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**Checkpoint inhibitors in gastrointestinal cancers: Expectations and reality**

**Kourie HR *et al*. Checkpoint inhibitors in GI cancers**

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**Abstract**

Immune checkpoint inhibitors represent revolutionary anti-cancer agents, being rapidly approved in different malignancies and settings. Gastrointestinal (GI) cancers represent a wide variety of tumors with specific characteristics and different responses to various therapeutic alternatives; while some are chemo-sensitive others are chemo-resistant and only respond to more aggressive cytotoxic regimens, targeted therapies or a combination of both. Preliminary results of immune checkpoint inhibitors in some GI cancers are promising, namely in hepatocellular carcinoma, anal cancers and microsatellite instability high colorectal cancers. A impressive number of immune checkpoint inhibitors are being evaluated in different indications in GI cancers as single agents or in combination with other agents. We reported in this paper ongoing and published trials evaluating immune checkpoint inhibitors in hepatocellular carcinoma and biliary tract cancers, esophageal, gastric, pancreatic, colorectal and anal cancers and we discussed the future perspectives of these agents in GI cancers.

**Key words:** immunotherapies; gastrointestinal; cancers; digestive; checkpoint inhibitors

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**C****ore tip:** Immune checkpoint inhibitors represent new promising anti-cancer therapies, rapidly approved in different malignancies and settings. We aimed in this editorial to report all the ongoing and published trials evaluating these agents in gastro-intestinal malignancies, to focus on the past expectations and the reality of the results and finally, to discuss the future perspectives of these agents in this field.

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**Introduction**

Since the emergence of immune checkpoint inhibitors (ICI) in the last few years, hundreds of trials have been attempting to test their efficacy in the treatment of various malignancies and in different settings[1]. Melanomas, non-small cell lung cancer (NSCLC), renal cell carcinomas and bladder cancer are the three malignancies, where these agents have presently gained approval, mainly in metastatic as first line treatment in melanomas and in the second line setting for the three others[2-5]. Most importantly, one of these agents, ipilimumab, has been approved in the adjuvant setting for the treatment of melanoma[6].

Similar response rates (RR) have been reported in different malignancies ranging between 15% to 25%, except for sarcomas, colorectal cancers (CRC), pancreatic, breast and prostate cancers, where efficacy has not been demonstrated or is still under evaluation in clinical trials. Preliminary results from phase 1 and 2 trials are reporting response rates between 15% to 25% in esophageal, gastric, hepato-biliary and anal cancer, similar to those described in other malignancies. Two exceptions in gastrointestinal (GI) cancers are pancreatic and CRC. In pancreatic cancer, we still do not have any preliminary results from trials looking into anti-PD1 agents and those evaluating anti-CTLA4 agent were mostly disappointing[7]. After several trials failed to demonstrate the value of ICI in CRC, it was initially believed that these agents would not easily find their way into the preexisting the therapeutic arsenal. It was only after one patient with MMR-deficient CRC demonstrated a spectacular response to anti-PD1 agent that a potential predictive biomarker was brought to light. Effectively, the RR in this subgroup of patients exceeded 40%[8].

Despite the promising results in GI malignancies, ICI have not yet been approved in any of the aforementioned tumors. Herein, we briefly summaries the results of select trial with results that might have an impact on our clinical practice in the foreseeable future (Table 1).

**Checkpoint inhibitors results in GI cancers**

***Esophageal cancer***

Results from two phase II trials evaluating nivolumab and pembrolizumab in esophageal cancers demonstrated an acceptable safety profile, meaningful clinical activity and RR of around 20% in heavily pretreated patients[9]. Nivolumab is evaluated in squamous cell carcinoma regardless of PD-L1 status, while pembrolizumab is mainly being tested in patients with squamous cell carcinoma (77%), but PDL1 positivity was set as an inclusion criteria[10].

***Gastric cancer***

In gastric adenocarcinomas, tremelimumab (anti-CTLA4) showed a response rate of 5% in a phase I trial[11]. A phase II trial testing nivolumab in pretreated metastatic adenocarcinoma of the stomach and the gastroesophageal junction reported response rates around 12%, independently of the PDL1 status[12], while a phase Ib trial evaluating pembrolizumab in pretreated metastatic adenocarcinoma of the stomach and the junction showed response rates exceeding the 30% in PD-L1 positive patients[13]. In ASCO 2016, a trial tested avelumab as second line treatment and as maintenance treatment of advanced gastric or gastro- esophageal junction, the RR in second line setting was 18% in PD-L1 positive tumors and 9% in PD-L1 negative tumors; the disease control rate (DCR) was 29%[14]. The combination of ipilimumab and nivolumab was tested at two different doses in phase I/II trial in gastric or gastro-esophageal adenocarcinoma, progressing after chemotherapy; the RR was 26% with the combination of nivolumab 1 mg/kg and ipilimumab 3 mg/kg and 14% with nivolumab[15].

***Pancreatic***

A phase II trial evaluating ipilimumab in pancreatic cancer failed to discern any clinical activity as no response were reported in a any of the 26 patients (0%)[7]. Moreover, we do not have any preliminary results with anti-PD1 agents; three ongoing trials are evaluating nivolumab as single agent, nivolumab in combination with ipilimumab and nivolumab in combination with gemcitabine, which might act as a stimulant for neo-antigen expression.

*Hepatocellular and biliary tract carcinoma*

### The safety profile and antitumor activity tremelimumab, in patients with hepatitis-C-induced liver cirrhosis and subsequent advanced hepatocellular carcinoma (HCC), was promising with RR of approximately 17% and stable disease of 76%[16]. Additionally, Nivolumab was tested in patients with sorafenib-refractory or sorafenib-intolerant HCC regardless of hepatitis status. Preliminary results were promising with RR of 23% (15% in uninfected and 32% in infected HCC)[17]. Not only do these trials highlight the efficacy of ICI in this subset of patients, but they also provide valuable information in regards to the potential use of immunotherapy in patients with less than vigorous liver function. An ongoing trial randomized, multicenter, phase III study is comparing nivolumab to sorafenib in first-line treatment in patients with advanced hepatocellular carcinoma ([NCT02576509](http://clinicaltrials.gov/show/NCT02576509)).

Pembrolizumab was also tested in pretreated, PDL1 positive, adenocarcinoma of the gallbladder and biliary tract - excluding ampullary carcinomas - with promising results; RR of 17% and SD of 17%[18].

***Colorectal cancer***

As previously mentioned, various phase I trials of anti-CTLA4 or anti-PD1 agents in CRC came to naught, even in patients with PD-L1 positive tumors[19-21]. Only one heavily pretreated patient presented a remarkable response to nivolumab and this patient was later found to harbour a MMR-deficient CRC. As such, one phase II study demonstrated significant RR (40%) in MMR-deficient CRC patients versus 0% in MMR proficient CRC patients treated with pembrolizumab[8]. Therefore, MMR status is now believed to be a valuable predictor of response to anti-PD1 agents, even more valuable than PD-L1 status for that matter. This finding also extends beyond CRC as it highlights the importance of mutational burden as a predictor to ICI response since patients with MMR deficient malignancies tend to have higher rates of intra-tumoral mutations and a subsequent expression of cell surface neo-antigens leading to a more potent immune response.

***Anal cancer***

### A phase Ib trial evaluating pembrolizumab in pretreated squamous cell anal cancer showed response rates of 20% and a stable disease in 40% of patients PDL1 positive tumors[22]. A multi-institutional eETCTN phase II study of nivolumab in refractory metastatic squamous cell carcinoma of the anal canal was presented in ASCO 2016 including 37 patients, some of them carrying HIV or hepatitis B or C. The results showed RR of 21% and DCR of 70%; it was not reported more severe adverse events in HIV positive patients[23].

### Future perspectives

With the express approval of checkpoint inhibitors in different malignancies, these agents will most likely be gain approval for the treatment of some GI malignancies in the very near future.

Anti-CTLA4 agents are unlikely to yield substantial value in the treatment of GI cancers, especially as single agents, because of lacking clinical activity, except of tremelimumab in HCV-induced HCC.

Anti-PD1 agents will soon be considered for the second line treatment of metastatic squamous cell carcinoma of the oesophagus, metastatic gastric adenocarcinoma and advanced cholangiocarcinoma after standard platinum-based therapy. The new molecular classification of gastric adenocarcinoma will help better define patients that might benefit from these therapies, mainly those expressing PDL1 and EBV positive gastric adenocarcinomas. Anti-PD1 agents will also be considered as second line treatment in advanced HCC while viral hepatitis status should be considered as a predictive biomarker for response since it clearly does not prevent the use of ICI.

Moreover, anti-PD1 agents will most likely be approved MMR-deficient colorectal cancers, which represent 10% to 15% of these tumors. Second line treatment of metastatic anal squamous cell carcinoma will also benefit from the emergence of these new agents after standard therapy, and HPV status should be looked into as a predictive biomarker.

With the increasing popularity of chemo-immunotherapy, it is also likely that such combinations will soon emerge and hasten the approval process in first line settings[24].

**References**

1 **Kourie HR**, Awada G, Awada AH. Learning from the "tsunami" of immune checkpoint inhibitors in 2015. *Crit Rev Oncol Hematol* 2016; **101**: 213-220 [PMID: 27051042 DOI: 10.1016/j.critrevonc.2016.03.017]

2 **Robert C**, Long GV, Brady B, Dutriaux C, Maio M, Mortier L, Hassel JC, Rutkowski P, McNeil C, Kalinka-Warzocha E, Savage KJ, Hernberg MM, Lebbé C, Charles J, Mihalcioiu C, Chiarion-Sileni V, Mauch C, Cognetti F, Arance A, Schmidt H, Schadendorf D, Gogas H, Lundgren-Eriksson L, Horak C, Sharkey B, Waxman IM, Atkinson V, Ascierto PA. Nivolumab in previously untreated melanoma without BRAF mutation. *N Engl J Med* 2015; **372**: 320-330 [PMID: 25399552 DOI: 10.1056/NEJMoa1412082]

3 **Brahmer J**, Reckamp KL, Baas P, Crinò L, Eberhardt WE, Poddubskaya E, Antonia S, Pluzanski A, Vokes EE, Holgado E, Waterhouse D, Ready N, Gainor J, Arén Frontera O, Havel L, Steins M, Garassino MC, Aerts JG, Domine M, Paz-Ares L, Reck M, Baudelet C, Harbison CT, Lestini B, Spigel DR. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. *N Engl J Med* 2015; **373**: 123-135 [PMID: 26028407 DOI: 10.1056/NEJMoa1504627]

4 **Motzer RJ**, Escudier B, McDermott DF, George S, Hammers HJ, Srinivas S, Tykodi SS, Sosman JA, Procopio G, Plimack ER, Castellano D, Choueiri TK, Gurney H, Donskov F, Bono P, Wagstaff J, Gauler TC, Ueda T, Tomita Y, Schutz FA, Kollmannsberger C, Larkin J, Ravaud A, Simon JS, Xu LA, Waxman IM, Sharma P. Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. *N Engl J Med* 2015; **373**: 1803-1813 [PMID: 26406148 DOI: 10.1056/NEJMoa1510665]

5 **Hoffman-Censits JH**, Grivas P, Van Der Heijden MS, Dreicer R, Loriot Y, Retz M, Vogelzang NJ, Perez-Gracia JL, Rezazadeh A, Bracarda S, Yu EY, Hoimes CJ, Bellmunt J, Quinn DI, Petrylak DP, Hussain SA, Cui N, Mariathasan S, Abidoye OO, Rosenberg JE. IMvigor 210, a phase II trial of atezolizumab (MPDL3280A) in platinum-treated locally advanced or metastatic urothelial carcinoma (mUC). *J Clin Oncol* 2016; **34**: 355 [doi: 10.1200/jco.2016.34.2\_suppl.355]

6 **Eggermont AM**, Chiarion-Sileni V, Grob JJ, Dummer R, Wolchok JD, Schmidt H, Hamid O, Robert C, Ascierto PA, Richards JM, Lebbé C, Ferraresi V, Smylie M, Weber JS, Maio M, Konto C, Hoos A, de Pril V, Gurunath RK, de Schaetzen G, Suciu S, Testori A. Adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma (EORTC 18071): a randomised, double-blind, phase 3 trial. *Lancet Oncol* 2015; **16**: 522-530 [PMID: 25840693 DOI: 10.1016/S1470-2045(15)70122-1]

7 **Royal RE**, Levy C, Turner K, Mathur A, Hughes M, Kammula US, Sherry RM, Topalian SL, Yang JC, Lowy I, Rosenberg SA. Phase 2 trial of single agent Ipilimumab (anti-CTLA-4) for locally advanced or metastatic pancreatic adenocarcinoma. *J Immunother* 2010; **33**: 828-833 [PMID: 20842054 DOI: 10.1097/CJI.0b013e3181eec14c]

8 **Le DT**, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD, Skora AD, Luber BS, Azad NS, Laheru D, Biedrzycki B, Donehower RC, Zaheer A, Fisher GA, Crocenzi TS, Lee JJ, Duffy SM, Goldberg RM, de la Chapelle A, Koshiji M, Bhaijee F, Huebner T, Hruban RH, Wood LD, Cuka N, Pardoll DM, Papadopoulos N, Kinzler KW, Zhou S, Cornish TC, Taube JM, Anders RA, Eshleman JR, Vogelstein B, Diaz LA. PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. *N Engl J Med* 2015; **372**: 2509-2520 [PMID: 26028255 DOI: 10.1056/NEJMoa1500596]

9 **Kojima T**, Hara H, Yamaguchi K, Hironaka S, Iwasa S, Kato K, Tsushima T, Yasui H, Ura T, Muro K, Satoh T, Doki Y, Ohtsu A, Hamamoto Y, Kitagawa Y. Phase II study of nivolumab (ONO-4538/BMS-936558) in patients with esophageal cancer: Preliminary report of overall survival. *J Clin Oncol* 2016; **34**: TPS175 [DOI: 10.1200/jco.2016.34.4\_suppl.tps175]

10 **Doi T**, Piha-Paul SA, Jalal SI, Mai-Dang H, Yuan S, Koshiji M, Csiki I, Bennouna J. Pembrolizumab (MK-3475) for patients (pts) with advanced esophageal carcinoma: Preliminary results from KEYNOTE-028. *J Clin Oncol* 2015; **33**: 4010 [DOI: 10.1200/jco.2015.33.15\_suppl.4010]

11 **Ralph C**, Elkord E, Burt DJ, O'Dwyer JF, Austin EB, Stern PL, Hawkins RE, Thistlethwaite FC. Modulation of lymphocyte regulation for cancer therapy: a phase II trial of tremelimumab in advanced gastric and esophageal adenocarcinoma. *Clin Cancer Res* 2010; **16**: 1662-1672 [PMID: 20179239 DOI: 10.1158/1078-0432.CCR-09-2870]

12 **Le DT**, Bendell J, Calvo E, Kim J, Ascierto P, Sharma P, Ott PA, Bono P, Jaeger D, Evans J, de Braud F, Chau I, Tschaika M, Harbison CT, Lin CS, Janjigian YY. Safety and Activity of Nivolumab Monotherapy in Advanced and Metastatic Gastric or Gastroesophageal Junction Cancer (GC/GEC): Results From the CheckMate-032 Study. *J Clin Oncol* 2016; **34**: 6

13 **Muro K**, Chung HC, Shankaran V, Geva R, Catenacci D, Gupta S, Eder JP, Golan T, Le DT, Burtness B, McRee AJ, Lin CC, Pathiraja K, Lunceford J, Emancipator K, Juco J, Koshiji M, Bang YJ. Pembrolizumab for patients with PD-L1-positive advanced gastric cancer (KEYNOTE-012): a multicentre, open-label, phase 1b trial. *Lancet Oncol* 2016; **17**: 717-726 [PMID: 27157491 DOI: 10.1016/S1470-2045(16)00175-3]

14 **Chung HC**, Arkenau HT, Wyrwicz L, Oh DY, Lee KW, Infante JR, Mita AC. Avelumab (MSB0010718C; anti-PD-L1) in patients with advanced gastric or gastroesophageal junction cancer from JAVELIN solid tumor phase Ib trial: Analysis of safety and clinical activity. *J Clin Oncol* 2016; **34**: 4009

15 **Janjigian YY**, Bendell JC, Calvo E, Kim JW, Ascierto PA, Sharma P, Evans TR. CheckMate-032: Phase I/II, open-label study of safety and activity of nivolumab (nivo) alone or with ipilimumab (ipi) in advanced and metastatic (A/M) gastric cancer (GC). *J Clin Oncol* 2016; **34**: 4010

16 **Sangro B**, Gomez-Martin C, de la Mata M, Iñarrairaegui M, Garralda E, Barrera P, Riezu-Boj JI, Larrea E, Alfaro C, Sarobe P, Lasarte JJ, Pérez-Gracia JL, Melero I, Prieto J. A clinical trial of CTLA-4 blockade with tremelimumab in patients with hepatocellular carcinoma and chronic hepatitis C. *J Hepatol* 2013; **59**: 81-88 [PMID: 23466307 DOI: 10.1016/j.jhep.2013.02.022]

17 **El-Khoueiry AB**, Melero I, Crocenzi TS, Welling TH, Yau TC, Yeo W, Chopra A, Grosso J, Lang L, Anderson J, Dela Cruz CM, Sangro B. Phase I/II safety and antitumor activity of nivolumab in patients with advanced hepatocellular carcinoma (HCC): CA209-040. *J Clin Oncol* 2015; **33**: LBA101 [doi: 10.1200/jco.2015.33.18\_suppl.lba101]

18 **Bang YJ**, Doi T, De Braud F, Piha-Paul S, Hollebecque A, Abdul Razak AR, Lin CC, Ott PA, He AR, Yuan SS, Koshiji M, Lam B, Aggarwal R. 525 Safety and efficacy of pembrolizumab (MK-3475) in patients (pts) with advanced biliary tract cancer: Interim results of KEYNOTE-028. *Eur J Cancer* 2015; **51**: S112 [DOI: 10.1016/S0959-8049(16)30326-4]

19 **Chung KY**, Gore I, Fong L, Venook A, Beck SB, Dorazio P, Criscitiello PJ, Healey DI, Huang B, Gomez-Navarro J, Saltz LB. Phase II study of the anti-cytotoxic T-lymphocyte-associated antigen 4 monoclonal antibody, tremelimumab, in patients with refractory metastatic colorectal cancer. *J Clin Oncol* 2010; **28**: 3485-3490 [PMID: 20498386 DOI: 10.1200/JCO.2010.28.3994]

20 **Topalian SL**, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, Powderly JD, Carvajal RD, Sosman JA, Atkins MB, Leming PD, Spigel DR, Antonia SJ, Horn L, Drake CG, Pardoll DM, Chen L, Sharfman WH, Anders RA, Taube JM, McMiller TL, Xu H, Korman AJ, Jure-Kunkel M, Agrawal S, McDonald D, Kollia GD, Gupta A, Wigginton JM, Sznol M. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med* 2012; **366**: 2443-2454 [PMID: 22658127 DOI: 10.1056/NEJMoa1200690]

21 **Brahmer JR**, Tykodi SS, Chow LQ, Hwu WJ, Topalian SL, Hwu P, Drake CG, Camacho LH, Kauh J, Odunsi K, Pitot HC, Hamid O, Bhatia S, Martins R, Eaton K, Chen S, Salay TM, Alaparthy S, Grosso JF, Korman AJ, Parker SM, Agrawal S, Goldberg SM, Pardoll DM, Gupta A, Wigginton JM. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. *N Engl J Med* 2012; **366**: 2455-2465 [PMID: 22658128 DOI: 10.1056/NEJMoa1200694]

22 **Ott PA**, Piha-Paul SA, Munster P, Pishvaian MJ, Van Brummelen E, Cohen R, Gomez-Roca C, Ejadi S, Stein M, Chan E, Simonelli M, Morosky A, Yuan SS, Koshiji M, Bennouna J. 500 Pembrolizumab (MK-3475) for PD-L1-positive squamous cell carcinoma (SCC) of the anal canal: Preliminary safety and efficacy results from KEYNOTE-028. *Eur J Cancer* 2015; **51**: S102 [DOI: 10.1016/S0959-8049(15)30008-3]

23 **Morris VK**, Ciombor KK, Salem ME, Nimeiri HS, Iqbal S, Singh PP, Bekaii-Saab TS. NCI9673: A multi-institutional eETCTN phase II study of nivolumab in refractory metastatic squamous cell carcinoma of the anal canal (SCCA). *J Clin Oncol* 2016; **34**: 3503

24 **Kourie HR**, Klastersky JA. Side-effects of checkpoint inhibitor-based combination therapy. *Curr Opin Oncol* 2016; **28**: 306-313 [PMID: 27136134 DOI: 10.1097/CCO.0000000000000295]

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**Table 1 summarizes publish and ongoing clinical trials evaluating checkpoint inhibitors in gastrointestinal cancers**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  |  |  |  |
| **Ref.** | **Phase/*n*** | **Agent** | **Histology distribution**  | **Chemotherapies** | **ORR**  | **SD** | **OS** |
| **Esophageal cancer**  |
| Kojima *et al*[9], 2016 | II/65 | Nivolumab | 100% squamous | Median prior regimen 3 | 17.2% | 25% | 12.1 |
| Doi *et al*[10], 2015 | Ib/23 | Pembrolizumab | 77% squamous | 87% received ≥ 2 prior therapies for metastatic disease | 23% | 18% | N/A |
| **Gastric cancer** |
| Christy *et al*[11], 2010 | II/18 | Tremelimumab | Adenocarcinoma (Gastric and esophageal) | 15 received one line , 3 two lines | 5% | 22% | N/A |
| Muro *et al*[12], 2016 | Ib/39 | Pembrolizumab | Adenocarcinoma of the stomach and the junction | Pretreated | 31% | NA | 11.4 |
| Le *et al*[13], 2016  | II/59 | Nivolumab | Adenocarcinoma of the stomach and the junction | 83 % received ≥ 2 prior therapies for metastatic disease | 12% | 21% | 6.8 |
| Chung *et al*[14], 2016 | Ib/62 | Avelumab | Adenocarcinoma of the stomach and the junction | Second line treatment | 18.2(PDL1+) | NA | 6.3 (PDL1+) |
| Jangiguian *et al*[15], 2016 | I/II / 160 | NivolumabN(3)+I (1)N(1)+I (3) | Adenocarcinoma of the stomach and the junction | ≥ 2 prior therapies for metastatic disease | 14%10%25% | NA | 54.66.9 |
| **Pancreatic cancer/hepatocellular carcinoma/biliary tract cancers** |
| Royal *et al*[7], 2010 | II/26 | Ipilimumab | Pancreatic adenocarcinoma | Pretreated | 0% | 1/26 after progression | NA |
| Sangro *et al*[16], 2013  | I/20 | Tremilimumab | Advanced hepatocellular carcinoma HCV-induced liver cirrhosis | Pretreated  | 17.6 % | 76.4% | NA |
| El-Khoueiry *et al*[17], 2015 | I/II /41 | Nivolumab | Child-Pugh (CP) score ≤ B7 and progressive disease (PD) on, intolerant of, or refusing sorafenib | 77% prior sorafenib | 23% | NA | 72% at 6m |
| Bang *et al*[18], 2015 | Ib/24 | Pembrolizumab | Adenocarcinoma of the gallbladder and biliary tree excluding cancer of the ampulla of Vater | > or = 1 chemotherapy and 38% > or = 3 | 17% | 17% | NA |
| **Colon cancer**  |
| Chung *et al*[19], 2010 | Phase II /47 | Tremelimumab | Adenocarcinoma of colorectal cancer | Extensive prior chemotherapy | 2% | 2% | 4.8 months |
| Topalian *et al*[20], 2012 | I/17 | Nivolumab | Advanced colorectal cancer | Heavily pretreated | 1/17 | 0 | NA |
| Brahmer *et al*[21], 2012 | I/18 | BMS-936559 | Advanced colorectal cancer | Pretreated | 0% | NA | NA |
| Le *et al*[8], 2015 | Phase II | Pembrolizumab | Adenocarcinoma of colorectal carcinoma (MMR proficient versus MMR deficient) | Pretreated | 0% versus 40% | NA | 2.2 monnths versus NR |
| **Anal cancer**  |
| Ott *et al*[22]. 2015 | Ib/25 | Pembrolizumab | Refractory metastatic squamous cell carcinoma of the anal canal | Prior systemic therapies | 20% | 40% | NA |
| Morris *et al*[23], 2016 | II/39 | Nivolumab | Refractory metastatic squamous cell carcinoma of the anal canal | Previously treated , immunotherapy naïve | 21% | 58% | NA |

ORR: Objective response rate; OS: overall survival; MMR: mismatch repair; NR: not reached; NA: not available.