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## Supplementary information

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# Trends in kinase drug discovery: targets, indications and inhibitor design

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Supplementary Table 1 | **Approved drugs targeting kinases: small-molecule kinase inhibitors and monoclonal antibodies**

| INN                                                      | Binding type | Indication(s)                                                                    | Company              | First approval year | Approval | Type | Class | Targets                              |
|----------------------------------------------------------|--------------|----------------------------------------------------------------------------------|----------------------|---------------------|----------|------|-------|--------------------------------------|
| <b>Sirolimus</b><br>(Rapamune)                           | Rapalog      | Prophylaxis of organ rejection                                                   | Pfizer, Wyeth        | 1999                | FDA      | SM   | Rapa  | MTOR                                 |
| <b>Imatinib</b><br>(Glivec;<br>Gleevec)                  | Type 2       | CML, Ph-positive B-ALL, CMML, HES, GIST                                          | Novartis             | 2001                | FDA      | SM   | ABL   | BCR-ABL; PDGFRB; KIT                 |
| <b>Gefitinib</b><br>(Iressa)                             | Type 1       | NSCLC                                                                            | AstraZeneca          | 2003                | FDA      | SM   | HER   | EGFR                                 |
| <b>Erlotinib</b><br>(Tarceva)                            | Type 1       | NSCLC, pancreatic cancer                                                         | OSI                  | 2004                | FDA      | SM   | HER   | EGFR                                 |
| <b>Sorafenib</b><br>(Nexavar)                            | Type 2       | RCC, HCC                                                                         | Bayer Healthcare     | 2005                | FDA      | SM   | RAF   | BRAF; FLT1; KDR; FLT4; PDGFRB; KIT   |
| <b>Dasatinib</b><br>(Sprycel)                            | Type 1       | CML, ALL                                                                         | Bristol-Myers Squibb | 2006                | FDA      | SM   | ABL   | BCR-ABL; PDGFRB; KIT; SRC            |
| <b>Sunitinib</b><br>(Sutent)                             | Type 1       | RCC, imatinib resistant GIST                                                     | CPPI CV (Pfizer)     | 2006                | FDA      | SM   | VEGFR | FLT1; KDR; PDGFRA; PDGFRB; FLT3; KIT |
| <b>Lapatinib</b><br>(Tykerb)                             | Type 1.5     | BC                                                                               | SmithKline Beecham   | 2007                | FDA      | SM   | HER   | EGFR; ERBB2                          |
| <b>Nilotinib</b><br>(Tasigna)                            | Type 2       | CML                                                                              | Novartis             | 2007                | FDA      | SM   | ABL   | BCR-ABL; PDGFRB; KIT                 |
| <b>Temsirolimus</b><br>(Torisel)                         | Rapalog      | RCC                                                                              | PF Prism CV (Pfizer) | 2007                | FDA      | SM   | Rapa  | MTOR                                 |
| <b>Pazopanib</b><br>(Votrient)                           | Type 1       | RCC, STS                                                                         | GSK                  | 2009                | FDA      | SM   | VEGFR | FLT1; KDR; FLT4; PDGFRB; PDGFRA      |
| <b>Everolimus</b><br>(Certican;<br>Afinitor;<br>Votubia) | Rapalog      | RCC, SEGA, Prophylaxis of organ rejection, TSC-associated partial-onset seizures | Novartis             | 2009                | FDA      | SM   | Rapa  | MTOR                                 |
| <b>Ruxolitinib</b><br>(Jakafi)                           | Type 1       | GVHD, PV, MF with JAK2V617F                                                      | Incyte Corporation   | 2011                | FDA      | SM   | JAK   | JAK1; JAK2; JAK3                     |
| <b>Vemurafenib</b><br>(Zelboraf)                         | Type 1       | Metastatic melanoma with BRAFV600E                                               | Hoffmann La Roche    | 2011                | FDA      | SM   | RAF   | BRAF                                 |
| <b>Vandetanib</b><br>(Caprelsa)                          | Type 1       | MTC                                                                              | IPR Inc (AZ)         | 2011                | FDA      | SM   | VEGFR | KDR; EGFR; RET                       |
| <b>Crizotinib</b><br>(Xalcori)                           | Type 1       | NSCLC with ALK translocations                                                    | PF Prism CV          | 2011                | FDA      | SM   | ALK   | ALK; ROS1; MET                       |
| <b>Bosutinib</b><br>(Bosulif)                            | Type 1       | CML resistant/intolerant to therapy                                              | Wyeth Inc            | 2012                | FDA      | SM   | ABL   | BCR-ABL                              |
| <b>Regorafenib</b><br>(Stivarga)                         | Type 2       | CRC, GIST, HCC                                                                   | Bayer Healthcare     | 2012                | FDA      | SM   | RAF   | BRAF; FLT1; KDR; FLT4; TEK           |

|                                                 |                     |                                                                   |                            |      |     |    |       |                                                             |
|-------------------------------------------------|---------------------|-------------------------------------------------------------------|----------------------------|------|-----|----|-------|-------------------------------------------------------------|
| <b>Cabozantinib</b><br>(Cometriq)               | Type 1              | MTC, RCC, HCC                                                     | Exelixis                   | 2012 | FDA | SM | RET   | RET; KDR;<br>PDGFRB;<br>KIT; FLT3                           |
| <b>Tofacitinib</b><br>(Xeljanz;<br>Tasocitinib) | Type 1              | RA, PA, UC                                                        | PF Prism CV<br>(Pfizer)    | 2012 | FDA | SM | JAK   | JAK3                                                        |
| <b>Axitinib</b><br>(Inlyta)                     | Type 1              | RCC                                                               | Pfizer                     | 2012 | FDA | SM | VEGFR | FLT1; KDR;<br>FLT4; KIT;<br>PDGFRB;<br>RET; CSF1R;<br>FLT3  |
| <b>Ponatinib</b><br>(Iclusig)                   | Type 1              | CML: T315<br>resistant, ALL                                       | Ariad                      | 2012 | FDA | SM | ABL   | BCR-ABL<br>(T315I)                                          |
| <b>Ibrutinib</b><br>(Imbruvica)                 | Type 1:<br>Covalent | MCL, CLL, WM,<br>MZL, GVHD                                        | Pharmacyclics<br>Inc       | 2013 | FDA | SM | BTK   | BTK                                                         |
| <b>Dabrafenib</b><br>(Tafinlar)                 | Type 1              | Metastatic<br>melanoma with<br>BRAFV600E,<br>NSCLC, ATC           | GSK                        | 2013 | FDA | SM | RAF   | BRAF                                                        |
| <b>Trametinib</b><br>(Mekinist)                 | Type 3              | Metastatic<br>melanoma with<br>BRAFV600E                          | GSK                        | 2013 | FDA | SM | MEK   | MAP2K1;<br>MAP2K2                                           |
| <b>Afatinib</b><br>(Tomtovok)                   | Type 1:<br>Covalent | NSCLC with EGFR<br>activating<br>mutations                        | Boehringer<br>Ingelheim    | 2013 | FDA | SM | HER   | EGFR;<br>ERBB2;<br>ERBB4                                    |
| <b>Nintedanib</b><br>(Intedanib)                | Type 1              | IPF, ILDs                                                         | Boehringer<br>Ingelheim    | 2014 | FDA | SM | VEGFR | FLT1; KDR;<br>FLT4;<br>FGFR1;<br>FGFR2;<br>FGFR3;<br>PDGFRB |
| <b>Idelalisib</b><br>(Zydelig)                  | Type 1              | Leukaemia and<br>lymphomas                                        | Gilead<br>Sciences         | 2014 | FDA | SM | PI3K  | PIK3CD                                                      |
| <b>Ceritinib</b><br>(Zykadia)                   | Type 1              | NSCLC with ALK<br>translocations                                  | Novartis                   | 2014 | FDA | SM | ALK   | ALK                                                         |
| <b>Palbociclib</b><br>(Ibrance)                 | Type 1              | Advanced or<br>metastatic BC                                      | Pfizer                     | 2015 | FDA | SM | CYC   | CDK4; CDK6                                                  |
| <b>Alectinib</b><br>(Alecensa)                  | Type 1              | ALK-rearranged<br>NSCLC                                           | Roche                      | 2015 | FDA | SM | ALK   | ALK; RET                                                    |
| <b>Cobimetinib</b><br>(Cotellic)                | Type 3              | Melanoma; BC;<br>other solid<br>tumours                           | Genentech/<br>Exelixis Inc | 2015 | FDA | SM | MEK   | MAP2K1;<br>MAP2K2                                           |
| <b>Lenvatinib</b><br>(Lenvima)                  | Type 1              | Progressive,<br>differentiated<br>thyroid cancer,<br>advanced RCC | Eisai Inc                  | 2015 | FDA | SM | VEGFR | FLT1; KDR;<br>FLT4; RET                                     |
| <b>Osimertinib</b><br>(Tagrisso)                | Type 1:<br>Covalent | NSCLC with<br>T790M positive                                      | AstraZeneca                | 2015 | FDA | SM | HER   | EGFR<br>T970M                                               |
| <b>Brigatinib</b><br>(Alunbrig)                 | Type 1              | ALK-rearranged<br>metastatic NSCLC                                | ARIAD                      | 2017 | FDA | SM | ALK   | ALK; EGFR<br>T790M                                          |
| <b>Midostaurin</b><br>(Rydapt)                  | Type 1              | AML (FLT3<br>mutation+), aSM,<br>MCL                              | Novartis                   | 2017 | FDA | SM | FLT3  | FLT3                                                        |
| <b>Netarsudil</b><br>(Rhopressa)                | Type 1              | Glaucoma/ocular<br>hypertension                                   | Aerie                      | 2017 | FDA | SM | ROCK  | ROCK1;<br>ROCK2                                             |

|                                     |                     |                                                                         |                                   |      |     |    |      |                                             |
|-------------------------------------|---------------------|-------------------------------------------------------------------------|-----------------------------------|------|-----|----|------|---------------------------------------------|
| <b>Neratinib</b><br>(Nerlynx)       | Type 1:<br>Covalent | HER2-positive BC                                                        | Puma<br>Biotechnology<br>, Inc    | 2017 | FDA | SM | HER  | ERBB2                                       |
| <b>Abemaciclib</b><br>(Verzenio)    | Type 1              | HR/HER2-positive,<br>advanced or<br>metastatic BC                       | Eli Lilly                         | 2017 | FDA | SM | CYC  | CDK4; CDK6                                  |
| <b>Ribociclib</b><br>(Kisqali)      | Type 1              | HR/HER2-positive,<br>advanced or<br>metastatic BC                       | Novartis                          | 2017 | FDA | SM | CYC  | CDK4; CDK6                                  |
| <b>Acalabrutinib</b><br>(Calquence) | Type 1:<br>Covalent | MCL, at least one<br>prior therapy; CLL                                 | AstraZeneca<br>(Acerta<br>Pharma) | 2017 | FDA | SM | BTK  | BTK                                         |
| <b>Copanlisib</b><br>(Aliqopa)      | Type 1              | Relapsed follicular<br>lymphoma                                         | Bayer                             | 2017 | FDA | SM | PI3K | PIK3CA;<br>PIK3CB                           |
| <b>Baricitinib</b><br>(Olumiant)    | Type 1              | RA                                                                      | Incyte/Eli Lilly                  | 2017 | FDA | SM | JAK  | JAK1; JAK2                                  |
| <b>Lorlatinib</b><br>(Lorviqua)     | Type 1              | ALK positive<br>metastatic NSCLC                                        | Pfizer                            | 2018 | FDA | SM | ALK  | ALK                                         |
| <b>Encorafenib</b><br>(Braftovi)    | Type 1              | BRAF mutant<br>melanoma, CRC                                            | Array<br>BioPharma                | 2018 | FDA | SM | RAF  | BRAF<br>(Mutant<br>forms)                   |
| <b>Binimetinib</b><br>(Mektovi)     | Type 3              | BRAF mutant<br>melanoma                                                 | Array<br>BioPharma                | 2018 | FDA | SM | MEK  | MAP2K1;<br>MAP2K2                           |
| <b>Duvelisib</b><br>(Copiktra)      | Type 1              | CLL, SLL & FL                                                           | Verastem<br>Oncology              | 2018 | FDA | SM | PI3K | PIK3C2G;<br>PIK3CD                          |
| <b>Gilteritinib</b><br>(Xospata)    | Type 1              | FLT3 mutant AML                                                         | Astellas<br>Pharma                | 2018 | FDA | SM | FLT3 | FLT3                                        |
| <b>Dacomitinib</b><br>(Vizimpro)    | Type 1:<br>Covalent | Mutation positive<br>NSCLC                                              | Pfizer                            | 2018 | FDA | SM | HER  | EGFR;<br>ERBB2;<br>ERBB4<br>(EGFR<br>T790M) |
| <b>Fostamatinib</b><br>(Tavalisse)  | Type 1              | Persistent/chronic<br>ITP                                               | Rigel Pharms                      | 2018 | FDA | SM | SYK  | SYK                                         |
| <b>Larotrectinib</b><br>(Vitrakvi)  | Type 1              | Solid tumours<br>with NTRK fusions                                      | Loxo<br>Oncology                  | 2018 | FDA | SM | TRK  | NTRK1;<br>NTRK2;<br>NTRK3                   |
| <b>Erdafitinib</b><br>(Balversa)    | Type 1              | Advanced or<br>metastatic<br>urothelial<br>carcinoma, FGFR-<br>altered  | Janssen                           | 2019 | FDA | SM | FGFR | FGFR1;<br>FGFR2;<br>FGFR3;<br>FGFR4         |
| <b>Alpelisib</b><br>(Piqray)        | Type 1              | Advanced or<br>metastatic,<br>HR/HER2 positive,<br>PIK3CA-mutated<br>BC | Novartis                          | 2019 | FDA | SM | PI3K | PIK3CA                                      |
| <b>Zanubrutinib</b><br>(Brukinsa)   | Type 1:<br>Covalent | MCL                                                                     | Beigene                           | 2019 | FDA | SM | BTK  | BTK                                         |
| <b>Upadacitinib</b><br>(Rinvoq)     | Type 1              | Moderate/severe<br>active RA                                            | AbbVie                            | 2019 | FDA | SM | JAK  | JAK1                                        |
| <b>Entrectinib</b><br>(Rozlytrek)   | Type 1              | NTRK positive<br>solid tumours,<br>ROS1 positive<br>NSCLC               | Genentech                         | 2019 | FDA | SM | TRK  | NTRK1;<br>NTRK2;<br>NTRK3;<br>ROS1; ALK     |

|                                   |        |                                                     |                          |      |     |     |       |                                         |
|-----------------------------------|--------|-----------------------------------------------------|--------------------------|------|-----|-----|-------|-----------------------------------------|
| <b>Fedratinib</b><br>(Inrebic)    | Type 1 | Primary & secondary MF                              | Celgene                  | 2019 | FDA | SM  | JAK   | JAK2                                    |
| <b>Pexidartinib</b><br>(Turalio)  | Type 2 | Tenosynovial giant cell tumour                      | Daiichi Sankyo           | 2019 | FDA | SM  | CSFR  | CSF1R; KIT; FLT3-ITD                    |
| <b>Tucatinib</b><br>(Tukysa)      | Type 1 | Advanced or metastatic, pretreated HER2 positive BC | Seattle Genetics         | 2020 | FDA | SM  | HER   | ERBB2                                   |
| <b>Ripretinib</b><br>(Quinlock)   | Type 2 | Advanced GIST                                       | Deciphera                | 2020 | FDA | SM  | KIT   | KIT; PDGFRA (KIT D816V; PDGFRA D842V)   |
| <b>Pemigatinib</b><br>(Pemazyre)  | Type 1 | FGFR2 mutant advanced cholangio-carcinoma           | Incyte                   | 2020 | FDA | SM  | FGFR  | FGFR1; FGFR2; FGFR3                     |
| <b>Capmatinib</b><br>(Tabrecta)   | Type 1 | MET mutation positive NSCLC                         | Novartis                 | 2020 | FDA | SM  | MET   | MET (mutant form)                       |
| <b>Pralsetinib</b><br>(Gavreto)   | Type 1 | Metastatic RET fusions NSCLC, MTC, Thyroid cancer   | Blueprint Medicines      | 2020 | FDA | SM  | RET   | RET                                     |
| <b>Selumetinib</b><br>(Koselugo)  | Type 3 | Neuro-fibromatosis type 1 plexiform neurofibromas   | Astra Zeneca             | 2020 | FDA | SM  | MEK   | MAP2K1; MAP2K2                          |
| <b>Avapritinib</b><br>(Ayvakit)   | Type 1 | PDGFRA exon 18 mutation (incl D842V) positive GIST  | Blueprint Medicines      | 2020 | FDA | SM  | KIT   | KIT; PDGFRA (D816 V KIT; D842 V PDGFRA) |
| <b>Selpercatinib</b><br>(Retevmo) | Type 1 | RET fusions NSCLC & MTC, Thyroid cancer             | Eli Lilly                | 2020 | FDA | SM  | RET   | RET (mutant forms and fusions)          |
| <b>Tirbanibulin</b><br>(Klisyri)  | -      | Actinic keratosis                                   | Athenex                  | 2020 | FDA | SM  | SRC   | SRC (& tubulin polymerization)          |
| <b>Tepotinib</b><br>(Tepmetko)    | Type 1 | MET mutation positive NSCLC                         | Merck                    | 2021 | FDA | SM  | MET   | MET (mutant form)                       |
| <b>Tivozanib</b><br>(Fotvida)     | Type 2 | RCC, advanced                                       | EUSA Pharma (UK) Limited | 2021 | FDA | SM  | VEGFR | FLT1; FLT4; KDR                         |
| <b>Trilaciclib</b><br>(Cosela)    | Type 1 | Small Cell Lung Cancer Myelo-preservation Therapy   | G1 Therapeutics          | 2021 | FDA | SM  | CYC   | CDK4; CDK6                              |
| <b>Umbralisib</b><br>(Ukoniq)     | Type 1 | MZL, FL                                             | TG Therapeutics          | 2021 | FDA | SM  | PI3K  | PIK3CD                                  |
| <b>Trastuzumab</b><br>(Herceptin) |        | EGFR positive tumours                               | Genentech                | 1998 | FDA | mAb | HER   | EGFR                                    |
| <b>Cetuximab</b><br>(Erbix)       |        | EGFR positive CRC                                   | Eli Lilly                | 2004 | FDA | mAb | HER   | EGFR                                    |
| <b>Panitumumab</b><br>(Vectibix)  |        | EGFR positive CRC                                   | Amgen                    | 2006 | FDA | mAb | HER   | EGFR                                    |

|                                                   |                     |                                                                    |                           |      |                |     |            |                         |
|---------------------------------------------------|---------------------|--------------------------------------------------------------------|---------------------------|------|----------------|-----|------------|-------------------------|
| <b>Pertuzumab</b><br>(Perjeta)                    |                     | HER2-positive BC                                                   | Genentech                 | 2012 | FDA            | mAb | HER        | ERBB2                   |
| <b>Trastuzumab<br/>emtansine</b><br>(Kadcyla)     |                     | HER2-positive<br>tumours                                           | Genentech                 | 2013 | FDA            | mAb | HER        | ERBB2                   |
| <b>Ramucirumab</b><br>(Cyramza)                   |                     | Metastatic NSCLC,<br>metastatic CRC,<br>HCC                        | Eli Lilly                 | 2014 | FDA            | mAb | VEGFR      | KDR                     |
| <b>Necitumumab</b><br>(Portrazza)                 |                     | NSCLC                                                              | Eli Lilly                 | 2015 | FDA            | mAb | HER        | EGFR                    |
| <b>Olaratumab</b><br>(Lartruvo)                   |                     | Soft tissue<br>sarcoma                                             | Eli Lilly                 | 2016 | FDA            | mAb | PDGFR<br>A | PDGFRA                  |
| <b>Trastuzumab<br/>deruxtecan</b><br>(Enhertu)    |                     | Breast cancer                                                      | Daiichi<br>Sankyo         | 2019 | FDA            | mAb | HER        | ERBB2                   |
| <b>Margetuximab</b><br>(Margenza)                 |                     | Metastatic HER2-<br>positive BC                                    | MacroGenics               | 2020 | FDA            | mAb | HER        | ERBB2                   |
| <b>Icotinib*</b><br>(Conmana)                     |                     | Advanced-stage<br>NSCLC with EGFR<br>mutation                      | Beta Pharma               | 2011 | Other:<br>NMPA | SM  | HER        | EGFR                    |
| <b>Apatinib*</b><br>(Rivoceranib)                 |                     | Advanced or<br>metastatic gastric<br>cancer                        | Advenchen<br>Laboratories | 2014 | Other:<br>NMPA | SM  | VEGFR      | KDR; KIT;<br>SRC        |
| <b>Pyrotinib*</b><br>(Irene)                      |                     | HER2-positive,<br>advanced or<br>metastatic BC (in<br>combination) | Shanghai<br>Hengrui       | 2018 | Other:<br>NMPA | SM  | HER        | EGFR;<br>ERBB2          |
| <b>Fruquintinib*</b><br>(Elunate)                 | Type 1              | Metastatic<br>colorectal cancer                                    | Chi-Med/Eli<br>Lilly      | 2018 | Other:<br>NMPA | SM  | VEGFR      | FLT1; FLT4;<br>KDR      |
| <b>Catequentinib*</b><br>(Anlotinib;<br>Zepzelca) | Type 1              | NSCLC                                                              | Advenchen<br>Laboratories | 2018 | Other:<br>NMPA | SM  | VEGFR      | FLT1; FLT4;<br>KDR      |
| <b>Flumatinib*</b><br>(Hansoh Xinfu)              |                     | CML                                                                | Hansoh                    | 2019 | Other:<br>NMPA | SM  | ABL        | BCR-ABL;<br>PDGFRB; KIT |
| <b>Almonertinib*</b><br>(Ameile)                  | Type 1:<br>Covalent | Advanced<br>mutation positive<br>NSCLC                             | Hansoh                    | 2020 | Other:<br>NMPA | SM  | HER        | EGFR<br>T970M           |
| <b>Orelabrutinib*</b>                             |                     | MCL or CLL/SLL                                                     | InnoCare<br>Pharma        | 2020 | Other:<br>NMPA | SM  | BTK        | BTK                     |
| <b>Nimotuzumab*</b><br>(BIOMAb EGFR)              |                     | Head and neck<br>neoplasms                                         | Biotech                   | 2014 | Other:<br>NMPA | mAb | HER        | EGFR                    |
| <b>Filgotinib*</b><br>(Jyseleca)                  | Type 1              | RA                                                                 | Gilead/Galapa<br>gos      | 2020 | Other:<br>EMA  | SM  | JAK        | JAK1                    |
| <b>Ripasudil*</b><br>(Glanatec)                   | Type 1              | Glaucoma/ocular<br>hypertension                                    | Kowa<br>Company           | 2014 | Other:<br>PMDA | SM  | ROCK       | ROCK1;<br>ROCK2         |
| <b>Peficitinib*</b><br>(Smyraf)                   | Type 1              | RA                                                                 | Astellas<br>Pharma        | 2019 | Other:<br>PMDA | SM  | JAK        | JAK3                    |
| <b>Delgocitinib*</b>                              | Type 1              | Atopic dermatitis                                                  | Japan<br>Tobacco Co       | 2020 | Other:<br>PMDA | SM  | JAK        | JAK1; JAK2              |
| <b>Tirabrutinib*</b>                              | -                   | Recurrent or<br>refractory primary<br>CNS lymphoma                 | Ono                       | 2020 | Other:<br>PMDA | SM  | BTK        | BTK                     |

|                               |                     |                              |                                          |      |                         |    |      |                               |
|-------------------------------|---------------------|------------------------------|------------------------------------------|------|-------------------------|----|------|-------------------------------|
| <b>Fasudil*</b><br>(Eril)     | Type 1              | Cerebral<br>vasospasm        | Chuanwei/Eril                            | 1995 | Other:<br>PMDA;<br>NMPA | SM | ROCK | ROCK1;<br>ROCK2               |
| <b>Radotinib*</b><br>(Supect) | Type 2              | CML                          | Il-Yang<br>Pharm. Co.,<br>Ltd            | 2012 | Other:<br>MFDS          | SM | ABL  | BCR-ABL;<br>PDGFRA;<br>PDGFRB |
| <b>Olmudinib*</b><br>(Olita)  | Type 1:<br>Covalent | NSCLC with<br>T790M positive | Boehringer<br>Ingelheim and<br>Hanmi Co. | 2016 | Other:<br>MFDS          | SM | HER  | EGFR                          |

The first approval year prioritizes FDA approvals. \* Denotes agents approved by other regulating body than US FDA.

Abbreviations used in this table: ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; aSM, advanced systemic mastocytosis; ATC, Anaplastic thyroid cancer; BC, breast cancer; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; CMML, chronic myelomonocytic leukemia; CRC, colorectal cancer; EMA, European Medicines Agency; FL, follicular lymphoma; GIST, gastrointestinal stromal tumors; GVHD, graft versus host disease; GSK, GlaxoSmithKline; HCC, hepatocellular cancer; HES, hypereosinophilic syndrome; ILDs, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; ITP, immune thrombocytopenia; mAb, monoclonal antibody; MCL, mantle cell lymphoma; MF, myelofibrosis; MFDS, Ministry of Food and Drug Safety (South Korea); MTC, medullary thyroid cancer; MZL, marginal zone lymphoma; NMPA, National Medical Products Administration (China); NSCLC, non-small cell lung cancer; PMDA, Pharmaceuticals and Medical Devices Agency (Japan); PV, polycythemia vera; RA, rheumatoid arthritis; RCC, renal cell carcinoma; SEGA, subependymal giant cell astrocytoma; SLL, small lymphocytic lymphoma; SM, small molecule; WM, Waldenström's macroglobulinemia. Tirbanibulin targets the peptide substrate site of SRC.

Supplementary Table 3 | **Calculating the success rate of kinase inhibitors through phase transition probabilities of agents in clinical trials**

|                                                           | Phase I | Phase II | Phase III |
|-----------------------------------------------------------|---------|----------|-----------|
| Number of agents entering phase                           | 516     | 358      | 159       |
| Number of agents successfully transitioning to next phase | 328     | 159      | 71        |
| Number of active agents still in phase                    | 57      | 119      | 78        |
| Number of not active agents still in phase                | 127     | 83       | 11        |

The phase transition probabilities were calculated for 546 small-molecule kinase inhibitors that have entered clinical development (475 clinical SMKIs plus 71 FDA-approved KIs). Information from nearly 3,700 clinical trials on investigative agents was used. Successful phase transitions from phase I to phase II to phase III were extrapolated for the 71 already approved agents.

Agents that began early phase I or phase I/phase II trials that did not proceed further were considered (active or not active) agents still in phase I. If an agent entered phase I/phase II trials and transitioned to another phase II then it was considered as entering phase I and successfully transitioning to phase II trials. If an agent began phase I and proceeded to another phase I/phase II trial then it was considered as successfully transitioning to phase II trials. The phase transition probabilities were calculated as described by Hay et al. (1) and based on DiMasi and Grabowski (2) analyses: the number of agents that successfully transitioned to the next phase divided by the number of agents that successfully transitioned to the next phase plus the number of drugs that were suspended (or in this analysis, considered *not active*). Note there are 28 agents that began with phase II trials only – no information on phase I trials was available. Also four agents began with phase I/phase II trials (recorded as entering phase I trials) and proceeded to phase III trials.

Agents were considered not active for several reasons: information could be found that development was discontinued with them through press releases; they were not found in development pipelines anymore; they had reached a completed, terminated, suspended or unknown trial status prior to 2015 and no development had since been reported. Any agents with one of those statuses post-2015 were researched and definitively identified as active or discontinued (and labelled not active).

## References

1. Hay M, Thomas DW, Craighead JL, Economides C, Rosenthal J. Clinical development success rates for investigational drugs. *Nat Biotechnol.* 2014 Jan;32(1):40–51.
2. DiMasi JA, Grabowski HG. Economics of New Oncology Drug Development. *J Clin Oncol.* 2007 Jan 10;25(2):209–16.

Supplementary Table 4 | **Kinases for which the clinical development of modulators is presumed discontinued**

| <b>Kinase group</b> | <b>Family</b> | <b>Kinase(s)</b> | <b>Highest clinical stage</b> | <b>Year completed trials</b> | <b>Disease indications</b>                                            |
|---------------------|---------------|------------------|-------------------------------|------------------------------|-----------------------------------------------------------------------|
| <b>TKL</b>          | MLK           | MLK1-3           | Phase 2/3                     | 2005                         | Parkinson's disease                                                   |
| <b>CMGC</b>         | MAPK:JNK      | MAPK8-10         | Phase 2                       | 2017                         | Myeloid leukaemia, lupus, idiopathic pulmonary fibrosis, hearing loss |
| <b>CAMK</b>         | MAPKAPK       | MAPKAPK5         | Phase 2                       | 2011                         | Rheumatoid arthritis                                                  |
| <b>AGC</b>          | PDK           | PDK1             | Phase 1                       | 2013                         | Solid tumours, lymphoma                                               |
| <b>Other</b>        | TKK           | MSP1             | Phase 1                       | 2018                         | Cancer                                                                |
| <b>TKL</b>          | LISK          | LIMK2            | Phase 1/2                     | 2012                         | Glaucoma, ocular hypertension                                         |

Supplementary Table 5 | **Chemical probes and historical compounds targeting kinases****Chemical probes**

| Probe name   | Primary target(s)                                 | Established or novel | Target class | Subclass        | Reviews | Published on |
|--------------|---------------------------------------------------|----------------------|--------------|-----------------|---------|--------------|
| TL13-112     | ALK                                               | Established          | PK           | Tyrosine Kinase | 0       | 12-Nov-20    |
| Asciminib    | BCR-ABL                                           | Established          | PK           | Tyrosine Kinase | 0       | 23-Nov-20    |
| GDC-0834     | BTK                                               | Established          | PK           | Tyrosine Kinase | 0       | 17-Nov-20    |
| BSJ-03-123   | CDK6                                              | Established          | PK           | CMGC            | 0       | 12-Nov-20    |
| CP-10        | CDK6                                              | Established          | PK           | CMGC            | 0       | 01-Dec-20    |
| WZ4002       | EGFR                                              | Established          | PK           | Tyrosine Kinase | 0       | 25-Nov-20    |
| AZD4547      | FGFR1, FGFR2, FGFR3                               | Established          | PK           | Tyrosine Kinase | 0       | 03-Dec-20    |
| G749         | FLT3                                              | Established          | PK           | Tyrosine Kinase | 0       | 27-Nov-20    |
| AZ-960       | JAK2                                              | Established          | PK           | Tyrosine Kinase | 0       | 27-Nov-20    |
| Capmatinib   | MET                                               | Established          | PK           | Tyrosine Kinase | 2       | 26-Oct-20    |
| AMG 337      | MET                                               | Established          | PK           | Tyrosine Kinase | 1       | 26-Nov-20    |
| MK-8033      | MET, MST1R                                        | Established          | PK           | Tyrosine Kinase | 0       | 26-Nov-20    |
| AC710        | PDGFR $\alpha$ , PDGFR $\beta$ , KIT, FLT3, CSF1R | Established          | PK           | Tyrosine Kinase | 0       | 27-Nov-20    |
| AZD-6482     | PIK3CB                                            | Established          | PK           | Lipid           | 3       | 26-Oct-20    |
| PI-3065      | PIK3CD                                            | Established          | LK           | Lipid           | 0       | 17-Dec-20    |
| BAY-549      | ROCK1, ROCK2                                      | Established          | PK           | AGC             | 2       | 06-Jun-20    |
| GNF-5837     | TRKA, TRKB, TRKC                                  | Established          | PK           | Tyrosine Kinase | 0       | 17-Nov-20    |
| BAY1125976   | AKT1, AKT2                                        | Novel in CT          | PK           | AGC             | 3       | 10-Aug-20    |
| XMD-12       | AURKA, AURKB, AURKC                               | Novel in CT          | PK           | Other           | 2       | 14-Oct-20    |
| THZ531       | CDK12, CDK13                                      | Novel in CT          | PK           | CMGC            | 1       | 14-Oct-20    |
| THAL-SNS-032 | CDK9, CDK10                                       | Novel in CT          | PK           | CMGC            | 0       | 12-Nov-20    |
| GNE-9822     | ITK                                               | Novel in CT          | PK           | Tyrosine Kinase | 0       | 03-Dec-20    |
| A-770041     | LCK                                               | Novel in CT          | PK           | Tyrosine Kinase | 1       | 25-Nov-20    |
| MLi-2        | LRRK2                                             | Novel in CT          | PK           | TKL             | 2       | 17-May-20    |

|                               |                       |                 |    |                 |   |                     |
|-------------------------------|-----------------------|-----------------|----|-----------------|---|---------------------|
| NIK SMI1                      | MAP3K14               | Novel in CT     | PK | STE             | 1 | 27-Oct-20           |
| FS-694                        | MAPK14                | Novel in CT     | PK | CMGC            | 1 | 17-May-20           |
| SR-318                        | MAPK14                | Novel in CT     | PK | CMGC            | 1 | 02-Jun-20           |
| BAY-3827                      | PRKAA1, RPS6KA1       | Novel in CT     | PK | CAMK            | 1 | 03-Aug-20           |
| GSK2982772                    | RIPK1                 | Novel in CT     | PK | TKL             | 3 | 21-Oct-20           |
| BAY-826                       | TIE1, TEK, DDR1, DDR2 | Novel in CT     | PK | Tyrosine Kinase | 1 | 15-Jun-20           |
| ULK-101                       | ULK1, ULK2            | Novel in CT     | PK | Other           | 2 | 17-Jun-20           |
| Adavosertib                   | WEE1                  | Novel in CT     | PK | Other           | 1 | 26-Oct-20           |
| XMD8-87                       | ACK1(TNK2)            | Novel not in CT | PK | Tyrosine Kinase | 1 | 13-Oct-20           |
| BAY-1816032                   | BUB1                  | Novel not in CT | PK | Other           | 2 | 20-Jul-20           |
| BAY-885                       | MAPK7                 | Novel not in CT | PK | CMGC            | 3 | 17-May-20           |
| MBM-55                        | NEK2                  | Novel not in CT | PK | Other           | 1 | 22-Oct-20           |
| TBK1 PROTAC 3i                | TBK1                  | Novel not in CT | PK | Other           | 2 | 12-Nov-20           |
| BAY-985                       | TBK1, IKBKE           | Novel not in CT | PK | Other           | 3 | 16-May-20           |
| Phorbol12-myristate13-acetate | pan-PKC               | Novel in CT     | PK | AGC             |   | undergoing curation |
| CH5424802                     | ALK                   | Established     | PK | Tyrosine Kinase | 3 | 10-Dec-15           |
| GNF-5                         | BCR-ABL               | Established     | PK | Tyrosine Kinase | 3 | 10-Dec-15           |
| Bafetinib                     | BCR-ABL, LYN          | Established     | PK | Tyrosine Kinase | 4 | 10-Dec-15           |
| Imatinib                      | BCR-ABL, PDGFR, KIT   | Established     | PK | Tyrosine Kinase | 3 | 10-Dec-15           |
| GDC-0879                      | BRAF V600E            | Established     | PK | TKL             | 3 | 10-Dec-15           |
| CGI1746                       | BTK                   | Established     | PK | Tyrosine Kinase | 3 | 10-Dec-15           |
| AVL-292                       | BTK                   | Established     | PK | Tyrosine Kinase | 3 | 10-Dec-15           |
| PD0332991                     | CDK4, CDK6            | Established     | PK | CMGC            | 3 | 10-Dec-15           |
| Afatinib                      | EGFR, ERBB2           | Established     | PK | Tyrosine Kinase | 3 | 10-Dec-15           |
| CP-724714                     | ERBB2                 | Established     | PK | Tyrosine Kinase | 3 | 10-Dec-15           |
| TX1-85-1                      | ERBB3                 | Established     | PK | Tyrosine Kinase | 3 | 10-Dec-15           |

|             |                            |             |    |                 |   |           |
|-------------|----------------------------|-------------|----|-----------------|---|-----------|
| BGJ-398     | FGFR1, FGFR2, FGFR3, FGFR4 | Established | PK | Tyrosine Kinase | 3 | 10-Dec-15 |
| BLU9931     | FGFR4                      | Established | PK | Tyrosine Kinase | 3 | 14-Mar-17 |
| AC220       | FLT3                       | Established | PK | Tyrosine Kinase | 3 | 10-Dec-15 |
| Filgotinib  | JAK1                       | Established | PK | Tyrosine Kinase | 3 | 10-Feb-17 |
| Ruxolitinib | JAK1, JAK2                 | Established | PK | Tyrosine Kinase | 3 | 10-Dec-15 |
| Tofacitinib | JAK1, JAK2, JAK3           | Established | PK | Tyrosine Kinase | 3 | 10-Dec-15 |
| BMS-911543  | JAK2                       | Established | PK | Tyrosine Kinase | 3 | 29-Jul-16 |
| JAK3i       | JAK3                       | Established | PK | Tyrosine Kinase | 3 | 09-Sep-16 |
| FM-381      | JAK3                       | Established | PK | Tyrosine Kinase | 3 | 24-Apr-17 |
| WH-4-023    | LCK, SRC                   | Established | PK | Tyrosine Kinase | 5 | 10-Dec-15 |
| Selumetinib | MAP2K1                     | Established | PK | STE             | 3 | 10-Dec-15 |
| SGX-523     | MET                        | Established | PK | Tyrosine Kinase | 3 | 10-Dec-15 |
| Rapamycin   | MTOR                       | Established | PK | Atypical        | 3 | 10-Dec-15 |
| AZD2014     | MTOR                       | Established | PK | Atypical        | 3 | 10-Dec-15 |
| eCF309      | MTOR                       | Established | PK | Atypical        | 3 | 17-Oct-16 |
| CP-673451   | PDGFR $\beta$              | Established | PK | Tyrosine Kinase | 3 | 10-Dec-15 |
| BYL-719     | PIK3CA                     | Established | LK | Lipid           | 3 | 10-Dec-15 |
| Pictilisib  | PIK3CA, PIK3CD             | Established | LK | Lipid           | 4 | 10-Dec-15 |
| eCF506      | SRC                        | Established | PK | Tyrosine Kinase | 4 | 23-Feb-17 |
| PRT062607   | SYK                        | Established | PK | Tyrosine Kinase | 3 | 10-Dec-15 |
| 2-MT 63     | TEK                        | Established | PK | Tyrosine Kinase | 3 | 13-Mar-17 |
| VE-821      | ATR                        | Novel in CT | PK | Atypical        | 3 | 10-Dec-15 |
| MK-5108     | AURKA                      | Novel in CT | PK | Other           | 3 | 10-Dec-15 |
| AMG900      | AURKA, AURKB, AURKC        | Novel in CT | PK | Other           | 3 | 10-Dec-15 |
| AZD1152     | AURKB                      | Novel in CT | PK | Other           | 3 | 10-Dec-15 |
| BMX-IN-1    | BMX                        | Novel in CT | PK | Tyrosine Kinase | 3 | 10-Dec-15 |

|               |                                                  |             |    |                 |   |                     |
|---------------|--------------------------------------------------|-------------|----|-----------------|---|---------------------|
| BMS-265246    | CDK, CDK2                                        | Novel in CT | PK | CMGC            | 3 | 10-Dec-15           |
| THZ1          | CDK7                                             | Novel in CT | PK | CMGC            | 3 | 10-Dec-15           |
| Cortistatin A | CDK8, CDK19                                      | Novel in CT | PK | CMGC            | 3 | 09-Sep-16           |
| CCT251545     | CDK8, CDK19                                      | Novel in CT | PK | CMGC            | 3 | 13-Jan-17           |
| PF-477736     | CHEK1                                            | Novel in CT | PK | CAMK            | 3 | 10-Dec-15           |
| CCT244747     | CHEK1                                            | Novel in CT | PK | CAMK            | 3 | 09-Sep-16           |
| CCT241533     | CHEK2                                            | Novel in CT | PK | CAMK            | 3 | 10-Dec-15           |
| KH-CB19       | CLK1, CLK4, DYRK1A                               | Novel in CT | PK | CMGC            | 3 | 10-Dec-15           |
| CX-4945       | CSNK2A1                                          | Novel in CT | PK | CMGC            | 3 | 10-Dec-15           |
| DDR1-IN-1     | DDR1                                             | Novel in CT | PK | Tyrosine Kinase | 3 | 10-Dec-15           |
| CHIR-99021    | GSK3A, GSK3B                                     | Novel in CT | PK | CMGC            | 3 | 16-Jul-15           |
| NVP-AEW541    | IGF1R                                            | Novel in CT | PK | Tyrosine Kinase | 3 | 10-Dec-15           |
| Linsitinib    | IGF1R, INSR, INSRR                               | Novel in CT | PK | Tyrosine Kinase | 3 | 27-Jun-17           |
| GNE7915       | LRRK2                                            | Novel in CT | PK | TKL             | 3 | 10-Dec-15           |
| BIX-02188     | MAP2K5                                           | Novel in CT | PK | STE             | 3 | 10-Dec-15           |
| SCH772984     | MAPK1, MAPK3                                     | Novel in CT | PK | CMGC            | 3 | 10-Dec-15           |
| VX-745        | MAPK14                                           | Novel in CT | PK | CMGC            | 3 | 10-Dec-15           |
| Skepinone-L   | MAPK14                                           | Novel in CT | PK | CMGC            | 3 | 15-Mar-17           |
| JNK-IN-8      | MAPK8, MAPK9, MAPK10                             | Novel in CT | PK | CMGC            | 3 | 10-Dec-15           |
| PF3644022     | MAPKAPK2                                         | Novel in CT | PK | CAMK            | 3 | 10-Dec-15           |
| UNC2025       | MERTK, FLT3                                      | Novel in CT | PK | Tyrosine Kinase | 3 | 06-Apr-17           |
| URMC-099      | MLK1(MAP3K9),<br>MLK2(MAP3K10),<br>MLK3(MAP3K11) | Novel in CT | PK | TKL             | 3 | 10-Dec-15           |
| MPS1-IN-1     | MPS1(TTK)                                        | Novel in CT | PK | Other           | 3 | 10-Dec-15           |
| CFI402257     | MPS1(TTK)                                        | Novel in CT | PK | Other           |   | Undergoing curation |
| Empesertib    | MPS1(TTK)                                        | Novel in CT | PK | Other           |   | Undergoing curation |
| NVS-PAK1-1    | PAK1                                             | Novel in CT | PK | STE             | 3 | 29-Nov-16           |

|                 |                                    |                 |    |          |   |                     |
|-----------------|------------------------------------|-----------------|----|----------|---|---------------------|
| GNE-2861        | PAK4, PAK5, PAK6                   | Novel in CT     | PK | STE      | 3 | 30-May-17           |
| GF109203X       | pan-PKC                            | Novel in CT     | PK | AGC      |   | Undergoing curation |
| GSK2334470      | PDK1                               | Novel in CT     | PK | AGC      | 3 | 10-Dec-15           |
| CFI-400945      | PLK4                               | Novel in CT     | PK | Other    | 3 | 10-Dec-15           |
| 8-CPT-cAMP      | PRKACA, PRKACG                     | Novel in CT     | PK | AGC      |   | Undergoing curation |
| GSK481          | RIPK1                              | Novel in CT     | PK | TKL      | 3 | 16-Feb-17           |
| BI-D1870        | RPS6KA1, RPS6KA2, RPS6KA3, RPS6KA6 | Novel in CT     | PK | AGC      | 3 | 10-Dec-15           |
| BIX-02565       | RPS6KA3                            | Novel in CT     | PK | AGC      |   | Undergoing curation |
| GW788388        | TGFBR1, ACVR1B, ACVR1C, TGFBR2     | Novel in CT     | PK | TKL      |   | Undergoing curation |
| KU-60019        | ATM                                | Novel not in CT | PK | Atypical | 3 | 10-Dec-15           |
| STO609          | CAMKK1, CAMKK2                     | Novel not in CT | PK | Other    | 3 | 10-Dec-15           |
| PF-4800567      | CSNK1E                             | Novel not in CT | PK | CK1      | 3 | 10-Dec-15           |
| AZ191           | DYRK1B                             | Novel not in CT | PK | CMGC     | 3 | 10-Dec-15           |
| CHEMBL-3421981  | DYRK1B                             | Novel not in CT | PK | CMGC     |   | Undergoing curation |
| AMG-18          | ERN1                               | Novel not in CT | PK | Other    | 3 | 08-Dec-16           |
| GNE-3511        | MAP3K12                            | Novel not in CT | PK | TKL      |   | Undergoing curation |
| 5Z-7-Oxozeaenol | MAP3K7, MAPK1, MAP2K7              | Novel not in CT | PK | CMGC     |   | Undergoing curation |
| XMD8-92         | MAPK7                              | Novel not in CT | PK | CMGC     | 3 | 10-Dec-15           |
| AX15836         | MAPK7                              | Novel not in CT | PK | CMGC     | 3 | 05-Dec-16           |
| WZ4003          | NUAK1, NUAK2                       | Novel not in CT | PK | CAMK     | 3 | 10-Dec-15           |
| G-5555          | PAK1, PAK2, PAK3                   | Novel not in CT | PK | STE      | 3 | 29-Nov-16           |
| PF-3758309      | PAK1, PAK4, PAK5, PAK6             | Novel not in CT | PK | STE      | 3 | 10-Dec-15           |
| BI2536          | PLK1, PLK2, PLK3                   | Novel not in CT | PK | Other    | 3 | 10-Dec-15           |
| GSK583          | RIPK2                              | Novel not in CT | PK | TKL      | 3 | 09-Mar-17           |
| HG-9-91-01      | SIK1, SIK2, SIK3                   | Novel not in CT | PK | CAMK     | 3 | 10-Dec-15           |

Data are obtained from ChemicalProbes.org (<https://www.chemicalprobes.org/>). Identification of *established* or *novel* in clinical trials (CT) or *novel not in CT* was determined from our dataset.

## Historical compounds targeting kinases

| Historical compound       | Primary target(s) | Note about activity    | NoT | Refs |
|---------------------------|-------------------|------------------------|-----|------|
| 4-anilinopyrimidine 15a   | MAPK8             | Non selective compound | 100 | [1]  |
| 4-anilinopyrimidine 8c    | MAPK8             | Non selective compound | 105 | [1]  |
| 6-Bromoindirubin-3'-oxime | CDK5              | Non selective compound | 108 | [1]  |
| A-674563                  | AKT1              | Non selective compound | 165 | [1]  |
| AST 487                   | ABL1              | Non selective compound | 224 | [1]  |
| Axitinib                  | ABL1              | Non selective compound | 114 | [1]  |
| BMS-387032                | CDK2              | Non selective compound | 116 | [1]  |
| CHEMBL1649761             | CSNK2A1           | Non selective compound | 102 | [1]  |
| CHEMBL2062936             | CDC7              | Non selective compound | 118 | [1]  |
| Chlorpromazine            | DRD2              | Non selective compound | 174 | [1]  |
| Crizotinib                | ALK               | Non selective compound | 166 | [1]  |
| CX5011                    | CSNK2A1           | Non selective compound | 215 | [1]  |
| CYC-116                   | CDK2              | Non selective compound | 133 | [1]  |
| Dovitinib lactate         | FGFR3             | Non selective compound | 237 | [1]  |
| Doxorubicin               | ABCB1             | Non selective compound | 143 | [1]  |
| Ellagic acid              | CSNK2A1           | Non selective compound | 156 | [1]  |
| Enzastaurin hydrochloride | PRKCB             | Non selective compound | 104 | [1]  |
| Fedratinib                | JAK2              | Non selective compound | 274 | [1]  |
| Flavopiridol              | CDK2              | Non selective compound | 179 | [1]  |
| Fluoxetine glucuronide    | MTOR              | Non selective compound | 203 | [1]  |
| Gw8510                    | GSK3B             | Non selective compound | 102 | [1]  |
| Ilorasertib               | KDR               | Non selective compound | 102 | [1]  |
| Intedanib                 | ABL1              | Non selective compound | 223 | [1]  |
| JNJ-28312141              | FLT3              | Non selective compound | 203 | [1]  |

|                 |                                    |                                                                                                                                                              |     |     |
|-----------------|------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|-----|
| JNJ-7706621     | CDK1                               | Non selective compound                                                                                                                                       | 184 | [1] |
| Kenpaullone     | CDK1                               | Non selective compound                                                                                                                                       | 110 | [1] |
| Kinome_1054     | CDC7                               | Non selective compound                                                                                                                                       | 105 | [1] |
| Kinome_1194     | PTK2                               | Non selective compound                                                                                                                                       | 122 | [1] |
| Kinome_1199     | MAPK8                              | Non selective compound                                                                                                                                       | 100 | [1] |
| Kinome_1901     | PIM2                               | Non selective compound                                                                                                                                       | 106 | [1] |
| Kinome_2079     | FER                                | Non selective compound                                                                                                                                       | 105 | [1] |
| Kinome_635      | ALK                                | Non selective compound                                                                                                                                       | 113 | [1] |
| KW-2449         | ABL1                               | Non selective compound                                                                                                                                       | 273 | [1] |
| Lestaurtinib    | FLT3                               | Non selective compound                                                                                                                                       | 363 | [1] |
| Linifanib       | KDR                                | Non selective compound                                                                                                                                       | 142 | [1] |
| NVP-TAE 226     | ALK                                | Non selective compound                                                                                                                                       | 115 | [1] |
| NVP-TAE684      | ALK                                | Non selective compound                                                                                                                                       | 299 | [1] |
| PD173955        | ABL1                               | Non selective compound                                                                                                                                       | 157 | [1] |
| PF-03814735     | AURKA                              | Non selective compound                                                                                                                                       | 123 | [1] |
| PF-562271       | PTK2B                              | Non selective compound                                                                                                                                       | 144 | [1] |
| Quercetin       | AKR1B1                             | Non selective compound                                                                                                                                       | 312 | [1] |
| SCHEMBL3814469  | PLK1                               | Non selective compound                                                                                                                                       | 114 | [1] |
| Staurosporine   | PRKCB                              | Non selective compound                                                                                                                                       | 395 | [1] |
| SU14813         | ABL1                               | Non selective compound                                                                                                                                       | 239 | [1] |
| Sunitinib       | KDR                                | Non selective compound                                                                                                                                       | 307 | [1] |
| Trifluoperazine | DRD2                               | Non selective compound                                                                                                                                       | 117 | [1] |
| Vandetanib      | KDR                                | Non selective compound                                                                                                                                       | 141 | [1] |
| ZINC04335977    | MAPK8                              | Non selective compound                                                                                                                                       | 146 | [1] |
| Lck inhibitor   | LCK                                | Available data reveal limited profiling against kinases, and insufficient evidence to establish that this compound is acting on the intended target in cells |     | [2] |
| Famitinib       | Broad specificity kinase inhibitor |                                                                                                                                                              |     | [3] |

|              |                                             |                                                                                                                                                                                                                                                                                                                                         |  |          |
|--------------|---------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|----------|
| Saracatinib  | Pan-SFK inhibitor                           | Limited validation data are available regarding the activity of this compound against kinases                                                                                                                                                                                                                                           |  | [4]      |
| Tozasertib   | Broad specificity kinase inhibitor          |                                                                                                                                                                                                                                                                                                                                         |  | [5]      |
| Dasatinib    | Broad specificity kinase inhibitor          |                                                                                                                                                                                                                                                                                                                                         |  | [5]      |
| Sorafenib    | Broad specificity kinase inhibitor          |                                                                                                                                                                                                                                                                                                                                         |  | [5]      |
| Entrectinib  | Broad specificity kinase inhibitor          |                                                                                                                                                                                                                                                                                                                                         |  | [6]      |
| NS-018       | JAK, SRC family kinases                     |                                                                                                                                                                                                                                                                                                                                         |  | [7]      |
| LFM-A13      | BTK                                         | Sufficiently potent to be a chemical probe                                                                                                                                                                                                                                                                                              |  | [8]      |
| KT5720       | PKA                                         |                                                                                                                                                                                                                                                                                                                                         |  | [9]      |
| Rottlerin    | PKC kinases                                 | Broad specificity kinase inhibitor                                                                                                                                                                                                                                                                                                      |  | [9]      |
| Ninetedanib  | Broad specificity tyrosine kinase inhibitor |                                                                                                                                                                                                                                                                                                                                         |  | [10]     |
| Ki-20227     | CSF1R                                       | Available data reveal limited profiling against kinases, and insufficient evidence to establish that this compound is acting on the intended target in cells                                                                                                                                                                            |  | [11]     |
| ENMD-2076    | Aurora kinases                              |                                                                                                                                                                                                                                                                                                                                         |  |          |
| Foretinib    | MET                                         |                                                                                                                                                                                                                                                                                                                                         |  |          |
| Epiblastin A | CK1                                         | Given the low potency and poor selectivity we consider Epiblastin A an historical compound and we do suggest its use to interrogate target activity in cells                                                                                                                                                                            |  |          |
| AMG-458      | cMET                                        | AMG-458 is more potent against RON and inhibits multiple kinases within 10-fold of its IC50 for MET                                                                                                                                                                                                                                     |  |          |
| Enzastaurin  | GSKbeta                                     | Broad specificity kinase inhibitor                                                                                                                                                                                                                                                                                                      |  |          |
| FRAX1036     | PAK1                                        | FRAX1036 is a lipophilic compound with insufficient potency or selectivity to be a chemical probe                                                                                                                                                                                                                                       |  |          |
| MLN8054      | Aurora A                                    |                                                                                                                                                                                                                                                                                                                                         |  | [12]     |
| OTSSP167     | MELK                                        | MELK knock-out cell lines remain sensitive to OST167 indicating that this compound mediates its anti-growth activity via another target                                                                                                                                                                                                 |  | [13]     |
| SL0101       | RSK2                                        | Limited validation data are available regarding the activity of this compound against kinases                                                                                                                                                                                                                                           |  | [14]     |
| TG10129      | JAK2                                        | TG10129 also potently inhibits BRD4, FLT3 and RET                                                                                                                                                                                                                                                                                       |  | [15]     |
| Gefitinib    | EGFR, ERBB2                                 | In proteomic experiments, gefitinib interacts with several protein tyrosine kinases BRK, YES, CSK, and EPHB4, and the serine/threonine kinases RICK (RIPK2, RIP2, and CARDIAK), GAK, CaMKII, Aurora A, JNK2 and p38. In AML and EGFR-expressing cells, gefitinib binds to and modulates the activity of histamine receptors (H2 and H4) |  | [16, 17] |

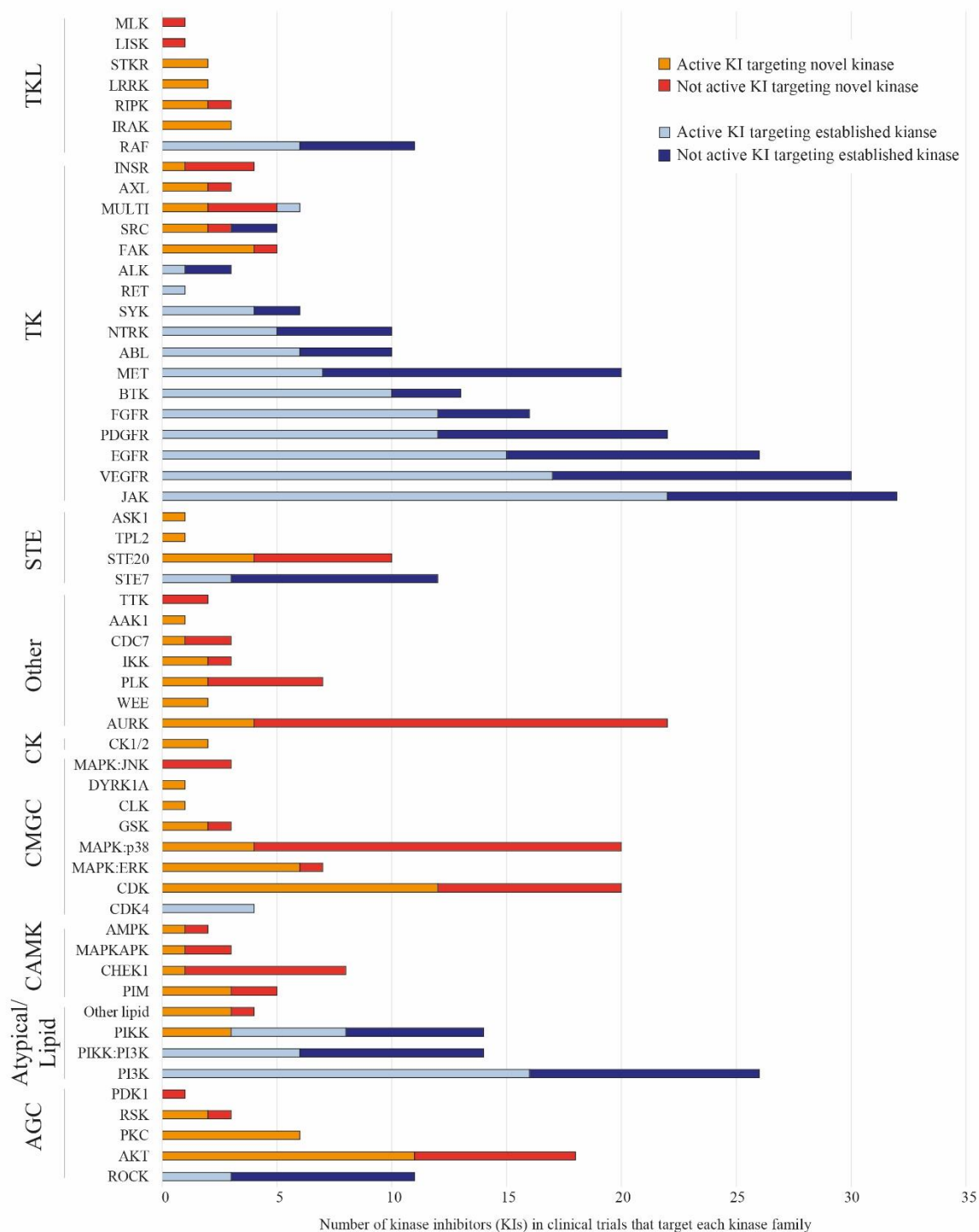
|              |                                                     |                                                                                                                                                                                                   |  |  |
|--------------|-----------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|--|
| Decerinib    | JAK3                                                | More potent and selective JAK3 probes available                                                                                                                                                   |  |  |
| Cerdulatinib | pan JAK, SYK                                        | Non-selective, more selective pan JAK probes available                                                                                                                                            |  |  |
| Pacritinib   | JAK2, FLT3                                          | More potent and selective JAK2 probes are available                                                                                                                                               |  |  |
| Dorsomorphin | AMPK                                                | Non selective compound                                                                                                                                                                            |  |  |
| LY294002     | PI3K                                                | Non selective compound                                                                                                                                                                            |  |  |
| Aloisine     | Broad specificity kinase inhibitor                  | Non selective compound                                                                                                                                                                            |  |  |
| Dinaciclib   | CDK                                                 | Non selective compound                                                                                                                                                                            |  |  |
| Tandutinib   | FLT3                                                | Non selective compound                                                                                                                                                                            |  |  |
| XL-647       | RTKs                                                | Non selective compound                                                                                                                                                                            |  |  |
| IPA-3        | PAK1                                                | While this compound is a selective, covalent binder of PAK1 (targeting its autoregulatory domain), its redox activity makes it a poor tool                                                        |  |  |
| XMD17-109    |                                                     | While this compound is selective among the kinases, it also inhibits bromodomains. The bromodomain-binding activity is sufficient to explain all of the compound's reported biological activities |  |  |
| LJI308       | RSKs                                                |                                                                                                                                                                                                   |  |  |
| PD166285     | WEE1, MYT1, EERB1, FGFR1, PDGFRb, SRC, LCK          | Broad specificity tyrosine kinase inhibitor                                                                                                                                                       |  |  |
| Rebastinib   | FLT3, TIE2, KDR, LYN, BCR-ABL, TRKA, ABL1, and YES1 | Broad specificity tyrosine kinase inhibitor                                                                                                                                                       |  |  |

All data are obtained from ChemicalProbes.org (<https://www.chemicalprobes.org/>). Number of Targets: NoT.

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Supplementary Figure 1 | **Active and not active small-molecule kinase inhibitors targeting established and novel kinases.** KI, kinase inhibitor.