



## Review Article

## Targeting the hallmarks of ovarian cancer: The big picture

M. Petrillo <sup>a,\*</sup>, C. Nero <sup>a</sup>, G. Amadio <sup>a</sup>, D. Gallo <sup>b</sup>, A. Fagotti <sup>a,c</sup>, G. Scambia <sup>a</sup><sup>a</sup> Department of Obstetrics and Gynecology, Catholic University of the Sacred Heart, Rome, Italy<sup>b</sup> Department of Obstetrics and Gynecology, Centre for Translational Medicine for Women and Children Health, Catholic University of the Sacred Heart, Rome, Italy<sup>c</sup> University of Perugia, Italy

## HIGHLIGHTS

- Genomic instability and angiogenesis appear as the cornerstone in molecularly-driven therapy in high-grade serous OC.
- Targeting sustained proliferative signaling seems the most promising approach for low-grade and clear cell OC.
- Evasion of immune destruction is the emerging target in high-grade serous OC.

## ARTICLE INFO

## Article history:

Received 3 March 2016

Received in revised form 20 March 2016

Accepted 29 March 2016

Available online 7 April 2016

## Keywords:

Molecular pathways  
Epithelial ovarian cancer  
Cancer hallmarks

## ABSTRACT

**Objective.** As a result of relevant achievements in the field of translational research, several active drugs and multiple biological targets are available in ovarian cancer (OC). In this complex scenario, there is an urgent need to effectively summarize the available data in order to update conclusions, and outline perspectives.

**Methods.** The results in terms of target identification and drug development have been summarized using the well-known hallmarks of cancer firstly described, and recently modified by Hanahan and Weinberg [1–2]. Published data from clinical trials have been retrieved from PubMed, Embase, CINAHL and Cochrane database. Ongoing clinical trials were searched using [clinicaltrials.gov](http://clinicaltrials.gov) web platform, and identified using NCT number.

**Results.** Genomic instability and angiogenesis are the most actively investigated hallmarks in high-grade serous OC, and the inhibition of tumor immune evasion appears as the emerging strategy for molecularly-driven therapy. Targeting sustained proliferative signaling through MEK and mTOR inhibitors seems the most promising approach in clear cell, and low-grade serous OC.

**Conclusions.** This substantial amount of data suggests that targeted therapies are already part of the clinical and therapeutic management of OC patients. The expectations of getting from translational research a better knowledge of tumor biology and therefore personalized drugs are high and worthy of maximum effort from referral centers.

© 2016 Elsevier Inc. All rights reserved.

## Contents

1.	Introduction . . . . .	177
2.	Enabling characteristics . . . . .	178
2.1.	Genomic instability . . . . .	178
2.1.1.	Poly(ADP-ribose) polymerase (PARP) inhibitors . . . . .	178
2.2.	Inflammatory state . . . . .	178
2.2.1.	Cyclooxygenase (COX) inhibitors . . . . .	178
3.	Hallmarks of ovarian cancer . . . . .	178
3.1.	Sustained proliferative signaling . . . . .	178
3.1.1.	EGFR/HER pathway inhibitors . . . . .	178
3.1.2.	Folate receptor pathway . . . . .	178
3.1.3.	Cytoplasmic tyrosine kinases and phosphates-AKT/mTOR pathway . . . . .	179
3.1.4.	MEK inhibitors . . . . .	180
3.1.5.	PI3K inhibitors . . . . .	180

\* Corresponding author at: Department of Obstetrics and Gynecology, Catholic University of the Sacred Heart, Largo A. Gemelli, 8, 00168 Rome, Italy.  
E-mail address: [marco.petrillo@gmail.com](mailto:marco.petrillo@gmail.com) (M. Petrillo).

3.2.	Evasion of growth suppressors	180
3.2.1.	Restoring the functionality of retinoblastoma protein (pRB) pathway	180
3.2.2.	Targeting p53 network	180
3.3.	Evasion of immune destruction	180
3.3.1.	Targeting programmed Death-Ligand1 (PD-L1)	180
3.3.2.	Targeting cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4)	180
3.3.3.	Transforming growth factor- $\beta$ (TGF- $\beta$ )	180
3.3.4.	Targeting nuclear factor- $\kappa$ B (NF- $\kappa$ B) pathways	180
3.4.	Replicative immortality	181
3.5.	Resistance to cell death	181
3.5.1.	Inhibition of IGF-1/IGFR pathway	181
3.6.	Angiogenesis	181
3.6.1.	Inhibition of VEGFA/B	181
3.6.2.	Inhibition of angiopoietins 1–2	181
3.6.3.	Tyrosine kinase blockade (small molecule inhibitors)	181
3.6.4.	Activation of invasion and metastasis	181
3.6.5.	Inhibitors of focal adhesion kinase (FAK)	181
3.6.6.	Inhibitors of E and N-cadherin	181
3.6.7.	Inhibitors of HGF/c-MET axis	181
3.7.	Energy metabolism	181
4.	Conclusions	182
	Conflict of interest statement	182
	Acknowledgments	182
	References	182

**1. Introduction**

In the last decade, the close and synergistic exchange between basic and clinical science has represented the cornerstone of research effort on ovarian cancer (OC). As a result of this global commitment, a plethora of active pharmaceutical compounds targeting different biological

pathways have been actively tested in clinical trial on OC patients. In this big picture, there is an urgent need to effectively summarize the available data in ways that enable to update conclusions, and outline perspectives.

A conceptual approach to rationalize the complexity of cancer has been successfully introduced since 2000 by Hanahan and Weinberg

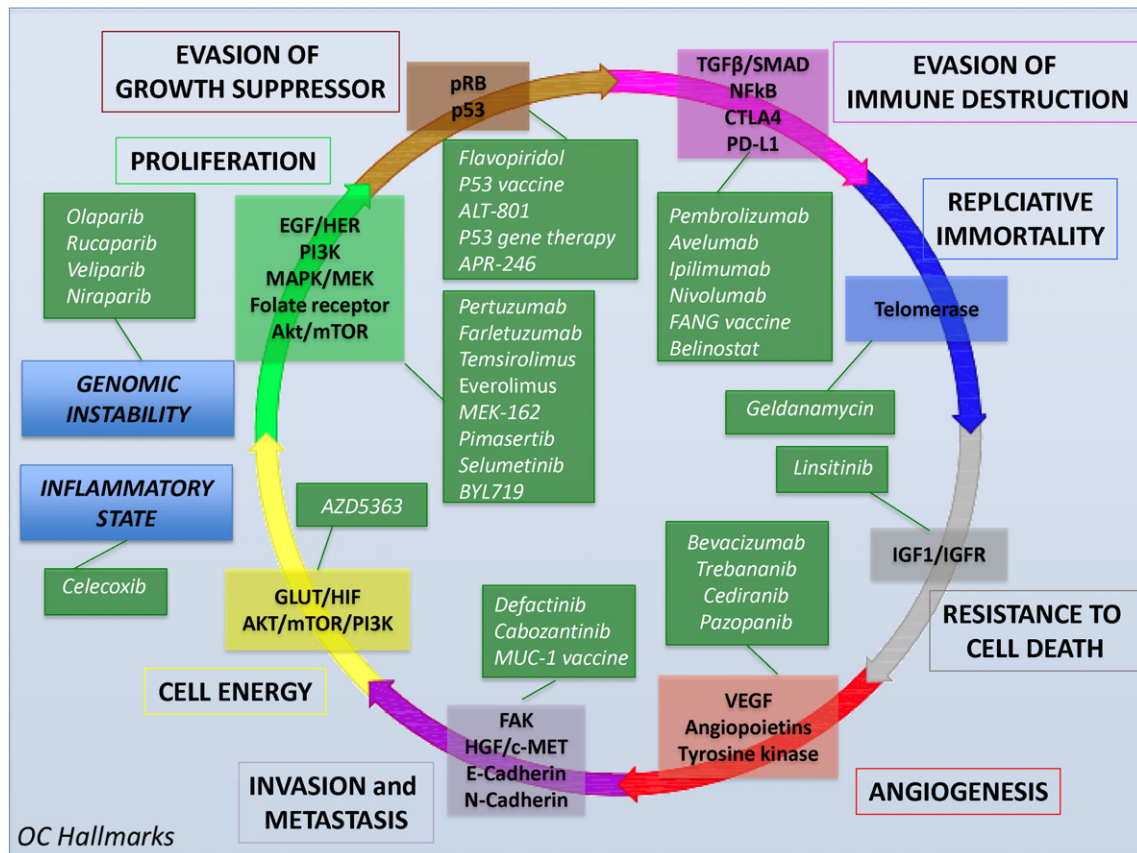


Fig. 1. Tumor hallmark and molecularly-driven drugs approved, or under evaluation in OC.

Download English Version:

<https://daneshyari.com/en/article/3945407>

Download Persian Version:

<https://daneshyari.com/article/3945407>

[Daneshyari.com](https://daneshyari.com)