**Table S1: relevant clinical trials investigating targeted therapies for T-ALL treatment**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Therapeutic agent | Target | Association with T-ALL subtype/ outcome | Trial identifier and year posted on clinicaltrials.gov | Tumor type | Phase/status | Results |
|
| BH3 mimetics | Higher BCL2 expression | Higher in ETP-ALL |  |  |  |  |
| Venetoclax  (ABT-199) | NCT03236857 (p, ya); 2017 | R/R malignancies | I (R) |  |
|
| NCT03808610 (a); 2019 | R/R ALL (with chemo) | I/II (R) |  |
| Navitoclax  (ABT-263) | Higher BCL2 and BCLXL expression |  | NCT00406809 (a); 2006 | R/R lymphoid malignancies | I/II (C) | Thrombo-cytopenia and neutro-penia (1) |
| NCT03181126 (p, a); 2017 | R/R ALL or LBL (with chemo) | I (A) |  |
| AZD-5991 | Higher MCL1 expression |  | NCT03218683 (a); 2017 | R/R hematologicmalignancies  (also with venetoclax) | I (A) |  |
| NOTCH1 inhibitors | *NOTCH1* activating mutations | Favourable outcome |  |  |  |  |
| Brontictuzumab (OMP-52M51) | NCT01703572 (a); 2012 | R/R lymphoid malignancies | I (C) |  |
| γ-secretase inhibitors |  |  |  |  |
| LY3039478 | NCT02518113 (p, a); 2015 | T-ALL/T-LBL (with dexa) | I/II (C) |  |
| BMS-906024 | NCT01363817 (a); 2011 | R/R T-ALL/LBL (alone or in combination with dexa) | I (C) |  |
| PF-3084014 | NCT00878189 (ya; a); 2009 | R/R T-ALL/LBL and solid tumors | I (C) | Anti T-ALL activity (2) |
| CXCR4 inhibitors |  |  |  |  |  |  |
| Plerixafor (AMD3100) |  |  | NCT01319864 (p, a); 2011 | R/R ALL, AML, and MSD (with cytarabine and etoposide) | I (C) | No response in ALL patients (3) |
| BL-8040 | NCT02763384 (a); 2016 | R/R T-ALL/LBL (with nelarabine) | II (R) |  |
| BET inhibitors | BRD4 activity; aberrant Myc activity |  |  |  |  |  |
| OTX015  (MK-8628) | NCT01713582 (a); 2012 | R/R acute leukemia and MM | I (C) |  |
| GSK525762 | NCT01943851 (a); 2013 | R/R hematologic malignancies | I/II (C) |  |
| ABL/SRC inhibitors | *ABL1* fusions |  |  |  |  |  |
| Dasatinib | NCT03117751 (p); 2017 | Dx ALL/LL (with chemo) | II/III (R) |  |
| Imatinib | NCT02551718 (p, a); 2015 | R/R acute leukemia | N/A (R) |  |
| JAK1/2 inhibitor | *IL7Ra, JAK1/3* and *STAT5B* mutations | Higher in ETP-ALL; associated with steroid resistance |  |  |  |  |
| Ruxolitinib | NCT01251965 (ya, a); 2010 | R/R ALL/AML | I/II (T) | No clinical benefit \* |
| NCT03613428 (p, a); 2018 | R/R ETP-ALL (with chemo) | I/II (NR) |  |
| NCT03117751 (p); 2017 | Dx ALL/LL (with chemo) | II/III (R) |  |
| NCT03515200 (p, ya); 2018 | R/R ALL (with chemo) | I (T) |  |
| Pan-PI3K inhibitors |  |  |  |  |  |  |
| Buparlisib (BMK120) | *PIK3R1* and *PIK3CA/D* mutations; *AKT* mutations; *PTEN* deletions; | Poor prognosis, therapy failure and relapse | NCT01396499 (a); 2011 | R/R acute leukemia | I (C) |  |
| NCT01833169 (a); 2013 | PIK3-activated solid and hematologicmalignancies | II (C) |  |
| Selective-PI3K inhibitors |  |  |  |  |
| Duvelisib  (IPI-145, γ/δ inhibitor) | NCT02711852 (a); 2016 | R/R  hematologicmalignancies | II (A) |  |
| Idelalisib  (CAL-101, δ inhibitor) | NCT03742323 (a); 2018 | R/R ALL | I/II (R) |  |
| mTOR inhibitors |  |  |  |  |
| Everolimus (rapamycin, RAD001) | NCT00968253 (p, a); 2009 | R/R ALL (with chemo) | I/II (C) | The combination is tolerated with moderate activity in T-ALL (4) |
| NCT01523977 (p, ya); 2012 | R/R ALL (with chemo) | I (C) | The combination is feasible (5) |
| NCT00874562 (p, a); 2009 | R/R ALL (with steroids) | I (C) |  |
| NCT03740334 (p,a); 2018 | R/R ALL (with dexa and ribociclib) | I (R) |  |
| Temsirolimus (CCI-799) | NCT00084916 (a); 2004 | R/R leukemia | II (C) |  |
| NCT01403415 (p, ya); 2011 | >2 relapses ALL/LBL (with re-induction chemo) | I (C) | Excessive toxicity (6) |
| Dual PI3K/mTOR inhibitors | NCT01756118 (a); 2012 | R/R acute leukemia | I (A) |  |
| Dactolisib  (NVP-BEZ235) |
| AKT inhibitors | NCT01231919 (p, ya); 2010 | R/R solid tumors or leukemia | I (C) |  |
| MK-2206 (allosteric) |
| MEK inhibitors |  |  |  |  |  |  |
| Selumetinib | *NRAS/ KRAS* mutations | Higher in ETP-ALL; associated with steroid resistance | NCT03705507 (p, a); 2018 | R/R ALL (with dexa) | I/II (R) |  |
|
| Trametinib | NCT00920140 (a); 2009 | R/R leukemias | I/II (C) |  |
| NCT02551718 (p, a); 2015 | R/R acute leukemias | N/A (R) |  |
| Binimetinib (MEK162) | NCT01885195 (a); 2013 | RAS/RAF/MEK-activated malignancies | II (C) |  |
| CDK4/6 inhibitors |  |  |  |  |  |  |
| Ribociclib  (LEE011) | *CDKN2A/B* down- regulation; *CDKN1B* deletions; *CCND3* up- regulation | Lower incidence in ETP-ALL | NCT02187783 (a); 2014 | CDK4/6-activated tumors | II (C) |  |
| NCT03740334 (p, a); 2018 | R/R ALL (with dexa and everolimus) | I (R) |  |
| NCT02813135 (p); 2016 | R/R cancer | I/II (R) |  |
| Palbociclib  (PD-332991) | NCT03792256 (p); 2019 | R/R ALL/LL  (with re-induction chemo) | I (R) |  |
| NCT03132454 (ya, a); 2017 | R/R leukemia (with sorafenib, decitabine or dexa) | I (R) |  |
| NCT03515200 (p, ya); 2018 | R/R ALL (with chemo) | I (T) |  |
| Purine analog | Rapid DNA synthesis |  |  |  |  |  |
| Nelarabine | NCT02551718 (p, a); 2015 | R/R acute leukemia | N/A (R) |  |
|
| NCT00866671 (p, ya); 2009 | R/R T-ALL/LBL with ≥2 prior treatments | IV (C) | The risk–benefit profile is positive (7) |
| NCT00408005 (p, ya); 2006 | Dx T-ALL/LBL | III (A) | Increased disease-free survival rate (8) |
| MDM2 inhibitors | MDM2 over- expression |  |  |  |  |  |
| Idasanutlin | NCT04029688 (p, ya); 2019 | R/R acute leukemia or solid tumors (with chemo or venetoclax) | I/II (R) |  |
| HDM201 | NCT02143635 (a); 2014 | p53-WT advanced tumors, including ALL | I (C) |  |
| ALRN-6924 | NCT03654716 (p, ya); 2018 | Pediatric cancer, including R/R ALL | I (R) |  |
| Immunotherapy |  |  |  |  |  |  |
| Daratumumab | CD38 expression |  | NCT00501826 (p, a); 2007 | T-ALL/T-LBL (with chemo) | II (R) |  |
| NCT03384654 (p); 2017 | R/R ALL/LBL (with chemo) | II (R) |  |
| Isatuximab | NCT03860844 (p); 2019 | R/R ALL or AML (with chemo) | II (R) |  |
| CAR T |  |  |  |  |  |  |
| Anti-CD5 CAR T | CD5 expression |  | NCT03081910 (p, a); 2017 | R/R T-cell malignancies | I (R) |  |
| Anti-CD7 CAR T | CD7 expression |  | NCT03690011 (p, a); 2018 | R/R T-cell malignancies | I (NR) |  |
| OTHER DRUGS |  |  |  |  |  |  |
| XPO1 inhibitor | Nuclear export of oncogenic proteins/  mRNA |  |  |  |  |  |
| Selinexor  (KPT-330) | NCT02212561 (p, ya); 2014 | R/R ALL, AML, or MSD | I (C) | Drug is safe with promising activity (9) |
| NCT02091245 (p, ya); 2014 | R/R ALL and AML | I (A) |  |
| HDAC inhibitors | High HDAC expression and activity |  |  |  |  |  |
| Panobinostat | NCT00723203 (a); 2008 | R/R ALL or AML | II (T) | Lack of efficacy \* |
| NCT02518750 (p); 2015 | R/R T-ALL/LBL (with bortezomib and chemo) | II (T) | Slow accrual \* |
| NCT01321346 (p); 2011 | R/R acute leukemias (with cytarabine) and lymphomas | I (C) |  |
| Vorinostat | NCT03117751 (p); 2017 | Dx ALL/LBL (with chemo) | II/III (R) |  |
| NCT01483690 (p, ya); 2011 | R/R ALL (with decitabine and chemo) | I/II (T) | Excessive toxicity \* |
| NCT02553460 (p); 2015 | Dx ALL (with bortezomib and chemo) | I/II (R) |  |
| Methyltransferase inhibitors | DNA methyl-transferase activity |  |  |  |  |  |
| 5-Azacitidine | NCT02551718 (p,a); 2015 | R/R acute leukemias | N/A (R) |  |
| NCT01861002 (p); 2013 | R/R ALL or AML (with chemo) | I (C) |  |
| Decitabine | NCT02551718 (p, a); 2015 | R/R acute leukemias | N/A (R) |  |
| NCT01483690 (p, ya); 2011 | R/R ALL (with vorinostat and chemo) | I/II (T) | Excessive toxicity \* |
| NCT00349596 (p, a); 2006 | R/R ALL | I (C) |  |
| NCT03132454 (ya, a); 2017 | R/R ALL or AML (with palbociclib) | I (R) |  |
| Proteasome inhibitors |  |  |  |  |  |  |
| Bortezomib | Rapid protein turnover |  | NCT02518750 (p); 2015 | R/R T-ALL/LBL (with chemo) | II (T) | Slow accrual \* |
| NCT02553460 (p); 2015 | Dx ALL (with vorinostar and chemo) | I/II (R) |  |
| NCT02551718 (p, a); 2015 | R/R acute leukemias | N/A (R) |  |
| NCT00440726 (p); 2007 | R/R ALL (with chemo) | I/II (C) |  |
| NCT04224571 (p, ya); 2020 | R/R ALL (with chemo) | II (R) |  |
| NCT00873093 (p, a); 2009 | 1st relapse ALL/LBL (with chemo) | II (C) | Promising results for T-ALL (10) |
| NCT02112916 (p, ya); 2014 | Dx T-ALL-LBL (with chemo) | III (A) |  |
| NCT03590171 (p); 2018 | R ALL (with chemo) | II (R) |  |
| NCT03117751 (p); 2017 | Dx ALL/LBL (with chemo) | II/III (R) |  |
| NCT03643276 (p); 2018 | Dx ALL (with chemo) | III (R) |  |
| NAE inhibitor |  |  |  |  |
| Pevonedistat (MLN49243) | NCT03349281 (ya, a); 2017 | R/R ALL (with chemo) | I (R) |  |
| AURK inhibitors | AURK over expression |  |  |  |  |  |
| Alisertib | NCT01154816 (p, ya); 2010 | R/R ALL, AML, and solid tumors | II (C) | Response rate <5%  (11) |
| AT-9283 | NCT01431664 (p); 2011 | R/R acute leukemia | I (C) | No efficacy (12) |

List of clinical trials investigating the targeted agents described in this review. The clinical trials listed were chosen based on the following two selection criteria: the targeted drug investigated belongs to one of the categories of agents described in the text (modifiers of apoptosis, inhibitors of transcription regulation, signal transduction, cell cycle or immunotherapies) and the trial includes T-ALL patients.

\* Source: <https://clinicaltrials.gov/>

Abbreviations: p= pediatric, ya= young adult, a= adults; ALL= acute lymphoblastic leukemia, LBL= lymphoblastic lymphoma, AML= acute myeloid leukemia, MDS= myelodysplastic syndrome, MM= multiple myeloma, Dx= newly diagnosed, R/R= refractory/relapsed; chemo= chemotherapy; dexa= dexamethasone; WT= wild-type; N/A= not applicable, R= recruiting, A= active, C= completed, T= terminated, NR= not yet recruiting.

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