晚期、持续性或复发性宫颈癌靶向治疗进展

广西柳州市工人医院　贺红英

2019-11-16　广州

目录

- 宫颈癌流行病学特点
- 晚期、持续性或复发性宫颈癌的治疗现状
- 靶向药物的分类及相关进展

宫颈癌流行病学特点

2012年高收入国家发病率占女性恶性肿瘤第11位，死亡率第9位；中低收入国家发病率居第2位，死亡率居第3位；非洲和拉丁美洲宫颈癌是女性癌症特异性死亡的最主要原因

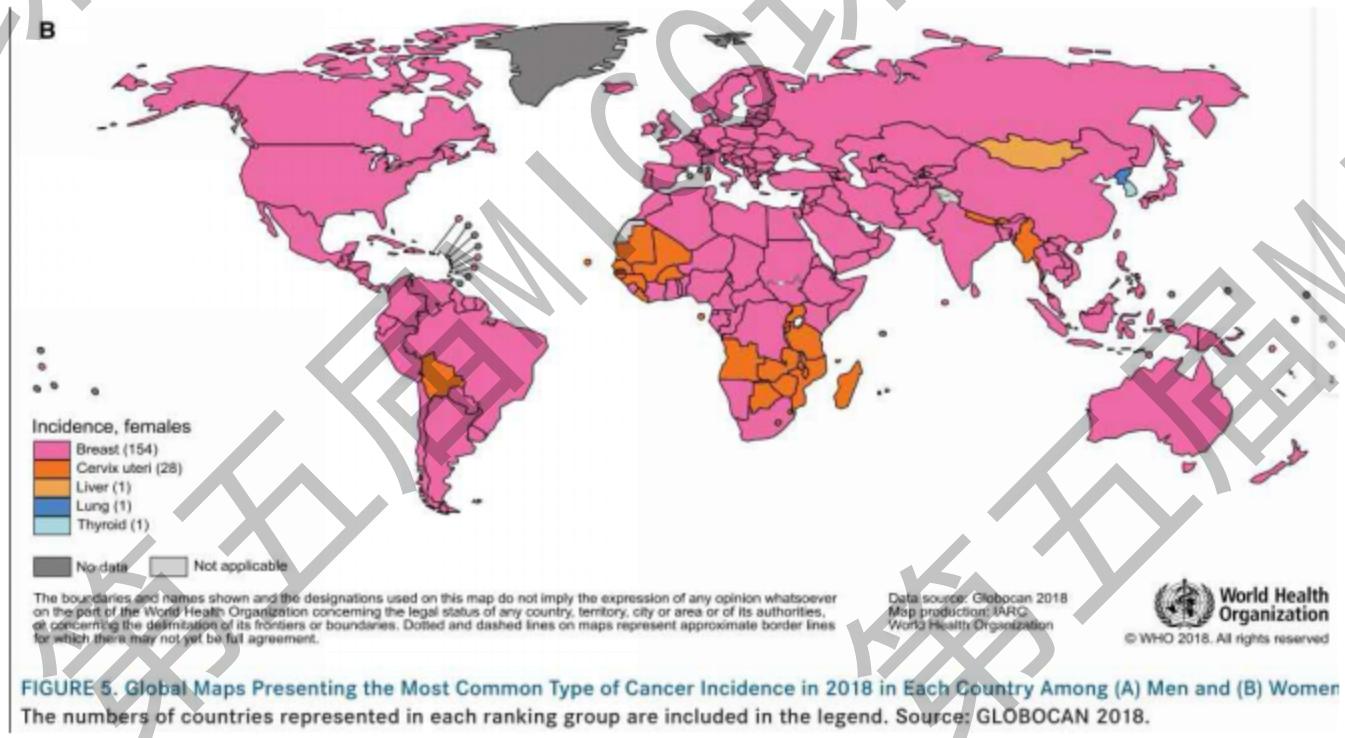


FIGURE 5. Global Maps Presenting the Most Common Type of Cancer Incidence in 2018 in Each Country Among (A) Men and (B) Women
The numbers of countries represented in each ranking group are included in the legend. Source: GLOBOCAN 2018.

Paul A Cohen, AnjuaJhingran, Ana Oaknin, et al. Cervical cancer. Lancet,2019; 393: 169-82

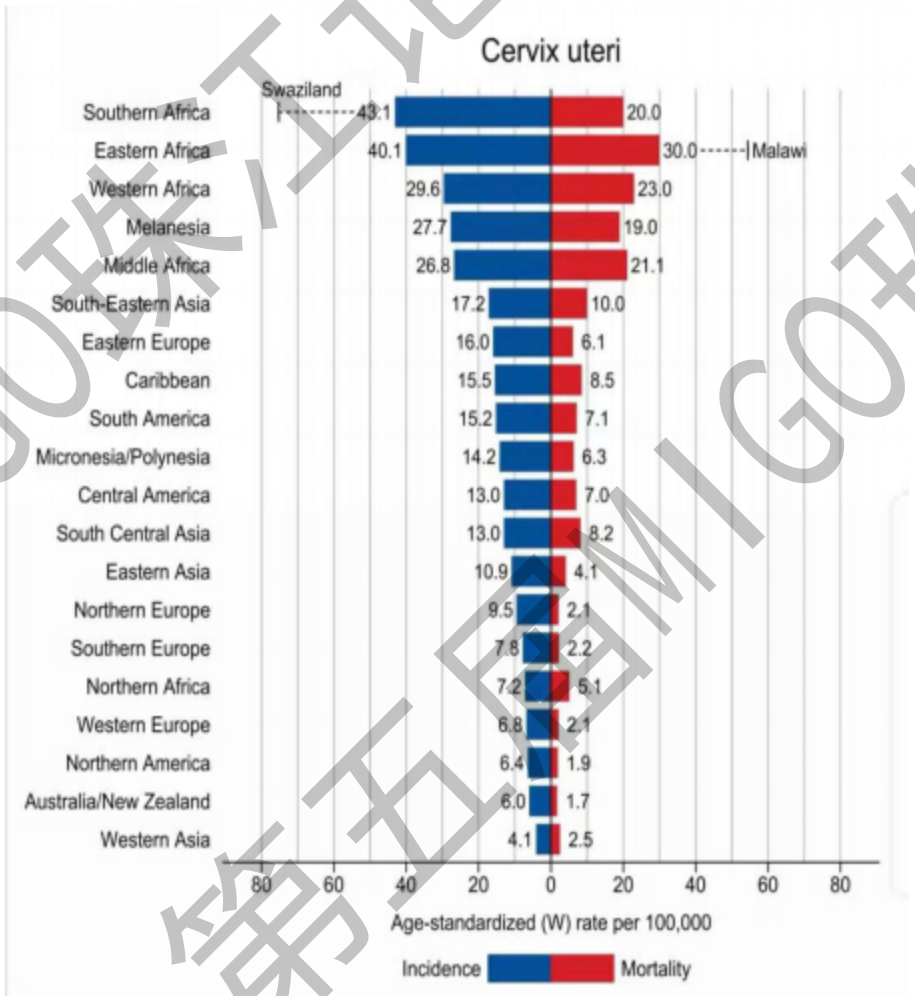
宫颈癌流行病学特点

- **发病年龄：**中位47岁(美国)
- **5年生存率68%**
- **全球新发病例（2018）**

569847例，死亡311365例

- **我国新发病例（2015）**

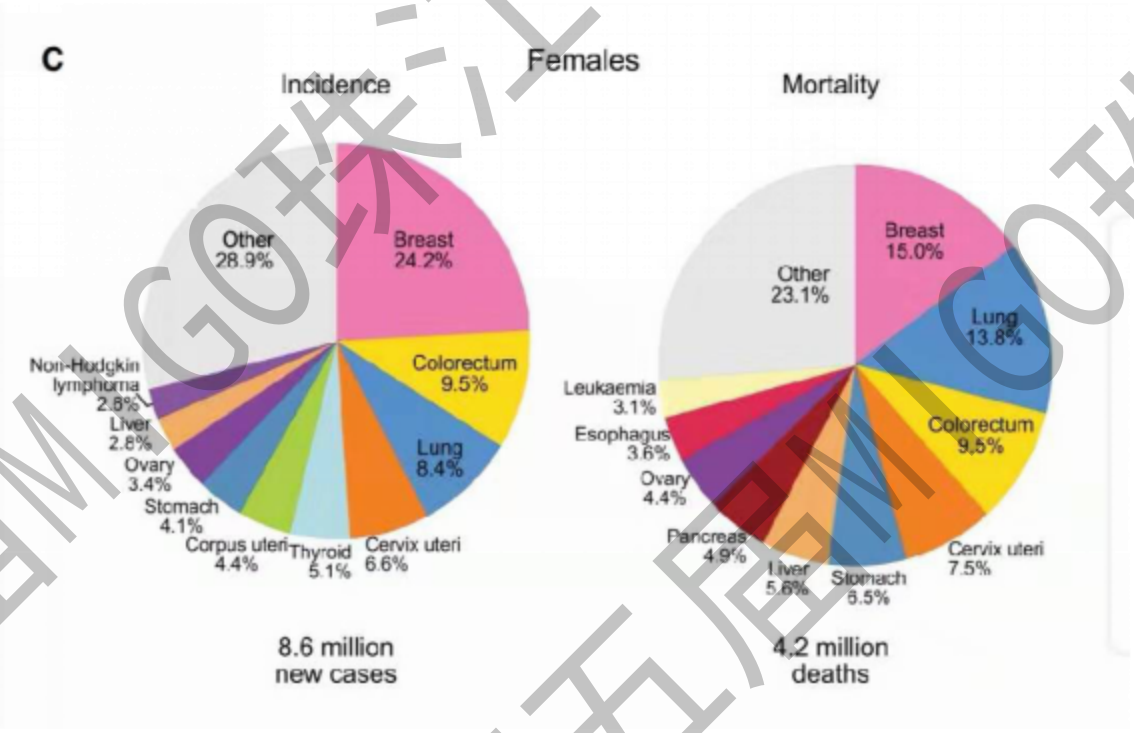
10.643万（15.7%），死亡4.77万



Bray F, Ferlay Jet al.. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018; 68: 394–424.

宫颈癌流行病学特点

- 尽管HPV疫苗及宫颈癌筛查的普及，但仍有5%的患者诊断时已处于晚期，其5年生存率为10-20%。持续性、复发性宫颈癌患者，其5年生存率低于5%



Bray F, Ferlay Jet al.. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018; 68: 394–424.

现代肿瘤治疗方法

治疗方法	分类	作用机制	优点	缺点
传统方法	手术	切除	简单 相对便宜	杀伤正常组织 有剂量限制 有耐药
	放疗	高能辐射		
	化疗	化学杀伤		
靶向治疗	分子靶向药	特异性结合致癌位点切断肿瘤发生通路	有选择性 不良反应轻 高效	治疗范围窄 耐药性
	单克隆抗体			
免疫治疗	肿瘤疫苗	调动机体免疫系统，利用天然防御机制控制杀伤肿瘤细胞	阻止肿瘤进展 对晚期有效 副反应轻 改善生活质量	可能损伤正常组织 治疗过程复杂 费用高
	免疫检测点抑制剂			
	细胞免疫			
	溶瘤病毒			
	双特异性抗体			
	细胞因子			
基因治疗	基因剪辑	实现变异基因正常化	从源头抑制肿瘤发生发展	技术要求高 治疗复杂

晚期、持续性及复发性宫颈癌仍是临床重大挑战

- 以铂为基础的联合化疗有效率**20%-30%**，中位生存期**8-12**个月，探索新的有效药物及方案势在必行
  - 靶向治疗
  - 免疫治疗
  - 基因治疗

晚期、持续性或复发宫颈癌的治疗现状

确立铂类最佳给药方案

（GOG-26c、GOG-43、GOG-64、GOG-77）

↓

寻找可延长生存的铂类联合给药方案

（GOG-110、GOG-149、GOG-169、GOG-179、GOG-204）

↓

寻找铂类基础的化疗联合靶向治疗最佳方案

（GOG240）

↓

免疫治疗

（Keynote-028、Keynote158）

贝伐单抗用于晚期、持续、复发性宫颈癌的关键研究

GOG277C：NCCN采纳贝伐单抗二线治疗宫颈癌研究

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Phase II Trial of Bevacizumab in the Treatment of Persistent or Recurrent Squamous Cell Carcinoma of the Cervix: A Gynecologic Oncology Group Study

ABSTRACT

Purpose

Patients and Methods

Results

Conclusion

INTRODUCTION

Phase II Trial of Bevacizumab in the Treatment of Persistent or Recurrent Squamous Cell Carcinoma of the Cervix: A Gynecologic Oncology Group Study

贝伐单抗治疗顽固性/复发宫颈鳞癌的II期临床研究：来自GOG的研究

J Clin Oncol. 2009.27:1069-1074

贝伐单抗单药用于复发或转移性宫颈癌二线治疗（2B）

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SYSTEMIC THERAPY REGIMENS FOR CERVICAL CANCER[a]
(Strongly consider clinical trial)

Chemoradiation		
Preferred Regimens • Cisplatin • Carboplatin if patient is cisplatin intolerant **Other Recommended Regimens** • Cisplatin/fluorouracil		
Recurrent or Metastatic Disease		
First-line combination therapy[b,c]	**Possible first-line single-agent therapy[c]**	**Second-line therapy[d]**
Preferred Regimens • Cisplatin/paclitaxel/bevacizumab[1] (category 1) • Carboplatin/paclitaxel/bevacizumab • Topotecan/paclitaxel/bevacizumab[1] (category 1) • Cisplatin/paclitaxel (category 1)[2,3] • Carboplatin/paclitaxel[4,5] (category 1 for patients who have received prior cisplatin therapy) • Topotecan/paclitaxel[1] **Other Recommended Regimens** • Cisplatin/topotecan[6]	**Preferred Regimens** • Cisplatin[3] **Other Recommended Regimens** • Carboplatin[7] • Paclitaxel[8,9]	**Preferred Regimens** • Pembrolizumab for PD-L1–positive[e] or MSI-H/dMMR tumors **Other Recommended Regimens** (All agents listed here are category 2B unless otherwise noted) • Bevacizumab • Albumin-bound paclitaxel • Docetaxel • Fluorouracil • Gemcitabine • Ifosfamide • Irinotecan • Mitomycin • Pemetrexed • Topotecan • Vinorelbine

GOG240：贝伐单抗联合化疗的首个III期研究

THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Improved Survival with Bevacizumab in Advanced Cervical Cancer

Krishnansu S. Tewari, M.D., Michael W. Sill, Ph.D., Harry J. Long III, M.D., Richard T. Penson, M.D., Helen Huang, M.S., Lois M. Ramondetta, M.D., Lisa M. Landrum, M.D., Ana Oaknin, M.D., Thomas J. Reid, M.D., Maria M. Leitao, M.D., Helen E. Michael, M.D., and Bradley J. Monk, M.D.

ABSTRACT

BACKGROUND

Vascular endothelial growth factor (VEGF) promotes angiogenesis, a mediator of disease progression in cervical cancer. Bevacizumab, a humanized anti-VEGF monoclonal antibody, has single-agent activity in previously treated, recurrent disease. Most patients in whom recurrent cervical cancer develops have previously received cisplatin with radiation therapy, which reduces the effectiveness of cisplatin at the time of recurrence. We evaluated the effectiveness of bevacizumab and nonplatinum combination chemotherapy in patients with recurrent, persistent, or metastatic cervical cancer.

METHODS

Using a 2×by-2 factorial design, we randomly assigned 452 patients to chemotherapy with or without bevacizumab at a dose of 15 mg per kilogram of body weight. Chemotherapy consisted of cisplatin at a dose of 50 mg per square meter of body-surface area, plus paclitaxel at a dose of 135 or 175 mg per square meter or topotecan at a dose of 0.75 mg per square meter on days 1 to 3, plus paclitaxel at a dose of 175 mg per square meter on day 1. Cycles were repeated every 21 days until disease progression, the development of unacceptable toxic effects, or a complete response was documented. The primary end point was overall survival; a reduction of 30% in the hazard ratio for death was considered clinically important.

RESULTS

Groups were well balanced with respect to age, histologic findings, performance status, previous use or nonuse of a radiosensitizing platinum agent, and disease status. Topotecan–paclitaxel was not superior to cisplatin–paclitaxel (hazard ratio for death, 1.201). With the data for the two chemotherapy regimens combined, the addition of bevacizumab to chemotherapy was associated with increased overall survival (17.0 months vs. 13.3 months; hazard ratio for death, 0.71; 95% confidence interval, 0.54 to 0.95; P=0.004 in a one-sided test) and higher response rates (48% vs. 36%; P=0.008). Bevacizumab, as compared with chemotherapy alone, was associated with an increased incidence of hypertension of grade 2 or higher (25% vs. 2%), thromboembolic events of grade 3 or higher (8% vs. 2%), and gastrointestinal fistulas of grade 3 or higher (5% vs. 0%).

CONCLUSIONS

The addition of bevacizumab to combination chemotherapy in patients with recurrent, persistent, or metastatic cervical cancer was associated with an improvement of 3.7 months in median overall survival. (Funded by the National Cancer Institute; GOG 240 ClinicalTrials.gov number, NCT00803062.)

The New England Journal of Medicine

Improved Survival with Bevacizumab in Advanced Cervical Cancer

贝伐单抗改善晚期宫颈癌患者生存

N Engl J Med 2014;370:734-43.

GOG240结论

- 贝伐珠单抗联合化疗显著改善IVB期、复发、持续宫颈癌的OS
  - OS改善3.5个月具有临床显著性意义
  - 中位PFS和ORR也得到改善
  - 顺铂+紫杉醇是目前的标准方案，联合贝伐珠单抗获益更大
- 贝伐珠单抗组的不良事件发生率更高，但并无新的安全顾虑
- 贝伐珠单抗组延长OS的同时，并不降低健康相关的生活质量

Lancet Oncol 2015; 16: 301–11

贝伐联合化疗用于复发/转移性宫颈癌一线治疗（1类）

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(Strongly consider clinical trial)

Chemoradiation

Preferred Regimens
- Cisplatin
- Carboplatin if patient is cisplatin intolerant

Other Recommended Regimens
- Cisplatin/fluorouracil

推荐含铂/非铂化疗联合抗血管生成治疗是复发或转移宫颈癌的一线标准方案

Recurrent or Metastatic Disease

First-line combination therapy[b,c]	Possible first-line single-agent therapy[c]	Second-line therapy[e]
Preferred Regimens • Cisplatin/paclitaxel/bevacizumab[d,1] (category 1) • Carboplatin/paclitaxel/bevacizumab[d] • Topotecan/paclitaxel/bevacizumab[d,1] (category 1) • Cisplatin/paclitaxel (category 1)[2,3] • Carboplatin/paclitaxel[4,5] (category 1 for patients who have received prior cisplatin therapy) • Topotecan/paclitaxel[1] **Other Recommended Regimens** • Cisplatin/topotecan[6]	**Preferred Regimens** • Cisplatin[3] **Other Recommended Regimens** • Carboplatin[7] • Paclitaxel[8,9]	**Preferred Regimens** • Pembrolizumab for PD-L1–positive[f] or MSI-H/dMMR tumors **Other Recommended Regimens** (All agents listed here are category 2B unless otherwise noted) • Bevacizumab[d] • Albumin-bound paclitaxel • Docetaxel • Fluorouracil • Gemcitabine • Ifosfamide • Irinotecan • Mitomycin • Pemetrexed • Topotecan • Vinorelbine

免疫治疗用于晚期宫颈癌

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Safety and Efficacy of Pembrolizumab in Advanced, Programmed Death Ligand 1–Positive Cervical Cancer: Results From the Phase Ib KEYNOTE-028 Trial

Jean-Sebastien Frenel, Christophe Le Tourneau, Bert O'Neil, Patrick A. Ott, Sarina A. Piha-Paul, Carlos Gomez-Roca, Emilie M.J. van Brummelen, Hope S. Rugo, Shari Thomas, Sanatan Saraf, Reshma Rangwala, and Andrew Varga

Author affiliations and support information (if applicable) appear at the end of this article.

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Clinical trial information: NCT02054806.

Corresponding Author: Jean-Sebastien Frenel, MD, Institut de Cancérologie de l'Ouest, Centre René Gaudducheau, 11 Blvd Jacques Monod, 44800 Saint-Herblain, France; e-mail: JeanSebastien.Frenel@ico.unicancer.fr.

0732-183X/17/3536-4041/$20.00

ABSTRACT

Purpose
The KEYNOTE-028 trial (ClinicalTrials.gov identifier: NCT02054806) was designed to assess the safety and efficacy of pembrolizumab in 20 programmed death ligand 1–positive, advanced solid tumor cohorts. Here, we present the results from the cohort of patients with advanced cervical cancer.

Methods
Patients were treated with pembrolizumab 10 mg/kg every 2 weeks for up to 24 months. Response was assessed every 8 weeks for the first 6 months and every 12 weeks thereafter. The primary end point was overall response rate per Response Evaluation Criteria in Solid Tumors, version 1.1, by investigator review. Safety was a secondary end point.

Results
Twenty-four patients were enrolled in the cervical cancer cohort. The median age was 42 years (range, 26 to 62 years), 22 patients (92%) had received prior radiation therapy, and 15 patients (63%) had received two or more lines of therapy, including bevacizumab (10 of 24 patients), for advanced disease. At the data cutoff, median follow-up duration was 11.0 months (range, 1.3 to 32.2 months). Overall response rate was 17% (95% CI, 5% to 37%); four patients (17%) achieved a confirmed partial response, and three patients (13%) had stable disease. Median duration of response for the four patients who achieved a partial response was 5.4 months (4.1 to 7.5 months). Treatment-related adverse events (AEs) were experienced by 18 patients (75%); only rash (n = 5; 21%) and pyrexia (n = 4; 17%) and occurred in ≥ 10% of patients. Five patients experienced grade 3 treatment-related AEs. No grade 4 treatment-related AEs or deaths were observed.

Conclusion
In patients with programmed death ligand 1–positive advanced cervical cancer, pembrolizumab demonstrated antitumor activity and exhibited a safety profile consistent with that seen in other tumor types.

J Clin Oncol 35. © 2017 by American Society of Clinical Oncology

INTRODUCTION

Although the use of screening programs and the introduction of vaccines protecting against the human papillomavirus (HPV) have dramatically reduced the incidence of cervical cancer, the disease remains a problem in populations without access to adequate health care.[1] Consequently, cervical cancer is the second most commonly diagnosed malignancy in women in the developing world, with 87% of all cervical cancer deaths occurring in developing regions.[1,2]

In the United States, 46% of patients diagnosed with cervical cancer will present with localized disease.[3] The prognosis for these patients is good, with a 5-year survival rate of 91%.[4] In contrast, the prognosis for patients with advanced disease is poor, with a 5-year survival rate of only 17%.[4,5] For recurrent or metastatic disease, cisplatin-based therapy has been a common treatment option[6,7]; however, outcomes are disappointing, with response rates ranging from 13% with cisplatin alone to 36% with cisplatin-containing doublet therapy.[8-10] Recently, bevacizumab in combination with chemotherapy

ASSOCIATED CONTENT

Data Supplement
DOI: https://doi.org/10.1200/JCO.2017.74.5471

DOI: https://doi.org/10.1200/JCO.2017.74.5471

Safety and Efficacy of Pembrolizumab in Advanced, Programmed Death Ligand 1–Positive Cervical Cancer:
Results From the Phase Ib KEYNOTE-028 Trial

Pembrplizumab治疗
晚期PD-L1阳性宫颈癌的IB期临床研究

J Clin Oncol.2017 35(36):4035-4041

免疫治疗用于晚期宫颈癌

- ***KEYNOTE-158：关于帕博利珠单抗治疗晚期实体瘤的2期多队列研究***

- 年龄>18岁
- 组织学或细胞学确认的晚期宫颈癌
- 至少经过一线标准治疗后进展或不能耐受
- ECOG≤1
- 能够提供用于PD-L1和其它生物标志物检测的肿瘤样品

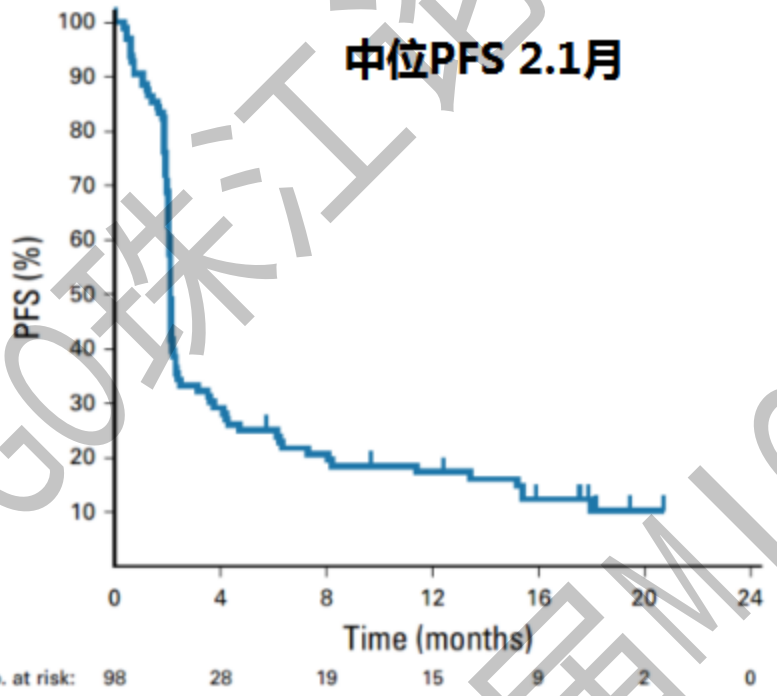
→ 帕博利珠单抗 200mg IV Q3W → 治疗2年或直到PD、不能耐受或研究取消 → 生存随访

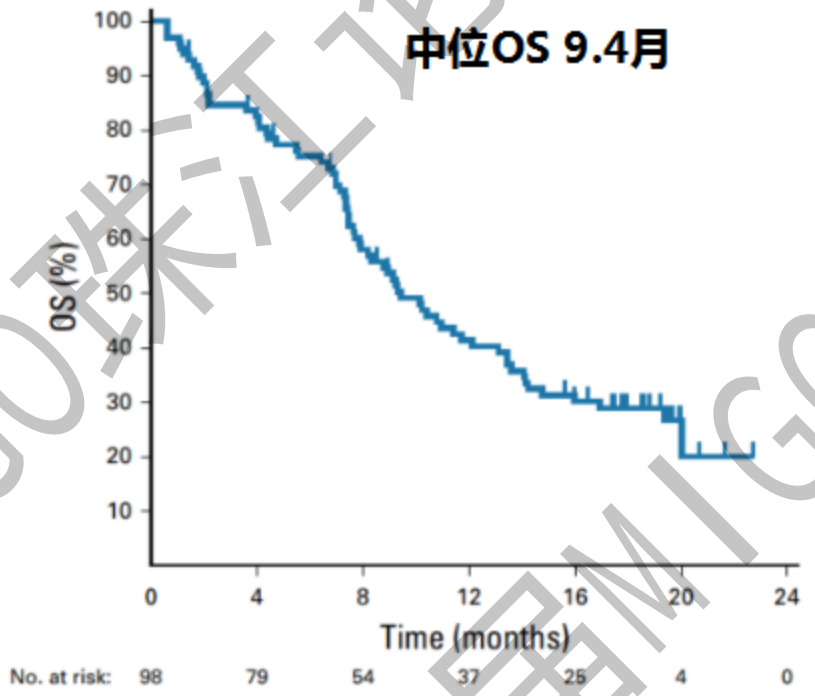
- **主要终点：ORR**
- **次要终点：PFS、OS、缓解维持时间、安全性**
- **探索性终点：在生物标记物亚组的疗效**

第1年每9周评估一次缓解情况，此后每12周一次

2018 ASCO

KEYNOTE-158：2019 ASCO





共入组98例复发/转移性宫颈癌患者，82例为PD-L1阳性肿瘤，其中，5例腺癌和1例鳞癌患者的PD-L1表达呈阳性。患者中位年龄为46.0岁，65.3%患者的ECOG评分为1分，93.9%是IVb期。总体上，21.4%的患者之前接受过辅助和/或新辅助治疗，30.6%的患者接受过3线或以上的治疗，大部分患者（86.7%）曾接受过放疗。中位随访时间10.2个月，ORR为12.2%，中位PFS为2.1月，中位持续治疗时间为2.9个月， 84例患者（85.7%）出现疾病进展或死亡。

Hyun Cheol Chung, et al. J Clin Onco, 2019, l 37:1470-1478.

Pembrolizumab用于PD-L1阳性宫颈癌二线治疗（2B）

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靶向治疗的分类及相关进展

- 抗血管生成剂
- 表皮生长因子受体
- 信号转导阻滞药物
- 细胞周期调控药物
- 聚腺苷二磷酸核糖聚合酶（PARP）抑制剂
- 其余靶向药物

01

➢抗血管生成剂

—— 贝伐珠单抗(Bevacizumab，avastin)

帕唑帕尼（Pazopanib）

➢贝伐珠单抗是重组人源化单克隆抗体，与人血管内皮生长因子A（VEGFA）结合抗肿瘤血管生成。GOG240研究结果显示化疗联合贝伐珠单抗延长了患者的OS和PFS，且不影响生命质量

➢帕唑帕尼（Pazopanib）是血管内皮生长因子受体(VEGFR)-1、-2、-3、血小板源性生长因子受体(PDGFR)α/β以及c-KIT等多靶点的小分子酪氨酸激酶抑制剂。有研究证实帕唑帕尼用于晚期和复发性宫颈癌的治疗表现较好生物活性及较小毒性作用

Penson RT，et al．Bevacizumab for advanced cervical cancer：patient··reported outcomes of a randomised，phase 3 trial(NRG Oncology Gynecologic Oncology Group protocol 240)[J]．Lancet Oncol，2015,16(3)：301-311

Monk BJ．Survival data from a phase II．open-labelstudy of pazopanib or lapatinib monotherapy in patients with advanced and recurrent cervical cancer[J]．J Ctin Oncol，2011，29 (36)：4845

02

表皮生长因子受体拮抗剂

约80%的宫颈鳞癌表达表皮生长因子受体(EGFR)。目前EGFR的靶向治疗药物一般分为小分子酪氨酸激酶抑制剂和单克隆抗体

➢ **EGFR小分子酪氨酸激酶抑制剂(TKIs)**

吉非替尼(Gefitinb)

Goncalves等[23]的Ⅱ期临床研究显示，吉非替尼作为治疗复发、晚期宫颈癌的二线或三线药物，中位PFS和OS分别为37d和107d

安罗替尼（ Anlotinib ）

是一种多靶点（VEGFR、PDGFR、FGFR）酪氨酸激酶抑制剂，抑制血管新生和肿瘤生长

Goncalves A，et al．A phase II trial to evaluate gefitinib as second-or third-line treatment in patients with recutting locoregionally advanced or metastatic cervical cancer[J]．Gynecol Oncol，2008，108(1)：42-46

02 表皮生长因子受体拮抗剂

抗EGFR单克隆抗体

西妥昔单抗(Cetuximab)

可以竞争性阻断EGF和其他配体与EGFR的结合，阻断细胞内增殖信号的转导，从而抑制癌细胞的增殖，诱导癌细胞的凋亡。西妥昔单抗单药治疗晚期宫颈癌有效性欠佳，且不良反应大

尼妥珠单抗（Nimotuzumab）

人源性抗EGFR抗体，可联合传统化疗治疗晚期宫颈癌，入组17例患者，疗效为SD者占35%，中位PFS为163 d，OS为299 d，患者耐受性可

Farley J，et al．Phase U study of cisplatin plus cetuximab in advanced，recurrent，and previously treated cancels of the cervix and evaluation of epidermal growth factor receptor immunohistochemical expression：a Gynecologic Oneology Group study[J]．Gynecol Oncol，2011,121(2)：303-308

.Cetina L，et al，A pilot study of nimotuzumab plus single agent chemotherapy as second·-or third—line treatment or more in patients with recurrent persistent or metastatic cervical cancer[J]．Cancer Biol Ther，2015，16(5)：684-689．

03 信号转导阻滞药物

哺乳动物雷帕霉素靶蛋白(mammalian target of rapamycin，mTOR)：
mTOR在血管形成，细胞的增殖和分化过程中起到重要的作用，是PI3K/Akt通路的主要靶点

- **替西罗莫司（Temsirolimus）**
  是一种mTOR抑制剂，与细胞内蛋白（FKBP-12）结合，形成药物-蛋白复合物，抑制mTOR活性，从而控制细胞增殖。Tinker等的研究中，使用替西罗司治疗38例宫颈癌患者，19例患者出现平均6.5个月的病情稳定期，1例患者出现肿瘤部分缓解，6个月的疾病无进展发生率约28%

Tinker AV，et al. Phase Ⅱ study of temsirolimus（CCI-779）in women with recurrent，unresectable，locally advanced or metastatic carcinoma of the cervix. A trial of the NCIC Clinical Trials Group（NCIC CTG IND 199）[J].Gynecol Oncol，2013，130（2）：269-274.

04 细胞周期调控药物

- **组蛋白去乙酰化酶(histone deacetylase，HDAC)**
  如**丙戊酸，**是一类蛋白酶，与基因表达调控及染色体的结构修饰有关

- **HDAC 抑制剂**
  能够诱导乙酰化组蛋白在子宫颈癌细胞染色质P21WAF1 基因中的积累，抑制与子宫颈癌细胞系相关的恶性表型基因的表达

- **载基因纳米粒注射剂(Rexin-G)** 是第一个获准上市的细胞周期调节因子类靶向抗肿瘤药，已广泛用于治疗各种顽固性癌症

05 PARP抑制剂

PARP是存在于多数真核细胞中的一个多功能蛋白质翻译后修饰酶。它通过识别结构损伤的DNA片段而被激活，对损伤的DNA进行修复。研究发现PARP抑制剂能够有效杀灭顺铂耐药的宫颈癌细胞

- **维利帕尼（Veliparib）**

  是一种口服的PARP抑制剂，GOG评估维利帕尼加拓扑替康治疗持续或复发性宫颈癌的Ⅰ～Ⅱ期临床研究显示临床疗效有限，但发现PARP-1免疫组织化学弱表达与PFS(P=0.02)和OS(P=0.005)相关

Kunos C,et al. A phase I-II evaluation of veliparib(NSC737664)，topotecan，and filgrastim or pegfilgrastim in the treatment of persistent or recurrent carcinoma of the uterine cervix：an NRG Oncology／Gyneologic Oncology Group study[J]. Int J Gynecol Cancer，2015，25(3)：484-492.

06 其余靶向药物

- 免疫检查点抑制剂

  - **伊匹单抗**（单克隆抗CTLA-4抗体）维持治疗的临床试验正在进行中（NCT01711515）

  - **纳武单抗**（Nivolumab）（PD-L1抑制剂）目前也正用于治疗晚期复发或转移的宫颈癌患者（NCT02257528）

06 其余靶向药物

WEE1蛋白抑制剂

WEE1是丝氨酸/苏氨酸蛋白激酶家族中一员，可使细胞过早的进行有丝分裂，产生大量不可修复的DNA和促进分裂后细胞的死亡

目前评估WEE1蛋白抑制剂联合拓扑替康和顺铂治疗晚期宫颈癌的临床试验正在进行中（NCT01076400）

Hirai H，et al. MK-1775，a small molecule Wee1 inhibitor enhances anti-tumor efficacy of various DNA damaging agents，including 5-fluorouracil [J] .Cancer Biol Therap，2010，9（7）：514-522

小 结

- 晚期、持续性或复发性宫颈癌仍是重要的临床挑战
- 化疗联合抗血管生成药物是目前主要的治疗手段
- 免疫治疗的应用初现端倪，如何筛选有效的生物标记，以及联合治疗亟待探索

THANKS FOR YOUR ATTENTION!