Spotlight on landmark oncology trials: the latest evidence and novel trial designs

Helena Earl¹, Stefano Molica² and Piotr Rutkowski³*

Abstract

The era of precision oncology is marked with prominent successes in the therapy of advanced soft tissue sarcomas, breast cancer, ovarian cancer and haematological neoplasms, among others. Moreover, recent trials of immune checkpoint inhibitors in melanoma, non-small cell lung carcinoma, and head and neck cancers have significantly influenced the therapeutic landscape by providing promising evidence for immunotherapy efficacy in the adjuvant setting in high-risk locoregional disease. To speed up the introduction of targeted therapy for cancer patients, novel phase II trials are being designed, and may likely form the basis for the ‘landmark trials’ of the future. A special article collection in BMC Medicine, “Spotlight on landmark oncology trials”, features articles from invited experts on recent clinical practice-changing trials.

Keywords: Cancer, Clinical trials, Oncology, Randomised trials, Targeted therapy, Trial design

Background

The era of precision medicine has led to significant developments in the therapy of advanced soft tissue sarcomas (STS), breast cancer, ovarian cancer and haematological neoplasms, among others. However, cancer research also faces challenges in the effective development and assessment of targeted therapeutics [1], including the need for early evaluation of potential biomarkers by translational and correlative studies.

In this editorial, we discuss the special article collection entitled “Spotlight on landmark oncology trials” recently published in BMC Medicine, which focuses on the core clinical trials of selected solid tumours (lung cancer [2], melanoma [3, 4], STS [5], head and neck cancer [6]). We also highlight selected and recent practice-changing trials in chronic lymphocytic leukaemia as well as breast and gynaecological cancers, and review the advances offered by the development of novel clinical trial designs.

Recent landmark immunotherapy trials – melanoma, non-small cell lung carcinoma (NSCLC), head and neck cancer

The first articles in the special article collection focus on landmark clinical trials in selected advanced solid tumours, with special attention on the most studied tumours with regards to immunotherapy development, namely melanoma [3, 4], NSCLC [2], and head and neck cancer [6]. Recent developments and approvals in immunotherapy have significantly changed the landscape of melanoma and NSCLC therapy in the metastatic setting, and open various possibilities for adjuvant treatment in high-risk locoregional disease [7–10]. In this article series, worldwide renowned experts in their fields provided an extensive overview on the state of the art in immunotherapy and discussed the possible future paths in these, still difficult, types of malignancies.

The current results of anti-PD-1 therapy with pembrolizumab or nivolumab monotherapy in melanoma indicated a median overall survival (OS) of approximately 2 years, but the combination of anti-PD-1 and anti-CTLA-4 (nivolumab with ipilimumab) was shown to be superior in terms of progression-free survival (PFS) and OS (Table 1) [11–15]. Further clinical trials are under way to determine how best to integrate combination immunotherapy and other treatment modalities as well as to establish the correct sequence of therapy with targeted treatment in BRAF-mutated cases.
The team led by Professor Jean-Charles Soria discussed the successes and failures of immunotherapy in the first-line treatment of NSCLC [2]. Moreover, three anti-PD-1/anti-PD-L1 agents, pembrolizumab, nivolumab and atezolizumab, have been approved for second-line therapy of NSCLC [16–17]; however, contrary to melanoma, patient selection to therapy should be based on PD-L1 expression level of tumour cells.

Recent landmark trials in STS
Another topic featured in this article collection is systemic therapy in STS [5], which is a heterogeneous group of rare solid tumours. Despite optimal local treatment, approximately 50% of adult patients with localised STS develop distant metastases and die of metastatic disease. A limited number of drugs have shown activity in advanced disease, and due to the rarity of these tumours, clinical trials in sarcoma include many subtypes and are mainly initiated by academic research groups.

Recent developments in the classification of STS, insights into their molecular pathogenesis and the optimal treatment strategies have evolved considerably during the past decades and have led to the introduction of new therapies. Nevertheless, the selection of systemic therapy must be strictly individualised and based upon several factors, including the histology and biological behaviour of the disease. A summary of recent pivotal trials for systemic therapy in advanced STS is presented in Table 2 [19–22].

Recent landmark trials in breast and gynaecological cancers
Recent landmark trials in HER2-positive breast cancer include those using dual HER2-targeted therapy pertuzumab and trastuzumab with docetaxel. In the neoadjuvant setting, the NeoSphere trial demonstrated significantly improved pathological complete response rates [23] and a trend favouring improved PFS and OS at 5 years [24]. Results from the CLEOPATRA trial in the metastatic setting of the same treatment have produced remarkable results [25]; the same combination produced a 56.5-month median OS compared with 40.8 months achieved with trastuzumab and docetaxel alone, showing an increase of 15.7 months to OS in the pertuzumab group. These results clearly demonstrate the superiority of dual HER2-directed therapy. In ER-positive, HER2-negative metastatic disease, the landmark trial (PALOMA 3) uses the CDK 4/6 inhibitor, palbociclib [26,27]. Median PFS was 9.5 months in the fulvestrant plus palbociclib group and 4.6 months in the fulvestrant plus placebo group with a hazard ratio of 0.46, which was highly statistically significant. However, translational research did not discover any predictive biomarker subgroups [27] for the palbociclib effect.

The landmark phase III trials in high-grade serous ovarian cancer are testing PARP inhibitors as maintenance therapy after response to platinum-based therapy in relapsed disease. Study 19 [28, 29] used olaparib against placebo and demonstrated a PFS of 11.2 months in BRCA-mutated patients compared with 4.3 months for wild-type patients (hazard ratio, 0.18; \( P < 0.0001 \)). A more recent niraparib study had similar results [30], where patients in the niraparib group had a significantly longer PFS than the placebo group in all cohorts tested (21.0 vs. 5.5 months in the gBRCA cohort; 12.9 vs. 3.8 months in the non-gBRCA cohort for patients who had tumours with homologous recombination deficiency; and 9.3 vs. 3.9 months in the overall non-gBRCA cohort; \( P < 0.001 \)). Both trials demonstrated significant benefit for maintenance PARP inhibitors in all subgroups of platinum-sensitive relapsed high-grade serous ovarian cancer.

Recent landmark trial in chronic lymphocytic leukaemia (CLL): upfront therapy with ibrutinib in elderly with chronic lymphocytic leukaemia (The RESONATE-2 Trial)
With the advent of novel oral agents that are well tolerated and highly efficacious, the therapeutic landscape of CLL underwent radical changes [31]. In phase 3 trials, ibrutinib, a first-in-class Bruton tyrosine kinase (BTK)
The landmark oncology trials highlighted in the Novo trial designs and conclusions – and rituximab [34 mab or obinutuzumab, are now the standard of care in pa-
CD2O monoclonal antibody, such as rituximab, ofatumu-
CLL [26]. Combinations of chlorambucil with an anti-
chlorambucil is no longer regarded an adequate therapy in
stered continuously and provide indefinite disease suppres-
the good 'vantage over chlorambucil despite the study
.sign. The strength of the study also relies on the good
were shown to be superior for patients who received ibruti-
study [33], a head-to-head clinical trial in which outcomes
peutic options in patients with relapsed or refractory CLL
inhibitor, showed efficacy over traditional salvage thera-
potential shortcoming with the upfront use of ibrutinib
elderly unfit patients and in those with high-risk disease.
inhibitor demonstrated a survival adva-
strategy of ibrutinib, which allows it to be adminis-
termed continuously and provide indefinite disease suppress-
even in elderly or unfit CLL patients. However, a
market phase II trial using an adaptive randomised design,
innovative trial designs will also require the matching of novel
can be accelerated. In the phase I setting, there is a press-
ing need to develop better trial methodologies for novel
mised phase III trials as required for licensing of new
reviewing practice-changing results for patients. These trials rep-
represent the end of the long process of translating scientific
innovation and drug discovery, through first-in-man
studies, followed by phase II trials and finally by rando-
mised phase III trials as required for licensing of new
Novel trial designs and conclusions
The landmark oncology trials highlighted in the BMC Medicine series “Spotlight on landmark oncology trials” and this editorial are recent trials that have produced
practice-changing results for patients. These trials rep-
resent the end of the long process of translating scientific
innovation and drug discovery, through first-in-man
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| Tumour type, phase [reference] | Line of therapy | Arms (experimental vs. control) | Response rate | Clinical benefit | Median PFS (months, \(P \) value) | Median OS (months, \(P \) value) |
|-------------------------------|-----------------|---------------------------------|--------------|-----------------|-------------------------------|-------------------------------|
| Non-adipocytic soft tissue sarcoma, phase 3, \(n = 369\) [19] | Second or later (after anthracycline) | Pazopanib 800 mg/m² vs. placebo | 6% vs. 0% | 73% vs. 38% | 4.6 vs. 1.6 \((P < 0.00001)\) | 12.5 vs. 10.7 \((P = 0.25)\) |
| Liposarcoma and leiomyosarcoma, phase 3, \(n = 518\) [20] | Second or later (after anthracycline) | Trabectedine 1.5 mg/m³ vs. dacarbazine 1000 mg/m² | 10% vs. 7% | 61% vs. 42% | 4.2 vs. 1.5 \((P < 0.001)\) | 12.4 vs. 12.9 \((P = 0.37)\) |
| Liposarcoma and leiomyosarcoma, phase 3, \(n = 452\) [21] | Third or later (after anthracycline) | Eribulin mesylate 1.4 mg/m³ vs. dacarbazine 850–1200 mg/m² | 5% vs. 4% | 57% vs. 52% | 2.6 vs. 2.6 \((P = 0.23)\) | 13.5 vs. 11.5 \((P = 0.01)\) |
| Soft tissue sarcoma, phase 2, \(n = 133\) [22] | First line | Olaratumab 15 mg/kg plus doxorubicin 75 mg/m² vs. doxorubicin alone 75 mg/m² | 18.2% vs. 11.9% | 77.3% vs. 62.7% | 6.6 vs. 4.1 \((P = 0.06)\) | 26.5 vs. 14.7 \((P = 0.0003)\) |

**Table 2** Summary of recent pivotal clinical trials in advanced soft tissue sarcomas

**OS overall survival; PFS progression-free survival**
of the pair to a phase III trial, along with the rapid rejection of novel drugs that did not work. More effective and cost-efficient phase II trial designs would rapidly lead to landmark trials and practice-changing results.

**Authors' contributions**

HE, SM and PR contributed equally to drafting, editing and revision of the manuscript. All authors read and approved the final manuscript.

**Authors' information**

HE is an academic clinician in Medical Oncology and currently Professor of Clinical Cancer Medicine at the University of Cambridge, Department of Oncology and a Principal Investigator of the NIHR Cambridge Biomedical Research Centre and Cambridge Experimental Cancer Medicine Centre. He is co-lead for the Breast Cancer Programme at the Cancer Research UK Cambridge Cancer Centre and significantly contributes to the translational endeavour in precision medicine and the development of personalised treatment pathways in breast cancer. In Cambridge, she is the cancer lead in the collaborative work stream for novel adaptive trial designs. She is an Editorial Board Member for BMC Medicine.

SM is Chief of the Department Haematology-Oncology at the Azienda Ospedaliera Pugliese-Ciaccio Catanzaro, Italy. Being a member of the American Society Clinical Oncology (ASCO), American Society Hematology (ASH), European Society Hematology, he is actively involved in the GIMEMA (Gruppo Italiano Malattie Ematologiche Adulti) lymphoproliferative working group as a member of the working party. His current research is focused on investigating the impact of novel laboratory parameters for assessing prognosis of CLL. From a clinical standpoint, he is actively involved in the management and treatment of patients with hematological malignancies and, particularly, those suffering from lymphoproliferative disorders. He has published more than 180 peer-reviewed papers primarily in the field of CLL and CLL-related disorders. He was/is member of the editorial board of Leukemia and Lymphoma, BMC Medicine, ISRN Hematology and International Journal of Hematologic Oncology. SM currently serves as referee for several haematology and oncology journals such as Journal Clinical Oncology, Blood, Haematologica, Leukemia Research, Leukemia, Leukemia & Lymphoma, European Journal Haematology, Cancer, British Journal of Haematology, and Lancet Haematology.

PR is Professor of Surgical Oncology at the Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology in Warsaw, Poland. He is the Head of the Department of Soft Tissue/Bone Sarcoma and Melanoma, the Plenipotentiary Director of Institute for Clinical Trials at the Maria Sklodowska-Curie Memorial Cancer Center as well as the President of the Scientific Council of Maria Sklodowska-Curie Memorial Cancer Center. He has participated in several investigator-driven trials in melanoma and sarcoma. He is also Coordinator of the Polish Clinical GST Registry, and a reviewer for several international scientific journals, as well as a member of the Editorial Board of Annals of Surgical Oncology, BMC Medicine and European Journal of Surgical Oncology. PR is an active member of the EORTC Soft Tissue and Bone Sarcoma Group, where he chaired the Local Treatment Subcommittee and the Membership Committee of the EORTC Board. He is also an active member of the EORTC Melanoma Group and the Global Melanoma Task Force. He is a member of several Polish and international scientific societies (Board member and Past-President of Polish Society Surgical Oncology and Ex-member of the Board of Directors of the Connective Tissue Oncology Society). He has authored or co-authored over 120 scientific papers in Polish and international journals (with an impact factor of above 1200, index-H=32, citation index > 4000), and is co-author of national and international recommendations for sarcoma and melanoma. He works very closely with national patient advocacy groups for GIST and sarcoma and is Chairman of the Melanoma Academy in Poland.

**Competing interests**

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**Author details**

1. University of Cambridge Department of Oncology, NIHR Cambridge Biomedical Research Centre, and Hon Consultant in Medical Oncology, Cambridge University Hospital NHS Foundation Trust, Cambridge, UK.
2. Department Hematology-Oncology, Azienda Ospedaliera Pugliese-Ciaccio, 88100 Catanzaro, Italy.
3. Department of Soft Tissue/Bone Sarcoma and Melanoma, Maria Sklodowska-Curie Institute - Oncology Center, Roentgena 5, 02-781 Warsaw, Poland.

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