CNS progression was delayed compared with non-CNS progression, whether or not baseline CNS metastasis was present. Because lorlatinib is likely to be better tolerated than platinum-pemetrexed chemotherapy and is able to effectively treat and prevent CNS progression, it represents a good treatment option in the case of crizotinib failure.

The analysis of baseline *ROS1* resistance mutations in the study by Shaw and colleagues provides an insight into resistance mechanisms to crizotinib. *ROS1* mutations were detected in 15% of plasma samples and in 24% of tumour tissue samples. Gly2032Arg was the most common mutation detected. The response was lower in patients with *ROS1* mutations detected in plasma samples (none of six patients) compared with those without mutations detected (nine [27%] of 33 patients), and higher in patients with *ROS1* mutations detected in tissue samples (two [40%] of five patients) compared with those without (one [9%] of 11 patients). Of note, no responses to lorlatinib were observed in the six patients with Gly2032Arg mutations. We must be cautious in interpreting the results from this small dataset. Nevertheless, preclinical evidence of lorlatinib activity on Gly2032Arg does not seem to translate to the clinic.[7] The proportion of *ROS1* mutations in plasma samples was lower than previously reported, highlighting the limitations of plasma genotyping in this setting. The detection of *ROS1* mutations is not yet a reliable biomarker of lorlatinib clinical activity and further dedicated studies are needed.

This study establishes lorlatinib as an effective treatment option after crizotinib failure in *ROS1*-positive patients. A chemotherapy-free crizotinib-lorlatinib sequence is emerging as a treatment strategy of choice, with an expected cumulated progression-free survival of up to 27–28 months. Combined with the median overall survival of 51·4 months seen in crizotinib-treated patients in the PROFILE 1001 trial,[1] these data highlight the importance of systematic, reliable ROS1 molecular testing in all patients with non-squamous advanced NSCLC. Many other ROS1 TKIs with promising activity, such as entrectinib, brigatinib, repotrectinib, and DS-6051b, are being investigated and could extend the survival of *ROS1*-positive patients.

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Tumour Treating Fields for mesothelioma: controversy versus opportunity

The challenge of improving standard-of-care chemotherapy with pemetrexed and cisplatin for mesothelioma has proven to be virtually insurmountable since 2004. The addition of novel agents to standard chemotherapy in phase 3 trials has not succeeded in changing practice. Therefore, the front-line treatment setting remains a formidable hurdle for drug developers.

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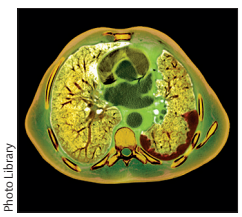
See **Articles** page 1702



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In *The Lancet Oncology*, Giovanni L Ceresoli and colleagues[1] report the results of a non-invasive intervention combined with standard chemotherapy in the STELLAR trial. This single-arm trial used an innovative technology involving alternating electric field therapy, known as Tumour Treating Fields (TTFields). TTFields have shown clinical efficacy in the glioblastoma setting,[2] where a randomised phase 3 evaluation of maintenance TTFields plus temozolomide achieved superiority over temozolomide alone, with a 3-month improvement in progression-free survival and a hazard ratio (HR) of 0·62 (95% CI 0·43–0·89). These results established a proof-of-concept for TTFields, garnering an approval from the US Food and Drug Administration (FDA) on May 23, 2019.

The STELLAR investigators hypothesised that TTFields could achieve an ambitious improvement in overall survival of 5·5 months beyond the overall survival expected for standard therapy alone (ie, 12·1 months). The study met its primary endpoint, and TTFields received FDA approval for treatment of mesothelioma on May 23, 2019. However, the question as to whether or not there truly exists a measurable and positive incremental benefit in overall survival conferred by TTFields over historical controls in 2019, remains unanswered.

Single-arm trials are notoriously subject to potential sampling bias in what is a particularly heterogeneous cancer such as mesothelioma. Another potentially confounding factor is the effect of post-study therapy. For instance, the control groups of the recent, large, phase 3 trial MAPS1 overperformed compared with historical data, showing a notable improvement in overall survival to 16·1 months. There is no licensed therapy for relapsed mesothelioma. Despite this, re-challenge platinum doublet chemotherapy,[3] vinorelbine,[4] and immunotherapy[5–7] have all shown promising signals of efficacy. Last year in Japan, nivolumab received an approval based on results of the single-arm Merit phase 2 trial. Given that more than half of patients received post-study therapy in STELLAR, including vinorelbine and immunotherapy, we cannot rule out the substantial effect of this sub-population on the measured overall survival, particularly given the similarity in response and progression-free survival relative to historical controls.

Notably, STELLAR enrolled a mixed population of patients comprising 27 (34%) of 80 patients with the more aggressive non-epithelioid subtype. Despite this, overall survival was 18·2 months in the whole population, longer than the overall survival of 15·2 months for the control group of the LUME-Meso phase 3 trial,[8] which was enriched for epithelioid-only patients. This positive finding is consistent with a signal of efficacy for TTFields and is reinforced by the substantial overall survival of 21·2 months in the epithelioid subgroup of STELLAR.

First-line systemic therapy for mesothelioma is rapidly evolving. In the non-epithelioid setting, metabolic therapy targeting loss of argininosuccinyl synthetase is being explored in the ATOMIC phase 2–3 trial (NCT02709512), based on promising monotherapy and combination data. Immunochemotherapy has led to an astounding transformation in the treatment of non-small-cell lung cancer,[9] and is currently undergoing phase 3 evaluation for mesothelioma in the BEAT-Meso trial (NCT03762018) and the IND227 trial (NCT02784171). In this changing landscape, a phase 3 randomised evaluation of TTFields is clearly warranted to assess the magnitude of both the efficacy and health economic benefit conferred by this novel treatment approach, and to support its wider adoption. From a biological perspective, TTFields target microtubule stability, disrupting the mitotic spindle;[10] however, the molecular determinants which affect sensitivity remain elusive. Identifying predictive biomarkers of efficacy could play a role in enabling selection of patients who are likely to benefit from TTFields. In summary, systemic therapy remains the first-line therapy for mesothelioma, but STELLAR presents a promising signal of efficacy that urgently needs reinforcement via the gold-standard of randomised evaluation.

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Quality of life and CAR T-cell therapy in children, adolescents, and young adults with haematological malignancies

Remarkable treatment advances have been made over the past two decades in haematological research, making the evaluation of quality of life and of other types of patient-reported outcomes (PROs) crucial to clinical decision making.[1] Development of chimeric antigen receptor (CAR) T-cell therapies for patients with haematological malignancies is a recent example of this outstanding progress, and poses some specific challenges to the assessment of PROs.[2]

In *The Lancet Oncology,* Theodore Laetsch and colleagues[3] assessed quality of life in children and young adults with relapsed or refractory B-cell acute lymphoblastic leukaemia treated with CAR T-cell therapy, a single infusion of tisagenlecleucel.[3] Although efficacy and safety data of tisagenlecleucel were previously documented in the pivotal study,[4] leading to the approval of this therapy by the US Food and Drug Administration and European Medicines Agency, only by reading Laetsch and colleagues' Article[3] can we appreciate how this therapy has affected patients' lives, from their own perspective. The comprehensive quality-of-life analysis[3] is of particular value, as a recent systematic review on studies using CAR T-cell therapies, both in solid and haematological malignancies, has found no full-length published articles (ie, no abstracts) reporting data on patient-reported quality-of-life outcomes.[5]

In Laetsch and colleagues' study,[3] 58 patients with relapsed or refractory B-cell acute lymphoblastic leukaemia aged 8 years or older were eligible for analysis of quality of life, which was evaluated at baseline (before infusion of tisagenlecleucel) and then at day 28 and months 3, 6, 9, and 12, using two validated questionnaires: the Pediatric Quality of Life Inventory (PedsQL) and the European Quality of Life-5 Dimensions (EQ-5D) questionnaire.

Baseline compliance with quality-of-life assessment was good: 50 (86%) of patients completed PedsQL and 48 (83%) completed the EQ-5D visual analogue scale. The level of compliance is notable considering the multicentre and international setting of the study, which included children and young adults with a highly debilitating and potentially life-threatening condition. Indeed, already at the time of study inclusion, the quality-of-life profiles of participants were substantially impaired compared with the general population, and more than 50% of them had undergone at least one haemopoietic stem-cell transplantation.

Laetsch and colleagues[3] found some improvements in quality of life measures as assessed with both questionnaires, albeit not clinically meaningful, as early as day 28. At this very early timepoint, the scale showing the greatest positive change from the PedsQL questionnaire was emotional functioning. Further improvements were increasingly found at subsequent timepoints up to 12 month and, notably, these were also clinically meaningful across several quality-of-life domains, with the largest improvement found for the physical functioning scale of the PedsQL. In additional subgroup analyses, improvements in quality of life from baseline to month 12 were also found for patients who reported a severe grade of cytokine release syndrome or neurotoxicity status, but these improvements

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See **Articles** page 1710