

# Clinical Impact of the Epithelial-Mesenchymal Transition in Lung Cancer as a Biomarker Assisting in Therapeutic Decisions

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## Keywords

Non-small-cell lung cancer · Epithelial-mesenchymal transition · Therapy · Resistance

## Abstract

Lung cancer is one of the most common solid cancers and represents the leading cause of cancer death worldwide. Over the last decade, research on the epithelial-mesenchymal transition (EMT) in lung cancer has gained increasing attention. Here, we review clinical and histological features of non-small-cell lung cancer associated with EMT. We then aimed to establish potential clinical implications of EMT in current therapeutic options, including surgery, radiation, targeted therapy against oncogenic drivers, and immunotherapy.

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## Introduction

Lung cancer is responsible for the highest number of cancer-related deaths worldwide. About 85% of lung cancers are classified as non-small-cell lung cancers (NSCLC),

which are histologically subdivided into adenocarcinoma (AC) (about half of NSCLC cases) and squamous cell carcinoma (SCC) (about 30% of NSCLC cases). Regarding staging, more than half of the cases are diagnosed at a metastatic or advanced stage without curative options. Over the past years, innovative therapies such as molecularly targeted drugs and immunotherapies, have emerged and have led to overall improvements in cancer treatment. However, global 5-year survival rate for NSCLC patients remains under 20% [Hirsch et al., 2017; Bray et al., 2018]. Even in localized stages with a surgically resectable tumor, 5-year survival rates drastically drop from 60% for stage IIA disease to 36% for stage IIIA disease according to the 8th edition staging project of the International Association for the Study of Lung Cancer (IASLC) [Goldstraw et al., 2016]. Promising and innovative strategies are ongoing, especially in neoadjuvant [Uprety et al., 2020] and adjuvant [Broderick, 2020; NCT02595944; NCT02486718; NCT02504372] contexts, which could improve the dramatic landscape of NSCLCs [Otaibi et al., 2019; Kris et al., 2020]. Nevertheless, this fateful prognosis also highlights the need to further refine tumor characteristics in order to improve clinical patient management.

Research on the epithelial-mesenchymal transition (EMT) in lung cancer has gained major interest in the last decade. EMT is a term widely used now to describe the loss of epithelial features and the acquisition of mesenchymal traits by epithelial cells in various physiological and pathological conditions. In cancer, EMT is considered as a dynamic and reversible process, thereby generating various phenotypes. Some hybrids may have enhanced plasticity allowing them to adapt to various tumor microenvironments (TMEs) encountered during cancer progression and metastatic dissemination [Dongre and Weinberg, 2019; Bhatia et al., 2020; Yang et al., 2020]. As such, EMT has been shown to endow tumor cells with many properties that may provide them a selective advantage to master different steps of cancer progression, including enhanced invasive potential, enhanced survival, stimulation of angiogenesis, immune escape, resistance to apoptotic signals, and niching properties [Francart et al., 2018; Pastushenko and Blanpain, 2019]. EMT is molecularly complex, diversified, and context dependent. This complexity certainly contributes to slow down the implementation of EMT consideration in clinical routine. EMT programs may indeed be triggered by several factors, such as transforming growth factor- $\beta$  (TGF- $\beta$ ) [Miyazono et al., 2018], fibroblast growth factor (FGF) [Kato and Nakagama, 2014], epidermal growth factor (EGF) [Shaurova et al., 2020], Notch, or Wnt signaling pathways [Yuan et al., 2014; Patel et al., 2019]. Activated signaling pathways converge onto a set of transcription factors, such as Snail, ZEB, and Twist family [Zeisberg and Neilson, 2009]. A dynamic balance finally represses expression of epithelial-related genes such as E-cadherin and induces expression of genes coding for mesenchymal markers such as vimentin. Importantly, EMT rather supports early steps of the metastatic dissemination, i.e., tumor invasion, survival in the blood stream, and early niching. After an eventual period of dormancy, a reversal towards more epithelial phenotypes, so-called mesenchymal-epithelial transition (MET), is considered to occur at secondary sites to support metastatic outgrowth. Although EMT features have been described for many years in numerous histological types of cancer, discussion remains regarding EMT characterization in tumors. Pan-cancer studies are based on most consensual and proposed canonical markers, such as E-cadherin (*CDH1*), vimentin (*VIM*), N-cadherin (*CDH2*), and fibronectin (*FNI*). Using NSCLC cell lines and tumor samples, some studies established EMT signatures. From these NSCLC reports, some markers such as *DSP*, *TJP1*, *CLDN4*, *ERBB3*, *GALNT3*, and *CDS1* appear commonly associated with

*CDH1* epithelial-related genes while *MMP-2*, *AXL*, *ZEB1/2*, *NRP-1*, and *TWIST* clustered with *VIM* and *FNI* mesenchymal-related genes [Wushou et al., 2014; Zheng and Kang, 2014; Antony and Huang, 2017; Goossens et al., 2017; Wong et al., 2018; Karacosta et al., 2019; Shao et al., 2019].

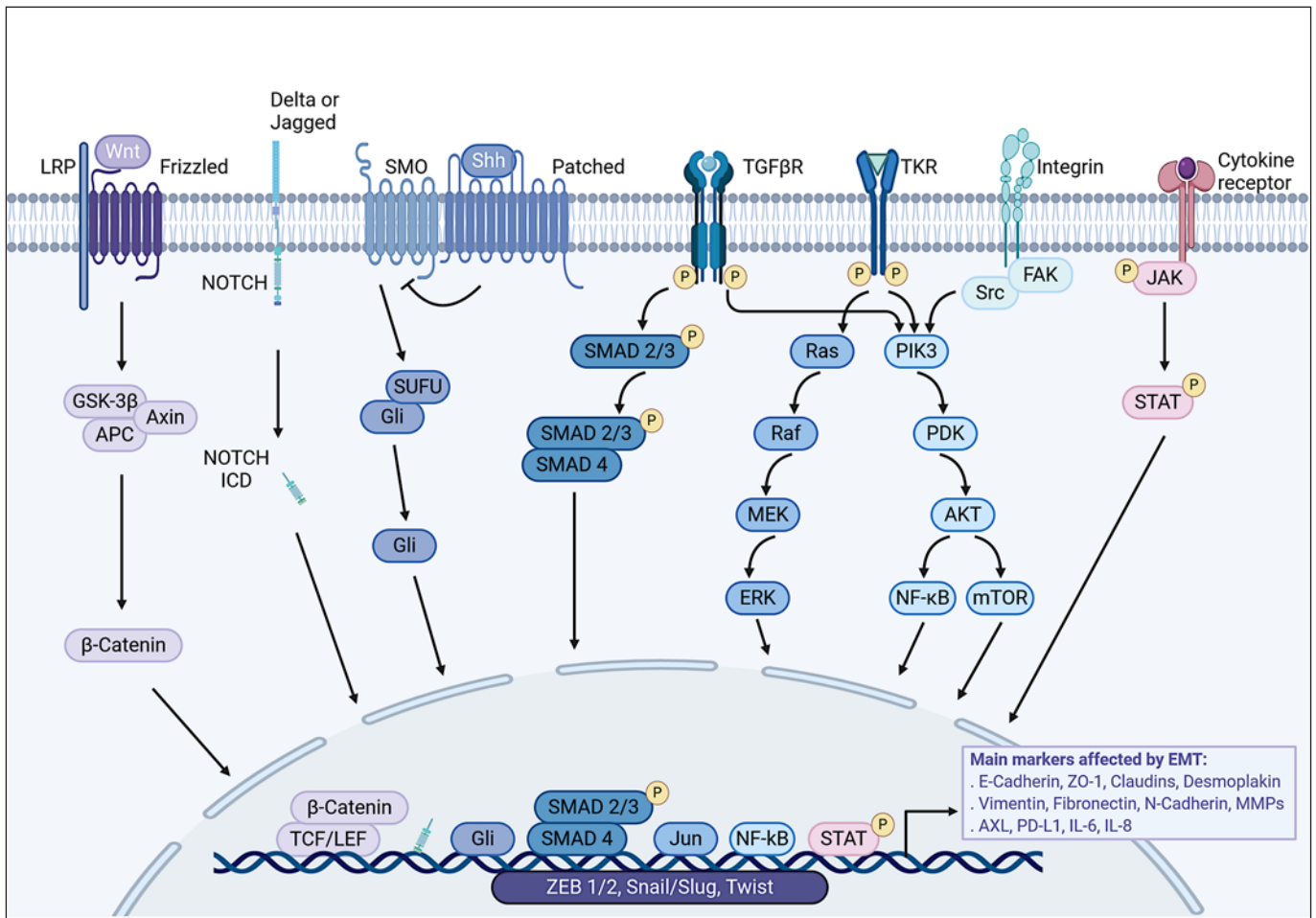
We discuss here the potential utility of examining and considering EMT in clinical practice. Although some reports highlight a contribution of EMT in small-cell lung cancer [Ito et al., 2017] and malignant pleural mesothelioma [Schramm et al., 2010] with specific implications respective to their cell type origin, we will focus this review on NSCLC, the most frequent lung cancer in which EMT has now been extensively analyzed. We aim at pointing to clinically relevant features related to the EMT process that could help clinicians to identify disease contexts. We further propose to examine the beneficial contribution of EMT in the clinical management of early/advanced stages to metastatic conditions in order to meet current clinical challenges. Considering the poor outcome of resectable lung cancer, a crucial challenge is indeed to identify independent and powerful predictors of global patient outcomes that are currently lacking. On the hand, advanced and metastatic conditions are associated with inevitable therapy resistance to currently available strategies, including chemotherapies, radiotherapy, targeted therapies, and immunotherapies. In these clinical conditions, considering EMT as a biomarker could allow a refinement of patient management.

### NSCLC Biomarkers Related to EMT

Aiming at defining the clinical relevance of EMT as a biomarker, we will first confront the EMT status with pathological features of lung tumor cells, and then unravel relationships bridging EMT to two cornerstones of both lung carcinogenesis and clinical management that are oncogenic drivers and immune profiles.

#### *EMT and Histopathological Features*

The literature emphasizes that EMT features are quite commonly observed in lung cancer both in AC and in SCC [Kidd et al., 2014; Mittal, 2018]. For example, in a study by Dauphin et al. [2013], up to 50% of tumor cells had a mesenchymal phenotype. Mesenchymal traits were shown to be even more frequent in other lung histological types, such as large-cell neuroendocrine carcinomas [Galván et al., 2014], sarcomatoid carcinomas [Thomas et al., 2012], or pleomorphic carcinomas, which are typi-



**Fig. 1.** Main EMT markers and activation pathways. Major actors of main signaling pathways involved in EMT are represented. APC, adenomatous polyposis coli; ERK, extracellular signal-regulated kinase; FAK, focal adhesion kinase; GSK-3 $\beta$ , glycogen synthase kinase-3 $\beta$ ; ICD, intracellular domain; JAK, Janus kinase; LRP, lipoprotein receptor-related protein; MMPs, matrix metalloproteinases; mTOR, mechanistic target of rapamycin kinase; NF- $\kappa$ B, nuclear factor  $\kappa$ B; P, phosphorylation; PDK, pyruvate de-

hydrogenase kinase; PD-L1, programmed death ligand 1; PI3K, phosphatidylinositol kinase; Shh, sonic hedgehog; SMO, smoothened; STAT, signal transducers and activators of transcription; SUFU, suppressor of fused homolog; TCF/LEF, lymphoid enhancer factor/T cell factor; TGF $\beta$ R, transforming growth factor  $\beta$  receptor; TKR, tyrosine kinase receptor; ZO-1, zonula occludens-1. This figure was created with BioRender.com.

cally reflect the mesenchymal switch [Miyahara et al., 2015; Kondo et al., 2018]. Mesenchymal features have also been associated with a low degree of differentiation in NSCLC [Dauphin et al., 2013; Matsubara et al., 2014; Bian et al., 2019; Z. Wang et al., 2019]. Otherwise, the spatial distribution of EMT features within a tumor is very heterogenous. EMT attributes have thus frequently been reported in so-called invasive fronts, at the interface with extracellular matrix, correlating with invasiveness and metastatic potential [Maeng et al., 2014]. EMT has also been associated with hypoxic zones and inflammation-rich areas [Dominguez et al., 2017], emphasizing a major

contribution of specific TMEs in EMT induction/regulation [Yang and Wu, 2008; Hung et al., 2009; Foster et al., 2014]. Accordingly, experimental data strongly support that EMT may be induced/regulated by extracellular matrix components, inflammatory mediators, and other soluble factors secreted by stromal cells, and hypoxia [Lou et al., 2016; Mittal et al., 2016]. Inversely, EMT-positive tumor cells have also been reported to secrete higher levels of soluble factors crucially impacting TME (e.g., VEGF stimulating angiogenesis, chemokines impacting immune cell recruitment). Finally, effects on the immune system are classically examined clinicopathological pa-

rameters in lung cancer. Thus, EMT also modulates immune cell infiltration [Dominguez et al., 2017; De Matteis et al., 2019] through well-identified molecular regulatory networks [Markopoulos et al., 2019]. For instance, Chae et al. [2018] reported reduced CD4 T-cell and CD4/CD8 T-cell infiltration in lung AC and SCC, respectively, with tumor cells displaying mesenchymal attributes (EMT positive). Inversely, increases in activated B cells and regulatory T cells were reported, although some differential infiltration patterns need to be further defined between AC and SCC. Additionally, EMT-positive tumors were also found to overexpress multiple immunosuppressive cytokines, such as IL-10, TGF- $\beta$ , IL-6, or IL-11 [Q. Zhang et al., 2017; Zhao et al., 2018; Jiang et al., 2019; Zheng et al., 2019]. A narrow crosstalk and regulatory loops between stromal cells and EMT-derived cells are thus established, contributing to the formation of particular areas favoring tumor invasion and dissemination. Main EMT-associated markers and activation pathways are illustrated and summarized in Figure 1.

In addition to EMT determination in lung primary tumors, examining EMT in circulating tumor cells (CTCs) has also gained major interest. Presently, CTCs indeed appear as promising biomarkers in lung cancer [Y. Li et al., 2018; Milano et al., 2018; Maly et al., 2019]. Unlike tumor biopsies, CTCs allow a live assessment of disease progression and could thus help to predict metastasis and monitor therapeutic response. Today, numerous studies report the presence of EMT-shifted hybrid CTCs and CTC clusters in NSCLC patients [Lindsay et al., 2017; G. Li et al., 2018; Sawabata et al., 2020]. Interestingly, Manjuntha et al. [2019] observed that the intensity of EMT marker staining (vimentin and fibronectin) was higher in EMT-positive CTCs than in patient-matched NSCLC tumor tissues. Validating the importance of EMT characterization and supporting its utility for clinicians, Wu et al. [2015] classified CTCs into 3 subpopulations (epithelial, intermediate, and mesenchymal phenotypes) and reported that mesenchymal CTCs were more commonly found in patients in the metastatic stages of different types of cancers. Additionally, several reports associated a mesenchymal shift in CTCs as predictor of a poor outcome in NSCLC [Li et al., 2017, p. 4; Liu et al., 2018]. Miguel-Perez et al. [2019] thus identified mesenchymal CTCs as an independent prognostic factor for relapse-free survival, with an impact on overall survival in resected lung ACs. Moreover, similar data were obtained in a prospective and controlled cohort [Manjunath et al., 2019]. Among metastatic stages, EMT subclassification could allow to further refine those with a poor evolution

profile [Y. Wang et al., 2019]. EMT status in CTCs could also be useful as a predictor of therapeutic response [Liao et al., 2014; Togo et al., 2017; Milano et al., 2018]. Despite these numerous data validating the clinical relevance of examining EMT in CTCs, the variability of methodologies used to enrich and isolate CTCs combined with the molecular complexity of EMT certainly introduces biases in our comprehension of EMT-related CTC heterogeneity. It seems worth mentioning that many CTC isolation devices are based on the expression of specific epithelial biomarkers (such as EpCAM). Subpopulations of EMT-derived CTCs, supposedly expressing lower levels of many membrane epithelial markers, may thus fail to be detected by such methods. To address this limitation, alternative enrichment devices exploiting physical properties of CTCs are developed to isolate label-free CTCs and facilitate the study of EMT heterogeneity in the CTC population [Alix-Panabières et al., 2017; Nicolazzo et al., 2019; Genna et al., 2020].

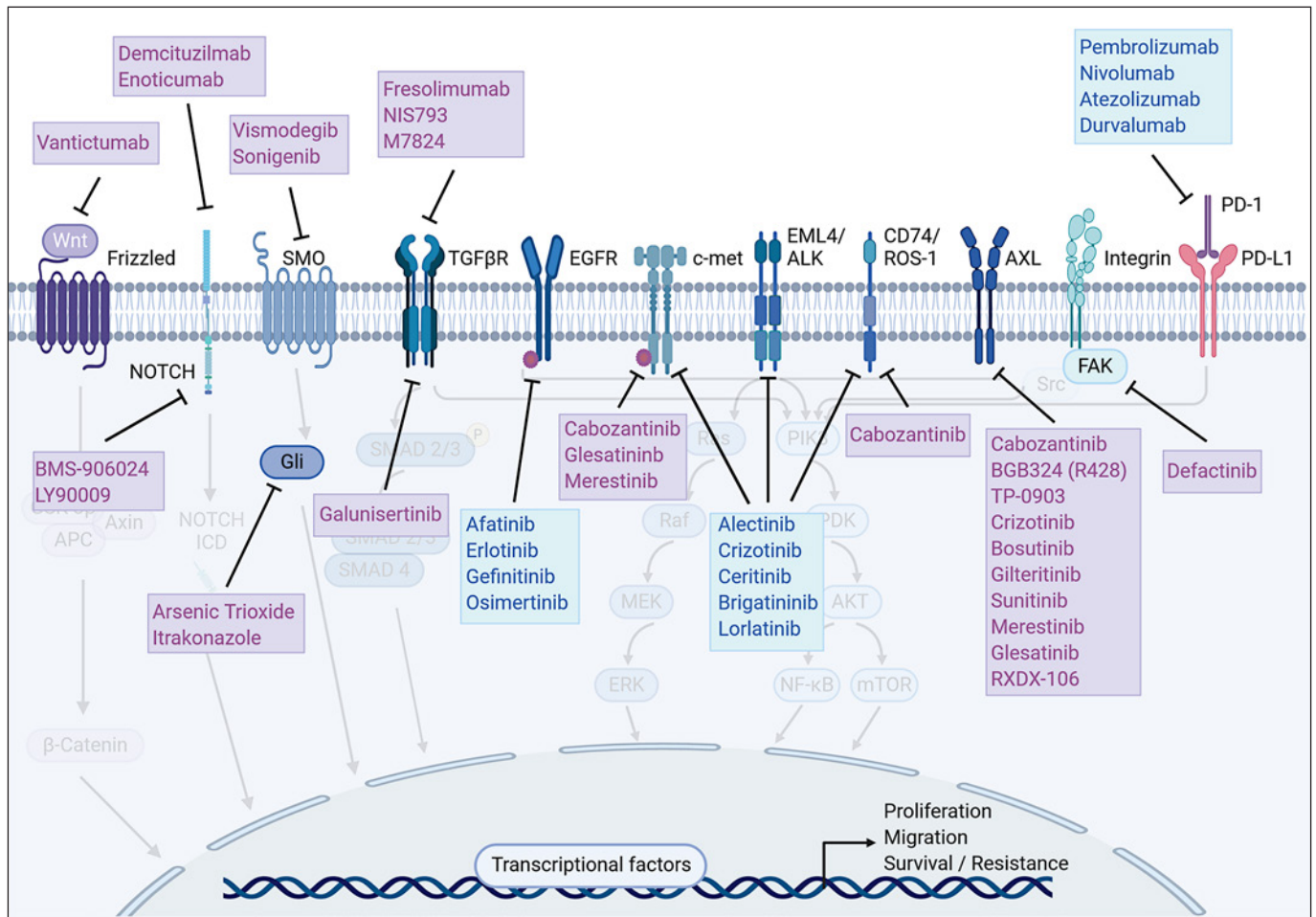
All in all, EMT is a frequent event in NSCLC, which is observable both at the primary tumor site and in CTCs. Its association with unfavorable clinicopathological features justifies the proposition to consider EMT as a potential marker to predict patient outcome. Methodological standardization and identification of the most relevant molecular markers are nevertheless necessary steps before routine clinical application.

#### *EMT and Oncogenic Drivers*

Our growing molecular knowledge of cancer somehow shook some dogmas and continuously redirects lung cancer management. Several targeted therapies constitute the current arsenal to combat lung cancer, most of which are specifically directed against recognized oncogenic drivers of lung cancer (Fig. 2). Among major genetic modifications associated with NSCLC, KRAS, EGFR, and ALK, additive mutations or alterations are probably the main ones [Arbour and Riely, 2019].

#### KRAS

To date, KRAS mutation is the most common molecular alteration encountered in NSCLC but remains with no effective therapies targeting tumors harboring the mutant KRAS variant despite many clinical trials [Aran and Omerovic, 2019; Yang et al., 2019]. Experimental data suggest that KRAS mutations contribute to mesenchymal changes, either alone, but often also combined with other EMT-inducing factors [Arner et al., 2019]. For instance, mutant KRAS and TP53 cell lines established from a lung cancer transgenic mouse model were found to display im-



**Fig. 2.** Inhibitors currently used in NSCLC management. Inhibitors EMT inhibitors in NSCLC. EML4/ALK, echinoderm microtubule-associated protein-like 4/anaplastic lymphoma kinase fusion. See legend to Figure 1 for further abbreviations. This figure was created with BioRender.com.

promisingly analyzed in clinical trials are also depicted. Drugs currently available and used in lung cancer management with potential impact on EMT are depicted in blue. Additionally, drugs in pink represent molecules in development of potential interest as

portant EMT/MET plasticity. A shift towards a mesenchymal phenotype was shown to depend on a well-described miR-200/ZEB regulatory loop and to promote metastasis [Gibbons et al., 2009]. Deciphering further *KRAS* mutant/EMT relationships, Singh et al. [2009] showed that, within *KRAS* mutant cell lines, 2 subgroups were distinguished based on their *KRAS* dependency to maintain their viability. In contrast to the untreated cell line, the *KRAS*-dependent NSCLC cell line treated with the classical EMT inducer (TGF- $\beta$ 1) acquired *KRAS* independency. Thus, mesenchymal-switched NSCLC cell lines harbor *KRAS* independency and, inversely, support a close relationship between EMT and loss of oncogene addiction. Examining *KRAS* molecular status and EMT

phenotype as tandem biomarkers could thus harbor a particular significance and also refine patient stratification and therapeutic strategies. Considering until now deceiving effectiveness for drugs targeting *KRAS* addiction, selected patients with *KRAS*-mutant NSCLC harboring the epithelial phenotype could thus benefit from *KRAS* inhibitors.

### EGFR

As the second most common molecular addiction occurring in NSCLC, activating mutations of the EGF receptor (EGFR) gene are especially involved in lung ACs without smoking history. A large majority of these activating mutations (85–90%) occurs by exon 19 deletion

(about 45%) or exon 21 L858R mutation (about 45%) [Castellanos et al., 2017]. In *EGFR*-mutated advanced lung cancer patients, many randomized phase III trials have revealed that treatment with first-, second-, and now third-generation *EGFR* tyrosine kinase inhibitors (TKIs) resulted in improved outcome compared to standard first-line chemotherapy [Soria et al., 2018]. Erlotinib even provided efficacy similar to chemotherapy as second-line therapy in *EGFR* wild-type tumors with no additional adverse events [Ciuleanu et al., 2012]. However, cancer progression is fatal after a median 12-month treatment, and almost all patients who strongly responded to *EGFR*-TKIs acquire resistance over time. Frequently, the mechanism of resistance is an acquired *EGFR* mutation [Rotow and Bivona, 2017]. In half of the cases, this second mutation is a T790M point mutation in exon 20 of the *EGFR* gene [Kobayashi et al., 2005] that can be triggered by osimertinib, a dedicated *EGFR*-TKI [Carlisle and Ramalingam, 2019]. In patients with a tumor harboring a mutation in *EGFR* and developing *EGFR*-TKI resistance, a significant part does not exhibit mechanisms of genotypic resistance. Such an *EGFR*-independent mechanism of resistance includes EMT, which occurs in about 5% of cases [Bronte et al., 2018; Lim et al., 2018]. Interestingly, tumors from patients developing resistance to TKIs exhibit mesenchymal traits while maintaining their original *EGFR*-activating mutation. Moreover, Sequist et al. [2011] did not observe EMT features in patients developing a resistance mechanism mediated by a T790M *EGFR* mutation, supporting that T790M does not drive EMT. In patients harboring a T790M mutation and treated with osimertinib, unfortunately, progression also occurs, and a C797S tertiary mutation has been identified. A tertiary resistance could be also associated with and/or supported by EMT, even in non-C797S mutation-harboring patients, although *MET* gene amplification may more frequently drive the underlined mechanism of resistance in this context [Del Re et al., 2019]. Those clinical observations linking *EGFR*-TKI resistance to the emergence of EMT phenotypes are supported by *in vitro* and *in vivo* preclinical studies [Tulchinsky et al., 2019; X. Zhu et al., 2019]. For example, TGF- $\beta$ 1, insulin-like growth factor 1 receptor (IGF1R), and Notch-1 pathways, known to be potent EMT inducers, seem to be crucial actors in resistance mechanisms [Rho et al., 2009; Suda et al., 2011; Cortot et al., 2013; Xie et al., 2013; Soucheray et al., 2015; Zhou et al., 2015]. This phenotypical switch appears to be reversible and could thus be promising in combined therapies [Witta et al., 2006]. By using dasatinib, Sesumi et al. [2017] inhibited EMT induction by TGF- $\beta$  in *EGFR*-mu-

tant NSCLC cell lines. For NSCLC already harboring erlotinib resistance with mesenchymal features, dasatinib monotherapy failed to restore both an epithelial phenotype and sensitivity to *EGFR*-TKIs. However, combining erlotinib and dasatinib prevented EMT-mediated resistance to *EGFR*-TKI and resulted in T790M mutation resistance.

## ALK

Among molecular alterations in ALK, ALK translocations with a fusion partner correspond to the second targetable oncogenic driver to date in NSCLC [Du et al., 2018]. Following the ALEX trial, alectinib became the gold standard of ALK-rearranged related TKIs with an increase in overall survival [Hida et al., 2017]. As similarly observed in *EGFR* inhibitor management, some ALK inhibitor resistance inevitably occurs and is mediated most of the time by an acquired *ALK* mutation [Katayama, 2018]. As for resistance to *EGFR*-TKI, EMT has been observed and proposed as a nononcogenic resistance pathway [Peters and Zimmermann, 2018]. Gainor et al. [2016] explored different mechanisms of ceritinib resistance in 12 re-biopsies and observed that 5 specimens displayed mesenchymal traits. Interestingly, some of them also harbored a concomitant second *ALK* mutation of resistance. Similarly, Gower et al. [2016] described acquired EMT characteristics in tumors harboring ALK-TKI resistance. However, reversible models of EMT did not allow to restore sensitivity to ALK inhibitors, suggesting that the EMT process may be associated with but is not required for ALK-TKI resistance. Deciphering further this EMT/*ALK* mutation status, Fukuda et al. [2019] performed microdissection analyses in a tumor resistant to ALK-rearranged related TKI. This tumor concomitantly harbored an acquired *ALK* mutation of resistance (L1196M) in epithelial-like tumor area while no additive mutation was found in the mesenchymal-switched tumor area. Taken together, those observations suggest that EMT can be both independent of and additive to mechanisms underlying ALK-TKI-resistant cancers. To investigate the EMT and ALK-TKI resistance relationship, Kogita et al. [2014] established an NSCLC cell line with EML4-*ALK* rearrangement and showed that the hypoxic condition was associated with ALK-TKI resistance by EMT-dependent signaling. Beyond molecular mechanisms involving hypoxia-induced actors, e.g., epithelial splicing regulatory protein 1 (ESRP1) [Voena et al., 2016], 3 other EMT-related pathways were involved in ALK-mutant cancers such as proteoglycans, HIF-1, and FoxO signaling, and extracellular matrix-receptor interaction, as re-

ported by Wei et al. [2018]. Altogether, these observations suggest that resistance to ALK-TKI can be associated with mesenchymal features even though EMT is not the sole driver of resistance.

#### Others

Among other targetable oncogenic drivers, some molecular alterations seemed related to EMT. For example, the EMT process has been described as dysregulated in BRAF-mutant cancers, such as primary cutaneous melanoma or papillary thyroid carcinoma [Mitchell et al., 2016]. Possibly due to the low prevalence of BRAF-mutant lung cancer (<1%), only few works reported on the BRAF/EMT interplay in NSCLC [Urbanska et al., 2020]. With a structural similarity to ALK but lower prevalence, ROS1 alterations are also oncogenic drivers targetable in clinical management [Lin and Shaw, 2017]. Gou et al. [2018] described a mesenchymal polarization in the NSCLC cell line with a CD74-ROS1 G2032R mutation, leading to increased aggressiveness and, interestingly, supporting resistance to ROS1-TKI (crizotinib). Regarding the EMT process, our laboratory observed a more frequent mesenchymal switch in NSCLC cell lines and tumors harboring HER2 activation, classically related to aggressiveness. Interestingly, anti-HER2 therapies allowed to restore epithelial features and reduce invasiveness [Da Silva et al., 2020]. Finally, c-MET molecular alterations are also described in a minority of NSCLC, and many pre-clinical and clinical trials have been designed in lung cancer. However, NSCLC harbor a large heterogeneity in c-MET molecular modification, such as overexpression, amplification, and point mutations, that could explain many controversial results to date [Drilon et al., 2017], although exon-14-skipping mutations seem promising [Pasquini and Giaccone, 2018].

In conclusion, both common and uncommon oncogenic drivers seem intrinsically linked to EMT processes. A large part of studies reported that mesenchymal features are associated with resistance to various drugs. Whether EMT is a consequence of or a prerequisite to drug resistance are 2 nonmutually exclusive possibilities. Elucidation of those phenomena may lead to innovative pharmacological strategies.

#### *EMT and Immune Profile*

Among EMT-induced properties contributing to enhanced metastatic potential, the ability of tumor cells to escape immune surveillance has gained major interest along with the emergence of immunotherapies. Thus, numerous studies report a positive correlation between a

mesenchymal switch and the expression of immune checkpoint proteins. As a cornerstone in immunotherapy management, PD-(L)1 has been largely explored in NSCLC context. Several in vitro and preclinical studies reported an induction of PD-L1 expression by different EMT pathways and EMT transcription factors, and PD-L1/EMT transcription factor coexpression has been reported in human lung cancer specimens [Noman et al., 2017; Asgarova et al., 2018; Li et al., 2018]. This coexpression has actually been observed in many histological types [Alsuliman et al., 2015; Ock et al., 2016; Chen et al., 2017] and largely reported in NSCLC, from metastatic to local and resected lung cancers [Kim et al., 2016; Ancel et al., 2019], and in CTCs [Manjunath et al., 2019]. Other reports studying PD-1 and PD-L1 expression further corroborated this association with EMT phenotypes [Kim et al., 2016; Mak et al., 2016]. Additionally, EMT seems to affect other immune checkpoint systems including CTLA-4 and TIM-3, but also PD-L1/2, PD-1, and B7-H3 that were also found overexpressed, suggesting a wide-ranging effect of EMT on tumoral immune escape [Lou et al., 2016]. Chae et al. [2018] observed that overexpression of druggable immune checkpoints, such as CTLA-4 and TIM-3 (but not PD-L1 in their study context), is associated with an EMT signature in NSCLC and with a lower infiltration of CD4 T cells. Thus, besides a direct effect on EMT in regulating the expression of immune checkpoint proteins in tumor cells, EMT also acts on immune cell infiltration (discussed later in the paper), which promotes an immunosuppressive TME in the vicinity of EMT-positive areas.

Overall, the EMT process appears as a promising biomarker intrinsically related to tumor aggressiveness in NSCLC. EMT could thus help refining tumor prognosis and clinicians in the choice of pharmacological strategies, especially regarding targetable oncogenic drivers and immunotherapies.

### **EMT in Clinical Lung Cancer Management**

Aiming at going beyond a descriptive level, we here below report how clinicians could benefit from examining EMT in NSCLC – both in early and metastatic stages.

#### *EMT as a Prognostic Marker of Early Lung Cancer*

As previously mentioned, 5-year survival rates in early-stage NSCLC remain poor, even after complete resection, and relapse is fatal in a large number of cases. Aiming at reducing this burden, adjuvant platinum-based

regimens are employed, though with limited effects. Many targeted therapies are currently available in lung cancer, but their use is restricted to advanced stages. For example, pre- and/or postoperative anti-PD-(L)1 cannot be employed although >50% tumor specimens harbor PD-L1-positive cells. This highlights a crucial need to further refine tumor characteristics in order to identify patients that could benefit from a personalized strategy such as immune checkpoint inhibitors. Identifying patients with worse outcomes is a key step to this end, and robust prognostic markers are thus needed. Considering the extensive literature bridging EMT to tumor aggressiveness, EMT has been explored, either solely or in combination with other markers, through different approaches that, as we discuss later in the review, still need to be optimized and validated in order to be beneficial in a clinical context. Chikaishi et al. [2011] thus described a noninformative EMT status based on vimentin,  $\gamma$ -catenin, fibronectin, and E-cadherin expression in 183 resected tumors, which was not able to predict patient outcome. These results could reflect the incorporation of a large number of stage IA tumors, which are known to display a specific, better prognosis, in the study cohort. Examining homogeneous and larger cohorts, many other studies reported a positive association between EMT-positive characteristics and poor outcome. The evaluation of the prognostic and predictive value of EMT in early stages of NSCLC (NCT03509779) is being examined in a prospective cohort (TWIST lung). In other studies, higher vimentin expression in tumor cells was proposed as a predictor of metastasis occurrence [Dauphin et al., 2013; Tsoukalas et al., 2017; Aruga et al., 2018; Y. Wang et al., 2019]. In SCCs, vimentin expression failed to establish an independent prognosis, but high S100A expression and lack of intercellular E-cadherin allowed to predict patients at a high risk of recurrence and poor prognosis [Zhang et al., 2013]. Both in ACs and SCCs, reduced membranous staining of E-cadherin and expression of vimentin were shown to be independent predictors of mortality [Che et al., 2015; Aruga et al., 2018; Shao et al., 2019].

Overcoming the clinical challenge to collect tumor biopsies, CTCs in peripheral blood were also explored as a predictor of outcome in early stages of lung cancers. Regarding CTCs, many parameters are faced, such as CTC count, CTC variation, or CTCs employed as liquid biopsy [Cabel et al., 2017; Syrigos et al., 2018]. Moreover, CTCs can be informative through their biomarker expression, and assessing EMT seems promising. Indeed, CTCs with a mesenchymal switch were associated with a poor outcome [Li et al., 2017, p. 4; Liu et al., 2018; de

Miguel-Pérez et al., 2019; Manjunath et al., 2019]. Thus, considering the EMT status in CTCs could allow to enhance the clinical relevance of CTCs in lung cancer management [Wu et al., 2015; Jin et al., 2017; Lowes and Allan, 2018].

To summarize the significance of prognostic markers, studies examining multiple EMT markers are numerous and mainly concordant, supporting the independent capacity of the EMT signature to predict patient outcome. However, it appears crucial to identify some of the most relevant markers to examine their expression in routine practice. In this regard, vimentin and E-cadherin expression seems promising.

#### *EMT in Advanced and Metastatic Lung Cancers*

In addition to promoting local and distant dissemination/recurrence, EMT was proposed by many authors to support resistance to therapies [Dudas et al., 2020]. We here explore the associations of EMT with the therapeutic options currently used in advanced stages of NSCLC, such as chemo/radiotherapies, targeted therapies, and immune checkpoint blocking antibodies.

#### *Resistance to Chemo/Radiotherapy*

Extensive literature today emphasizes a role of EMT in resistance to chemotherapies currently used clinically, such as cisplatin, paclitaxel, gemcitabine, and vinorelbine [Fischer et al., 2015; Toge et al., 2015; Han et al., 2016; Suda et al., 2017; van Staalduinen et al., 2018]. Particularly mesenchymal attributes have been associated with cisplatin resistance, the major first-line chemotherapy in NSCLC. This is supported by numerous in vitro and in vivo data [Chen et al., 2016; Guo et al., 2018; He et al., 2018; Jiang et al., 2019]. Similar findings also support a role of EMT in resistance to docetaxel, a cytotoxic gold standard drug in lung cancer typically used as second-line therapy [Chen et al., 2014; Shen et al., 2014]. Importantly, the majority of these reports emphasized reversible and flexible EMT-mediated resistance processes, offering targeting perspectives. Aiming at circumventing chemotherapy resistance, many interesting approaches are thus being developed to adapt combination treatment protocols and/or to block EMT and sensitize tumor cells to chemotherapy. For instance, examining different protocols of pemetrexed-cisplatin combination treatment on lung cancer cell lines, Tièche et al. [2016] identified a resistant cell subpopulation with EMT and cancer stem cell characteristics emerging in all tested treatment settings. Interestingly, the authors observed that a pretreatment with pemetrexed before the addition of cisplatin reduced the



emergence of this EMT/cancer stem cell phenotype and significantly enhanced the inhibitory effect of cisplatin on lung cancer cell growth. Another *in vitro* study reported an EMT-mediated resistance to antifolate pemetrexed chemotherapy and further showed that blocking EMT signaling with the flavonoid kaempferol restored pemetrexed sensitivity [Liang et al., 2015]. Using *in vitro* drug-resistant NSCLC cell models, Kurokawa et al. [2013] observed that acquired cisplatin resistance reduces the sensitivity of cancer cells to a subsequent treatment with gefitinib, an EGFR-TKI. Cisplatin-induced resistance to gefitinib was associated with acquisition of both EMT and induction of AXL, a now well-described EMT-associated tyrosine kinase receptor that may bypass EGFR signaling for survival and proliferation and that has become an attractive therapeutic target.

Regarding radioresistance, some studies have examined the relationships between EMT and ionizing radiation. Radiation was thus shown to induce EMT and enhance motility and invasiveness in various lung cancer cell lines [Jung et al., 2007; Gomez-Casal et al., 2013; Yao et al., 2016; Lu et al., 2018]. As observed for chemoresistance, radioresistance mediated by EMT seemed to be a reversible and targetable process. For instance, Notch-1-regulating flavonoid compounds [Rhamnetin and Cirsiliol] were found to inhibit EMT and induce radiosensitization in different NSCLC cell lines [Kang et al., 2013]. PD-L1 expression was also reported to be increased along with EMT after ionizing radiation. Down-regulating PD-L1 in radiation-resistant cells was shown to alleviate radiation resistance and to decrease EMT attributes, and radiotherapy combined with anti-PD-L1 antibody synergistically enhanced antitumor immunity in a xenograft mouse model [Gong et al., 2017].

Although limited to preclinical *in vitro* and *in vivo* studies, those observations highlight the importance of monitoring EMT to refine sequential therapy, drug combinations, and treatment regimens, and also to identify EMT pathways as potential targets to enhance or restore chemo/radiosensitivity.

#### EGFR-TKI Resistance

As mentioned earlier, EMT is involved in primary and acquired resistance to anti-EGFR drugs. Additionally, clinical studies and trials confirmed the potential significance of EMT in anti-EGFR therapies.

Only few clinical reports evaluated EMT in patients with tumors harboring activating EGFR mutations. Those observations associated mesenchymal features with EGFR-TKI resistance [Miyoshi et al., 2015; N. Zhang et

al., 2017; Poh et al., 2018]. As there are no validated markers of response to EGFR inhibitors in EGFR wild-type patients, numerous clinical trials assessed EMT as a predictor of response in this molecular context. Thus, Villalobos et al. [2019] examined E-cadherin and vimentin expression in a cohort of 104 advanced and metastatic NSCLC patients who were not selected regarding their EGFR status and treated with erlotinib/bevacizumab or a chemotherapy regimen. It appears that tumors with mesenchymal attributes exhibited increased progression-free survival in the chemotherapy group in comparison to the EGFR-TKI group suggesting better efficacy of standard chemotherapy in comparison to the erlotinib/bevacizumab combination for mesenchymal-like tumors [Villalobos et al., 2019]. Additionally, based on NSCLC cell lines and validated in clinical conditions in the BAT-TLE-1 cohort treated with erlotinib (Biomarker-Integrated Approaches of Targeted Therapy for Lung Cancer Elimination), Byers et al. [2013] described an EMT signature able to predict EGFR-TKI resistance. In this (BAT-TLE-1 NSCLC) cohort, the epithelial EMT signature predicted better disease control in patients receiving erlotinib in comparison to mesenchymal-switched NSCLC. EMT signature was not associated with a different response to other therapies, including platinum drugs, pemetrexed, docetaxel, and paclitaxel. Consequently, the ability to identify tumors that have not undergone EMT may help to select patients who would most likely benefit from EGFR inhibition, e.g., as second-line therapy of patients harboring a wild-type EGFR cancer. Additionally, *in vitro* studies support that targeting EMT may reverse or prevent acquisition of therapeutic resistance to EGFR inhibitors. This is for instance illustrated in an *in vitro* study reporting that the reversion of an epithelial phenotype through forced E-cadherin expression in NSCLC cell lines restored sensitivity to the EGFR inhibitor gefitinib [Witta et al., 2006].

In the same line of thought, examining EMT biomarkers resistant to anti-EGFR therapy may also point to EMT-induced alternative pathways that could overcome EGFR signaling for cell survival and growth. This is very well illustrated by numerous studies showing that, as we mentioned earlier, AXL is frequently overexpressed in EGFR inhibitor resistance [Zhang et al., 2012; Singh and Silakari, 2017; Karachaliou et al., 2018; Kim et al., 2019; F. Wang et al., 2019]. AXL is indeed considered a promising target to overcome EGFR resistance. AXL inhibitors have been generated, with some of them assessed in clinical trials such as cabozantinib, a small-size TKI targeting AXL, MET, RET, KIT, and VEGFR2 [Neal et al., 2016; Wakelee

et al., 2017; Nokihara et al., 2019]. In conclusion, it appears that, in addition to being a biological marker of tumor aggressiveness, EMT signature could be a marker of nonresponse to EGFR-TKIs in lung cancers.

### Immune Evasion

Cancer immunotherapy, including competing antibodies, checkpoint inhibitors, vaccines, and adoptive cell transfer, is based on restoring the immune response towards the tumor. Examining the interplay between EMT and the immune system has been proposed as a promising strategy to improve immunotherapy efficiency [Soundararajan et al., 2019; Horn et al., 2020]. To date, current practice solely relies on blocking antibodies that have already proven to be cornerstone options for patients with lung cancer [Doroshov et al., 2019]. Despite few contradictory results [Cooper et al., 2015; Okita et al., 2017], PD-L1 expression does not seem sufficient to accurately predict response to immune-related drugs [Duma et al., 2019; Xia et al., 2019], and examining potential companion biomarkers both in tumors and CTCs could enhance predictive significance [Kloten et al., 2019]. PD-L1 also remains a poor prognostic indicator of overall survival [Woodard et al., 2016; Takada et al., 2018].

In the PACIFIC study, PD-L1 inhibition by durvalumab showed an improvement in progression-free survival in a narrowly selected cohort of nonmetastatic advanced-stage patients who received chemoradiotherapy pretreatment. Even in doing so, the response rate only reached 28.4% [Antonia et al., 2018]. This objective response rate (ORR) seems lower and deceiving in comparison to ORRs observed in metastatic stages, showing a real need to refine predictive markers of response. With this in mind, EMT was proposed as a tandem marker with PD-L1 expression to predict resistance to immunotherapy [Jia et al., 2019]. Thus, considering both vimentin and PD-L1 expression in primary tumors [Ancel et al., 2019] or in CTCs [Manjunath et al., 2019] allows to redefine patients with dismal outcome. This subgroup coexpressing high levels of both vimentin and PD-L1 could be associated to worse ORR to immunotherapy.

Furthermore, Funaki et al. [2017] reported enhanced PD-L1 expression after a platinum-based regimen via TGF- $\beta$ -induced EMT in lung cell lines. In addition to the aggressiveness of lung cancer, a strong EMT-PD-L1 correlation could thus explain the efficacy observed for chemotherapies in combination with immunotherapies in NSCLC [Gandhi et al., 2018; Paz-Ares et al., 2018]. Indeed, response improved with durvalumab after chemo-

radiation therapy in advanced stages and with the pembrolizumab-chemotherapy combination as first-line therapy in metastatic stages. Considering the major role of EMT in immunosuppression exacerbating resistance to immunotherapies, many reports support the potential advantage of combination therapies to prevent and/or overcome treatment resistance [Soundararajan et al., 2019].

### Strategies in Development – Limitations and Perspectives

In the light of its extensively documented implication in promoting tumor aggressiveness in diverse tumor types and especially in lung cancer, EMT is thus today considered both as a promising companion prognostic/predictive biomarker and as a target for anticancer therapy. Along these lines, we discuss some propositions and explore the role of the EMT status as a companion biomarker or the effect of EMT inhibition cancer management in different contexts. These propositions are recapitulated in Figure 3.

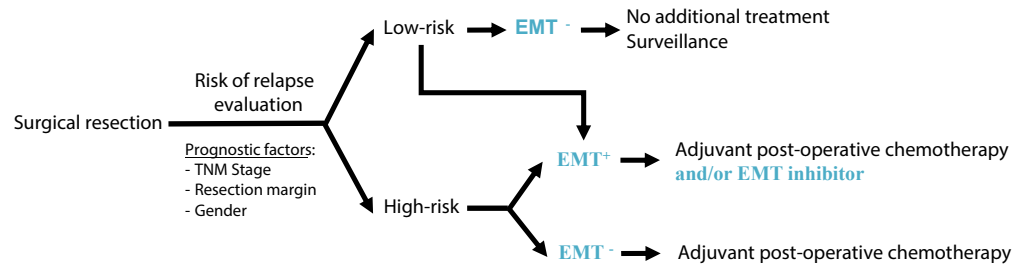
It is nevertheless important to emphasize that a major limitation to the exploitation of EMT in the clinic resides in the fact that reliable EMT signatures/biomarkers still need to be validated in clinical settings. In order to assess EMT polarization, mRNA expression signature [Rudisch et al., 2015; Chen et al., 2019; Gordian et al., 2019; Thompson et al., 2020] or specific EMT canonical markers are often analyzed. It is important to recognize that tumor cells broadly interplay with stroma, and particularly with stromal mesenchymal cells, including fibroblasts or immune-infiltrative cells that express frequently analyzed EMT markers. The examination of gene expression signature in total mRNA may thus introduce critical biases. Such explorative methods thus need to be further validated with concomitant analysis of tumor-specific marker expression or using other alternative methods such as single-cell sequencing [Karacosta et al., 2019; Ramirez et al., 2020], which is still restricted to the preclinical field.

**Fig. 3.** Proposal for potential refinements in NSCLC management according to the EMT status and considering that anti-EMT drugs are available. **a, b** The propositions solely concern cancer contexts in which the EMT status has been interrogated in published studies that are detailed in the main text. These hypothetical management scenarios have been elaborated considering that robust EMT markers/signatures can be validated in clinical practice. The figure thus does not present current therapeutic options.

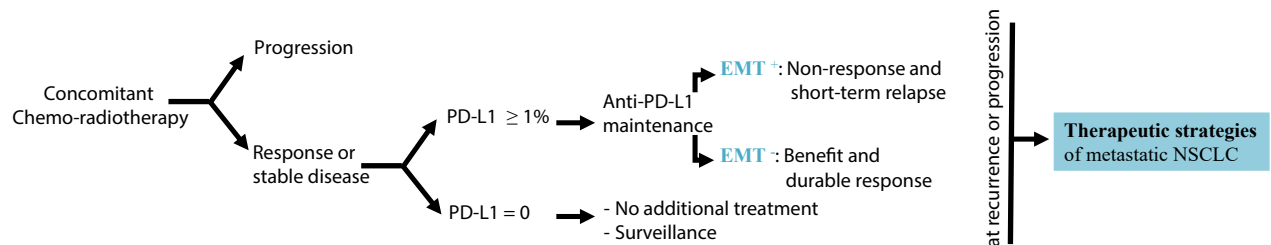
(For figure see next page.)

### Therapeutic strategies of non-metastatic NSCLC

#### Early and advanced resectable stages



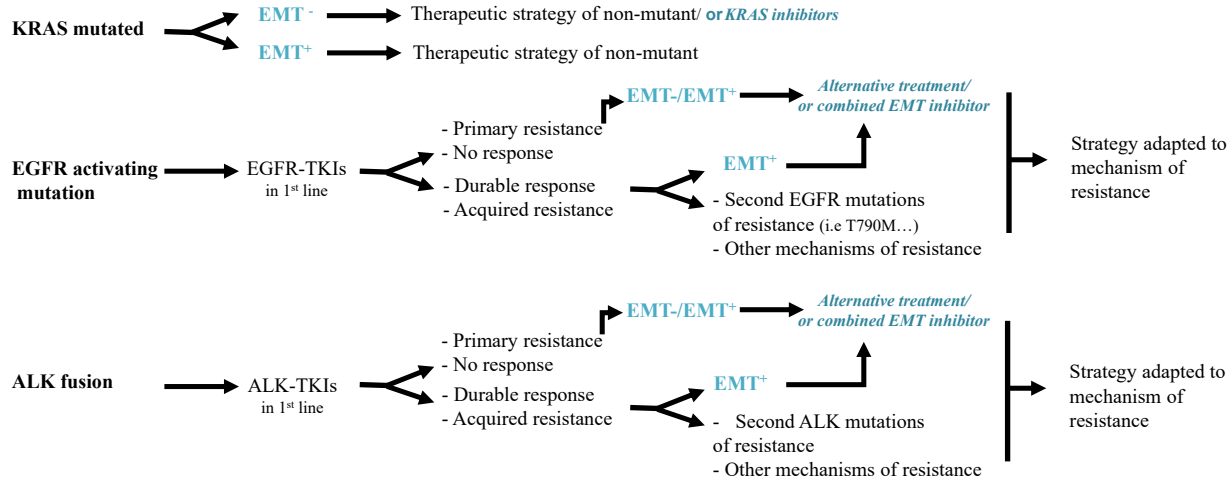
#### Advanced non-resectable stages



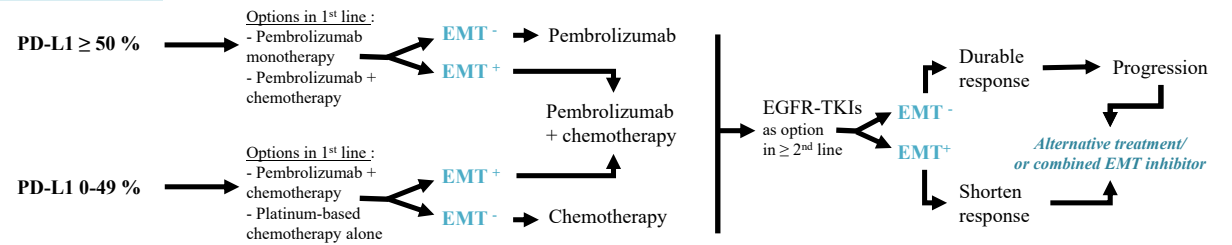
a

### Therapeutic strategies of metastatic NSCLC

#### Mutant NSCLC



#### Non-mutant NSCLC



b

3

Examining EMT by *in situ* approaches (immunohistochemistry in combination with epithelial markers such as cytokeratins, *in situ* hybridization) probably allows a more accurate analysis of EMT-associated gene expression modulations occurring in tumor cells. Nevertheless, determining thresholds and cutoff values to score and define the extent of EMT is also a thorny challenge that needs to be further evaluated in clinical trials, particularly in the context of immunostaining analyses. In this line of thought, to establish a numerical EMT index using selected validated biomarkers is a promising perspective of current EMT research to quantify the extent of EMT in tumors [Fici et al., 2017].

In addition, the tumor material to be analyzed for EMT is also a subject of discussion. In early-stage cancer, pathological examination of whole surgically resected tumors provides information on tumor heterogeneity in its entirety [Neelakantan et al., 2015]. In metastatic disease, EMT characterization based on biopsy samples is limited to fewer tumoral territories mostly in non-pre-treated condition. Furthermore, EMT being recognized as a dynamic process associated with tumor invasion and early dissemination, one can hypothesize that metastases would rather contain tumor cells that reverted to more epithelial phenotypes through METs. In order to develop a personalized medicine and to adapt treatments in a real-time manner taking EMT into account, it thus seems pertinent to propose that EMT characterization should be performed on lung primary tumor biopsies and on CTCs issued from timely and repeated liquid biopsies.

Concerning the exploitation of EMT as a therapeutic target, there are no dedicated EMT inhibitors used in the clinic. However, existing drugs impacting RTK (receptor tyrosine kinase) known to be involved in EMT (such as anti-TGF- $\beta$ , or Notch and Snail inhibitors) have been used for this purpose in preclinical models [Feng et al., 2020]. Elaborating EMT inhibitors is a very active sector, and many other anti-EMT compounds are being generated, some of which have been tested in NSCLC context [Otsuki et al., 2018]. Most of them are still in preclinical development, and we chose here to illustrate those confronted to clinical phases. RO4929097, a  $\gamma$  secretase inhibitor designed to target Notch signaling, has been employed in early phases for ovarian [Diaz-Padilla et al., 2015] and pancreatic [De Jesus-Acosta et al., 2014] cancers with limited results. Phase II trials unfortunately also failed to demonstrate its efficacy on advanced and metastatic NSCLC (NCT01193868) as well as in recurrent or refractory NSCLC (NCT01070927) alone or in combination with erlotinib (NCT01193881). To date, drug pro-

duction has been stopped. A well-designed and randomized phase II study of 132 patients evaluated the outcome of erlotinib combined or not to entinostat (isoform selective histone deacetylase inhibitor) as a potential inhibitor of EMT. Erlotinib combined with entinostat exhibited a safety profile but did not improve progression-free survival based on a 4-month follow-up in the study population. Interestingly, overall survival was longer in patients with high E-cadherin levels assessed at the time of diagnosis, demonstrating the need to identify predictive biomarkers to improve patient stratification [Witta et al., 2012]. With the aim to identify biomarkers indicating response to EGFR-TKIs in NSCLC patients, Reckamp et al. [2008] originally assessed EMT markers in serum samples from 22 patients. Decreased soluble E-cadherin and MMP-9 serum levels between baseline and the first follow-up were correlated with better response to the erlotinib-celecoxib combination. However, this combination did not seem to improve outcome in an unselected population in a phase II trial [Reckamp et al., 2015]. TLY3039478, which was also designed against Notch, has been tested in a phase I trial. Eight patients with advanced NSCLC were recruited, demonstrating safety with efficacy based on metabolic response or tumor necrosis [Massard et al., 2018]. A further clinical trial based on this drug is still recruiting (NCT02836600). Innovative strategies such as si-mi-RNAs could also represent an interesting approach in solid tumors [Naghizadeh et al., 2019], although their vectorization process is still insufficiently developed to date [Wang et al., 2014].

Targeting EMT in NSCLC could thus be beneficial alone but more probably in combination, specifically with chemotherapies to prevent and/or overcome resistance to actual treatments. Combining anti-EMT molecules with chemotherapy may also conceptually override a suspected implication of MET in metastatic outgrowth. Combination of anti-EMTs with other targeted therapies may also be beneficial. Additionally, the redundancy of EMT activation pathways (Fig. 2) also constitutes a clear challenge in targeting EMTs [Zoni et al., 2015; Yin et al., 2019] and pleads in favor of multitarget TKI approaches that are being examined [de Jonge et al., 2019; Hellerstedt et al., 2019; Wheatley-Price et al., 2019]. Multiple therapeutics against EMT-activating pathways (e.g., TGF $\beta$ , FAK, FGFR, or PDGFR) have been tested with no convincing effects [Giaccone et al., 2015; Paik et al., 2017; Han et al., 2018; Gerber et al., 2020], although research is still ongoing with FGFR [SenthilKumar et al., 2020] or FAK inhibitors [Mak et al., 2019]. Among EMT-associated targetable receptor pathways, AXL seems currently

one of the most promising [C. Zhu et al., 2019]. Accordingly, AXL small molecule inhibitors are currently being tested as monotherapy or in combination with chemotherapy or anti-EGFR therapy in clinical trials [Levin et al., 2016; Kim et al., 2020].

On the other hand, the high prevalence of PD-L1 expression in tumors with mesenchymal attributes and accumulating data evidencing resistance to immune checkpoint inhibitors suggest that the selection/management of patients that may benefit from anti-PD-L1 therapies may be refined. Thus, among patients with high PD-L1 expression, a mesenchymal switch would predict resistance to immunotherapies in comparison to tumors with an epithelial-like phenotype. As a hypothesis, patients with NSCLC harboring EMT+/PD-L1+ markers could thus benefit from a combination of immunotherapy with chemotherapy. Synergistic effects of TGF- $\beta$  inhibition combined with PD-L1 blockade are also explored [Sow et al., 2019; Lind et al., 2020].

## Conclusion

Numerous data emphasize a narrow relationship between EMT and lung cancer in early-advanced and metastatic stages. Examining EMT parameters as a routine biomarker is foreseen to improve personalized lung cancer management. For early-resected lung cancer, the detection of EMT traits could help identifying patients with worse outcomes and guide clinicians towards an adaptation of clinical surveillance and adjuvant strategies. For conventional therapies, immunotherapies, and oncogen-

ic driver-targeted therapies, EMT may appear as a predictive factor and/or marker of resistance and could steer clinicians to an alternative therapeutic option. Specific EMT actors may also represent promising, new therapeutic targets to be used in combination therapy. A better characterization of most relevant EMT actors to be considered for specific purposes seems crucial and will undoubtedly facilitate and speed up the implementation of EMT consideration in clinical practice.

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## Conflict of Interest Statement

The authors declare that they have no conflicts of interest.

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