

RECOMENDACIÓN T2

BÚSQUEDA Y SÍNTESIS DE EVIDENCIA DE EFECTOS DESEABLES E INDESEABLES Guía de Práctica Clínica Leucemia Aguda en personas de 15 años y más - 2018

A. PREGUNTA CLÍNICA

En personas con leucemia linfoblástica aguda Philadelphia positivo Ph (+) ¿Se debe usar quimioterapia más inhibidores de la tirosina quinasa (TKI) de 1era y 2ª generación, en comparación a realizar sólo quimioterapia?

Análisis y definición de los componentes de la pregunta en formato PICO

Población: Personas con leucemia linfoblástica aguda Philadelphia positivo Ph (+).

Intervención: Inhibidores de la tirosina quinasa (TKI) de 1era y 2ª generación.

Comparación: Quimioterapia.

Desenlace (outcome): Impacto clínico.

B. BÚSQUEDA DE EVIDENCIA

Se realizó una búsqueda general de revisiones sistemáticas asociadas al tema de “Acute lymphoblastic leukemia” y “Acute myeloid leukemia”. Las bases de datos utilizadas fueron: Cochrane database of systematic reviews (CDSR); Database of Abstracts of Reviews of Effectiveness (DARE); HTA Database; PubMed; LILACS; CINAHL; PsycINFO; EMBASE; EPPI-Centre Evidence Library; 3ie Systematic Reviews and Policy Briefs Campbell Library; Clinical Evidence; SUPPORT Summaries; WHO institutional Repository for information Sharing; NICE public health guidelines and systematic reviews; ACP Journal Club; Evidencias en Pediatría; y The JBI Database of Systematic Reviews and implementation Reports. No se aplicaron restricciones en base al idioma o estado de publicación. Dos revisores de manera independiente realizaron la selección de los títulos y los resúmenes, la evaluación del texto completo y la extracción de datos. Un investigador experimentado resolvió cualquier discrepancia entre los distintos revisores. En caso de considerarse necesario, se integraron estudios primarios.¹

Seleccionadas las revisiones sistemáticas o estudios primarios asociadas a la temática, se clasificaron en función de las potenciales preguntas a las que daban respuesta. Al momento de definir la pregunta la evidencia ya se encontraba previamente clasificada según intervenciones comparadas. Los resultados se encuentran alojados en la plataforma Living Overview of the Evidence (L·OVE), sistema que permite la actualización periódica de la evidencia.

¹ Para revisar la metodología, las estrategias y los resultados de la búsqueda, favor revisar el informe “Búsqueda sistemática de evidencia de los efectos deseables e indeseables” en la sección de método de la Guía de Práctica Clínica respectiva.

C. SÍNTESIS DE EVIDENCIA

Resumen de la evidencia identificada

No se identificaron revisiones sistemáticas pertinentes a la pregunta de interés. Se expandió la búsqueda a través de síntesis amplia, guías clínicas [1-3] y citación cruzada sin identificar ensayos evaluando la pregunta exacta.

Tabla 1: Resumen de la evidencia seleccionada

| | |
|----------------------|---|
| Revisión Sistemática | 0 |
| Estudios primarios | 0 |

Además, se analizaron 14 artículos provistos por el equipo de expertos participantes del panel convocado para elaborar la guía [4-17] y también se revisaron las referencias citadas en estos artículos y se buscaron artículos que citaran a los artículos provistos, dando un total de 80 artículos potencialmente relevantes [18-97].

Estimador del efecto

Se realizó un análisis de los artículos, identificando que si bien la mayoría de estos no responde la pregunta de interés, la identificación de ellos proviene por una búsqueda no sistemática, lo cual expone a un alto riesgo de sesgo de publicación, especialmente proviniendo de una intervención de costo elevado. De acuerdo a la metodología GRADE, la síntesis de evidencia siempre debe provenir de una búsqueda sistemática y exhaustiva de estudios primarios para minimizar el sesgo de publicación. Ya que en este caso, no se cumple la regla, el equipo de síntesis en conjunto con el equipo metodológico MINSAL decidió no construir la tabla de resumen de resultados.

Metanálisis

No aplica.

Tabla de Resumen de Resultados (Summary of Findings)

| INHIBIDORES DE TIROSINA KINASA PARA LEUCEMIA LINFOBLÁSTICA AGUDA PHILADELPHIA POSITIVO | | | |
|----------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|---------------------------------|--------------------------------------|
| Población | Personas con leucemia linfoblástica aguda Philadelphia positivo Ph (+). | | |
| Intervención | Inhibidores de tirosina kinasa más quimioterapia | | |
| Comparación | Quimioterapia. | | |
| Desenlaces | Efecto | Certeza de la evidencia (GRADE) | Mensajes clave en términos sencillos |
| Impacto clínico | Se decidió no construir la tabla de resumen de resultados. Ver detalles en estimador del efecto. | -- | -- |

GRADE: Grados de evidencia Grading of Recommendations Assessment, Development and Evaluation.
*Impacto clínico se refiere a cualquier desenlace que tenga impacto directo o indirecto en el manejo de los pacientes. Esto incluye a los desenlaces priorizados por el panel de expertos.
Fecha de elaboración de la tabla: Diciembre, 2018.

Referencias

1. Couban S, Savoie L, Mourad YA, Leber B, Minden M, Turner R, Palada V, Shehata N, Christofides A, Lachance S. Evidence-based guidelines for the use of tyrosine kinase inhibitors in adults with Philadelphia chromosome-positive or BCR-ABL-positive acute lymphoblastic leukemia: a Canadian consensus. *Current oncology (Toronto, Ont.)*. 2014;21(2):e265-309.
2. Hoelzer D, Bassan R, Dombret H, Fielding A, Ribera JM, Buske C, ESMO Guidelines Committee. Acute lymphoblastic leukaemia in adult patients: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of oncology : official journal of the European Society for Medical Oncology*. 2016;27(suppl 5):v69-v82.
3. Brown PA, Shah B, Fathi A, Wieduwilt M, Advani A, Aoun P, Barta SK, Boyer MW, Bryan T, Burke PW, Cassaday R, Coccia PF, Coutre SE, Damon LE, DeAngelo DJ, Frankfurt O, Greer JP, Kantarjian HM, Klisovic RB, Kupfer G, Litzow M, Liu A, Mattison R, Park J, Rubnitz J, Saad A, Uy GL, Wang ES, Gregory KM, Ogba N. NCCN Guidelines Insights: Acute Lymphoblastic Leukemia, Version 1.2017. *Journal of the National Comprehensive Cancer Network : JNCCN*. 2017;15(9):1091-1102
4. Chalandon Y, Thomas X, Hayette S, Cayuela JM, Abbal C, Huguet F, Raffoux E, Leguay T, Rousselot P, Lepretre S, Escoffre-Barbe M, Maury S, Berthon C, Tavernier E, Lambert JF, Lafage-Pochitaloff M, Lhéritier V, Chevret S, Ifrah N, Dombret H; Group for Research on Adult Acute Lymphoblastic Leukemia (GRAALL). Randomized study of reduced-intensity chemotherapy combined with imatinib in adults with Ph-positive acute lymphoblastic leukemia. *Blood*. 2015 Jun 11;125(24):3711-9
5. Chiaretti S, Foà R. Management of adult Ph-positive acute lymphoblastic leukemia. *Hematology Am Soc Hematol Educ Program*. 2015;2015:406-13
6. Daver N, Thomas D, Ravandi F, Cortes J, Garris R, Jabbour E, Garcia-Manero G, Borthakur G, Kadia T, Rytting M, Konopleva M, Kantarjian H, O'Brien S. Final report of a phase II study of imatinib mesylate with hyper-CVAD for the front-line treatment of adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. *Haematologica*. 2015 May;100(5):653-61
7. Fielding AK. How I treat Philadelphia chromosome-positive acute lymphoblastic leukemia. *Blood*. 2010 Nov 4;116(18):3409-17
8. Gökbüget N. How I treat older patients with ALL. *Blood*. 2013 Aug 22;122(8):1366-75
9. Lee KH, Lee JH, Choi SJ, Lee JH, Seol M, Lee YS, Kim WK, Lee JS, Seo EJ, Jang S, Park CJ, Chi HS. Clinical effect of imatinib added to intensive combination chemotherapy for newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia. *Leukemia*. 2005 Sep;19(9):1509-16
10. Leoni V, Biondi A. Tyrosine kinase inhibitors in BCR-ABL positive acute lymphoblastic leukemia. *Haematologica*. 2015 Mar;100(3):295-9
11. Ottmann OG, Larson RA, Kantarjian HM, le Coutre PD, Baccarani M, Hochhaus A, Kim DW, Fan X, Novick S, Giles FJ. Phase II study of nilotinib in patients with relapsed or refractory Philadelphia chromosome--positive acute lymphoblastic leukemia. *Leukemia*. 2013 Jun;27(6):1411-3
12. Ottmann OG, Pfeifer H. Management of Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL). *Hematology Am Soc Hematol Educ Program*. 2009:371-81
13. Ottmann OG, Wassmann B, Pfeifer H, Giagounidis A, Stelljes M, Dührsen U, Schmalzing M, Wunderle L, Binckebanck A, Hoelzer D; GMALL Study Group. Imatinib compared with

- chemotherapy as front-line treatment of elderly patients with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ALL). *Cancer*. 2007 May 15;109(10):2068-76
14. Rousselot P, Cayuela JM, Hayette S, Récher C, Leguay T, Salanoubat C, Agape P. Dasatinib (Sprycel®) and low intensity chemotherapy for first-line treatment in elderly patients with de novo Philadelphia positive ALL (EWALL-PH-01): kinetic of response, resistance and prognostic significance. *American Society of Hematology*. 2010
 15. Thomas DA, Faderl S, Cortes J, O'Brien S, Giles FJ, Kornblau SM, Garcia-Manero G, Keating MJ, Andreeff M, Jeha S, Beran M, Verstovsek S, Pierce S, Letvak L, Salvado A, Champlin R, Talpaz M, Kantarjian H. Treatment of Philadelphia chromosome-positive acute lymphocytic leukemia with hyper-CVAD and imatinib mesylate. *Blood*. 2004 Jun 15;103(12):4396-407
 16. Vignetti M, Fazi P, Cimino G, Martinelli G, Di Raimondo F, Ferrara F, Meloni G, Ambrosetti A, Quarta G, Pagano L, Rege-Cambrin G, Elia L, Bertieri R, Annino L, Foà R, Baccarani M, Mandelli F. Imatinib plus steroids induces complete remissions and prolonged survival in elderly Philadelphia chromosome-positive patients with acute lymphoblastic leukemia without additional chemotherapy: results of the Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) LAL0201-B protocol. *Blood*. 2007 May 1;109(9):3676-8
 17. Yanada M. Time to tune the treatment of Ph+ ALL. *Blood*. 2015 Jun 11;125(24):3674-5
 18. AK F, SM R, HM L, al. et. Does imatinib change the outcome in Philadelphia chromosome positive acute lymphoblastic leukaemia in adults? Data from the ukallxii/ecog2993 Study. *Blood [Internet]*. 2007;110
 19. AM C, Catania G, Pica G, al. et. Adult Philadelphia-positive acute lymphoblastic leukemia (Ph + all) treated at diagnosis with imatinib followed by 2nd line tki (imatinib or dasatinib) and stem cell transplantation. *Blood [Internet]*. 2009;114
 20. Anderlini P, Sheth S, Hicks K, Ippoliti C, Giralt S, Champlin RE. Re: Imatinib mesylate administration in the first 100 days after stem cell transplantation. *Biol Blood Marrow Transplant [Internet]*. 2004 Dec 18;10(12):883–4
 21. Arellano M, Muringampurath–John D, PJ S, al. et. Imatinib mesylate and hyper-cvad (im-hcvad) for Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ all). *Blood [Internet]*. 2009;114
 22. Aricò M, Valsecchi MG, Camitta B, Schrappe M, Chessells J, Baruchel A, et al. Outcome of treatment in children with Philadelphia chromosome-positive acute lymphoblastic leukemia. *N Engl J Med [Internet]*. 2000;342(14):998–1006
 23. Aricò M, Schrappe M, Hunger SP, Carroll WL, Conter V, Galimberti S, et al. Clinical outcome of children with newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia treated between 1995 and 2005. *J Clin Oncol Off J Am Soc Clin Oncol [Internet]*. 2010;28(31):4755–61
 24. Bachanova V, Marks DI, Zhang M-J, Wang H, de Lima M, Aljurf MD, et al. Ph+ ALL patients in first complete remission have similar survival after reduced intensity and myeloablative allogeneic transplantation: impact of tyrosine kinase inhibitor and minimal residual disease. *Leukemia [Internet]*. 2014;28(3):658–65
 25. Bassan R, Rossi G, EM P, al. et. Short chemotherapy-phased imatinib (im) pulses improve long-term outcome of adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ all). *Blood [Internet]*. 2009;114
 26. Bassan R, Rossi G, Pogliani EM, Di Bona E, Angelucci E, Cavattoni I, et al. Chemotherapy-phased imatinib pulses improve long-term outcome of adult patients with Philadelphia chromosome-

- positive acute lymphoblastic leukemia: Northern Italy Leukemia Group protocol 09/00. *J Clin Oncol Off J Am Soc Clin Oncol* [Internet]. 2010;28(22):3644–52
27. Biondi A, Schrappe M, De Lorenzo P, Castor A, Lucchini G, Gandemer V, et al. Imatinib after induction for treatment of children and adolescents with Philadelphia-chromosome-positive acute lymphoblastic leukaemia (EsPhALL): a randomised, open-label, intergroup study. *Lancet Oncol* [Internet]. 2012;13(9):936–45
 28. Brave M, Goodman V, Kaminskas E, Farrell A, Timmer W, Pope S, et al. Sprycel for chronic myeloid leukemia and Philadelphia chromosome-positive acute lymphoblastic leukemia resistant to or intolerant of imatinib mesylate. *Clin Cancer Res* [Internet]. 2008;14(2):352–9
 29. Burke MJ, Trotz B, Luo X, Baker KS, Weisdorf DJ, Wagner JE, et al. Allo-hematopoietic cell transplantation for Ph chromosome-positive ALL: impact of imatinib on relapse and survival. *Bone Marrow Transplant* [Internet]. 2009;43(2):107–13
 30. Carpenter PA, Snyder DS, Flowers MED, Sanders JE, Gooley TA, Martin PJ, et al. Prophylactic administration of imatinib after hematopoietic cell transplantation for high-risk Philadelphia chromosome-positive leukemia. *Blood* [Internet]. 2007 Dec 18;109(7):2791–3
 31. Chalandon Y, Thomas X, Hayette S, JM C, Abbal C, Huguet F, et al. Randomized study of reduced-intensity chemotherapy combined with imatinib in adults with Ph-positive acute lymphoblastic leukemia. *Blood* [Internet]. 2015 Dec 18;125(24):3711–9
 32. Chang H, LY S. Imatinib-induced tumor lysis syndrome: report of a case and review of the literature. *Chang Gung Med J* [Internet]. 2008;31(5):510–4
 33. Chiaretti S, Foà R. Management of adult Ph-positive acute lymphoblastic leukemia. *ASH Educ Progr B* [Internet]. 2015 Dec 18;2015(1):406–13
 34. Cortes J, DW K, Raffoux E, Martinelli G, Ritchie E, Roy L, et al. Efficacy and safety of dasatinib in imatinib-resistant or -intolerant patients with chronic myeloid leukemia in blast phase. *Leuk Off J Leuk Soc Am Leuk Res Fund, UK* [Internet]. 2008;22(12):2176–83
 35. Cortes J, Rousselot P, DW K, Ritchie E, Hamerschlak N, Coutre S, et al. Dasatinib induces complete hematologic and cytogenetic responses in patients with imatinib-resistant or -intolerant chronic myeloid leukemia in blast crisis. *Blood* [Internet]. 2007;109(8):3207–13
 36. DA T, Faderl S, Cortes J, al et. Update of the hypercvad and imatinib mesylate regimen in Philadelphia (Ph) positive acute lymphocytic leukemia (all). *Blood* [Internet]. 2004;104
 37. DA T, HM K, Cortes J, al. et. Outcome after frontline therapy with the hyper-cvad and imatinib mesylate regimen for adults with de novo or minimally treated Philadelphia chromosome (Ph) positive acute lymphoblastic leukemia (all). *Blood* [Internet]. 2008;112
 38. DA T, SM O, Faderl S, al. et. Long-term outcome after hyper-cvad and imatinib (im) for de novo or minimally treated Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph-all). *J Clin Oncol* [Internet]. 2010;28
 39. Daver N, Thomas D, Ravandi F, Cortes J, Garris R, Jabbour E, et al. Final report of a phase II study of imatinib mesylate with hyper-CVAD for the front-line treatment of adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. *Haematologica* [Internet]. 2015 Dec 18;100(5):653–61
 40. de Labarthe A, Rousselot P, Huguet-Rigal F, Delabesse E, Witz F, Maury S, et al. Imatinib combined with induction or consolidation chemotherapy in patients with de novo Philadelphia chromosome-positive acute lymphoblastic leukemia: results of the GRAAPH-2003 study. *Blood* [Internet]. 2007;109(4):1408–13

41. Delannoy A, Delabesse E, Lhéritier V, Castaigne S, Rigal-Huguet F, Raffoux E, et al. Imatinib and methylprednisolone alternated with chemotherapy improve the outcome of elderly patients with Philadelphia-positive acute lymphoblastic leukemia: results of the GRAALL AFR09 study. *Leukemia* [Internet]. 2006;20(9):1526–32
42. Dombret H, Witz F, S DB, al. et. Imatinib combined with intensive ham chemotherapy as consolidation of Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph1-all). Preliminary results of the AFR03 phase i/ii study. *Blood* [Internet]. 2004;104
43. Fielding AK. How I treat Philadelphia chromosome-positive acute lymphoblastic leukemia. *Blood* [Internet]. 2010;116(18):3409–17
44. Fielding AK, Rowe JM, Buck G, Foroni L, Gerrard G, Litzow MR, et al. UKALLXII/ECOG2993: addition of imatinib to a standard treatment regimen enhances long-term outcomes in Philadelphia positive acute lymphoblastic leukemia. *Blood* [Internet]. 2014;123(6):843–50
45. Fielding AK, Rowe JM, Richards SM, Buck G, Moorman A V, Durrant IJ, et al. Prospective outcome data on 267 unselected adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia confirms superiority of allogeneic transplantation over chemotherapy in the pre-imatinib era: results from the International ALL Trial MRC UKALLXII/ECOG2993. *Blood* [Internet]. 2009;113(19):4489–96
46. Foà R, Vitale A, Vignetti M, Meloni G, Guarini A, De Propriis MS, et al. Dasatinib as first-line treatment for adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. *Blood* [Internet]. 2011;118(25):6521–8
47. Gleissner B, Gökbuget N, Bartram CR, Janssen B, Rieder H, Janssen JWG, et al. Leading prognostic relevance of the BCR-ABL translocation in adult acute B-lineage lymphoblastic leukemia: a prospective study of the German Multicenter Trial Group and confirmed polymerase chain reaction analysis. *Blood* [Internet]. 2002;99(5):1536–43
48. Hematology AS of. Chalandon Y, Thomas X, Hayette S, et al; Group for Research on Adult Acute Lymphoblastic Leukemia (GRAALL). Randomized study of reduced-intensity chemotherapy combined with imatinib in adults with Ph-positive acute lymphoblastic leukemia. *Blood*. 2015;125(24):3711-3719. *Blood* [Internet]. 2015 Dec 18;126(10):1261
49. Jabbour E, Kantarjian HM, Thomas DA, Sasaki K, Ravandi F, Cortes JE, et al. Phase II Study of Combination of Hypercvad with Ponatinib in Front Line Therapy of Patients (pts) with Philadelphia Chromosome (Ph) Positive Acute Lymphoblastic Leukemia (ALL). *Blood* [Internet]. 2014 Dec 18;124(21):2289
50. JM R, Oriol A, Gonzalez M, al. et. Treatment of Philadelphia chromosome (Ph)-positive acute lymphoblastic leukemia (all) with concurrent chemotherapy and imatinib mesylate. *Blood* [Internet]. 2004;104
51. Kantarjian H, Giles F, Wunderle L, Bhalla K, O'Brien S, Wassmann B, et al. Nilotinib in imatinib-resistant CML and Philadelphia chromosome-positive ALL. *N Engl J Med* [Internet]. 2006;354(24):2542–51
52. Kantarjian HM, O'Brien S, Smith TL, Cortes J, Giles FJ, Beran M, et al. Results of Treatment With Hyper-CVAD, a Dose-Intensive Regimen, in Adult Acute Lymphocytic Leukemia. *J Clin Oncol* [Internet]. 2016 Dec 18
53. Koskenvesa P, Kreutzman A, Rohon P, Pihlman M, Vakkila E, Räsänen A, et al. Imatinib and pegylated IFN- α 2b discontinuation in first-line chronic myeloid leukemia patients following a major molecular response. *Eur J Haematol* [Internet]. 2014;92(5):413–20

54. KR S, WP B, Aledo A, WB S, Sather H, Devidas M, et al. Improved early event-free survival with imatinib in Philadelphia chromosome-positive acute lymphoblastic leukemia: a children's oncology group study. *J Clin Oncol* [Internet]. 2009;27(31):5175–81
55. Lee K-H, Lee J-SJ-H, Choi S-J, Seol M, Lee Y-S, Kim W-K, et al. Clinical effect of imatinib added to intensive combination chemotherapy for newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia | *Leukemia*. *Leukemia* [Internet]. 2018 Dec 18;19(9):1509–16
56. Lee S, DW K, YJ K, al. et. Minimal residual disease-based role of imatinib as a first-line interim therapy prior to allogeneic stem cell transplantation in Philadelphia chromosome-positive acute lymphoblastic leukemia. *Blood* [Internet]. 2003;102:3068–70
57. Lee S, Kim D-W, Cho B, Kim Y-J, Kim Y-L, Hwang J-Y, et al. Risk factors for adults with Philadelphia-chromosome-positive acute lymphoblastic leukaemia in remission treated with allogeneic bone marrow transplantation: the potential of real-time quantitative reverse-transcription polymerase chain reaction. *Br J Haematol* [Internet]. 2003;120(1):145–53
58. Lee S, Kim Y-J, Min C-K, Kim H-J, Eom K-S, Kim D-W, et al. The effect of first-line imatinib interim therapy on the outcome of allogeneic stem cell transplantation in adults with newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia. *Blood* [Internet]. 2005;105(9):3449–57
59. Leoni V, Biondi A. Tyrosine kinase inhibitors in BCR-ABL positive acute lymphoblastic leukemia. *Haematologica* [Internet]. 2015 Dec 18;100(3):295–9
60. Lesokhin AM, Ansell SM, Armand P, Scott EC, Halwani A, Gutierrez M, et al. Preliminary Results of a Phase I Study of Nivolumab (BMS-936558) in Patients with Relapsed or Refractory Lymphoid Malignancies. *Blood* [Internet]. 2014;124(21):291
61. Marks DI, Wang T, Pérez WS, Antin JH, Copelan E, Gale RP, et al. The outcome of full-intensity and reduced-intensity conditioning matched sibling or unrelated donor transplantation in adults with Philadelphia chromosome-negative acute lymphoblastic leukemia in first and second complete remission. *Blood* [Internet]. 2010;116(3):366–74
62. MB L, OG O, NP S, RA L, JJ R, Ehninger G, et al. Dasatinib 140 mg once daily versus 70 mg twice daily in patients with Ph-positive acute lymphoblastic leukemia who failed imatinib: Results from a phase 3 study. *Am J Hematol* [Internet]. 2010;85(3):164–70
63. OG O, RA L, HM K, al. et. Nilotinib in patients (pts) with relapsed/refractory Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ all) who are resistant or intolerant to imatinib. *Blood* [Internet]. 2007;110
64. OG O, Wassmann B, Pfeifer H, Giagounidis A, Stelljes M, Dührsen U, et al. Imatinib compared with chemotherapy as front-line treatment of elderly patients with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ALL). *Cancer* [Internet]. 2007 Dec 18;109(10):2068–76
65. Olivieri A, Locatelli F, Zecca M, Sanna A, Cimminiello M, Raimondi R, et al. Imatinib for refractory chronic graft-versus-host disease with fibrotic features. *Blood* [Internet]. 2009;114(3):709–18
66. Ottmann OG, Larson RA, Kantarjian HM, le Coutre PD, Baccarani M, Hochhaus A, et al. Phase II study of nilotinib in patients with relapsed or refractory Philadelphia chromosome-positive acute lymphoblastic leukemia. *Leukemia* [Internet]. 2013 Dec 18;27(6):1411–3
67. Ottmann O, Dombret H, Martinelli G, al. et, Simonsson B, Guilhot F, et al. Dasatinib induces rapid hematologic and cytogenetic responses in adult patients with Philadelphia chromosome

- positive acute lymphoblastic leukemia with resistance or intolerance to imatinib: interim results of a phase 2 study. *Blood* [Internet]. 2007;110(7):2309–15
68. Ottmann OG, Druker BJ, Sawyers CL, Goldman JM, Reiffers J, Silver RT, et al. A phase 2 study of imatinib in patients with relapsed or refractory Philadelphia chromosome-positive acute lymphoid leukemias. *Blood* [Internet]. 2002;100(6):1965–71
 69. Ottmann OG, Pfeifer H. Management of Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL). *ASH Educ Progr B* [Internet]. 2009 Dec 18;2009(1):371–81
 70. Ottmann OG, Pfeifer H, Cayuela J-M, Spiekermann K, Beck J, Jung WE, et al. Nilotinib (Tasigna®) and Chemotherapy for First-Line Treatment in Elderly Patients with De Novo Philadelphia Chromosome/BCR-ABL1 Positive Acute Lymphoblastic Leukemia (ALL): A Trial of the European Working Group for Adult ALL (EWALL-PH-02). *Blood* [Internet]. 2014 Dec 18;124(21):798
 71. Pfeifer H, Goekbuget N, Volp C, et al. Long-term outcome of 335 adult patients receiving different schedules of imatinib and chemotherapy as front-line treatment for Philadelphia-positive acute lymphoblastic leukemia (Ph+ all). *Blood* [Internet]. 2010;116
 72. Pfeifer H, Wassmann B, Bethge W, Dengler J, Bornhäuser M, Stadler M, et al. Randomized comparison of prophylactic and minimal residual disease-triggered imatinib after allogeneic stem cell transplantation for BCR-ABL1-positive acute lymphoblastic leukemia. *Leukemia* [Internet]. 2013;27(6):1254–62
 73. Pfeifer H, Wassmann B, Kabisch A, et al. Imatinib and interferon- alpha maintenance therapy for patients with Philadelphia-positive acute lymphoblastic leukemia (Ph+ all) ineligible for allogeneic stem cell transplantation (sct). *Blood* [Internet]. 2009;114:2042
 74. Pfeifer H, Wassmann B, WA B, et al. Updated long-term results of a randomized comparison of prophylactic and pre-emptive imatinib following allogeneic stem cell transplantation for Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ all). *ASH Annu Meet Abstr* [Internet]. 2011;118
 75. Pui C-H, Evans WE. Treatment of Acute Lymphoblastic Leukemia. *N Engl J Med* [Internet]. 2006 Dec 18;354(2):166–78
 76. Ravandi F, O'Brien S, Thomas D, Faderl S, Jones D, Garris R, et al. First report of phase 2 study of dasatinib with hyper-CVAD for the frontline treatment of patients with Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia. *Blood* [Internet]. 2010 Dec 18;116(12):2070–7
 77. Ribera J-M, Oriol A, González M, Vidriales B, Brunet S, Esteve J, et al. Concurrent intensive chemotherapy and imatinib before and after stem cell transplantation in newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia. Final results of the CSTIBES02 trial. *Haematologica* [Internet]. 2010;95(1):87–95
 78. Rousselot P, Cayuela JM, Hayette S, Récher C, Leguay T, Salanoubat C, et al. Dasatinib (Sprycel®) and Low Intensity Chemotherapy for First-Line Treatment In Elderly Patients with De Novo Philadelphia Positive ALL (EWALL-PH-01): Kinetic of Response, Resistance and Prognostic Significance. *Blood* [Internet]. 2010 Dec 18;116(21):172
 79. Rousselot P, Coudé MM, Huguet F, Lafage M, Leguay T, Salanoubat C, et al. Dasatinib (Sprycel®) and Low Intensity Chemotherapy for First-Line Treatment in Patients with De Novo Philadelphia Positive ALL Aged 55 and Over: Final Results of the EWALL-Ph-01 Study. *Blood* [Internet]. 2012 Dec 18;120(21):666
 80. Saglio G, Hochhaus A, YT G, Masszi T, Pasquini R, Maloisel F, et al. Dasatinib in imatinib-resistant or imatinib-intolerant chronic myeloid leukemia in blast phase after 2 years of follow-

- up in a phase 3 study: efficacy and tolerability of 140 milligrams once daily and 70 milligrams twice daily. *Cancer* [Internet]. 2010;116(16):3852–61
81. Sakamaki H, Ishizawa K, Taniwaki M, Fujisawa S, Morishima Y, Tobinai K, et al. Phase 1/2 clinical study of dasatinib in Japanese patients with chronic myeloid leukemia or Philadelphia chromosome-positive acute lymphoblastic leukemia. *Int J Hematol* [Internet]. 2009;89(3):332–41
 82. Schlegel P, Lang P, Zugmaier G, Ebinger M, Kreyenberg H, Witte K-E, et al. Pediatric posttransplant relapsed/refractory B-precursor acute lymphoblastic leukemia shows durable remission by therapy with the T-cell engaging bispecific antibody blinatumomab. *Haematologica* [Internet]. 2014;99(7):1212–9
 83. Schultz KR, Carroll A, Heerema NA, Bowman WP, Aledo A, Slayton WB, et al. Long-term follow-up of imatinib in pediatric Philadelphia chromosome-positive acute lymphoblastic leukemia: Children's Oncology Group study AALL0031. *Leukemia* [Internet]. 2014;28(7):1467–71
 84. Squibb B-M. Advanced Chronic Myelogenous Leukemia (CML) - Follow On: Study of BMS-354825 in Subjects With CML. *clinicaltrials.gov* [Internet]. 2005
 85. Stirewalt DL, Guthrie KA, Beppu L, Bryant EM, Doney K, Gooley T, et al. Predictors of relapse and overall survival in Philadelphia chromosome-positive acute lymphoblastic leukemia after transplantation. *Biol Blood Marrow Transplant J Am Soc Blood Marrow Transplant* [Internet]. 2003;9(3):206–12
 86. Talpaz M, NP S, Kantarjian H, Donato N, Nicoll J, Paquette R, et al. Dasatinib in imatinib-resistant Philadelphia chromosome-positive leukemias. *N Engl J Med* [Internet]. 2006;354(24):2531–41
 87. Thomas DA, Faderl S, Cortes J, O'Brien S, Giles FJ, Kornblau SM, et al. Treatment of Philadelphia chromosome-positive acute lymphocytic leukemia with hyper-CVAD and imatinib mesylate. *Blood* [Internet]. 2004 Dec 18;103(12):4396–407
 88. Tojo A, Usuki K, Urabe A, Maeda Y, Kobayashi Y, Jinnai I, et al. A Phase I/II study of nilotinib in Japanese patients with imatinib-resistant or -intolerant Ph+ CML or relapsed/refractory Ph+ ALL. *Int J Hematol* [Internet]. 2009;89(5):679–88
 89. Topp MS, Kufer P, Gökbuget N, Goebeler M, Klinger M, Neumann S, et al. Targeted therapy with the T-cell-engaging antibody blinatumomab of chemotherapy-refractory minimal residual disease in B-lineage acute lymphoblastic leukemia patients results in high response rate and prolonged leukemia-free survival. *J Clin Oncol Off J Am Soc Clin Oncol* [Internet]. 2011;29(18):2493–8
 90. Vignetti M, Fazi P, Cimino G, Martinelli G, Raimondo F Di, Ferrara F, et al. Imatinib plus steroids induces complete remissions and prolonged survival in elderly Philadelphia chromosome-positive patients with acute lymphoblastic leukemia without additional chemotherapy: results of the Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) LAL0201-B protocol. *Blood* [Internet]. 2007 Dec 18;109(9):3676–8
 91. Wassmann B, Gökbuget N, UJ S, Binckebanck A, Reutzel R, Gschaidmeier H, et al. A randomized multicenter open label phase II study to determine the safety and efficacy of induction therapy with imatinib (Glivec, formerly STI571) in comparison with standard induction chemotherapy in elderly (>55 years) patients with Philadelphia chromosome-positive (Ph+/BCR-ABL+) acute lymphoblastic leukemia (ALL) (CSTI571ADE 10). *Ann Hematol* [Internet]. 2003;82(11):716–20

92. Wassmann B, Pfeifer H, Goekbuget N, Beelen DW, Beck J, Stelljes M, et al. Alternating versus concurrent schedules of imatinib and chemotherapy as front-line therapy for Philadelphia-positive acute lymphoblastic leukemia (Ph+ ALL). *Blood* [Internet]. 2006;108(5):1469–77
93. Wassmann B, Pfeifer H, Stadler M, Bornhäuser M, Bug G, Scheuring UJ, et al. Early molecular response to posttransplantation imatinib determines outcome in MRD+ Philadelphia-positive acute lymphoblastic leukemia (Ph+ ALL). *Blood* [Internet]. 2005;106(2):458–63
94. Wetzler M, Stock W, Owzar K, al. et. Sequential imatinib and chemotherapy yield reverse-transcriptase polymerase chain reaction (rt-pcr)–negative peripheral stem cell collections in Philadelphia (Ph) chromosome positive acute lymphoblastic leukemia (all)—preliminary results of calgb 10001. *J Clin Oncol* [Internet]. 2006;24
95. Yanada M. Time to tune the treatment of Ph+ ALL. *Blood* [Internet]. 2015 Dec 18;125(24):3674–5
96. Yanada M, Sugiura I, Takeuchi J, Akiyama H, Maruta A, Ueda Y, et al. Prospective monitoring of BCR-ABL1 transcript levels in patients with Philadelphia chromosome-positive acute lymphoblastic leukaemia undergoing imatinib-combined chemotherapy. *Br J Haematol* [Internet]. 2008;143(4):503–10
97. Yanada M, Takeuchi J, Sugiura I, Akiyama H, Usui N, Yagasaki F, et al. High complete remission rate and promising outcome by combination of imatinib and chemotherapy for newly diagnosed BCR-ABL-positive acute lymphoblastic leukemia: a phase II study by the Japan Adult Leukemia Study Group. *J Clin Oncol* [Internet]. 2006;24(3):460–6