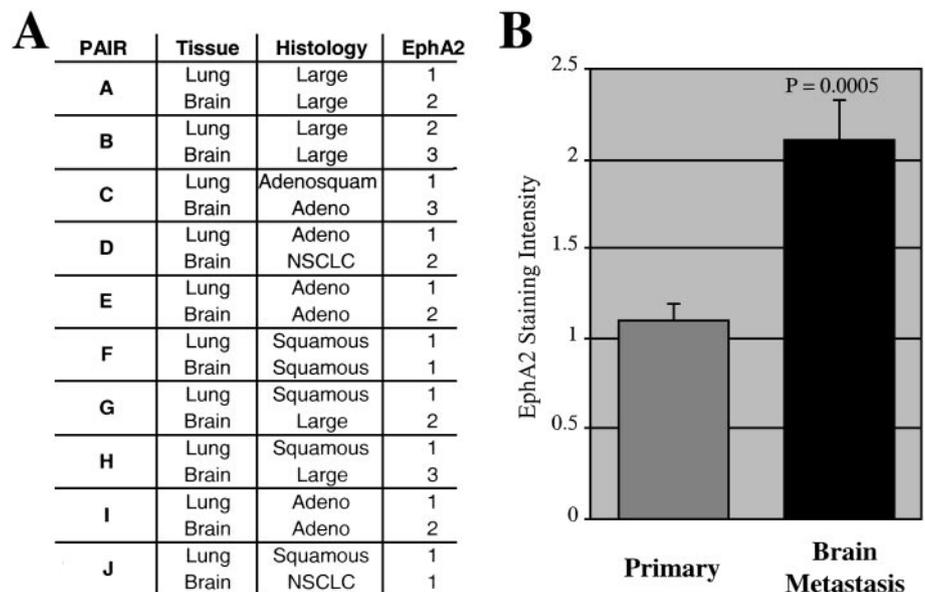
EphA2 levels in those patients who progressed to brain metastases differed from patients without recurrence ($P = 0.01$) and those who progressed to have metastases restricted to the contralateral lung ($P = 0.02$). Perhaps more importantly, removal of patients, whose disease was restricted to contralateral lung ($N = 7$), was sufficient to provide statistical significance about disease recurrence and present status ($P = 0.01$ and $P = 0.02$; respectively). Thus, high levels of EphA2 immunoreactivity appear to identify patients who develop metastases outside of the lung and also predict the recurrence of those metastases.

On the basis of the link between EphA2 and brain metastasis, the immunoreactivity of EphA2 in primary tumors and brain metastases was directly compared (Fig. 4). A matched set of clinical materials, obtained from the primary tumor or a brain metastasis of the same donor, was stained with EphA2 monoclonal antibodies (clone D7). The brain metastases demonstrated significantly higher levels of EphA2 than the matched primary tumor ($P = 0.0005$). These results provide additional evidence linking high levels of EphA2 with brain metastasis.

Discussion

The major findings of this study are that high levels of EphA2 apply to many NSCLCs and that EphA2 can convey important information about clinical outcomes. High levels of EphA2 can provide predictive information upon initial clinical outcome about the likelihood of subsequent relapse and survival. Interestingly, the highest levels of EphA2 are found in those patients who subsequently developed brain metastases, whereas low levels of EphA2 staining identified patients who did not relapse or who developed contralateral disease. Finally,

Fig. 4 EphA2 overexpression in brain metastases. **A**, EphA2 immunoreactivity was evaluated in matched sets of primary lung tumor and brain metastases, both isolated from the same patient. **B**, the pooled average intensity of EphA2 immunoreactivity was lower in primary tumors *versus* lung metastases ($P = 0.0005$). Note that these results were obtained using monoclonal EphA2 antibodies (clone D7), which accounts for the relatively low immunoreactivity of the primary tumors relative to previous results.



brain metastases themselves reveal higher levels of EphA2 than matched primary tumors.

One novel aspect of this study is a demonstration that EphA2 may convey important diagnostic and predictive information to assist the clinical management of lung cancer. High levels of EphA2 also apply to other tumor types and future studies could address whether EphA2 might similarly convey predictive information about clinical outcome.

As a transmembrane receptor, EphA2 could theoretically serve as a substrate for extracellular proteases and thus be shed into local fluids (*e.g.*, sputum, serum). Alternatively, circulating EphA2 DNA could provide a means of identifying patients with metastatic disease (7). Thus, accurate and sensitive detection of circulating EphA2 protein or DNA could provide a much-needed diagnostic marker for metastatic disease and also serve as a surrogate marker to assess and fine-tune clinical management of metastatic disease.

The causes of EphA2 overexpression in lung cancer remain largely unclear. What is known suggests that EphA2 expression is tightly regulated during development and in adults and that malignant transformation frequently circumvents these regulatory mechanisms (13, 16, 17, 19–24). For example, EphA2 expression is regulated by multiple members of the p53 family of transcription factors, which are generally understood to play critical roles in cancer (25). Additional studies have linked the up-regulation of EphA2 with intracellular signaling by oncogenic Ras (20, 22, 26). In light of evidence that the Ras signaling pathway is frequently up-regulated in aggressive lung cancers, this particular mechanism may account for much of the observed EphA2 overexpression in metastatic disease.

One of the more intriguing outcomes of this study is a demonstration of differential EphA2 expression in brain *versus* contralateral lung metastases. EphA2 overexpression does not seem to promote growth under ideal circumstance but instead favors the growth and survival of tumor cells in the context of a foreign microenvironment (13, 15). This hypothesis was based

on *in vitro* analyses of EphA2-overexpressing cells, but one interpretation of the present findings is that EphA2 plays a similar role *in vivo*. Specifically, the relatively low levels of EphA2 in patients who will develop contralateral disease might be consistent with the fact that the contralateral lung represents an accommodating local microenvironment that could facilitate tumor growth and survival without the need for EphA2. In contrast, the foreign microenvironment of the central nervous system might select for those metastatic cells that overexpress EphA2 and thus are capable of thriving under more adverse conditions. It is also tempting to speculate that high levels of EphA2 facilitate homing to the brain. This idea is consistent with the fact that Eph receptors and their ligands are primarily expressed in the CNS (27–29). Thus, the relative overexpression of EphA2 within brain metastases could reflect the consequences of the local brain microenvironment.

Antibody targeting of EphA2 can selectively target tumor cells while minimizing toxicities to normal cells (15). This finding offers an opportunity to target the large number of lung cancers that overexpress EphA2. On the basis of the fact that the highest levels of EphA2 are found in the most aggressive tumors (13, 14, 16, 20), selective targeting of EphA2 could provide an opportunity for therapeutic intervention against metastatic disease, which is imperative given the poor prognosis of patients with inoperable NSCLC brain metastases.

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Clin Cancer Res 2003;9:613-618.

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