Title given: Ph+ ALL: Is Chemo+TKI or Transplant the Best Road to Cure?

Title suggested: Curing Ph+ ALL: Assessing the relative contributions of chemotherapy, TKI and allogeneic stem cell transplant.

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Abstract

The understanding and treatment of Ph+ has changed rapidly in the past 10 years. The outcome is equally good as for Ph- disease and with targeted, TKI therapies in addition to chemotherapy, the novel immunotherapy approaches and the extension of allogeneic hematopoietic stem cell transplant (alloHCT) to older individuals, there is the potential to exceed this outcome. There is particular interest in reducing chemotherapy exposure and considering for whom alloHCT can be avoided. However, the patient population who can help test these options in clinical trials is limited in number and the available evidence is often from single arm studies. This paper summarises outcomes from recent approaches to *denovo* Ph+ ALL in the post-imatinib era and helps integrate all the available information to assist the reader make informed choices for their patients in an increasingly complex field.

Learning objectives

1. To understand and evaluate the range of treatment options for *denovo* Ph+ ALL.
2. To work through the options systematically to choose the best approach for your patient with newly diagnosed ALL based on recent evidence.

Clinical Case

A 63 year-old woman presents with intolerable bony pain after a few weeks of feeling generally tired and unwell. Bone marrow aspirate confirms the presence of a B-precursor ALL. The patient is started on a steroid 'pre-phase' pending the cytogenetics and BCR-ABL1 testing, which comes back 3 days later as showing t(9;22) by FISH and positivity for BCR-ABL1 p210 transcripts. Cytogenetics also shows del(9p). The patient consents and is enrolled onto the Ph+ pathway of the UK national trial UKALL60+ and begins imatinib combined with modest intensity chemotherapy, consisting of vincristine, steroid and intrathecal prophylaxis. She is unable to tolerate a dose of 600mg imatinib due to intractable nausea and facial oedema. By the end of one month of treatment the patient's blood count has normalised and bone marrow aspirate shows haematological complete remission (CR). Having been struggled to take continuous daily imatinib 400mg, throughout, she refuses to continue the agent any longer and is switched to dasatinib. BCR-ABL1 MRD result is 0.1% with an adequate control gene amplification. Tissue typing has demonstrated that none of her siblings are HLA-matched and an unrelated donor search is initiated. A sample is sent for BCR-ABL1 mutational analysis. At her next bone marrow evaluation, 1 month later, she has no detectable BCR-ABL1 and by this time a 10/10, CMV matched unrelated donor has been identified. During donor work-up the patient undergoes her next round of therapy with high dose methotrexate after which she receives a fludarabine/melphalan/alemtuzumab reduced intensity conditioned (RIC)alloHCT. Throughout this article, I will return to elements of why this patient was treated as described, with reference to the evidence.

Introduction

The outcome for the 25-30% of adult patients with Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukaemia (ALL) is now equivalent to or better than that for those with Ph- disease. Imatinib truly revolutionised outcome for patients with Ph+ ALL, as confirmed by numerous studies. Despite the lack of a large, randomised study, it was very clear from studies with comparable pre-imatinib era data [1,2] and large single arm studies, that the magnitude of the potential benefit was so great that regulatory and reimbursement authorities were readily convinced of its value. A table summarising the results of imatinib studies in Ph+ ALL is given in a prior review by the author[3]. Subsequent 2nd and 3rd generation TKI have likewise been tested to date only in single arm studies and no direct comparison between TKI has been done to date, although trials of imatinib compared to ponatinib are ongoing with commercial sponsor (NCT03589326) and planned as an academic trial (EWALL03). However, it is clear that the benefit of 2/3rd generation TKI over and above imatinib is not the same step change as occurred with the first introduction of TKI. Attempted comparisons using existing data based on comparing trials or propensity scores do suggest an advantage for 2/3rd generation[4 5]TKI, but by contrast, a small, non-randomised retrospective comparison of 77 patients treated at the Southern Medical University, Guangzhou showed no significant benefit for 1st versus 2nd generation TKI [6]. As a consequence, some health economies do yet not recommend or reimburse 2nd or subsequent generation TKI for therapy of *de novo* Ph+ ALL. As examples, Canadian evidence-based guidelines currently do not recommend subsequent generation TKI[7].

It is also important to note that the trials do date are unlikely to reflect what is possible in the general population because patients at highest risk of toxicities from

TKI are typically excluded from phase 2 studies. Furthermore, follow up from 3rd generation TKI trials is currently very short, meaning comparisons of long term survival are impossible. The long-term toxicity and drop-out rates are likely, in daily practice to be much higher than reported in trials. For this reason, this article will not offer a definitive, evidence-based response to the question of which, specific TKI should be used, in favour of simply reviewing the current evidence. It would not be wrong, in 2019, to treat patients with *denovo* ALL with imatinib.

My patient was started on imatinib because this is the only TKI that is routinely reimbursed for denovo Ph+ ALL in the UK and this was part of the trial protocol she received.

Dasatinib

As reviewed by Brattas et al**,** dasatinib inhibits not only the *BCR-ABL1* tyrosine kinase but also, at a relatively low IC_{50} SRC, LCK, and c-KIT. At higher concentrations, even more kinases are inhibited including FGFR1, VEGFR2, MEK, CDK2, Akt, and FAK suggesting that the antileukemic effect does not only depend on *BCR-ABL1* inhibition[8]. Dasatinib has now been evaluated in *de novo* Ph+ ALL both with and without chemotherapy. The GIMEMA LAL1205 trial investigated dasatinib combined with just prednisolone in 53 patients over a wide age range of 24–77 years[9]. Following a 100% CR rate, 20-month overall survival was 69% with DFS 51%. During the course of the study, 23 patients relapsed with 70% of tested relapse expressing the T315I mutation. Since post-remission therapy and longer term follow-up was not part of the trial, it is not possible to draw further conclusions. Dasatinib has been combined with more intensive therapy in the EWALL-Ph-01 “elderly” trial wherein 71 patients aged 55 years and older were assigned to receive dasatinib with vincristine (VCR) and dexamethasone (DEX) induction (CR rate was

96%), followed by 6 months of consolidation wherein cytarabine, asparaginase and methotrexate were added, followed by maintenance with dasatinib DEX/VCR pulses. 5-year OS was 36%. Of those tested for T315I mutation at relapse, 24/36 (75%) were positive[10]. Dasatinib has also been combined with the more intensive, myelosupressive chemotherapy regimen hyperCVAD. Long-term, 67-month follow-up of this study, in which 96% of patients had achieved CR and 12/72 (17%) patients had undergone alloHCT showed that 43% were alive in CR at 5 years. Yoon et al also alternated cycles of dasatinib with cycles of a medium intensive chemotherapy schedule in a trial which enrolled 51 patients with median age of 46 years, of whom 39 received alloHCT in CR1. Four year DFS was 52%[11]. The US intergroup study NCT00792948, evaluating dasatinib, chemotherapy and alloSCT is discussed in more detail in the alloHCT section. All studies reporting mutational analysis have reported T315I mutation as a primary association with relapse during first-line dasatinib treatment. Although generally well-tolerated, dasatinib puts patients at specific risk for pleural effusion. In a very large assessment across the dasatinib clinical trial program (N=2712) by Hughes et al[12], pleural effusion developed in 6-9% of patients at risk annually and drug-related pleural effusion occurred in 28% of patients in DASISION and in 33% of patients in 034/Dose-optimization, respectively. It is entirely possible that this problem is under appreciated in Ph+ ALL because many patients receive alloHCT and are not given (or do not need) long term TKI.

My patient was switched to dasatinib after clear evidence of intolerance of imatinib. This was fortuitous, as her BCR-ABL1 result showed evidence of slow response to her original regimen.

Nilotinib

Whilst efficacy against relapsed Ph+ ALL has been reported as comparable with that of dasatinib in patients with imatinib-resistant or intolerant Ph+ ALL[13], nilotinib has been less studied in *de novo* ALL. A single arm phase 2 study of nilotinib, combined with dose intensive cytotoxic chemotherapy was carried out in 91 patients with de novo Ph+ ALL by the Adult Acute Lymphoblastic Leukemia Working Party of the Korean Society of Hematology. CR rate was 91% with lack of CR being due to treatment related mortality (TRM). Fifty-seven patients received alloHCT. 2 year OS was 72%[14]. The EWALL-PH-02 study, as yet available only in abstract form[15] administered nilotinib throughout therapy at 400mg twice daily to 72 patients over 55 year (median age 66). 5-year OS was 47%. There was a much higher alloHCT rate than in EWALL01 and there was a 61% long term OS after alloHCT, despite the older age of the study participants.

Ponatinib

Ponatinib, a "3rd generation" potent, TKI is active against both unmutated and mutated *BCR-ABL*, including T315I mutation that is commonly observed when patients relapse after therapy with dasatinib. It was first demonstrated as having efficacy in 32 patients with relapsed Ph+ ALL enrolled in the PACE trial[16], 41% of whom hematologic response and 47% had a major cytogenetic response. Serious arterial thrombotic events were observed in 9% of patients. Interestingly, no single mutation was associated with resistance to ponatinib, although compound (≥2 mutations in the same *BCR-ABL* allele) mutations were associated with less deep or very abbreviated responses. Ponatinib has also been given in association with hyperCVAD in *de novo* Ph+ ALL. A 'long term' follow up of 76 patients (median age 47 years) in this study was published in December 2018[17], albeit the final patient had

been enrolled in April 2018. Two patients had died of ponatinib-related myocardial infarction prior to an amendment to reduce the dose from 45mg to 30mg after the first cycle. This was not a trivial treatment approach to offer patients; increased bilirubin (n=13, 17%), pancreatitis (n=13, 17%), hypertension (n=12, 16%), bleeding (n=10, 13%) stood out among other more typical grade 3/4 events such as infection. As a result, 48/76 (63%) of participants discontinued trial treatment (albeit 15 of these for alloHCT) despite an initial 100% CR. The modest numbers preclude seeing any statistically valid difference between those who did (N=15) and did not receive alloHCT. The reported 3-year OS at a median follow up of 36 months was 76% but only 43 of the 76 participants had reached the 3-year mark at the time of the report. Even if the combination of ponatinib with intensive myelosupressive chemotherapy is toxic, the rate of complete molecular remission is very high and the logical extension would be to reduce the toxicity by eliminating the myelosupressive chemotherapy. The LAL1811 study is so far reported only in abstract form[18]. Patients (N=44) over 60 years old received ponatinib 45mg plus steroid. CR rate was 90% at 8 weeks with a 45% complete molecular response. At week 24, only 15/42 patients still in the study could receive 45 mg of ponatinib daily. For physicians who are able to and choose to treat patients with *denovo* Ph+ using ponatinib, dose reductions from the initial 45mg dose are necessary after cycle 1 to avoid excess toxicity.

How much chemotherapy is appropriate ?

With enhanced potency of TKI and knowing the toxicity of intensive myelosupressive chemotherapy in older persons, the reduction in intensity of chemotherapy schedules reported above have been a natural corollary of wider use of these targeted therapies. Whilst the chemotherapy-free approach has been pioneered by Italian

investigators and will continue in this vein by investigating the combination 2nd or 3rd generation TKI with blinatumomab (NCT 02744768, dasatinib and blinatumomab), the GRAAPH-2005 validated the outcome equivalence of an induction regimen combining reduced-intensity chemotherapy and imatinib compared to combining it with hyperCVAD in a randomised trial. The early CR rate for the 'chemotherapy light' approach was 98.5% compared to 91% in the other arm due to TRM. The current study of the French/Belgian/Swiss cooperative uses nilotinib as TKI and is randomising patients to a further reduction in intensity during later parts of the protocol (NCT 02611492). Data from the UKALL14 study have clearly shown that the combination of pegylated-asparaginase and imatinib in older adults is particularly toxic, so where 'paediatric-inspired' regimens are used in adults, it would not be appropriate to extend them to adults with Ph+ ALL[19]. The balance of evidence suggests that at least during induction, which is the highest risk period for TRM, TKI combined with steroid and VCR can result in all patients achieving CR with minimal toxicity. This is a major advance for our patients.

My patient was enrolled on a trial for older individuals, UKALL60+, in which a less intensive dose of chemotherapy is used for Ph+ ALL, based on existing data from other groups.

Minimal residual disease (MRD) in Ph+ ALL

The existence of straightforward quantitative RQ-PCR assay which can precisely quantify BCR-ABL transcripts belies the considerable complexity of interpretation of MRD in Ph+ ALL. The subject bears an in-depth discussion, because, as treatments for the disease evolve and tend towards stratification to reduced therapy by perceived risk, clear guidance on how we should a) carry out and b) interpret

molecular monitoring is needed. The lack of guidance and the plethora of approaches used by both individual physicians and national study groups is underpinned by a genuine knowledge gap in the field. MRD in Ph+ ALL can be assessed by quantifying BCR-ABL transcripts for p190 or p210, identifying and quantifying patient-specific immunoglobulin heavy chain/T cell receptor (Ig/TCR) gene re-arrangements by PCR, by flow cytometry or by using next generation sequencing to quantify Ig/TCR.

BCR-ABL transcript quantification (using RNA) is relatively straightforward assay technically and, for p210 transcript quantification can be carried out and reported to international standards due to the work done in CML. However, the reports produced for CML characterise the molecular respond on a scale which is well validated for CML and is not validated and not suitable for Ph+ ALL. P190 quantification is less commonly available and is much less standardised. A highly significant effort for international standardisation of p190 quantification has been led by Heike Pfeifer on behalf of the EuroMRD consortium with 35 laboratories participating[20]. In this piece of work, successive quality control rounds demonstrated that standardised use of both “Europe Against Cancer” primer/probe sets and centrally prepared plasmid standards had the greatest impact on reducing inter-laboratory variability. Nonetheless, at the lowest levels of MRD there was still variation between labs and an appreciable false negative rate. The extremely detailed laboratory recommendations are a considerable move forward in p190 quantification.

Given we accept *BCR-ABL* assays on RNA can be carried out to a reasonable technical standard, what is the evidence that they are predictive of outcome and at what timepoints should they be measured? Whilst there is broad

agreement among studies that patients in whom *BCR-ABL1* does not significantly diminish during initial therapy after 2nd generation TKI are at higher risk for a poor outcome[10,11,14,21] the relationship between *BCR-ABL1* levels and outcome is not nearly so clear cut as that between Ig/TCR monitoring and outcome for Ph- disease. Of particular interest in this regard is data connecting *BCR-ABL1* and Ig/TCR monitoring. A recent study in childhood Ph+ ALL showed that the, overall concordance between the two methods was only 69% and Ig/TCR appeared more reliable at predicting outcome. An early MRD response was highly predictive of a favourable outcome[22]. The discrepancies between the two methods in a significant subset of patients has led to a highly important biological observation, the full clinical relevance of which is being investigated. Hovorkova et al flow-sorted different subsets of cells and demonstrated a *BCR-ABL1*-positive clonal haematopoiesis emanating from early progenitors, closely resembling a CML-like disease. These data suggest that at least some of the biological heterogeneity of *BCR-ABL1*-positive ALL may result from this[23].

In practical terms, these data suggest that wherever possible, *BCR-ABL1* should be monitored early and monitored often and if possible, both patient specific Ig/TCR re-arrangements and *BCR-ABL1* should be monitored.

Additional prognostic lesions

Additional genetic lesions have clear prognostic relevance in Ph+ ALL. Gross structural lesions such as del(9p) are clearly associated with a higher relapse rate, whereas high hyperploid is associated with a better outcome[24,25]. Several additional recent papers have also demonstrated deletions within CDKN2A/B (located at 9p21) are adverse, even in the TKI era[26,27] and there is evidence that this may not be

overcome by alloHCT[28]. Fedullo et al[27] noted that among 116 patients with de novo Ph+ ALL, those carrying simultaneous deletions of *IKZF1* plus *CDKN2A/B* and/or *PAX5* had a significantly lower disease-free survival rate (24.9% *versus* 43.3%; *P*=0.026) giving weight to the poor prognostic relevance of the "Ikaros+" phenotype. Whilst there is no additional targeted therapy directed at such lesions, they can be of great importance in counselling the patient about the possible outcome of various treatment strategies and is highly relevant to understanding more about the science of this disease. There is also evidence that the p190 and p210 transcripts may carry a different prognosis – Chiaretti et al[29] showed a significantly faster molecular response in p190 disease compared to p210 in the GIMEMA LAL0904 study.

My patient had del(9p). Although Pfeifer et al demonstrated an inferior outcome for patients with CDKN2A/B *deletions as compared with those without the deletion, the Kaplan-Meier curves for OS, DFS, and remission duration all reach an apparent plateau at a level that exceeds expectations from the pre-TKI era; certainly, the data do not suggest alloHCT is futile.*

Mutational analysis

Numerous mutations in BCR-ABL1 are associated with resistance to TKI. Most occur within the ATP-binding loop (also known as the P-loop) of the ABL kinase domain of which E255K/V is an example. The T315I mutation is at the contact site. By now, it is clear that such mutations can be detected at low levels at diagnosis using deep sequencing approaches [30,31] but the clinical relevance of these – when, how and under what pressure, if any, they may develop into resistant clones is completely unclear. Perhaps for this reason there are no consensus clinical recommendations

on when and how to do mutational testing. Presently, mutational analysis is done by Sanger sequencing but this technique does not identify low level clones. Soverini et al[32] used a NGS approach to look for low level mutated clones in patients who had switched from imatinib to a 2nd generation TKI without mutational analysis and looking back to those who had resistant disease, mutations with 1–20% abundance had clearly expanded suggesting that sensitive mutational analysis is a *sine-qua-non* to inform therapeutic decisions. However, it is important to note that mutational analysis of this type requires a minimum disease threshold of about 0.1% MRD. Schmitt and colleagues integrated single-molecule duplex sequencing of the *ABL1* gene in computational simulations. Their work predicted that the multiple preexisting resistant cells with single mutants may subtend the emergence of compound mutations following initial use of a TKI inhibitor that is susceptible to resistance from single point mutations [33] but there is no clinical trial proof of this interesting work to date. In a clinical scenario, the best advice that can be offered to date is to carry out mutational analysis in case of lack of response, rising MRD or overt relapse.

AlloHCT in Ph+ ALL

AlloHCT is a very active immunotherapy in ALL – there is strong evidence for a graft versus leukemia effect[34], reduced intensity conditioning (RIC) can also be applied with good effect in CR1[35,36], autologous transplant using the same TBI-based conditioning as for alloHCT is not better than chemotherapy[37] and there is preliminary evidence for the activity of donor lymphocyte infusion in minimal residual disease states post alloHCT[38]. The vast majority of the older literature, as I have previously summarised[39] is firmly in favour of alloHCT in this disease, even in the imatinib era. However, alloHCT as currently performed is undeniably a very toxic procedure with long term health impacts and an appreciable TRM of 15-20%. For

alloHCT to become dispensable in adult Ph+ ALL, the relapse risk would have to reliably exceed the TRM and it would have to be clear that the reduction in relapse risk was not contingent on long-term application of therapies that are unproven for long term safety. For example, if the only way to avoid alloHCT was to be dependent upon on lifelong ponatinib, this would raise new questions that the community are not yet able to answer. Extreme reluctance for alloHCT in children and young persons is completely understandable. However, in that setting, traditional, intensive chemotherapy combined with TKI is still applied. The AALL0622 study of dasatinib plus intensive chemotherapy recruited 60 patients. AlloHCT was recommended for patients at 'high risk' based on slow response as well as for those with a matched family donor regardless of response after at least 11 weeks of therapy. With very small numbers of patients in the comparison (N=9 for high risk and N=10 for sibling donor), there was no difference between those who did or did not receive alloHCT. Interestingly the 5 year OS did not differ from that of the AALL0031 study with imatinib as TKI[40]. By contrast in an older group of patients aged 18-60 years a US intergroup study of patients administered dasatinib plus hyperCVAD and applied alloHCT for all patients with a sibling or unrelated donor. Landmark analysis at 175 days from the time of CR/CRi (longest time to HCT), showed statistically superior advantages for RFS and OS (p=0.038 and 0.037, respectively) for the transplanted patients[41]. There were no MRD data from this study, so it is not known whether MRD could further inform alloSCT selection process.

Of course, alloHCT is not one specific approach and intensity of conditioning is a highly relevant decision – large registry data are helpful is showing that RIC conditioning can be completely appropriate for patients with Ph+ ALL[35,42 9]. The UKALL14 study has prospectively assessed RIC conditioning for all allografts in

patients over the age of 40. In a preliminary analysis in abstract form, the population as a whole pre-allograft MRD was highly relevant for outcome. Yoon et al compared myeloablative (N=116) with RIC (N=79) for patients in CR1 after imatinib or dasatinib-based therapy[43]. In a multivariate analysis, the conditioning intensity had no significant impact on transplantation outcomes. Wang et al[44] were able to conclude that whilst there was a benefit for alloHCT, this was no longer evident for patients with low presenting white blood counts and a rapid, deep MRD response.

My personal concern is that the very valid increasing reluctance for alloHCT in adults is contemporaneously accompanied by a trend towards reduction or cessation of cytotoxic chemotherapy without elucidation of clear evidence of what exactly constitutes low-risk Ph+ ALL. There is a risk that if a patient who has received ponatinib and immunotherapy without alloHCT relapses, there will be no effective salvage therapy as CR2 may be a very difficult goal. Hence, omitting alloHCT in favour of a reduced or non-chemotherapy approach is a risk which is hard to calculate. I would personally recommend omitting alloHCT *only* in the context of informed consent within a clinical trial. If a patient strongly wishes to avoid alloHCT by personal choice that is probably only safe to recommend if there is a complete and early disappearance of MRD by *BCR-ABL1* and Ig/TCR and extremely close monitoring of MRD.

My patient had several risk factors for poor outcome from Ph+ ALL including a poor early MRD response, del(9p) and intolerance of imatinib. On the balance she had achieved molecular remission prior to allograft, she was fit, well supported, motivated, had a low HCTCI score and very good donor. After discussion, the balance of risk fell in favour of alloHCT.

After alloHCT: how to monitor and TKI or not?

TKI are not well tolerated post alloHCT[45,46] and a randomised study of prophylactic administration of imatinib versus adding it only on evidence of *BCR-ABL1* detection did not show any clear evidence of benefit to prophylactic administration. Nontheless, many physicians choose to add TKI. A consensus position statement of the European Society for Blood and Marrow Transplantation, is an excellent reference for a clear-headed summary of all the available evidence and clarifies the lack of any grade 1 evidence for the use of posttransplant TKIs[47]. It is notable for recommending either extremely careful monitoring with re-start of TKI or possible prophylactic administration. Intensive MRD monitoring post alloHCT monitoring is critically important, perhaps more so where RIC has been used. Although peripheral blood is less sensitive, it can be done more often so a combination of initial monthly testing on blood interspersed with 2-3 monthly testing on bone marrow can be of value. In the UK, we also choose to add 3 monthly intrathecal chemotherapy to our 3 monthly BM testing after non-TBI-based, RIC allo stemming from a concern that the abbreviated initial therapies lack adequate CNS-directed prophylaxis. However, the evidence base for this approach compared to another is lacking. A genuine real-life problem, to which there is no adequate, evidence-based response is when to stop TKI, once started, especially if the patient has always been *BCR-ABL1* negative on monitoring. Every clinic will contain patients who have been taking TKI in these circumstances for decades and no-one dares stop. *My patient, whose disease was BCR-ABL1 negative prior to and remained so post RIC alloHCT, I preferred not to start TKI especially because of the prominent nausea during initial therapy. She developed grade 2 skin and gut GVHD after cyclosporinA was stopped and required an extension of immunosuppression until 1 year post-transplant. After 2 years of 3*

monthly IT and BM visits, she is now off all medication except prophylactic penicillin and has returned to work.

Immunotherapy

Immunotherapies and chemoimmunotherapy directed at CD19 (blinatumomab[48], chimeric antigen receptor T cells[49]) and CD22 (inotuzumab ozogamicin[50]) have all shown efficacy in relapsed Ph+ ALL and there is no reason to suspect the Ph status specifically impacts response to immunotherapy, hence these agents are likely to gain increasing prominence in the treatment of *denovo* Ph+ ALL as new data are available. Blinatumomab is currently being evaluated in denovo Ph+ ALL in 'chemotherapy-free' combinations with dasatinib (D-ALBA, NCT NCT02744768), and ponatinib NCT03263572

Summary

This is a very exciting time for the field of Ph+ ALL. Our patients can now expect to have at least an equivalent outcome to that for Ph- ALL and arguably, the outcome will soon surpass that of Ph- ALL given the combinations of TKI and immunotherapies. Additionally, such combinations may reduce the need for more toxic therapies such as alloHCT and allow optimal treatments to be expanded to older persons. Appropriate attention is also being paid to the best methods for sensitive and specific disease monitoring which will be absolutely key to get the best from our new agents. Given the modest numbers of patients with this disease, progress is commendable and relies, as always, on the close communication and cooperation of patients, physicians, scientists, and the pharmaceutical sector.

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