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Review

ALK translocation and crizotinib in non-small cell lung cancer: An evolving paradigm in oncology drug development

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Abstract Advances in our understanding of tumour biology have encouraged reassessment of tumour classification by the site of origin in favour of molecular characteristics and/or oncogenic drivers amenable to treatment**.** The identification of *EML4*-anaplastic lymphoma kinase (*ALK*) as an oncogenic driver in non-small cell lung cancer (NSCLC) early in the clinical development of crizotinib and the observation of promising clinical responses in patients with NSCLC harbouring *ALK* translocations accelerated its clinical development in *ALK*-positive NSCLC. Phase I and II trials of crizotinib in patients with *ALK*-positive advanced NSCLC reported notably high response rates that tended to be rapid and of prolonged duration. Crizotinib was well tolerated; treatment-related adverse events were typically gastrointestinal (grade 1/2) and visual disorders (almost exclusively grade 1). Crizotinib provided NSCLC symptom relief and maintained quality of life. Based on the phase I and II trial data, the US Food and Drug Administration granted approval of crizotinib in August 2011. The consistency of the crizotinib data to date suggests accurate selection of the target population for crizotinib treatment. The ability to molecularly select patients likely to respond to an investigational agent argues that future clinical development of targeted agents should be re-evaluated. Updated trial designs incorporating molecular testing, early use of enrichment biomarkers and intermediary endpoints may accelerate and optimise clinical evaluation of targeted agents. Such trial designs should allow rapid clinical evaluation, minimise exposure of patients to therapies unlikely to be of benefit and, potentially, allow accelerated drug approval in molecularly specified populations.

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1. Introduction

1.1. Personalised medicine: from organ-driven to molecular-driven pharmacologic intervention

Crizotinib clinical development has focused primarily on molecularly selected patients with anaplastic lymphoma kinase (ALK) translocations. Following the identification of *EML4-ALK* as an oncogenic driver in non-small cell lung cancer (NSCLC) early in the clinical development of crizotinib and the observation of promising clinical responses in patients with NSCLC harbouring *ALK* translocations, *ALK*-positive NSCLC became a focus for the clinical development of crizotinib.[1,2] Trials with crizotinib have consistently reported notably high response rates, with responses of prolonged duration, often rapidly achieved.[1–5] In addition, crizotinib was well tolerated and provided symptomatic relief whilst maintaining quality of life. Accelerated Food and Drug Administration (FDA) approval of crizotinib has been granted based on the phase I and II trial data.[4–7] Advances in our understanding of tumour biology are overturning the classification of tumours by site of origin in favour of grouping by molecular characteristics and key oncogenic drivers amenable to pharmacologic modulation.[8,9] This progress, together with the realistic expectation of achieving impressive tumour responses, argues that the current approach of evaluating drugs via large empirical trials in unselected patient populations should be re-evaluated for targeted drugs. Updated trial designs incorporating customised testing, use of enrichment biomarkers as early as possible and intermediary endpoints will accelerate and optimise clinical evaluation of targeted agents.[10]

Matching patients with tumours harbouring 'drugable' genetic abnormalities with appropriate molecularly targeted agents can have dramatic results. High response rates were reported with imatinib in interferon-resistant chronic myeloid leukaemia (CML) (target: BCR-ABL; cytogenetic response rate: 54%) and gastrointestinal stromal tumour (GIST) (target: KIT; objective response rate [ORR] 54%), and with dasatinib in imatinib-resistant Philadelphia chromosome-positive leukaemias (target: BCR-ABL; haematological response rate: 92% for patients with chronic-phase CML and 70% for patients with accelerated-phase CML, CML with blast crisis or Philadelphia chromosome-positive acute lymphoblastic leukaemia).[11–13] Treatment of women with breast cancer overexpressing human epidermal growth factor receptor 2 (HER2) with trastuzumab resulted in an obvious improvement in survival and dramatic responses to endothelial growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) were observed in patients with NSCLC harbouring *EGFR* sensitising mutations (approximately 10% of the unselected Caucasian patients enroled in early trials).[14–16] The IPASS trial, which compared gefitinib with combination chemotherapy in the first-line treatment of NSCLC, was a landmark study that not only redefined standard therapy for patients with *EGFR* sensitising mutations, but also clearly demonstrated that patient selection for targeted agents must be made on the basis of molecular characteristics.[15,17]

The relevance and ethical acceptability of randomised studies for clinical development are therefore highly questionable in poor-prognosis disease where the investigational arm is likely to be markedly more effective than the control arm. Recently, this issue came to the attention of the media when two young male cousins with melanoma enroled in a randomised trial of the investigational agent vemurafenib (PLX4032) versus a marginally active standard chemotherapy. The cousin diagnosed and randomised first received vemurafenib and responded within 2 months, whilst the cousin diagnosed second was randomised to the control arm and progressed quickly. With crossover disallowed, this was obviously very distressing for the patients, their families and the attending physician.[18] Conversely, imatinib entered phase II study in GIST on the basis of compelling preclinical data and a single highly encouraging case study.[12] Responses in the initial phase II trial were considered 'remarkable' and led to FDA approval in 2002.[12,19] The subsequent phase III study tested different doses of imatinib rather than including a control arm.[20] For GIST, it was recognised that there simply was no effective treatment option for comparison.[12] Timelines for the development of such agents are shortening as our understanding of tumour biology and our ability to select the true patient population increase; whilst 41 years elapsed between the discovery of BCR-ABL and initial trials with imatinib, it was less than 10 years for agents modulating more recently identified targets (KIT: 1998; BRAF: 2002).[21]

1.2. An evolving understanding of molecular drivers in NSCLC

Several potential oncogenic drivers have been identified in NSCLC, including *EGFR*, *BRAF*, *KRAS*, *MET*, *HER2* and *ALK*.[22–24] The investigation of driver mutations has led to the development of specific molecularly targeted therapies, most notably gefitinib and erlotinib (both EGFR inhibitors, now known to be effective first-line therapy for tumours with *EGFR* mutations).[15,25–27] The early development of gefitinib and erlotinib was hampered by the lack of detailed molecular knowledge of lung cancer and its molecular subtypes, and clinical progress was slow as a result. Continued research into *EGFR* mutations and diagnosis developed our understanding of the molecular basis of NSCLC, and made molecular testing a familiar concept in this disease.