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A REVIEW ARTICLE ON TALAZOPARIB – ANTI CANCER DRUG

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Abstract:

Talazoparib tosylate (BMN-673, Talzenna; Pfizer) is an oral poly [ADP-ribose] polymerase (PARP) inhibitor (PARPi) that has been approved by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of germline BRCA-mutated locally advanced or metastatic breast cancer (BC). In preclinical and clinical studies, talazoparib exerted superior efficacy and offered a significant clinical benefit in advanced or metastatic BC patients harbouring germline BRCA mutations compared with other PARPi and standard chemotherapy regimens through the concept of synthetic lethality. Thus, this review provides insight into the results of preclinical and clinical studies, highlights the current challenges of talazoparib and suggests innovative approaches to further improve its clinical efficacy and expand the use of talazoparib in advanced BC and/or triple-negative BC treatments beyond BRCA mutations.

Keywords: *BMN-673; BRCA-positive breast cancer; Cancer therapy; Poly [ADP-ribose] polymerase (PARP) inhibitors; Talazoparib to sylate.*

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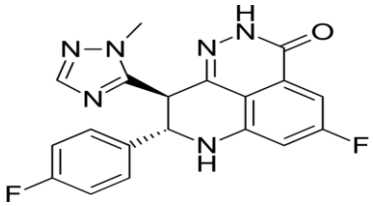
INTRODUCTION:

In the world of modern medicine, the discovery of novel drugs is an experimentation, and rigorous testing. One such promising drug that has emerged in recent years is Talazoparib. This article delves into the fascinating journey of Talazoparib, from its initial discovery to its potential as *a* breakthrough in cancer treatment.

Understanding PARP Inhibitor:

Talazoparib belongs to a class of drugs known as PARP (Poly ADP-ribose polymerase)inhibitors. PARP is an enzyme crucial for repairing damaged DNA in cells. When PARP is inhibited, cancer cells with defective DNA repair mechanisms become vulnerable, leading to their demise.



Discovery of* Talazoparib*:

Talazoparib, sold under the brand name Talzenna, is an orally available polyADP ribose polymerase(PARP)inhibitor developed by Pfizer for the treatment fadvanced breast cancer with Germaine BRCA mutations. Talazoparib is similar to the first in class PARP inhibitor ,olaparib. It was approved in October 2018, in the United States and June 2019, in the European Union for germline BRCA-mutated, HER2-negative locally advanced or metastatic breast cancer.

The journey of Talazoparib began with extensive research into identifying potential PARP inhibitors. Scientists and researchers were driven by the idea of finding targeted therapies for cancers associated with BRCA gene mutations, such as breast and ovarian cancer. Talazoparib emerged as a promising candidate in this pursuit.

Characterization of Talazoparib:

Talazoparib, a poly ADP-ribose polymerase (PARP) inhibitor, has gained attention in the field of oncology for its potential in treating various cancers, particularly those associated with BRCA gene mutations.

To fully appreciate its therapeutic capabilities and safety profile, it's essential to understand its characterization, including its chemical propertie**s.**

Chemical Structure and Properties:

Talazoparib, chemically known as 4-[(3S,4R)-3,4-dihydro-4-(4-hydroxy-3- methoxyphenyl) -2H-1-benzopyran-7-yl]-1(2H)-isoquinolinone, possesses a unique chemical structure. It is a synthetic small molecule with molecular formula C22H21NO5 and a molecular weight of approximately 375.41 g/mol. Key chemical properties of Talazoparib include its solubility, stability, and compatibility with pharmaceutical formulations.

IUPAC NAME:

(8S,9R)-5-Fluoro-8-(4-fluorophenyl)-9-(1-methyl-1H-1,2,4-triazol-5-yl)-2,7,8,9-tetrahydro-3H-pyrido[4,3,2-de]phthalazin-3-one.

Mechanism of action:

Talazoparib's mechanism of action lies in its ability to inhibit PARP enzymes. PARP enzymes play a crucial role in repairing damaged DNA in cells. When PARP is inhibited, DNA repair processes in cancer cells become compromised, leading to genomic instability and, ultimately, cell death. This mechanism is particularly effective insincerity BRCA gene mutations, as they have pre-existing DNA repair deficiencies.

Targeted therapy:

Talazoparib's selectivity for cancer cells over healthy cells is a hallmark of its characterization. This targeted approach minimizes harm to normal tissues, reducing the severity of side effects compared to conventional chemotherapy.

Clinical Applications:

Talazoparib has demonstrated its clinical significance in the treatment ofvarious cancer types, especially breast and ovarian cancers. It has been granted accelerated approval by regulatory agencies like the U.S. FDA for specific indications, further validating its potential in oncology.

Safety Profile:

Characterizing the safety profile of Talazoparib is essential for clinical use. Like any medication, it may

have side effects, including nausea, fatigue, anemia, and low platelet count. Close monitoring and individualized treatment crucial plans are to manage these side effects effectively.

Resistance Mechanisms:
Understanding potential resistance mechanisms is also part of Talazoparib's characterization. Over time, cancer cells may develop resistance to PARP inhibitors.Research continues to investigate these mechanisms to develop strategies to overcome resistance and improve long-term treatment outcomes.

Future Directions:
Talazoparib's characterization is an evolving process. Ongoing research seeks to expand its applications to other cancer types, explore combination therapies, optimize dosing regimens, and enhance its clinical utility.

In conclusion, Talazoparib's characterization is a multidimensional process that encompasses its chemical properties, mechanism of action, clinical applications, safety profile, and ongoing research. As our understanding of this PARP inhibitor deepens, it holds the potential to continue making a significant impact in the field of oncology, offering new hope to patients facing cancer diagnoses.

Formulation of Talazoparib:
Talazoparib was provided to the PPTP by Bio Marin Pharmaceutical Inc., through the Cancer Therapy Evaluation Program (NCI). Temozolomide was obtained through theNCI Drug Repository. Talazoparib was formulated in 10% dimethylacetamide/5% Solution HS 15/85% PBS and stored up to 7 days at 4°C. The solution was brought to ambient temperature and vortexes before oral dosing.

Talazoparib was administered twice daily for 5 days alone or in combination with daily temozolomide. Temozolomide was formulated in 1% carboxymethylcellulose in water and stored for up to 7 days at 4°C. Based upon single-agent talazoparib toxicity testing, the MTD (non tumored SCID mice) was 0.25 mg/kg twice daily. At 0.4 MTD of tolazoparib (0.1 mg/kg twice daily), temozolomide was tolerated at 30 mg/kg daily for 5 days (combination A). Talazoparib administered at its MTD could be combined with temozolomide at 12 mg/kg daily for 5 days (combination B). Talazoparib and temozolomide were provided to each consortium investigator in coded vials for blinded testing.

Pharmacokinetic Aspects and Drug Disposition:

1. **Absorption:** Talazoparib is orally administered and is well absorbed after ingestion. It is primarily absorbed in the small intestine.
2. **Distribution:** Ithasamoderate volume of distribution, indicating that it is distributed throughout the body's tissues. It binds to plasma proteins, including albumin.
3. **Metabolism:** Talazoparib undergoes metabolism primarily in the liver. It is metabolized by enzymes such as cytochrome P450 (CYP) enzymes, particularlyCYP1A1 and CYP1A2.
4. **Elimination:** Talazoparib is primarily eliminated through the hepatic (liver)route. It is excreted in the feces, primarily as metabolites, with a smaller portion excreted in the urine.
5. **Half-life:** The elimination half-life of talazoparib isapproximately8-10 hours, meaning it takes this amount of time for half of the drug to be removed from the body.
6. **Drug-Drug Interactions:** Talazoparib may interact with other drugs that affect CYP enzymes, potentially leading to drug interactions. Patients may be advised to avoid or adjust the dose of other medications while taking talazoparib.
7. **Special Populations:** Pharmacokinetics of talazoparib may vary in different patient populations, such as those with hepatic or renal impairment. Dose adjustments may be necessary in these cases.
8. **Food Effects:** Talazoparib can be taken with or without food, but taking it with a high-fat meal may increase its absorption.
9. **Excretion:** As mentioned earlier, a portion of the drug and its metabolites is eliminated through the feces and urine. It is essential to monitor renal and hepatic function in patients taking talazoparib.

Preclinical Toxicity Studies:
Preclinical toxicity studies are a critical step in the drug development process, and they involve evaluating the safety and potential side effects of a new

compound like talazoparib in animals before it progresses to human clinical trials.

Method and Results:
In the current study, an accurate and efficient liquid chromatography-tandem mass spectrometry (LC–MS/MS) analytical methodology was developed for TZB estimation in addition to its metabolic stability assessment. TZB and lapatinib (LAP) (which is chosen as an internal standard; IS) were separated using reversed phase elution system (Hypersil C18column) with an isocratic mobile phase.

The linearity range of the established method was 5–500 ng/mL ($r^2 \geq 0.999$) in the human liver microsomes (HLMs) matrix. Different parameters were calculated to confirm the method sensitivity (limit of quantification was 2.0 ng/mL), and reproducibility (intra- and inter-day precision and accuracy were below 3.1%) of our methodology. For evaluation of TZB metabolic stability in HLM matrix, intrinsic clearance (9.59 µL/min/mg) and in vitro half-life (72.7 mins) were calculated.
TZB treatment discontinuations were reported due to adverse events and dose accumulation, so in silico metabolic vulnerability (experimental and in silico) and toxicity assessment (in silico) of TZB were performed utilizing P450 Metabolism and DEREK modules of Star Drop software.

Conclusion:

TZB is slowly metabolized by the liver. TZB was reported to be minimally metabolized by the liver that approved our outcomes. We do recommend that plasma levelsbe monitored in cases when talazoparib is used for a long period oftime, since it is possible for TZB to bio accumulate after multiple doses to toxic levels. According to our knowledge, the current method is considered the first LC-MS/MS methodology for evaluating TZB metabolic stability. Further drug discovery studies can be done depending on this concept allowing the designing of new series of compounds with more safety profile through reducing side effects and improving metabolic Behaviour.

New Approaches in Drug Discovery:

Combinatorial chemistry:

Materials and methods:

Preparation of library of compounds and ligand-based virtual screening

The purchasable dataset of ZINC20 as a library for virtual screening of potential PARP inhibitors (~13.3 million compounds). Dataset was filtered using the PAINS filter. Thereafter the dataset was filtered based on the shape similarity to the talazoparib using Open Eyes scientific ROCS software. ROCS are a powerful ligand-based virtual screening tool which was used for the rapid identification of potentially active compounds by shape comparison to the talazoparib. ROCS perform shape-based overlays, which are based on a description of the molecules as atom centered Gaussian functions, of a candidate molecule toa reference molecule. Two scores were used to evaluate the tested compounds to the reference:

1) TheShapeTanimotocoefficientisusedtorankmolecu lesagainstthequerymolecule based on their shape similarity and

2) The Colour Tanimotoscore that counts appropriate overlap of groups that describe properties, such as H-bond donors and acceptors, cations, anions, rings, etc.

- **Structure-based virtual screening:**

Virtual screening was performed using the ICM-PRO software package. ICM-PRO demonstrated high accuracy based on the multiple benchmark studies for molecular docking and virtual screening software among both academic and commercial software. The docking algorithm of the ICM-PRO software is based on the Monte Carlo minimization approach.

The scoring function of ICM-PRO software is a weighted sum that includes van der Waals energy of the ligand-target interactions, internal force field energy of the ligand, hydrogen bonding interactions, hydrogen bond donor-acceptor desolation energy, hydrophobic free energy gain and others. The 3D structure of PARP in complex with one of the most potent inhibitors (talazoparib) was downloaded from Protein Data Bank (PDB ID: 7KK3) and used for virtual screening.

Re-scoringusing MMGBS Aapproach:
The algorithm for MMGBSA binding energy calculation includes three stages: 1) parametrization of the receptor and ligand, 2) minimization and 3) MMGBSA calculations. General Amber Force Field (GAFF) with AM1-BCC charge model was used for small molecule parametrization, while ff14SB force field is used to describe protein parameters.

Clusterization dendrogram and figures of chemical

structures were obtained using ICM-PRO. Comparative analysis of physicochemical features of the identified compounds with reference ligand (talazoparib) was performed using Open Eye ROCS's ROCS Report utility.

Molecular dynamics simulations:

AMBER20 package was used to carry out molecular dynamics simulations. Protein parametrization was performed using the ff14SB force field, while for ligand parametrization GAFF with AM1-BCC charge model was used. Minimized conformations of complexes of PARP1 protein with selected compounds obtained from previous stage (MMGBSA re- scoring) were used as starting positions for corresponding simulations. The complexes were solvatedinTIP3Pwater model and Na+/Cl− ions at 150mMconcentration. The Monte Carlo barostat with reference pressure at 1 bar and Langevin thermostat with collision frequency (gamma ln) 2 ps^{-1} were used to keep the temperature at 310.15 K. The Particle Mesh Ewald (PME) method with 1.0 nm cut-off was used for the long-range electrostatic interactions. Each simulation consisted of 5 ns of system minimization and equilibration and 100 ns of conventional molecular dynamics simulation. Finally, for every simulation, binding energies were calculated using MMPBSA.py program, using 250 snapshots with equal intervals collected from the last 20 ns of simulation. RMSD was calculated as indicator of stability of studied complexes during simulations. Besides, RMSF analysis was performed to measurethe average atomic flexibility of the Cα atoms of the docked complexes.

Results and discussion:

10,374,250 compounds remained as the result of filtration of the initial database (~13,276,808 compounds) using PAINS filter. These 10,374,250 compounds were additionally filtered for shape similarity to the reference ligand (talazoparib) usingOpenEye's ROCS tooland 500,000 compounds withhighest shape similaritytothe reference compound were selected for the following molecular docking study.

Molecular docking of the selected 500,000 compounds against the binding site of the catalytic domain of PARP1 enzyme (PDB ID: 7KK3, chain C) was performed using ICPRO software. As the result of molecular docking, 168 compounds demonstrated higher docking scores in comparison to the reference ligand .

With the goal of validation of obtained results, binding energies of identified 168 compounds were recalculated using MMGBSA method. MMGBSA re-scoring showed that only 74 compounds demonstrated close or higher binding energies in comparison to talazoparib [fig-1].

figure-1

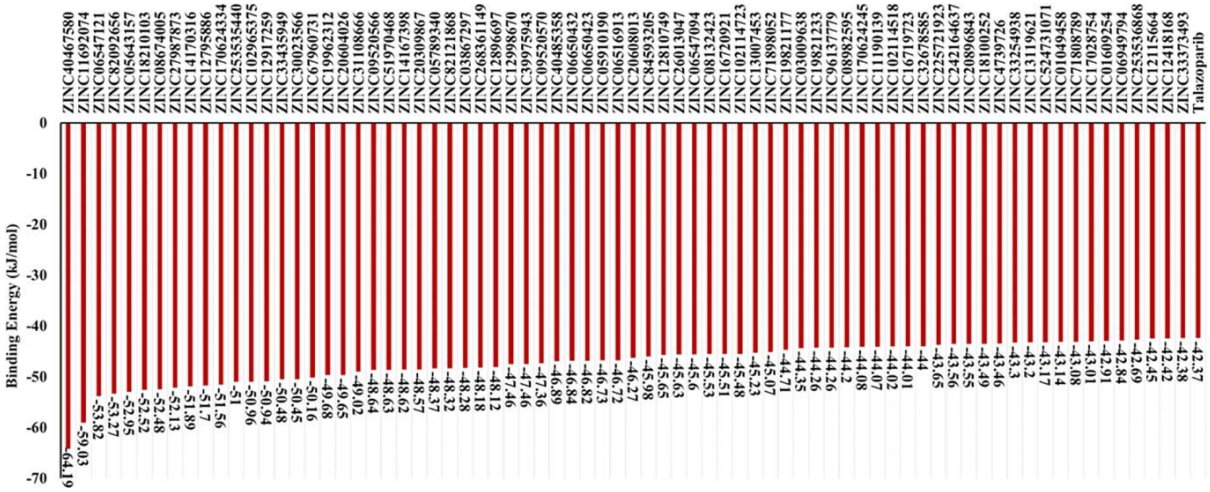


Fig1.MMGBSAbindingenergies.

Binding energies of identified compounds and Talazoparib (reference compounds) as the result of MMGBSA re-scoring.

These74compoundscanbedividedinto10clustersbasedontheirchemicalsimilarity[fig-2].

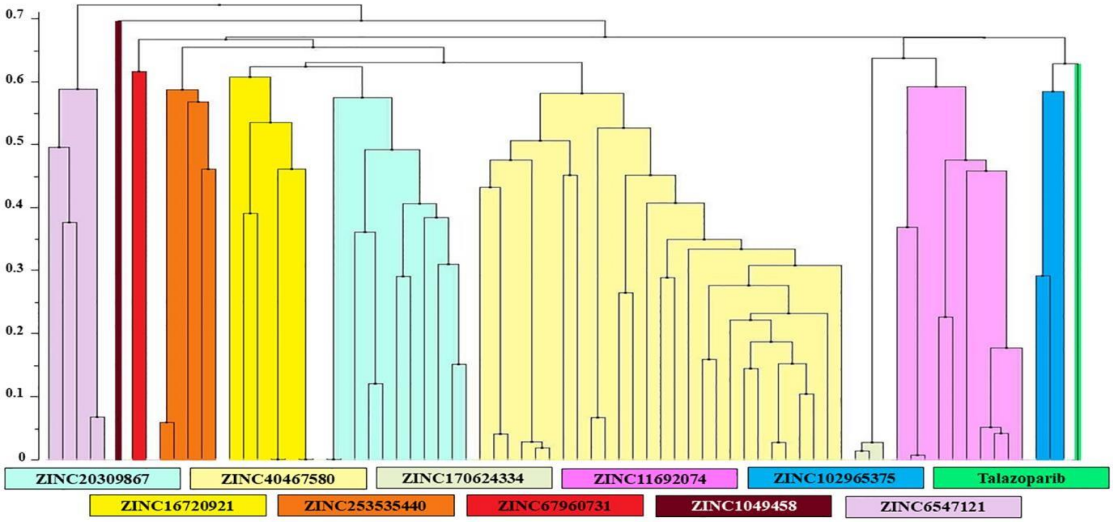
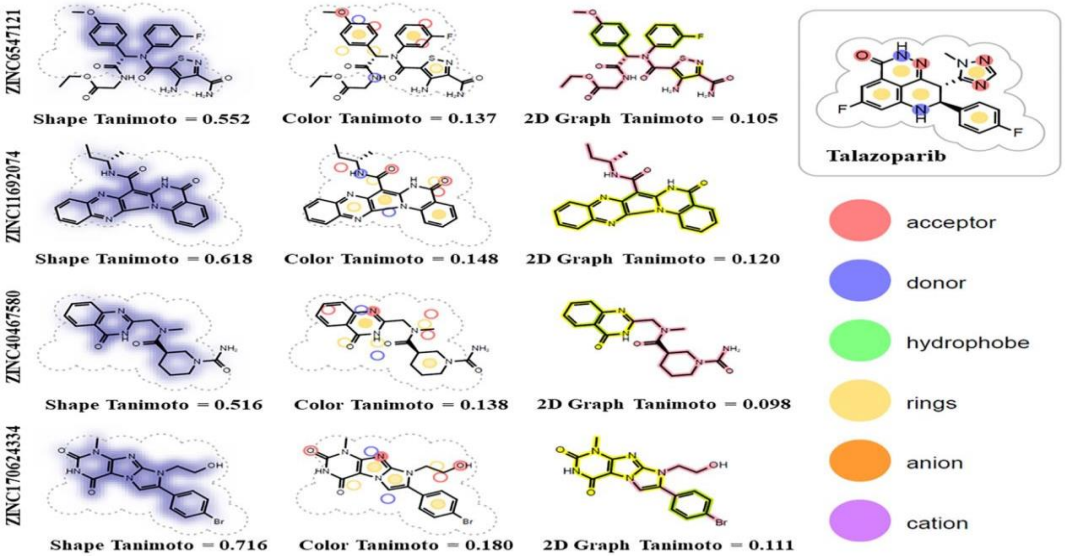


Fig2.Clusterization dendrogram.

Clusterization of the 74 identified compounds with higher binding energies in comparison to talazoparib. For each cluster ZINC ID of the representative compounds with highest estimated binding energy is labeled.

The compound with the highest estimated binding energy (ZINC40467580, -64.19 kJ/mol) lies within the biggest cluster. Identified compounds include derivatives of the dihydrophthalazine, dimethoxyphenyl, quinazolin, imidazole, tetrahydroisoquinoline, sulfonamide, fluoroaniline and others.

Similarity analysis of the four selected compounds (representative compounds of clusters with the highest estimated binding energies) and the reference drug-compound (talazoparib)demonstrated significant differences in both chemical structure and functional



groups[fig-3].

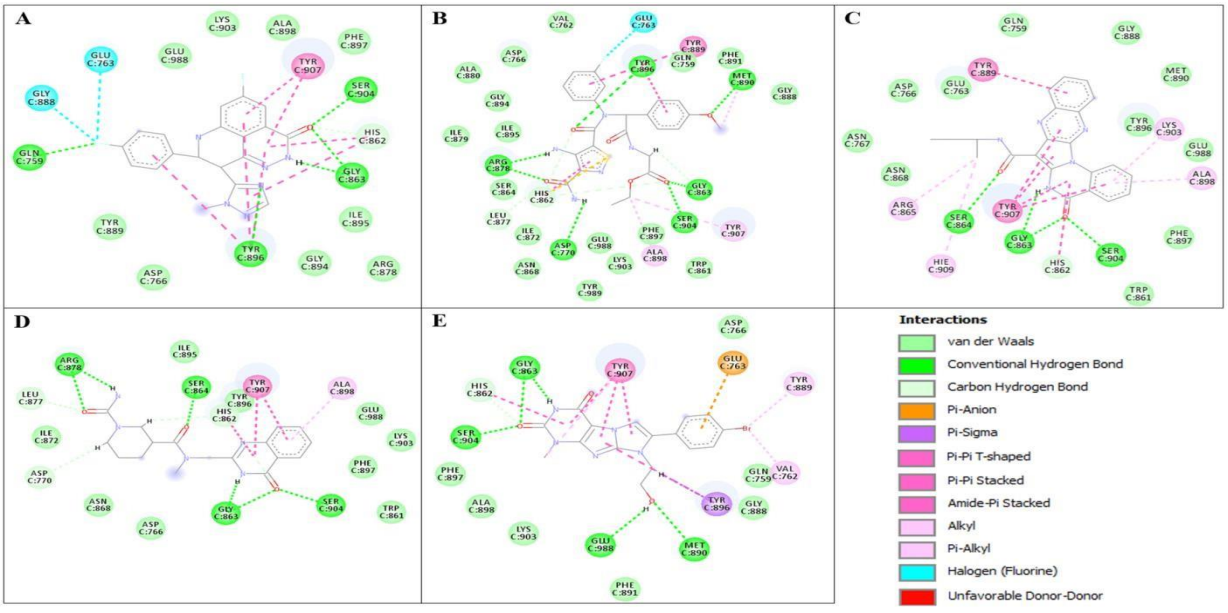
Fig3.Chemicalsimilarityanalysis:

Chemical similarity of top 4 identified compounds with talazoparib. In 2D Graph similarity score, pink colour highlights parts of the hit molecule that are dissimilar to the talazoparib, while "yellow to dark green" colour gradient highlights the bonds similarity. ZINC170624334(7-(4-bromophenyl)-6-(2-hydroxyethyl)-4-methylpurino[7,8-a] imidazole-1,3-dione) has the highest shape similarity (0.716) to the talazoparib among fouranalyzed compounds.

ZINC11692074 (N-[(2S)-butan-2-yl]-9-oxo-2,10,14,21-tetrazapentacyclo[11.8.0.02,11.03,8.015,20]henicosa-1(21),3,5,7,11,13,15,17,19-nonaene- 12-carboxamide), ZINC40467580 ((3R)-3-N-methyl-3- N-[(4-oxo-3H-quinazolin-2-yl)methyl]piperidine-1,3-dicarboxamide) and ZINC6547121, (ethyl2- [[(2S)-2-(N-(4-amino- 3-carbamoyl-1,2-thiazole-5-carbonyl)-3-fluoroanilino)-2-(4-methoxyphenyl)acetyl] amino] acetate)demonstrated following values of shape similarity to thetalazoparib:0.618,0.516 and 0.552, respectively.

Interaction of the selected compounds and reference ligand with the amino acid residues of the PARP1 active site are presented in fig4. Talazoparib forms 5 conventional hydrogen bonds with the following amino acid residues of the PARP1's active site: GLN759, GLY 863, TYR 896, SER 904. ZINC6547121 forms 7 conventional hydrogen bonds with 6 amino acid residues, from which 3 are similar to talazoparib (SER 904, GLY 863,TYR 896)and other 3(ASP 770, ARG 878, MET890) are different. ZINC11692074 forms 4 conventional hydrogen bonds with 3 amino acid residues of PARP1's active site: GLY 863, SER864andSER904, whereSER904andGLY863,again, are common interacting residues for both compounds. ZINC40467580 forms6conventionalbondswith5amino acid residues: GLY863,SER864,ARG878andSER904,whileZINC170624334forms5conventional hydrogenbondswithGLY863,MET890,SER904andGLU988.

Again, only SER 904 and GLY 863 are common interacting amino acid residues of PARP1involvedinhydrogenbondsformationforZINC40467580,ZINC170624334and reference drug compound talazoparib. Thus, all five studied compounds, including reference drug compound talazoparibformconventionalhydrogenbondswiththeSER904andGLY 863. Formation of hydrogen bonds with ASP 770 and GLU 988 is unique for the ZINC6547121 and ZINC170624334 respectively. ZINC6547121 and ZINC40467580 both form conventional hydrogen bonds with ARG 878. ZINC6547121 and ZINC170624334 interact with the MET 890.



Interaction of PARP1 active site's amino acid residues with A) Talazoparib, B) ZINC6547121, C) ZINC11692074, D) ZINC40467580, E) ZINC170624334.

To obtain information on stability of interactions and binding tendency of selected compounds and reference ligand, 5 molecular dynamics simulations were performed. Based on the RMSD values of studied compounds (<0.2 nm) and RMSF values of PARP1 amino acid residues during the performed molecular dynamics simulations, all studied interactions demonstrated stability [fig-5].

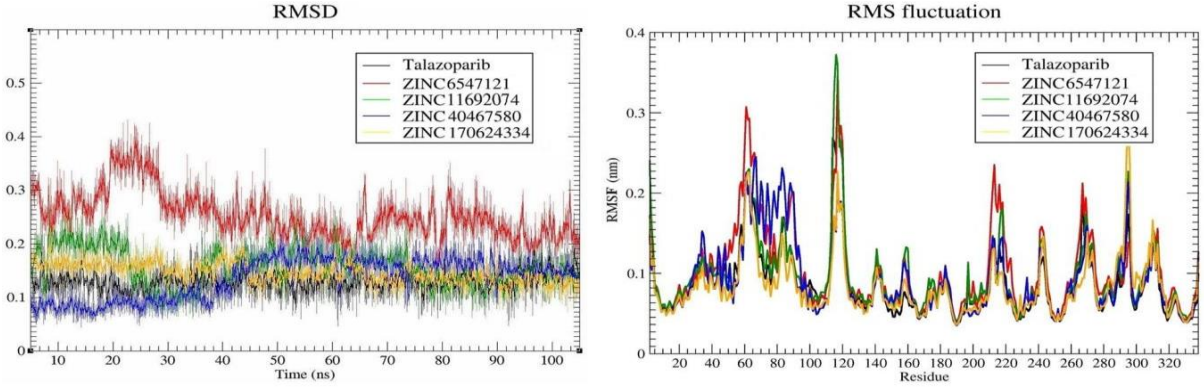
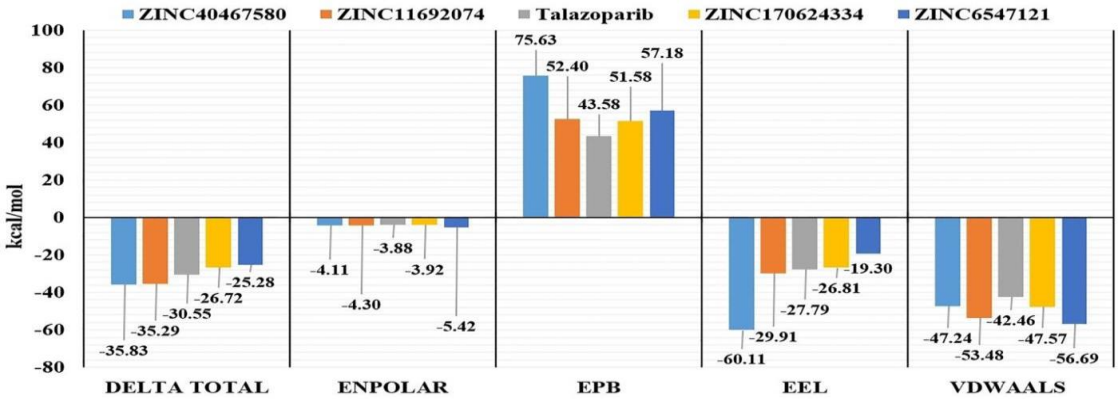


Fig 5. RMSD values of the top 4 compounds and talazoparib; and RMSF values of thePARP1 protein during performed molecular dynamics simulations.

Binding free energies of studied interactions were recalculated using MMPBSA approach, which is relatively more reliable and accurate method in comparison to the MMGBSA approach, based on the trajectories obtained fromperformed molecular dynamics simulations. Based on the "delta total" values , which is final estimated binding free energy calculated from other presented energetic terms, compounds ZINC40467580 (-35.83 kcal/mol) and ZINC11692074 (-35.29 kcal/mol) had lower binding energies than reference ligand talazoparib (-30.55), while other two compounds ZINC170624334 (-26.72 kcal/mol) and ZINC6547121 (-25.28 kcal/mol) demonstrated higher binding energies. Remarkably all studied compounds in comparison to talazoparib demonstrated relatively lower values of electrostatic energy and Vander Waals forces. However due to much higher electrostatic contribution of the studied compounds to the salvation free energy calculated by PB, overall "delta total" energy values of studied compounds are close to talazoparib. Differences in contribution of studied energetic terms to interaction of studied compounds, highlights additional interest and potential of selected compounds from drug design point of view.



Delta total final estimated binding free energy, En polar non polar contribution to the solvation free energy calculated by an empirical model. EPB the electrostatic contribution to the solvation free energy calculated by PB, VDWAALS vander Waals contribution, EEL electrostatic energy.

As the result of molecular docking and MMGBSA is re-scoring experiments several chemical compounds with close or higher binding energies to the PARPi active site havebeen identified. The 2D chemical similarity analysis showed that the identified compounds include alternative to talazoparib chemical components and scaffolds. Differences in the interaction patterns of these compounds and talazoparib with amino acid residues of theactive site of the catalytic domain of PARP1 enzyme indicate that these compounds might potentially have different therapeutically valuable properties. These compounds are of great interest for their further research as potential inhibitorsof the PARP1 enzyme.

CPCSEA GUIDELINES FOR THE CARE AND USE OF LABORATORY ANIMALS:

GOAL:

The goal of these Guidelines is to promote the humane care of animals used in biomedical and behavioral research and testing with the basic objective of providing specifications that will enhance animal well-being, quality in the pursuit of advancement of biological knowledge that is relevant to humans and animals.

VETERINARYCARE:

Adequate veterinary care must be provided and is the responsibility of a veterinarian ora person who has training or experience in laboratory animal sciences and medicine. Daily observation of animals can be accomplished by someone other than a veterinarian; however, mechanism of direct and frequent communication should be adopted so that timely and accurate information on problems in animal health, behavior, and well-being is conveyed to the attending veterinarian.

The veterinarian can also contribute to the establishment of appropriate policies and procedures for ancillary aspects of veterinary care, such as reviewing protocols and proposals, animal husbandry and animal welfare; monitoring occupational health hazards containment, and zoonosis control programs and supervising animal nutrition and sanitation. Institutional requirements will determine the need for full-time or part-time or consultative veterinary services.

QUARANTINE, STABILIZATION AND SEPARATION

Quarantine is the separation of newly received animals from those already in the facility until the health and possibly the microbial status of the newly received animals have been determined. An effective quarantine minimizes the chance for introduction of pathogens into an established colony. A minimum duration of quarantine for small lab animals is one week and large animals is 6 weeks (cat, dog and monkey) Effective quarantine procedures should be used for non-human primates to help limit exposure of human szoonotic infections.

Regardless of the duration of quarantine, newly received animals should be given a period for physiologic, psychological and nutritional stabilization before their use. The length of time stabilization will depend on the type and duration of animal transportation, the species involved and the intended use of the animals. Physical separation of animals by species is recommended to prevent interspecies disease physiological and behavioral changes due to interspecies conflict. Such separation is usually accomplished by housing different species in separate rooms; however, cubicles, laminar-flow units, cages that have filtered air or separate ventilation, and isolators shall be suitable alternatives. In some instances, it shall be acceptable to house different species in the same room, for example, if two species have a similar pathogen status and are behaviorally compatible.

SURVEILLANCE, DIAGNOSIS, TREATMENT AND CONTROL OF DISEASE

All animals should be observed for signs of illness, injury, or abnormal Behaviour by animal house staff. As a rule, this should occur daily, but more-frequent observations might be warranted, such as during postoperative recovery or when animals are ill or have a physical deficit. It is imperative that appropriate methods be in place for disease surveillance and diagnosis (Annexure 1 and 2).

Unexpected deaths and signs of illness, distress, or

other deviations from normal health condition in animals should be reported promptly to ensure appropriate and timely delivery of veterinary medical care. Animals that show signs of a contagious disease should be isolated from healthy animals in the colony. If an entire room of animals is known or believed to be exposed to an infectious agent (e.g. Mycobacterium Tuberculosis in non- human primates), the group should be kept intact and isolated during the process of diagnosis, treatment, and control. Diagnostic clinical laboratory may be made available.

ANIMAL EXPERIMENTATION INVOLVING HAZARDOUS AGENTS

Institutions should have policies governing experimentation with hazardous agents. InstitutionalBiosafetyCommitteewhosemembersarekn owledgeableabouthazardous agents are in place in most of the higher-level education, research institutes and in many pharmaceutical industries for safety issues. This committee shall also examine the proposal on animal experiments involving hazardous agents in addition to its existing functions (Annexure– 8). Since the use of animals in such studies requires special consideration, the procedures and the facilities to be used must be reviewed by both the Institutional Bio safety Committee and Institutional Animal Ethics Committee (IAEC).

DURATIONS OF EXPERIMENTS

No animal should be used for experimentation for more than 3 years unless adequate justification is provided.

PHYSICAL RESTRAINT

Brief physical restraint of animals for examination, collection of samples, and a variety of other clinical and experimental manipulations can be accomplished manually or with devices be suitable in size and design for the animal being held and operated properly to minimize stress and avoid injury to the animal. Prolonged restraint of any animal, including the chairing of non-human primates, should be avoided unless essential to research objectives. Less restrictive systems, such as the tether system or the pole and collar system, should be used when compatible with research objectives.

The following are important guidelines for the use of restraint equipment's: Restraint devices cannot be used simply as a convenience in handling or managing animals.

The period of restraint should be the minimum required to accomplish the research objectives. Animals to be placed in restraint devices should be given training to adapt to the equipment. Provision should be made for observation of the animal at appropriate intervals. Veterinary care should be provided if lesions orillness associated with restraint are observed. The presence of lesions, illness, or severe behavioral change should be dealt with by the temporary or permanent removal of the animal from restraint.

PHYSICAL FACILITIES:

(a) **Building materials**: should be selected to facilitate efficient and hygienic operation of animal facilities. Durable, moisture-proof, fire-resistant, seamless materials are most desirable for interior surfaces including vermin and pest resistance.

(b) Corridor(s): should be wide enough to facilitate the movement of personnel as well as equipment's and should be kept clean.

(c) Utilities: such as water lines, drain pipes and electrical connections should preferably be accessible through service panels or shafts in corridors outside the animal rooms.(d) Animal room: doors should be rust, vermin and dust proof. They should fit properly within their frames and provided with an observation window. Door closures may also be provided. Rodent barriers can be provided in the doors of the small animal facilities.

(e) Exterior windows: Windows are not recommended for small animal facilities. However, where power failures are frequent and backup power is not available, they may be necessary To provide alternate sources of light and ventilation. In primate rooms, window scan be provided.

(f) Floors: Floors should be smooth, moisture proof, nonabsorbent, skid-proof, resistant to wear, acid, solvents, adverse effects of detergents and disinfectants. They should be capable of supporting racks, equipment, and stored items without becoming gouged, cracked, or pitted, with minimum number of joints. A continuous moisture-proof membrane might be needed. If sills are installed at the entrance to a room, they should be designed to allow for convenient passage of equipment.

(g) Drains: Floor drains are not essential in all

rooms used exclusively for housing rodents. Floor in such rooms can be maintained satisfactorily by wet vacuuming or mopping with appropriate disinfectants or cleaning compounds. Where floor drains are used, the floors should be sloped and drain taps kept filled with water or corrosion free mesh. To prevent high humidity, drainage must be adequate to allow rapid removal ofwater and drying of surfaces.

(h) Walls and ceilings: Walls should be free of cracks, unsealed utility penetrations, or imperfect junctions with doors, ceilings, floors and corners. Surface materials should be capable of withstanding scrubbing with detergents and disinfectants and the impact of water under high pressure.

Preclinical studies:

The poly (adenosine diphosphate–ribose) inhibitor talazoparib has shown antitumor activity in patients with advanced breast cancer and germline mutations in BRCA1 and BRCA2 (BRCA1/2).

METHODS:

We conducted a randomized, open-label, phase 3 trial in which patients with advanced breast cancer and a germline BRCA1/2 mutation were assigned, in a 2:1 ratio, to receive talazoparib (1 mg once daily) or standard single-agent therapy of the physician's choice (capecitabine, eribulin, gemcitabine, or vinorelbine in continuous 21-daycycles). The primaryend point was progression-free survival, which was assessed by blinded independent central review.

RESULTS:

Of the 431 patients who underwent randomization, 287 were assigned to receive talazoparib and 144 were assigned to receive standard therapy. Median progression free survival was significantly longer in the talazoparib group than in the standard therapy group (8.6 months vs. 5.6 months; hazard ratio for disease progression or death, 0.54, 95% confidence interval [CI], 0.41 to 0.71; P=0.11 [57% of projected events]). The objective response rate was higher in the talazoparib group than in the standard-therapy group (62.6% vs. 27.2%; odds ratio, 5.0, 95% CI, 2.9 to 8.8, [P<0.001].

Hematologic grade 3–4 adverse events (primarily anemia) occurred in 55% of the patientswhoreceivedtalazoparibandin38%ofthepatient swhoreceivedstandardtherapy; non hematologic grade 3 adverse events occurred in 32% and 38% of the patients, respectively. Patient-reported outcomes favoured talazoparib significant overall improvements and significant delays in the time to clinically meaningful deterioration according to both the global health status–quality-of-life and breast symptoms scales were observed

CONCLUSIONS:

Among patients with advanced breast cancer and a germline BRCA1/2 mutation, single-agent talazoparib provided a significant benefit over standard chemotherapy with respect to progression-free survival. Patient-reported outcomes were superior witht alazoparib.

In a phase 1 trial, talazoparib monotherapy(at a dose of 1 mg once daily) resulted in a 50% response rate and an 86% clinical benefit rate at 24 weeks among 18 patients with advanced breast cancer and a germline BRCA1/2 mutation.8 The most common adverse events related to talazoparib were anemia, thrombocytopenia, and mild to moderate fatigue.8 In the phase 2 ABRAZO study (ClinicalTrials.gov number, NCT02034916), talazoparib also had single-agent activity in two cohorts of patients with metastatic breast cancer and a germline BRCA1/2 mutation.

The response rate was 21% among patients who had previously had a response to platinum chemotherapy and 37% among patients who had previously received three or more cytotoxic regimens for advanced breast cancer without previous exposure to platinum agents. 9 Our phase 3 trial (EMBRACA) compared the efficacy and safety of talazoparib with standard chemotherapy of the physician's choice for the treatment of locally advanced or metastatic breast cancer in patients with a germline BRCA1/2 mutation.

Patients:

Eligible patients were at least 18 years of age and had either locally advanced breast cancer that had not been amenable to curative therapy or metastatic breast cancer. Patients had a deleterious or suspected deleterious germline BRCA1/2 mutation detected by central testing with BRAC Analysis (Myriad Genetics). Patients had received no more than three previous cytotoxic regimens for advanced breast cancer, and they had received previous treatment with a taxane, an anthracycline, or both, unless this treatment was contraindicated. Previous neoadjuvant or adjuvant platinum-based therapy was permitted, provided the patient had had a disease-free interval of at least 6 months after the last dose; patients were

excluded if they had objective disease progression while receiving platinum chemotherapy for advanced breast cancer (i.e., the patient could not have had progressive disease according to Response Evaluation Criteria in Solid Tumors[RECIST], version1.1, withinapproximately8 weeks after the last dose).

There was no limit on the number of previous hormone therapies received by patients with hormone-receptor–positive breast cancer. Patients with central nervous system (CNS) Meta stases were eligible provided they had completed definitive local therapy, had stable CNS lesions on repeat brain imaging, and were receiving low-dose or no glucocorticoids. .

Trial Design and Oversight

The EMBRACA trial was an open-label, randomized, international, phase 3 trial comparing the efficacy and safety of talazoparib with a protocol specified single-agent therapy of the physician's choice (capecitabine, eribulin, gemcitabine, or vinorelbine). Patients with advanced breast cancer underwent randomization in a 2:1 ratio. Patients under went central randomization with stratification according to the number of previous cytotoxic chemotherapy regimens for advanced disease received (0 vs. 1to 3), hormone-receptor status (triple negative vs. hormone-receptor positive), and a history of CNS metastases (yes or no). Patients with human epidermal growth factor receptor type 2–positive breast cancer were not eligible for this trial. Patients who received talazoparib received a dose of 1 mg orally once daily continuously, with or without food. Laboratory values were monitored every 3 weeks, and decisions to withhold doses and dose reductions were made as outlined in the Methods section of the Supplementary Appendix.

The standard-therapy group received protocol specified chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine) in continuous 21-day cycles, in accordance with the institution's dose and regimen guidelines. The choice of standard therapy drug for each patient was determined before randomization. Treatment continued until disease progression, unacceptable toxic effects, or withdrawal of consent occurred, or unless the physician decided to end treatment. Crossover from the standard-therapy group to the talazoparib group was not permitted.

Local site investigators recruited patients, contributed to patient care, and collected patient data, which were analyzed by the sponsor. Three of the authors, one of whom was an employee of the sponsor, guided the initial drafting of the manuscript with medical-writing support that was funded by the sponsor and with input from all other authors. Three authors who were employees of the sponsor contributed to the data analysis and the reporting and review of the data and the manuscript. All authors had full access to the trial data after the primary analysis was conducted, contributed to the revision and approval of the manuscript, and participated in the decision to submit the manuscript for publication. The authors vouch for the accuracy and completeness of the data and analyses and for adherence of the trial conduct to the trial protocol.

End Points and Trial Assessments

The primary end point was radiologic progression–free survival, as determined by blinded independent central review (according to RECIST, version 1.1). Progression-free survival was defined as the time from randomization to the date of first documented radiologic progression according to RECIST or the date of death from any cause, whichever occurred first. Patients underwent imaging (computed tomography, magnetic resonance imaging, and nuclear-medicine bone imaging) at baseline, every 6 weeks until week 30, and the newer 9 weeks, with head imaging repeated during the trials clinically indicated and bone imaging every 12 weeks after week 30. All tumor imaging was centrally reviewed by two radiologists, with an adjudication assessment in case of disagreement regarding progression, according to the central imaging charter. Secondary efficacy end points included overall survival, the objective response rate, the clinical benefit rate at 24 weeks (defined as the rate of complete response, partial response, or stable disease at 24 weeks or more), and the duration of response. After discontinuation of the trial treatment, patients were followed every 12 weeks for survival and use of anticancer therapy after the trial. Safety was assessed according to adverse events, use of concomitant medications, and clinically relevant changes in laboratory values. Adverse events were graded with the use of the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

Patient-reported outcomes were measured with the use of the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30) and the breast cancer–specific QLQ-BR23 at baseline, the beginning of each treatment cycle, and the end of treatment as supportive prespecified exploratory end points (additional details are provided in the statistical analysis plan, version 4.0, in the Supplementary Appendix). The EORTC QLQ-C30 is a 30-item questionnaire composed of five

multiple item functional subscales, three multiple-item symptom scales, a global health status quality of life subscale, and six single-item symptom scales assessing other cancer-related symptoms.

Statistical Analysis:

We determined that a total of 288 events of disease progression or death following the enrolment of 429 patients would give the trial 90% power (at a two-sided alpha level of 5%) to show a significant difference in progression-free survival between the talazoparib group and the standard therapy group, with a targeted hazard ratio for disease progression or death of 0.67.

To maintain the overall two-sided type I error rate of 5%, the analyses for the primary end point (progression-free survival) and the key secondary end point (overall survival) were protected under a multiplicity-adjustment schema with the use of a gate keeping method. Additional details of the multiplicity-adjustment method are described in the statistical analysis plan, version 4.0, in the Supplementary Appendix. Efficacy analyses were performed in the intention-to-treat population. Progression-free survival was analyzed with the use of a stratified log-rank test (with the use of randomization factors) and summarized with the use of Kaplan–Meier methods.

We estimated stratified hazard ratios with two-sided 95% confidence intervals using a stratified Cox proportional-hazards model, with randomization factors. Subgroup analyses were performed and are detailed in the Methods section in the SupplementaryAppendix.10,11 Prespecified patient-reported outcome analyses included the overall mean change from baseline (estimated with the use of the longitudinal mixed-effects model) andthe time to clinically meaningful deterioration (analyzed with the use of a stratified log-rank test, summarized with the use of Kaplan–Meier methods). The time to clinically meaningful deteriorationaccordingtotheglobalhealthstatus–quality-of-lifescalewasdefinedasthe time from randomization to the first observation with a decrease of 10 points or more and no subsequent observations with a decrease of less than 10 points from baseline; the time to deterioration according to the breast symptoms scale on the breast cancer–specific QLQ-BR23 was defined as the time from randomization to the first observation with an increase of 10 points or more and no subsequent observations with an increase of less than 10 points from baseline.

Patients:

Between October 2013 and April 2017, patients underwent randomization at 145sites in16countries. Atotalof431patientswere included inthe intention-to-treat population. Of these patients, 287 were assigned to receive talazoparib and 144 were assigned to receive standard therapy (capecitabine [44%], eribulin [40%], gemcitabine [10%], and vinorelbine [7%]; percentages total >100% because of rounding). Eighteen patients who were randomly assigned to standard therapy and 1 patient in the talazoparib group withdrew conjsent without receiving treatment (Fig. S2 in the Supplementary Appendix). Baseline characteristics of the patients are shown in Table 1. The data cutoff date was September 15, 2017.

Efficacy:

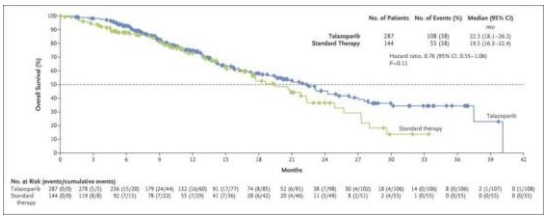
Wecalculatedthatthemediandurationoffollowupforprogression-freesurvivalwas 11.2 months onthe basis of the reverse Kaplan–Meier estimator of progression-free survival. The primary end point (radiologic progression-free survival) was assessed after 269 progression events or deaths were confirmed by blinded independent central review. The median progression-free survival among patients in the talazoparib group was longer than that among patients in the standard therapy group (8.6 months [95% confidence interval {CI},7.2to9.3] vs.5.6 months [95% CI,4.2to6.7];hazard ratio for disease progression or death,0.54;95%CI,0.41to0.71;P<0.001].

Characteristic	Talazoparib Group (N=287)	Standard- Therapy Group (N=144)
Age —yr		
Median	45	50
Range	27.0–84.0	24.0–88.0
Age<50yr—no. (%)	182(63.4)	67(46.5)
Femalesex —%	98.6	97.9
ECOGperformancestatusscore—%†		
0	53.3	58.3
1	44.3	39.6
2	2.1	1.4
Breastcancerstage—no.(%)‡		

Characteristic	Talazoparib Group (N=287)	Standard- Therapy Group (N=144)
Locallyadvanced	15(5.2)	9(6.2)
Metastatic	271(94.4)	135(93.8)
Measurablediseaseassessedbyinvestigator—no.(%)	219(76.3)	114(79.2)
HistoryofCNSmetastases —no.(%)	43(15.0)	20(13.9)
Visceraldisease—no.(%)	200(69.7)	103(71.5)
Hormone-receptorstatus—no.(%)		
Triple-negative	130(45.3)	60(41.7)
Hormone-receptor–positive	157(54.7)	84(58.3)
*BRCA*status—no.(%)§		
BRCA1-positive	133(46.3)	63(43.8)
BRCA2-positive	154(53.7)	81(56.2)
<12-modisease-freeintervalfrominitialdiagnosistoadvanced breast cancer — no. (%)	108(37.6)	42(29.2)
Previous adjuvant torneo adjuvant therapy—no. (%)	238(82.9)	121(84.0)
No.of previous hormone-therapy–based regimens for hormone- receptor–positive breast cancer in the talazoparib group (157 patients) and the standard-therapy group (84 patients)		
Median	2.0	2.0
Range	0–6	0–6
Previousplatinumtherapy—no.(%)	46(16.0)	30(20.8)
Previouscytotoxicregimensforadvancedbreastcancer—no. (%)		
0	111(38.7)	54(37.5)
1	107(37.3)	54(37.5)
2	57(19.9)	28(19.4)
3	12(4.2)	8(5.6)

A total of 37% of the patients in the talazoparib group and 20% of the patients in the standard-therapy group did not have disease progression or death at 1 year, as determined by independent review.

The hazard ratio for disease progression or death that was determined by investigator assessment was identical to the hazard ratio that was determined by independent review (0.54 [95%CI,0.42to0.69]). A sub



group analysis of progression-free survival in the talazoparib group and the standard therapy group is provided in Figure 1B. In all clinically relevant subgroups, the risk of disease progression was lower in the talazoparib group than in the standard-therapy group, with previous use of platinum agents resulting in the only 95% confidence interval with an upper bound exceeding.

At the time of the primary analysis, 163 patients had died (108 in the talazoparib group and 55 in the standard-therapy group). The median overall survival at the interim analysis was 22.3 months (95%CI,18.1to26.2) in the talazoparib group and 19.5months (95% CI, 16.3 to 22.4) in the standard-therapy group (hazard ratio for death, 0.76; 95% CI, 0.55 to 1.06, P=0.11) (Fig. 2). Anticancer therapy after the trial was received by 62% of the patients in the talazoparib group and 68% of the patients in the standard-therapy group.

Safety:

A summary of adverse events is shown in Table 3. Common adverse events included anemia, fatigue, and nausea in the talazoparib group and nausea, fatigue, and neutropenia in the standard-therapy group (Table S3 in the Supplementary Appendix). Grade 3 or 4 hematologic adverse events occurred in 55% of the patients in the talazoparib group and in 38% of the patients in the standard therapy group, whereas grade 3 non hematologic adverse events occurred in 32% of patients in the talazoparib group and in 38% of patients in the standard-therapy group. The majority of non-hematologic adverse events in the talazoparib group were grade 1 in severity. Adverse events resulting in discontinuation of the drug occurred in 5.9% of patients who received talazoparib and in 8.7% of patients who receivedto dose modification were anaemia, neutropenia, and thrombocytopenia in the talazoparib group and neutropenia, palmar–plantar erythrodysesthesia, nausea, and diarrhea in the standard-therapy group. An analysis of dose modification over time involving patients who had at least one hematologic adverse event was performed; this analysis reviewed dose modifications at months1, 2, 3, 4to 6, and7to 12, and at morethan12 months. Bymonths4 to 6 after the first dose of talazoparib, approximately half the patients had had at least one dose interruption or dose reduction. Serious adverse events related to the trial drug were reported in 9% of patients in both the talazoparib and standard-therapy groups, with anemia being the most common in the talazoparib group and neutropenia the most common in the standard-therapy group.

One case of acute myeloid leukaemia occurred in a 59-year-old female patient in the standard-therapy group who received capecitabine. She underwent randomization on August 26, 2014, and received a diagnosis of acute promyelocytic leukaemiaonMarch12, 2015. She had received a diagnosis of breast cancer in 1993, had relapses in 2007, 2010, and 2014, and had received multiple courses of radiation therapy and chemotherapy. One drug-related death was observed in each group: one patient in the talazoparib group had veno-occlusive disease that was diagnosed by the trial site investigator and noted on imaging without biopsy evidence or classic signs, and one patient in the standard-therapy group had sepsis. No clinically significant cardiovascular toxicity was observed. Hepatic toxicity was more common in the standard-therapy group than in the talazoparib group (20% vs. 9%). chemotherapy.

Adverse events resulting in dose modification (reduction or interruption) occurred in 66% of patients who received talazoparib and 60% of patients who received chemotherapy. The most common adverse events leading to dose modification were anemia, neutropenia and thrombocytopenia in the talazoparib group and neutropenia, palmar–plantar erythrodysesthesia, nausea, and diarrhea in the standard-therapy group. An analysis of dose modification over time involving patients who had at least one hematologic adverse eventwas performed; this analysis reviewed dose modifications at months 1, 2, 3, 4 to 6, and 7 to 12, and at more than 12 months.

By months 4 to 6 after the first dose of talazoparib, approximately half the patients had had at least one dose interruption or dose reduction. Serious adverse events related to the trial drug were reported in 9% of patients in both the talazoparib and standard-therapy groups, with anemia being the most common in the talazoparib group and neutropenia the most common in the standard-therapy group. One case of acute

myeloid leukaemia occurred in a 59-year-old female patient in the standard-therapy group who received capecitabine. She underwent randomization on August 26, 2014, and received a diagnosis of acute promyelocytic leukaemia on March 12, 2015. She had received a diagnosis of breast cancerin1993, had relapses in2007, 2010, and 2014, and had received multiple courses of radiation therapy and chemotherapy. One drug-related death was observed in each group: one patient in the talazoparib group had veno-occlusive disease that was diagnosed by the trial site investigator and noted on imaging without biopsy evidence or classic signs, and one patient in the standard-therapy group had sepsis. No clinicallysignificant cardiovascular toxicity was observed. Hepatic toxicity was more common in the standard-therapy group than in the talazoparib group (20% vs. 9%).

Patient-Reported Outcomes:

A significant improvement in the estimated overall mean change from baseline in the global health status–quality-of-life scale on the EORTC QLQ-C30 was documented in the talazoparib group, as compared with a significant deterioration in the standard-therapy group (3.0[95%CI,1.2to4.8]vs.−5.4[95%CI,−8.8to−2.0];P<0.001].Ascompared with standard therapy, treatment with talazoparib resulted in a significant delay in the onset of clinically meaningful deterioration according to the global health status–quality-of life scale (Fig. S4 in the Supplementary Appendix). In addition, there was a significant improvement in the estimated overall mean change from baseline in the scale for breast symptoms (EORTC QLQ-BR23) in the talazoparib group, as compared with a non-significant change in the standard therapy group (−5.1 [95% CI, −6.7 to −3.5] vs. −0.1 [95% CI, −2.9 to 2.6];P=0.002). As compared with standard therapy, treatment with talazoparib resulted in a significant delay in the onset of clinically meaningful deterioration according to the breast symptoms scale.

The EMBRACA trial was a controlled, phase 3 clinical trial involving patients with advanced breast cancer that expresses a germline BRCA1/2 mutation.

This trial compared a PARP inhibitor, talazoparib, with chemotherapy. The risk of disease progression or death, as assessed by blinded central review, was 46% lower in the talazoparib group than in the standard-therapy group (hazard ratio, 0.54; 95% CI, 0.41 to 0.71), with a doubling of the response rate (62.6% in the talazoparib group vs. 27.2% in the standard-therapy group). All clinically relevant subgroups in the analysis of progression-free survival favored talazoparib. All secondary efficacy end points favored Talazoparib over standard therapy, including the response rate and duration of response. Time-to event end points (progression-free and overall survival, duration of response, and time to clinically meaningful deterioration according to the global health status–quality-of-life and breast symptoms scales) were all superior with talazoparib.

Variable	Talazoparib Group (N=219)	Standard- Therapy Group (N=114)	Odds Ratio (95% CI)	P Value*
	number(percent)			
Best overall response among patients with measurable disease — no. (%)†				
Complete response	12(5.5)	0	—	—
Partial response	125(57.1)	31(27.2)	—	—
Stable disease	46(21.0)	36(31.6)	—	—
Could not be evaluated	4(1.8)	19(16.7)	—	—
Investigator-assessed overall objective response among patients with measurable disease—%of patients (95% CI)†	62.6(55.8–69.0)	27.2(19.3–36.3)	5.0 (2.9–8.8)	<0.001
Clinicalbenefitrateat24wkinintention-to-treat population				
Patients with clinical benefit—no./total no.	197/287	52/144	—	—
Percent of patients (95%CI)	68.6(62.9–74.0)	36.1(28.3–44.5)	4.3(2.7–6.8)	<0.001
Investigator-assessed response in subgroup of patients with objective response				
No.with response	137	31	—	—

Variable	Talazoparib Group (N=219)	Standard-Therapy Group (N=114)	Odds Ratio (95% CI)	P Value*
	number(percent)			
Median duration of response—mo	5.4	3.1	—	—
Inter quartile range	2.8–11.2	2.4–6.7	—	—

A subgroup of patients had long-lasting responses to talazoparib that were not seen with standard therapy. Correlative studies of archival tumour and blood specimens are under way to assess whether a biologic signature can predict these exceptional responses. This trial was prospectively designed to detect an improvement in overall survival; interim survival data are promising, although survival data are immature. These data are encouraging given that approximately one third of the patients received subsequent platinum therapy (in both groups), and 18% of the patients received a subsequent PARP inhibitor (in the standard-therapy group). Int he OlympiAD trial, olaparib was also associated with longer progression- free survival than standard therapy (hazard ratio for disease progression or death, 0.58; 95% CI, 0.43 to 0.80).

Baseline characteristics differed in the trial populations: the EMBRACA trial included patients with locally advanced breast cancer and had a lower proportion of patients with an Eastern Cooperative Oncology Group performance status of 0 (53.3% of the patients in the EMBRACA trial vs. 72.2% of the patients in the OlympiAD trial). It is important to note both the qualitative and quantitative differences in safety between talazoparib and standard chemotherapy for the treatment of patients with breast cancer.

Most grade 3–4 toxic effects associated with the use of talazoparib were hematologic laboratory abnormalities, were not associated with substantial clinical sequelae, and did not result in drug discontinuation. In both the patient-reported global health status–quality-of-life and the breast symptoms scales, significant overall improvements and significant delays in the times to clinically meaningful deterioration were noted. We are highlighting an improvement in progression-free survival of only 3 months. Much more progress is needed. One limitation of this phase 3 trial is the open label design, necessitated by the mix of oral and intravenous treatment options in the standard therapy group. Eighteen patients in the standard therapy group (as compared with one patient in the talazoparib group) withdrew consent before receiving the first dose of trial drug; this led to censoring of data for the primary efficacy end point. Of note, many of these patients consented to be followed for overall survival; all received further anticancer therapy (including agents that were received by patients in the standard-therapy group).

To ensure the robustness of the results of this open-label trial, the primary analysis was based on blinded independent central review of data in the intention-to-treat population. Several studies have evaluated the use of platinum agents in patients with germline BRCA mutations. Byrski et al. reported a response rate of 80% among 20 patients with a BRCA1 mutation who received cisplatin.

The results of the Triple Negative Breast Cancer Trial, reported during the course of the EMBRACA trial, showed an objective response rate of68% with carboplatin versus 33% with docetaxel among 43 patients with metastatic triple-negative breast cancer and a known BRCA mutation.15 The EMBRACA trial permitted the use of platinum-based agents before the trial (which occurred in approximately 20% of the patients) as long as patients had no objective disease progression while receiving platinum therapy for advanced disease or relapse within 6 months while receiving neoadjuvant or adjuvant platinum therapy.

Approximately one third of the patients received platinum-based agents after the trial. The failure to include platinum based agents as an option in the standard-therapy group is a limitation of this trial, and data from a head-to-head comparison of a PARP inhibitor with platinum therapy to understand the relative efficacy, toxicity, and effects on patient reported outcomes are lacking. In addition, the EMBRACA trial did not evaluate the sequencing of PARP and platinum-based drugs after disease progression with the use of either agent. Studies to compare platinum-based agents with PARP inhibitors and to compare the response rates after progression among classes of inhibitors are lacking.

Adverse Event	Talazoparib Group (N=286)	Standard-Therapy Group (N=126)
numberofpatients(percent)		
Anyadverseevent	282(98.6)	123(97.6)
Seriousadverseevent†	91(31.8)	37(29.4)
Seriousanddrug-relatedadverseevent	26(9.1)	11(8.7)
Grade3or4seriousadverseevent	73(25.5)	32(25.4)
Adverseeventresultinginpermanentdrug discontinuation	17(5.9)	11(8.7)

CONCLUSION: talazoparib resulted in a significantly longer progression-free survival than standard-of-care chemotherapy. Treatment-associated myelotoxicity was managed by dose modifications or delays. Improvements in patient-reported outcomes indicated that talazoparib had a good side-effect profile.

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