Poly (ADP-ribose) polymerase (PARP) engages in DNA base excision repair by inducing poly (ADP-ribosy)lation of itself and other target proteins (Sonnenblick et al., 2015). In addition, PARP has a less well-defined role in homologous recombination mediated (Bryant et al., 2009) and alternative non-homologous end-joining mediated double-strand break repair (Paddock et al., 2011). PARP inhibition has been shown to be an effective therapeutic strategy against tumors associated with germline mutations in double-strand DNA repair genes by inducing synthetic lethality (Sonnenblick et al., 2015).

ADP-ribose 多聚酶（PARP）通过催化其自身及其底物的多聚反应来参与在碱基层面的 DNA 单链修复(Sonnenblick et al., 2015)。除此之外，它还参与同源重组途径介导的或者替代的非同源重组末端连接介导的DNA 双链修复，但此功能并没有像单链修复功能那样被广泛报道。目前的临床数据显示PARP抑制剂对于含有遗传性突变而导致的双链DNA修复功能障碍的肿瘤有有效的治疗效果(Sonnenblick et al., 2015)。

One PARP inhibitor (PARPi), olaparib, was approved by the U.S. Food and Drug Administration (FDA) in 2014 for the treatment of germline BRCA-mutated (gBRCAm) advanced ovarian cancer (Kim et al., 2015). More recently, another PARPi, niraparib, which was shown to significantly prolong the progression-free survival in ovarian cancer patients, received a fast track designation from the FDA for the treatment of patients with recurrent platinum-sensitive ovarian cancer (Mirza et al., 2016).

美国食品与药物安全局在2014年批准了以一个PARP抑制剂 欧拉帕瑞博用于治疗有遗传性BRCA突变的晚期卵巢癌(Kim et al., 2015)。此外，另一个PARP抑制剂，尼若帕瑞博近期得到了美国食品与安全局临床批准的绿色通道，因为早期临床试验数据显示，其对于复发的，铂类药物敏感卵巢癌有明显的延长疾病无进展期 (Mirza et al., 2016)。

In addition to ovarian cancer, PARPi has demonstrated tremendous potential in breast cancer, and there are currently several active clinical trials evaluating PARPi-containing combination therapies for advanced breast cancer. Although the objective response rate to PARPi in patients with advanced breast cancer harboring BRCA1/2 mutations was reported as high as 41%, its response duration is still very limited with a 5.7-month median duration (Tutt et al., 2010).

除了卵巢癌之外，PARP抑制剂也在乳腺癌治疗中表现出优越的治疗效果。目前有多个临床实验在评估含有PARP抑制剂的治疗对于晚期乳腺癌的效果。尽管PARP抑制剂在有BRCA突变的晚期乳腺癌的客观有效率高达41%，然而其有效时间的中位数仅为5.7个月 (Tutt et al., 2010)。

The underlying resistance mechanisms to PARPi have mainly attributed to the restoration of double-strand break repair. For instance, secondary BRCA mutations that restore BRCA function (Edwards et al., 2008) and reduced 53BP1 expression leading to partial restoration of homologous recombination (Jaspers et al., 2013) have been described as the potential resistance mechanisms to PARPi. In order to enhance the cytotoxic effect of PARPi, several combinations of PARPi and targeted anticancer agents, such as inhibitors against phosphatidylinositol 3-kinase (Ibrahim et al., 2012; Juvekar et al., 2012), Wee1 kinase (Karnak et al., 2014), DNA topoisomerase I (Kummar et al., 2011), and DNA methyltransferase (Muvarak et al., 2016), have been proposed. In addition, c-Met-mediated phosphorylation of PARP was reported to contribute to PARPi resistance, suggesting that the combined inhibition of c-Met and PARP may benefit patients who do not respond to PARPi and whose tumors are associated with c-Met activation (Du et al., 2016). Thus, developing a rational combination therapy with PARPi may lead to effective anticancer strategy.

PARP抑制剂耐药性一般归结于双链DNA修复能力的恢复。有报道称，二次BRCA的突变可以恢复BRCA的DNA修复能力(Edwards et al., 2008)；还有报道称53BP1的减少表达导致了同源重组途径的DNA修复的恢复(Jaspers et al., 2013)。这些都可以成为PARP抑制剂耐药的原因。为了增强PARP抑制剂的治疗疗效，多个与其他靶向治疗药物的组合治疗方案被提出验证，如PI3K抑制剂(Ibrahim et al., 2012; Juvekar et al., 2012)，Wee1抑制剂 (Karnak et al., 2014)，DNA拓扑异构酶(Kummar et al., 2011)还有DNA甲基转移酶(Muvarak et al., 2016)。 初次之外，cMET介导的PARP磷酸化被报道称可以促进PARP抑制剂的耐药性(Du et al., 2016)，因而与cMET抑制剂连用的方案也被提出应用到cMET高表达的肿瘤病人。简而言之，研究出一个有理论支持的组合治疗方案能有有效增强PARP抑制剂的临床治疗效果。