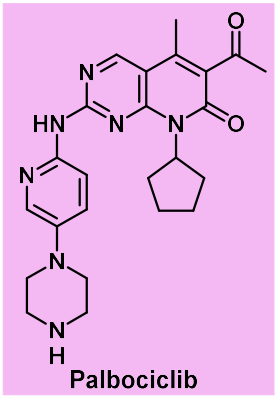
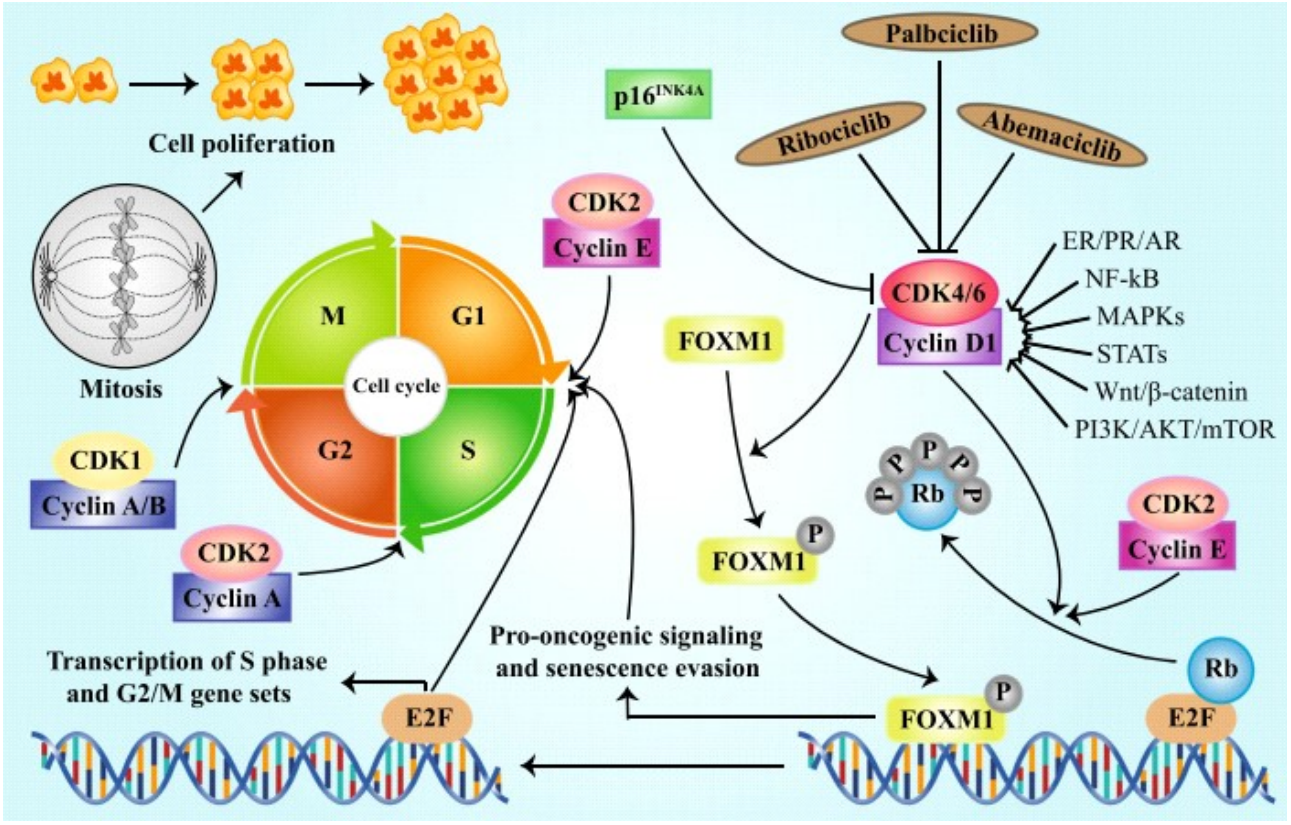
DOTW: Palbociclib (Ibrance)



- highly selective, reversible inhibitor of CDK 4/6
  - increased CDK 4/6 activity is typically observed in estrogen receptor-positive (ER+) breast cancer
  - induces G1-S cell cycle block by blocking the phosphorylation of RB and related proteins and down-regulating S-phase cyclins and mitotic regulatory genes as well as suppressing nucleotide biosynthesis and DNA replication
- used in combination with letraozole for treatment of postmenopausal women or men with ER+/ human epidermal growth factor receptor 2-negative (HER2-) advanced breast cancer
- 125 mg capsule taken orally once daily for 21 consecutive days followed by 7 days off treatment
- received accelerated approval from the FDA in Febuary 2015
- received regular approval from the FDA in March 2017
- third highest selling drug behind Prevnar 13 (pneumococcal vaccine) and Lyrica (nerve pain) with $4.1 billion in sales in 2018

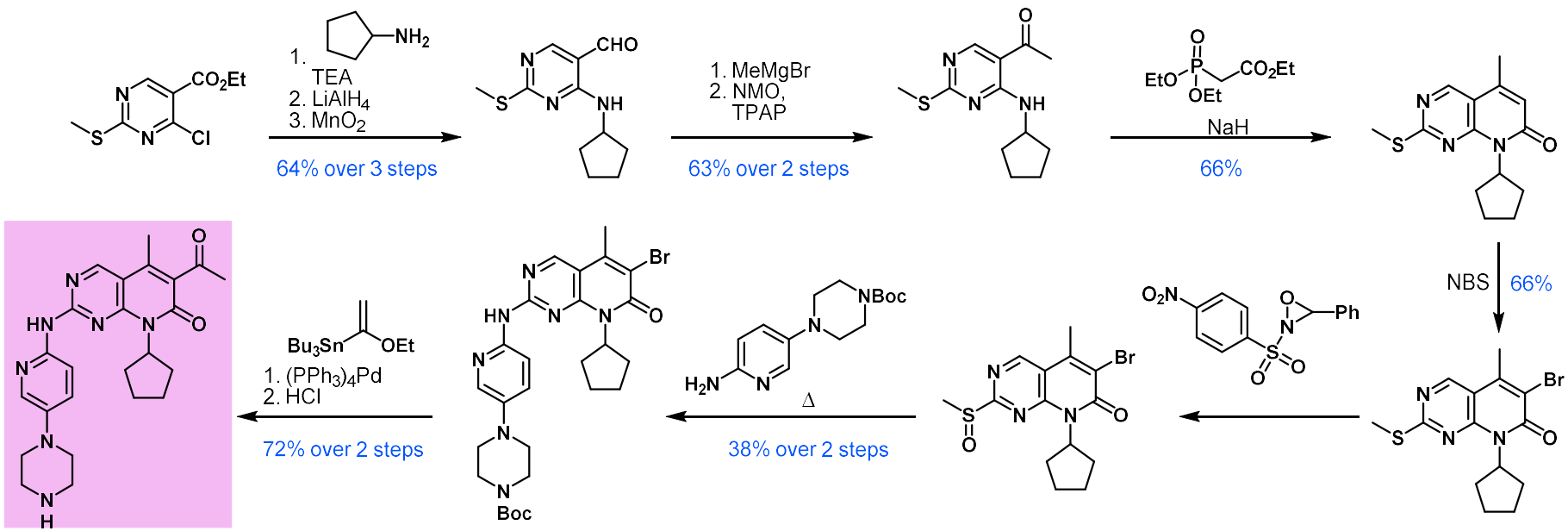


Regulation and function of CDK4/6 in cell cycle progression:
- complex of CDK4/6 and cyclin D1:
  - phosphorylates and inactivates retinoblastoma protein
    - Release of E2F (transcription factor) triggers up-regulation of E2F-positive gene, promoting cell proliferation at the G1/S transition
  - phosphorylates FOXM1 (transcription factor)
    - expression of FOXM1-dependent gene which protects cancer cells from cell cycle block
- kinase activity of CDK4/6 is supressed by:
  - $p16^{INK4A}$
  - palbociclib
  - ribociclib (Eli Lilly)
  - abemaciclib (Novartis)
- Cyclin D_1 is regulated by multiple pathways including:
  - ER/PR/AR
  - NF-kB
  - MAPKs
  - STATs
  - Wnt/β–catenin
  - PI_3K/AKT/mTOR

References:
Xu *et al. Journal of Hematology & Oncology* **2017,** *10*
https://s21.q4cdn.com/317678438/files/doc_financials/Quarterly/2018/q4/Q4-2018-PFE-Earnings-Release.pdf

DOTW: Palbociclib (Ibrance)

Discovery Route: Barvian *et al.*, *J. Med. Chem.* **2000**, *43*, 4606. Toogood *et al.*, *J. Med. Chem.* **2005**, *48*, 2388.



Procress Route: *Org. Process Res. Dev.* **2016**, *20*, 1191. *Org. Process Res. Dev.* **2016**, *20*, 1203. *Org. Process Res. Dev.* **2016**, 1217.