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BRAF inhibitor therapy in HCL

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Targeted treatment approaches are transforming the therapeutic landscape of cancer care. The discovery of the BRAF V600E mutation in most cases of classical hairy cell leukemia opens up unique opportunities for tumor specific treatment of HCL targeting the MEK/ERK signaling pathway.
The discovery and biological implications of BRAF V600E in HCL are summarized to form a basis for our current understanding of the potential for clinical exploitation. There is overwhelming clinical evidence for activity of inhibitors of BRAF in the disease. The review will review current trial activity as well as discuss novel trial concepts exploiting targeted treatment focusing on BRAF inhibition in HCL.

Introduction

The molecular pathogenesis of hairy cell leukemia (HCL) has been relatively obscure until the discovery of BRAF V600E mutations in virtually all cases of classical HCL [1].

BRAF mutations were first identified in a set of cancer cell lines and primary melanomas (59%), colorectal cancers, gliomas, and e.g. lung cancers [2]. The vast majority of mutations target codon 600 substituting Valine for Glutaminic acid (V600E) (http://cancer.sanger.ac.uk/cosmic/gene/overview?ln=BRAF). Although other codons are mutated by mainly single nucleotide variants, the proportion of mutations at codon 600 is >90% with some diversity across histological disease entities. Members of

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the Raf family (RAF1, ARAF1, and BRAF) encode serine/threonine kinases that act in the key cancer MAPK (mitogen-activated protein kinase) pathway to transduce regulatory signals from Ras to MEK1/2. These mutations are oncogenic by disrupting the interaction of the P-loop and the activation segment resulting in the loss of the inactive conformation [3], which leads to activation of the MAPK (mitogen-activated protein kinase) pathway (reviewed in Ref. [4]). BRAF has also been shown to be deregulated by translocations [5]. The RAS/RAF/MEK/ERK signaling pathway regulates many key cellular processes and is often targeted by mutations in human cancer. Active RAS-GTP binds in the membrane to multiple effector proteins including the three members of the RAF kinase family (ARAF, BRAF, and CRAF). Binding of these kinases to RAS-GTP leads to the activation of a cascade of kinases including RAF, MEK1/MEK2, and ERK1/ERK2. In the context of BRAF mutant cancer, this cascade is activated independent of upstream activation signal (Fig. 1).

Discovery of BRAF V600E in HCL

Using whole exome sequencing, Tiacci and colleagues identified BRAF V600E in HCL [6]. Validation showed that all HCL patients in the initial series showed this particular mutation, while a set of 195 B-cell lymphomas and leukemias did not show mutated BRAF. While a low incidence of BRAF mutations are found in leukemias and lymphoma (e.g. CLL) [7], this finding suggests that pathogenesis of HCL is driven by the activation of BRAF and the downstream MEK/ERK signaling pathway. The initial work has been confirmed in numerous studies and the detection of BRAF V600E has been developed using both sequencing and immunohistochemical techniques [8–11]. As the diagnosis of HCL can usually be based on FACS or IHC, the major implication of the BRAF V600E discovery, is likely to be the exploitation as a therapeutic target (see below) [8,12,13].

Downstream targets

As summarized above, the BRAF V600E oncogene activates central cellular signaling cascades. Both *in vitro* and in vivo work has demonstrated BRAF dependent pERK activation in HCL, which is an

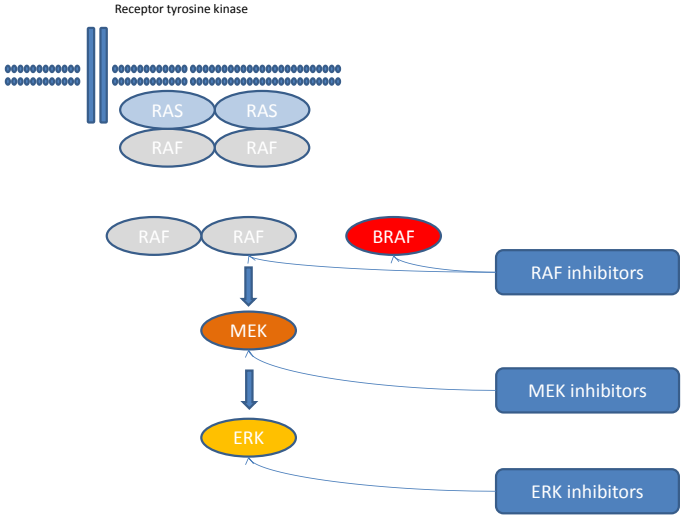

Fig. 1. /RAS/RAF/MEK/ERK signaling as a prime target for therapeutic intervention. Active RAS-GTP binds in the membrane to multiple effector proteins including the three members of the RAF kinase family (ARAF, BRAF, and CRAF). Binding of these kinases to RAS-GTP leads to their activation of a cascade of kinases including RAF, MEK1/MEK2, and ERK1/ERK2. In the context of BRAF mutant cancer, this cascade is activated independent op upstream activation signal. The pathway may be inhibited at multiple levels (e.g. vemurafenib, dabrafenib: BRAF; trametinib (MEK)).

acceptable biomarker of activity of the MEK/ERK signaling [6,13]. Some of the characteristic expression markers which allow pathological distinction of HCL may be activated based on MEK/ERK signaling. Aberrant cell cycle related proteins such as Cyclin D1 has been shown to be reversible using chemical inhibitors suggesting that expression is not a constitutive disease trait but elicited by MEK/ERK signaling induced by oncogenic BRAF mutations [13]. This concept may have important consequences regarding MRD assessment (in the context of inhibitor treatment) as the marker profile could be dynamic (Cyclin D1, CD25) as well as for targeted drug treatment which may be curtailed by on-target effect of inhibitors.

Discovery of MEK mutations

To understand the genetic mechanisms driving variant hairy-cell leukemia a group at NIH performed whole-exome sequencing and identified activating mutations in the MAP2K1 gene (encoding MEK1) in ~50% of patients with atypical HCL [14]. While the incidence has not unequivocally been confirmed [15], the mutational activation of a key downstream element of the same pathway is remarkable. Similarly to BRAF V600E the finding suggests potential new strategies for treating individuals with these diseases (Fig. 1).

Additional gene mutations in HCL

Cooperating genetic events that may contribute to HCL pathogenesis, in addition to BRAF V600E, have -until very recently- remained elusive. A recent study again used whole exome sequencing to explore the mutational landscape of purine analog refractory HCL [16]. The study identified mutations in known cancer associated genes such as EZH2, ARID1A as well as novel inactivating mutations of the cell cycle inhibitor CDKN1B (p27). 16% of HCL patients harbored deleterious CDKN1B mutations. In 11 of 13 patients the CDKN1B mutations were clonal, implying an early role of CDKN1B mutations in the pathogenesis of HCL. While clinical impact of CDKN1B mutations was not found, the data identify CDKN1B as the 2nd most commonly mutated gene in HCL. Based on the known function of CDNK1B in the control of cell cycle progression, the data suggest a novel role for alterations in regulation of cell cycle and senescence in HCL. While the function of these mutations remains to be elucidated in HCL, the documented ability of oncogenes such as BRAF V600E to induce senescence suggests a role in inactivating failsafe mechanisms e.g. senescence.

Therapeutic targeting of BRAF V600E

Inhibitors of BRAF have shown unique response in BRAF mutant melanoma [17], prolonging survival for patients with the disease. Both overall and progression-free survival in patients with metastatic melanoma harboring the *BRAF* V600E mutation were improved [17,18]. In contrast, a recent study demonstrated that only 5% of patients with *BRAF* V600E-positive colorectal cancer responded to vemurafenib, indicating that the mere presence of the mutation does not guarantee clinical activity (http://meetinglibrary.asco.org/content/50595-74).

Reports on clinical activity outside trials

Based on the discovery of BRAF V600E in virtually all patients with HCL as well as the success of BRAF inhibitor treatment in melanoma, it was intuitive that pharmacological inhibition should produce significant benefit to patients with HCL. The first patient exposed to the BRAF inhibitor vemurafenib indeed showed immediate and striking response, proving oncogene-dependence and clinical activity [12,13]. There are important lessons to be learned from the initial description: based on phase I data in melanoma the dose chosen was 240 mg bid, which is considerably lower than standard melanoma dosing (960 bid). While the dose was escalated to the melanoma dose, activity was demonstrated at low doses with reduction of HCL from the blood, resolution of splenomegaly and rising platelet counts. Indeed the initial melanoma study demonstrated response at the 240 mg bid level of dosing. Dose

finding studies often pick dose levels based on the incidence of side effects, rather than target inhibition. The data therefore may have implications for dosing in BRAF mutant cancer in general.

Soon after the initial report multiple studies confirmed efficacy of both vemurafenib and (because of availability) later dabrafenib. The reports also presented use in particularly challenging clinical situations including infection, where the lack of haematotoxicity may be particularly advantageous.

Follows et al. [19] used vemurafenib 240 mg BD and continued the dose with no breaks or escalation for 58d. Initially after treatment the blood hairy cell count increased, potentially by mobilization from other compartments. The hairy cell count then decreased to 0.002×10^9/l by the final day of treatment which was a 10 000-fold reduction in peripheral blood hairy cell numbers. Platelet count rose steadily after 2 weeks. Treatment was stopped after 58 d and the patient was observed off treatment for 2 months, before he needed retreatment with reemergence of HCL and dropping blood counts (Follows, personal communication).

Peyrade et al. used vemurafenib to treat a 72-year old patient who presented with relapsed HCL and the BRAF V600E mutation [20]. With vemurafenib at a dose of 240 mg twice daily (Day 0), the immunophenotyping and percentage of mutated cells showed comparable results to a healthy donor control at day 56. A bone marrow aspiration showed a $CD19^+/CD103^+$ cell frequency of 5% and the vemurafenib was stopped. One month after completion of the treatment (Day 90), the patient showed complete remission [21].

The first report of vemurafenib in standard dosing for HCL used vemurafenib 960 mg by mouth twice daily for 3 weeks [22]. Therapy was stopped because of arthralgia. At 4 months, blood counts remain normal, and repeat bone marrow aspirate and biopsy show a decrease in hairy cell leukemia infiltrate from 68% to less than 5% as estimated by morphology and approximately 10%–20% by immunohistochemistry stains.

Maurer et al. reported the use of vemurafenib in a patient with active infection [23]. After treatment with cladribine, rituximab, and interferon-α with no response, severe aspergillus pneumonia led to mechanical ventilation. On the intensive care unit, 960 mg BD vemurafenib was administered. HCL cells declined in the bone marrow while leukocytes and platelets increased. The aspergillus infection resolved with disappearance of the pulmonary fungal infiltrates. After a total of 54 days of treatment, vemurafenib was stopped. The case indicates that vemurafenib is a valuable salvage treatment option in primary refractory HCL and can even be successful when the patient suffers from a severe uncontrolled infection that prohibits intensive conventional HCL therapy. This data, as well as our personal experience suggests that due to accelerated response dynamics and reduced hematologic toxicity BRAF inhibitors may in fact be the first treatment option for patients with severe infections due to HCL to induce blood reconstitution (Table 1).

In a puzzling report, Samuel et al. present a patient with purine analog–refractory hairy-cell leukemia who had a biallelic BRAF V600E mutation and a high leukemic burden during treatment with vemurafenib [24]. Because of the high numbers of circulating hairy-cell leukemia cells, it was possible to study the effects of vemurafenib directly in vivo. Vemurafenib induced complete clinical remission with reduction of the viability of $CD103^+$ hairy-cell leukemia cells during therapy. A pull-down and kinase assay showed inhibition of BRAF in leukemic cells in vivo. However, BRAF inhibition was not associated with any major changes in phosphorylation of either MEK or ERK in vivo, as shown by means of both immunoblot and flow cytometry, despite prolonged exposure to vemurafenib.

Table 1
Dynamics of response to BRAF inhibition with vemurafenib.

	Lines of prior therapy	Dose (mg) (BRAFi)	Therapy-duration	BM response	Platelets >100.000/μl	Neutrophils >1000/μl	Hemoglobin >12 g/dl
Dietrich, 2012	5	2×240–2×960	56 d	CR d43	d28	d13	d55
Peyrade, 2013	2	2×240	56 d	CR d90	d33	d35	d90
Follows, 2013	4	2×240	58 d	PR d68	d35	G-CSF	d68
Samuel, 2014	5	2×240	167 d	PR d169	d35	d35	d58

BM: bone marrow, d: days, CR: complete remission, PR: partial remission.

The authors did not provide a mechanistic explanation for the data provided and postulate the existence of an alternative signaling pathway.

A few years after the first successful studies of BRAF inhibitor treatment, the first reports on successful retreatment emerged [25]. Bailleux et al. reported successful retreatment of a patient with a second line of vemurafenib. Based on the discontinuation of the inhibitor, it is not surprising that re-exposure would lead to sufficient disease control. In their report, vemurafenib at the dose of 240 mg once a day was sufficient to maintain a complete hematological remission after an initial induction treatment with low-dose vemurafenib (2×240 mg), a finding which suggests that optimal dosing of vemurafenib may warrant further studies.

Dabrafenib is a reversible BRAF inhibitor with a shorter half-life compared to vemurafenib which is licensed for melanoma. Two recent reports showed effectiveness of dabrafenib in HCL [26,27].

Vergote reported a 62-year-old male patient with refractory HCL who achieved a rapid, complete hematological response to treatment with the BRAF inhibitor dabrafenib. Dabrafenib was started at a reduced dose of 100 mg twice daily (day 0) as the patient received antifungal treatment for active Aspergillosis. The dose was increased to 150 mg twice daily, as recommended in metastatic melanoma. The neutrophil count increased and infection resolved, further supporting the notion that BRAF inhibitors are safe in acute infections. Marrow aspirate and biopsy performed after 79 days of treatment with dabrafenib revealed rare hairy cells morphologically and <1% hairy cells by flow cytometry. Dabrafenib was discontinued after 129 days. Blachly and colleagues [27] report similar results in a patient with co-occurrence of melanoma and HCL both carrying the BRAF p.V600E mutation. Dabrafenib lead to successful treatment of both cancers.

Taken together these studies provide definite evidence that BRAF inhibition is active in HCL. BRAF inhibitor treatment will lead to a considerable reduction of HCL load, and is sufficient to achieve CRs in a fraction of patients. Most reports used considerably lower doses of vemurafenib suggesting that dose finding studies are needed to define optimal schedules for HCL.

Reports on clinical activity in trials

Soon after the discovery of BRAF V600E in HCL investigators from the US and Europe designed phase II trials testing vemurafenib at standard dosing in HCL [27].

In a study lead by investigators at MSKCC patients with HCL who were resistant to/intolerant of purine analogs, or who have achieved suboptimal response to purine analogs were enrolled to the trial. Eligible pts received vemurafenib 960 mg bid continuously in cycles of 4 weeks for 3 cycles. Pts with partial response (PR) or complete response (CR) with detectable minimal residual disease (MRD) were allowed to receive vemurafenib for up to 3 additional cycles at the discretion of treating physicians. Systematic collection of samples during treatment will allow dissection of potential predictors of response to vemurafenib and identify genes collaborating with *BRAF* mutations in HCL pathogenesis.

The median age was 62 years (range 49–77 years), and the median number of treatments prior to the study was 3 (range 1–7). The most common adverse events included rash, photosensitivity, arthralgia, hand-foot syndrome, febrile neutropenia and tumor lysis syndrome. Patients developed new squamous cell carcinoma ($n = 3$) and cutaneous basal-cell carcinoma ($n = 1$) while on therapy and successfully underwent complete resection. Fourteen patients required dose reductions to 480 mg bid. All patients achieved complete hematologic recovery and 10/24 patients achieved CR. Responses were rapid as shown by flow cytometry. Plasma levels of sCD25 normalized within 2–3 weeks, and this correlated with a rapid decrease of BRAF+ hairy cells and dephosphorylation of ERK after one cycle. The results indicate that vemurafenib has potent antitumor activity in pts with relapsed/refractory *BRAF* mutant HCL and confirm the MAP kinase pathway as a rational promising therapeutic target in HCL.

The parallel study from Italy, described in the same report in the NEJM, presented data from their phase-2, single-arm, multicenter study (HCL-PG01; EudraCT 2011-005487-13) [28]. 28 BRAF-V600E + HCL patients were enrolled (15 patients were disease refractory to immediate prior therapy; 21 patients who relapsed early and/or repeatedly after PAs; one patient with severe myelotoxicity after PA). Vemurafenib was given for a median of 16 weeks and had to be reduced below 2×960 mg in 17 of 28 patients. Drug-related events were frequent, but reversible in all patients, and were typically grade

1–2. Three patients developed either cutaneous basal-cell carcinomas (n = 2) or superficial melanoma and were all successfully treated with a simple excision.

Overall response rate was 96% (25/26 patients): 9/26 (34.6%) CRs and 16/26 (61.4%) PRs, obtained after a median of 8 and 9 weeks respectively. In all CR patients immunohistochemistry showed minimal residual disease ($\leq$10%) at the end of treatment. A number of patients were recently retreated and responded to subsequent exposure. The median relapse-free survival was 9 months; the relapse-free survival was significantly longer among patients who had a complete response than among those who had a partial response (19 months vs. 6 months).

Recommendations on clinical use of BRAFi

The compelling evidence of clinical activity of BRAF inhibitors in HCL suggests that this class of drugs is very effective in inducing remissions in the disease. The distinctly different mechanism of action and the current lack of evidence for sustained remissions after drug discontinuation, call for the development of combination approaches. Based on the current data trials investigating BRAF/MEK inhibitors should not be limited to advanced disease, if treatment duration can be limited.

Currently, outside of trials-refractory and early relapsing patients, patients with extensive pretreatment as well as patients with active infections are candidates for BRAF inhibitor treatment. In the future MEK/ERK inhibitor combinations are likely to further improve results and side effect profile.

HCL offers unique opportunities to investigate optimal dosing, because of the availability of primary tumor tissue from blood or marrow.

Practice points and research agenda

- Compelling evidence of clinical activity of BRAF inhibitors in HCL.
- Refractory and early relapsing patients, patients with extensive pretreatment as well as patients with active infections are candidates for BRAF inhibitor treatment.
- Dosing and schedule of BRAF inhibitors need to be identified.
- Optimal combination treatment with BRAF inhibitors are an attractive research question.

Conflict of interest

None.

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References

[1] Tiacci E, Liso A, Piris M, Falini B. Evolving concepts in the pathogenesis of hairy-cell leukaemia. Nat Rev Cancer 2006 Jun; 6(6):437–48.
[2] Davies H, Bignell GR, Cox C, Stephens P, Edkins S, Clegg S, et al. Mutations of the BRAF gene in human cancer. Nature 2002 Jun 27;417(6892):949–54.
[3] Wan PT, Garnett MJ, Roe SM, Lee S, Niculescu-Duvaz D, Good VM, et al. Mechanism of activation of the RAF-ERK signaling pathway by oncogenic mutations of B-RAF. Cell 2004 Mar 19;116(6):855–67.
[4] Pratilas CA, Solit DB. Targeting the mitogen-activated protein kinase pathway: physiological feedback and drug response. Clin Cancer Res 2010 Jul 1;16(13):3329–34.

[5] Korshunov A, Meyer J, Capper D, Christians A, Remke M, Witt H, et al. Combined molecular analysis of BRAF and IDH1 distinguishes pilocytic astrocytoma from diffuse astrocytoma. Acta Neuropathol 2009 Sep;118(3):401–5.
[6] Tiacci E, Trifonov V, Schiavoni G, Holmes A, Kern W, Martelli MP, et al. BRAF mutations in hairy-cell leukemia. N Engl J Med 2011 Jun 16;364(24):2305–15.
[7] Jethwa A, Hullein J, Stolz T, Blume C, Sellner L, Jauch A, et al. Targeted resequencing for analysis of clonal composition of recurrent gene mutations in chronic lymphocytic leukaemia. Br J Haematol 2013 Nov;163(4):496–500.
[8] Andrulis M, Penzel R, Weichert W, von Deimling A, Capper D. Application of a BRAF V600E mutation-specific antibody for the diagnosis of hairy cell leukemia. Am J Surg Pathol 2012 Dec;36(12):1796–800.
[9] Arcaini L, Zibellini S, Boveri E, Riboni R, Rattotti S, Varettoni M, et al. The BRAF V600E mutation in hairy cell leukemia and other mature B-cell neoplasms. Blood 2012 Jan 5;119(1):188–91.
[10] Blombery PA, Wong SQ, Hewitt CA, Dobrovic A, Maxwell EL, Juneja S, et al. Detection of BRAF mutations in patients with hairy cell leukemia and related lymphoproliferative disorders. Haematologica 2012 May;97(5):780–3.
[11] Schnittger S, Bacher U, Haferlach T, Wendland N, Ulke M, Dicker F, et al. Development and validation of a real-time quantification assay to detect and monitor BRAFV600E mutations in hairy cell leukemia. Blood 2012 Mar 29;119(13):3151–4.
[12] Dietrich S, Glimm H, Andrulis M, von Kalle C, Ho AD, Zenz T. BRAF inhibition in refractory hairy-cell leukemia. N Engl J Med 2012 May 24;366(21):2038–40.
[13] Dietrich S, Hullein J, Hundemer M, Lehners N, Jethwa A, Capper D, et al. Continued response off treatment after BRAF inhibition in refractory hairy cell leukemia. J Clin Oncol 2013 Jul 1;31(19):e300–3.
[14] Waterfall JJ, Arons E, Walker RL, Pineda M, Roth L, Killian JK, et al. High prevalence of MAP2K1 mutations in variant and IGHV4-34-expressing hairy-cell leukemias. Nat Genet 2014 Jan;46(1):8–10.
[15] Dietrich S, Hullein J, Lee SC, Hutter B, Gonzalez D, Jayne S, et al. Recurrent CDKN1B (p27) mutations in hairy cell leukemia. Blood 2015 Jun 11. http://dx.doi.org/10.1182/blood-2015-04-643361.
[16] Dietrich S, Hullein J, Lee SC, Hutter B, Gonzalez D, Jayne S, et al. Recurrent CDKN1B (p27) mutations in hairy cell leukemia. Blood 2015 Aug 20;126(8):1005–8.
[17] Chapman PB, Hauschild A, Robert C, Haanen JB, Ascierto P, Larkin J, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med 2011 Jun 30;364(26):2507–16.
[18] Ribas A, Flaherty KT. BRAF targeted therapy changes the treatment paradigm in melanoma. Nat Rev Clin Oncol 2011 Jul;8(7):426–33.
[19] Follows GA, Sims H, Bloxham DM, Zenz T, Hopper MA, Liu H, et al. Rapid response of biallelic BRAF V600E mutated hairy cell leukaemia to low dose vemurafenib. Br J Haematol 2013 Apr;161(1):150–3.
[20] Peyrade F, Re D, Ginet C, Gastaud L, Allegra M, Ballotti R, et al. Low-dose vemurafenib induces complete remission in a case of hairy-cell leukemia with a V600E mutation. Haematologica 2013 Feb;98(2):e20–2.
[21] Grever MR. How I treat hairy cell leukemia. Blood 2010 Jan 7;115(1):21–8.
[22] Munoz J, Schlette E, Kurzrock R. Rapid response to vemurafenib in a heavily pretreated patient with hairy cell leukemia and a BRAF mutation. J Clin Oncol 2013 Jul 10;31(20):e351–2.
[23] Maurer H, Haas P, Wengenmayer T, Lubbert M, Duyster J, Zeiser R. Successful vemurafenib salvage treatment in a patient with primary refractory hairy cell leukemia and pulmonary aspergillosis. Ann Hematol 2014 Aug;93(8):1439–40.
[24] Samuel J, Macip S, Dyer MJ. Efficacy of vemurafenib in hairy-cell leukemia. N Engl J Med 2014 Jan 16;370(3):286–8.
[25] Bailleux C, Robert G, Ginet C, Re D, Thyss A, Sudaka I, et al. Successful re-treatment of a relapsed V600E mutated HCL patient with low-dose vemurafenib. Oncoscience 2015;2(1):44–9.
[26] Vergote V, Dierickx D, Janssens A, Verhoef G, Tousseyn T, Vandenberghe P, et al. Rapid and complete hematological response of refractory hairy cell leukemia to the BRAF inhibitor dabrafenib. Ann Hematol 2014 Dec;93(12):2087–9.
[27] Blachly JS, Lozanski G, Lucas DM, Grever MR, Kendra K, Andritsos LA. Cotreatment of hairy cell leukemia and melanoma with the BRAF inhibitor dabrafenib. J Natl Compr Canc Netw 2015 Jan;13(1):9–13. quiz.
[28] Tiacci E, Park JH, De Carolis L, Chung SS, Broccoli A, Scott S, et al. Targeting mutant BRAF in relapsed or refractory hairy-cell leukemia. N Engl J Med 2015 Sep 9. http://dx.doi.org/10.1056/NEJMoa1506583.