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Atezolizumab for the treatment of colorectal cancer: the latest evidence and clinical potential

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Abstract

Introduction: Atezolizumab is a fully humanized, engineered monoclonal antibody (MAb) of IgG1 isotype that specifically targets programmed death ligand 1 (PD-L1), a key molecule in the cancer-immunity pathway. Atezolizumab is currently approved for the treatment of metastatic non-small-cell lung cancer (NSCLC) and advanced urothelial carcinomas.

Areas covered: In this review, we will present the available (early phase clinical trials) data supporting the efficacy of atezolizumab for the treatment of metastatic colorectal cancer (mCRC). We will also provide an update on the ongoing / future clinical trials evaluating the role of atezolizumab for the treatment of colorectal cancer (CRC) in different settings (alone or in combination with other checkpoint inhibitors and/or targeted therapies). So far, a small subgroup of mCRC (those with deficiency in mismatch repair (dMMR) - also known as microsatellite instability high (MSI-H) – appear to benefit significantly from checkpoint inhibitors. As expected, further research is needed to develop biomarkers, effective therapeutic strategies and novel combinations to overcome immune escape resistance and achieve better clinical responses with minimal toxicities.

Expert opinion: Interim analyses from ongoing early-phase clinical trials have shown encouraging activity of atezolizumab for the treatment of mCRC in combination with chemotherapy and/or targeted therapies, especially with MEK inhibitor cobimetinib. Within the next few years, this PD-L1 checkpoint inhibitor will likely be included as one of the standard treatment options for CRC, at least for patients with dMMR.
Keywords: atezolizumab; colorectal; PD-L1; immunotherapy; checkpoint inhibitors.

1. Introduction
Colorectal cancer (CRC) is the third most common cancer in the world\(^1\). In 2013, there were 14,962 new cases of CRC diagnosed in Australia. In 2017, it is estimated that 16,682 new cases of CRC will be diagnosed in Australia\(^2\). The treatment of metastatic colorectal cancer (mCRC) has substantially improved over the last two decades, achieving unprecedented median overall survivals (mOS) of over 30 months with the combination of multiple chemotherapy agents and targeted therapies\(^3\,4\,5\).

In recent years a better understanding of molecular biology and a more profound knowledge of cancer immunology have led to a new forefront in oncology treatment: immunotherapy in general and checkpoint inhibitors in particular\(^6\). Programmed death 1 (PD-1) is an inhibitory cell-surface receptor expressed on the surface of T-cells, B-cells and natural-killer cells. The effector functions of T-cells that express PD-1 in the tumor microenvironment can be downregulated upon activation by its ligands (PD-L1 or PD-L2), which are expressed by the tumoral cells. Inhibition of PD-1/PD-L1 and/or cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) signaling pathway by monoclonal antibodies (MAbs) to release the anti-tumor activity of pre-existing tumor specific T-cell immunity has initiated a new era for tumor immunotherapy\(^7\,8\). These checkpoint inhibitors (anti-PD-1 MAb such as nivolumab or pembrolizumab, anti-PD-L1 MAb such as atezolizumab, avelumab or durvalumab and CTLA-4 inhibitors like ipilimumab) may achieve durable clinical responses in patients with different tumor types, including melanoma\(^9\), non-small-cell lung cancer (NSCLC)\(^10\), renal-cell carcinoma\(^11\), bladder cancer\(^12\), and Hodgkin’s lymphoma\(^13\). At a clinical level, up until now the objective response rates (ORR) and toxicity profiles seem broadly similar across the inhibitor classes, even though they have different targets within the tumoral microenvironment\(^14\). There has been no head-to-head trial to date comparing PD-1 vs PD-L1 inhibitors in any of the tumoral areas described above, although some differences may emerge with further research. Nor is it known yet whether metastatic patients can be treated with PD-L1 inhibitors following PD-1 inhibition failure (or vice versa). More research is needed to answer all these relevant questions\(^15\).

When these drugs were first tested in mCRC patients the results were very disappointing, demonstrating little activity in most patients\(^16\). It was hypothesized that the response rates
were directly related to the mutational burden of the tumors and CRC is usually associated with low mutational burden\cite{17}. However, further research has revealed a small subgroup of mCRC patients whose tumors do respond to the immunotherapy, specifically, those with deficiency in mismatch repair (dMMR) (also known as microsatellite instability high, MSI-H)\cite{18}. However, this subpopulation only constitutes 15-20\% in early-stage CRC and between 3-5\% in advanced stages\cite{19,20}, highlighting a need for novel therapies for the remaining MSI-low or Microsatellite Stable (MSS) mCRC. In order to increase responses to immunotherapy in this setting, current clinical trials are looking at better patient selection for immunotherapy treatment, a newer next generation of checkpoint inhibitors and novel combinations of immunotherapeutic agents and/or immunotherapy and targeted therapies. In this review we examine preclinical as well as clinical data of atezolizumab in the therapy of mCRC, challenges for potential markers of efficacy and future research with this anti-PD-L1 MAb\cite{21}.

2. Overview of atezolizumab

2.1. Pharmacodynamics
Atezolizumab (Tecentriq™, MPDL3280A, F. Hoffmann-La Roche Ltd. / Genentech, Inc.) is a fragment crystallizable (Fc)-engineered humanized immunoglobulin G1 (IgG1) MAb that directly binds to PD-L1 and blocks interactions with the PD-1 and B7.1 (CD80) receptors. This releases the PD-L1/PD-1 pathway-mediated inhibition of the immune response in the tumoral microenvironment (Fig.1). In syngeneic mouse tumor models, blocking PD-L1 pathway results in tumor growth inhibition\cite{22}. 

2.2. Pharmacokinetics of atezolizumab
Atezolizumab presents linear pharmacokinetics over a dose range of 5 – 20mg/kg, including the labelled 3-weekly 1,200mg dose. In murine studies, complete saturation of PD-L1 in blood was reached at serum concentration >0.5μg/mL. The volume of distribution at steady state is 6.9L. The terminal half-life is 27 days and population drug clearance is 0.2L/day\textsuperscript{[23]}. Dose escalation studies, in which patients received up to 20mg/kg every 3 weeks, reported no dose limiting toxicities and that no maximum tolerated dose was reached\textsuperscript{[24]}. Specific populations including positive anti-therapeutic antibody status, albumin levels, mild or moderate renal impairment and mild hepatic impairment, and PD-L1 expression have no impact on systemic exposure of the drug\textsuperscript{[25]}. Early clinical studies showed that atezolizumab is active in numerous malignancies, including mCRC\textsuperscript{[26]}. 

2.3. Approved indications of atezolizumab
Atezolizumab is the first U.S Food and Drug Administration (FDA)-approved PD-L1–targeted immunotherapy. It is currently indicated for the treatment of previously treated metastatic NSCLC and for patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-based chemotherapy[27].

3. Evidence of atezolizumab in mCRC

3.1. Phase Ib GP28328 study – mCRC cohort

The phase Ib GP28328 study (NCT01633970)[28] is an ongoing (although not recruiting participants at present), open-label, multi-center clinical trial evaluating the safety, pharmacology and preliminary efficacy of atezolizumab in combination with bevacizumab and/or chemotherapy in patients with locally advanced or metastatic solid tumors. The study is a 6-treatment-arm trial with an initial dose escalation part followed by tumor specific expansion cohorts. Eligible patients are ≥18 years old and had histologically or cytologically documented advanced solid tumors and measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria, an Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 to 1, and adequate hematologic and end-organ function. Patients with mCRC are enrolled to arms A and B. Arm A includes mCRC patients whose tumors are refractory to all available or standard therapies and these patients are treated with atezolizumab and bevacizumab. These patients receive a bevacizumab 15mg/kg intravenous (IV) infusion on day 1 of cycle 1 followed by an atezolizumab 1,200mg IV infusion every 3 weeks after days 5-7 and then 3-weekly atezolizumab 1,200mg and bevacizumab 15mg/kg on day 1 of all subsequent cycles until disease progression or unacceptable toxicity. Arm B includes patients who are oxaliplatin-naïve or patients who did not have oxaliplatin within 12 months prior to the diagnosis of metastatic disease. Arm B patients are treated with atezolizumab in combination with bevacizumab plus oxaliplatin, leucovorin, and 5-fluorouracil (5-FU) (FOLFOX). In this arm, patients are assigned to receive FOLFOX on day 1 of each cycle 1. For all subsequent cycles, patients receive atezolizumab 800mg IV and FOLFOX every 2 weeks with bevacizumab 10mg/kg every 2 weeks on day 1. In arm A, the median age was 56 years, 29% were male and all had ≥3 prior systemic regimens. In arm B, the median age was 57 years, 53% were male and 70% had no prior systemic therapy.

Updated data from this phase Ib study has been analysed (data cut-off 29th September 2014)[29, 30]. At the time of the analysis, 14 mCRC patients were recruited in arm A and 30 patients in arm B. Investigator-assessed, unconfirmed ORR of 7% and 40% were observed
in arms A and B, respectively. No complete responses (CR) were objectivized. Progression-
free survival (PFS) ranged from 10 to 61 weeks. In 23 first-line patients in arm B who had 1
year of additional follow-up, the ORR was 52%, the median duration of response was 11.4
months, and the median PFS was 14.1 months. Seven patients had stable disease (SD) and
4 patients had progressive disease (PD).

As regards adverse events (AEs) attributed to atezolizumab, the vast majority of AEs were
grade 1-2. The most common AE of any grade considered possibly related to atezolizumab
included fatigue (21% in arm A vs 47% in Arm B), nausea (29% vs 27%), and pyrexia (21%
vs 20%). The most common grade 3 events across both arms were neutropenia (7%),
increased aspartate aminotransferase (AST) (5%), increased alanine aminotransferase
(ALT) (2%), diarrhea (2%), fatigue (2%), and hypophosphatemia (2%). No grade 4 or 5 AEs
considered possibly related to atezolizumab were observed. Three Grade 5 AEs occurred
that were not attributed to atezolizumab by the investigators. Details on these AEs were not
reported. The median duration of treatment was 124 days (range, 21-533 days) for 6/10
patients in arm A and 217 days (range, 28-525 days) for patients in arm B[29].

3.1.2. Phase Ib GP28328 study – MSI-H mCRC subset
A safety expansion cohort of the previously described phase 1b GP28328 study evaluated
the safety, tolerability and preliminary efficacy of the combination of atezolizumab plus
bevacizumab in 10 refractory MSI-H mCRC patients[31]. Participants received bevacizumab
15mg/kg and atezolizumab 1,200mg IV every 3 weeks (data cut-off, 30th August 2016 results
were presented at the Gastrointestinal Cancers Symposium in San Francisco, CA; January
2017.). At baseline, the median age was 52.5 years (range, 28-66 years), 60% were male,
60% had an ECOG PS of 1. Tumor location was right-sided in 80% of patients and left-sided
in 20%. Thirty percent of patients had received 1 prior systemic regimen, 40% had received
2 lines of treatment, 10% had received 4, and 20% had received 5. At the time of analysis,
median treatment duration was 13.5 months with atezolizumab and 10.1 months with
bevacizumab.

Median duration of response was not reached by either RECIST v1.1 (range, 1.6-12.4
months) or immune-related response criteria (irRC) (range, 7.8-12.4 months). The confirmed
ORR per RECIST v1.1 was 40% (95% CI, 12%-74%) and 30% via irRC (95% CI, 7%-65%)
after a median duration of follow-up of 14.8 months. Neither median PFS (range, 1.5-21.9
months) nor median overall survival (OS) (range, 2.6-23.7 months) were reached. The
disease-control rate was 90%: four out of 10 patients who were treated with the combination of atezolizumab and bevacizumab had PR and 5 others had SD.

After a median safety follow-up of 13.7 months, treatment-related grade 3-4 AEs were reported in 40% of patients and included proteinuria, anaemia, hypertension, hypokalaemia, nausea, non-cardiac chest pain, and small-intestinal obstruction (n=1 [10%] each). No treatment-related grade 5 events were reported. The most common all-grade treatment-related AEs included fatigue (70%), diarrhea (50%), proteinuria (40%), arthralgia (40%), and sinusitis (40%). Adverse events resulting in withdrawal from bevacizumab and atezolizumab occurred in 30% and 10% of patients, respectively; grade 3 intestinal perforation and grade 2 embolism led to bevacizumab discontinuation and grade 3 congestive cardiac failure led to both bevacizumab and atezolizumab discontinuation.

The authors therefore concluded that atezolizumab and bevacizumab combination therapy showed encouraging antitumor activity in heavily pre-treated patients with MSI-H mCRC. In patients who responded to atezolizumab and bevacizumab, responses appeared to be durable, with a median duration of more than 12 months. Further follow-up in this patient population is ongoing.

3.2. Phase Ib GP28363 study – mCRC cohort
As mentioned in the introductory section, the responses of MSI-L or MSS mCRC to checkpoint inhibitors have been very disappointing so far. However, there is an increasing interest in discovering ways to enhance the susceptibility of MSS /MSI-L mCRC to immunotherapy. For example, inhibiting the Raf/MEK/ERK pathway has been hypothesized to lead to increased expression of major-histocompatibility complex I (MHC-I) in cancer cells and increased CD8 T-cell infiltration in tumors, both of which could synergistically potentiate the efficacy of checkpoint inhibitors in MSS mCRC. Bendell et al presented very exciting updated results of the phase Ib GP 28363 (NCT01988896) at the 2018 American Society of Clinical Oncology (ASCO) Gastrointestinal Cancers Symposium. This phase Ib study is an ongoing, open-label, multi-center clinical trial evaluating the safety and tolerability of atezolizumab plus MEK inhibitor cobimetinib in patients with locally advanced, recurrent, or metastatic solid tumors. This 2-stage trial includes a dose-escalation and expansion phase, enrolling tumor-specific expansion cohorts in the second phase. Eligible patients are ≥18 years old and have measurable disease by RECIST v1.1, an ECOG PS of 0 to 1, and adequate hematologic and end organ functions.
As of the 4th September 2017 data cut-off, 84 previously treated mCRC patients were enrolled during escalation and expansion. They each received 800mg IV every 2 weeks plus cobimetinib 20 to 60mg daily during dose escalation and 60 mg during dose expansion (14/14 or 21/7 d on/off schedule).

At baseline, the median age was 56.5 years, 45% of patients had an ECOG PS of 0, and 79% (n=66) had received at least 5 prior lines of therapy. Microsatellite status was MSI-H in 1 patient, MSI-low in 11%, MSS in 50%, and unknown in 38%. KRAS mutations were seen in 68% of the patients.

After a median safety follow-up of 17 months, the median OS was 9.8 months and 12-month OS rate was 43%. Seven patients had a confirmed partial response: 4 had MSS and 1 had MSI-low mCRC, while the remaining 2 had unknown MSI status. Responses were durable, with a median duration of response of 14.3 months. Across all 84 patients, median PFS was 1.9 months, with 6-month PFS at 18%. For patients with MSS disease (n=42), median PFS was 2.5 months, with 6-month PFS at 27%.

The median follow-up for safety in this analysis was 17 months. Treatment-related grade 3 to 4 adverse events were noted in 37% of patients. Rash, diarrhoea, fatigue, and increased blood creatine phosphokinase were the most frequent treatment-related grade 3-4 AEs reported (5% each). No all-cause or treatment-related grade 5 events were reported. Treatment related AEs resulting in withdrawal from cobimetinib occurred in 24% of patients; on the other hand, 13% of patients required withdrawal from atezolizumab.

3.3. Phase Ib WP29945 study

This is an ongoing, open-label, multi-center, dose-escalation and expansion phase Ib clinical trial (NCT02650713) evaluating the safety, tolerability, pharmacokinetics and therapeutic activity of RO6958688 in combination with atezolizumab in patients with locally advanced or metastatic carcinoembryonic antigen (CEA)-positive solid tumors[33]. RO6958688 is a CEA T-cell bispecific antibody (CEA-TCB) used to recognize CEA and CD3e via a novel molecular composition (2:1) that induces T cell-mediated killing of CEA over-expressing tumors. CEA-TCB antibody inhibits tumor growth and promotes inflammation within the tumor microenvironment[34].
At an interim analysis with a data cut-off of 3rd March 2017, 45 patients had been enrolled, of which 35 had mCRC. Twenty-five of the 35 patients received CEA-TCB at multiple ascending doses of 5-160mg in combination with atezolizumab 1,200mg IV every 3 weeks and had on-treatment tumor assessments. Eleven patients had MSS mCRC and were treated with CEA-TCB 80 or 160mg[^35].

The confirmed best ORR according to RECIST v1.1 was PR in 3 patients (12%), SD in 10 patients (40%), and disease control in 13 patients (52%). Twelve patients (48%) had PD. Of the 11 MSS patients dosed at 80 or 160mg of CEA-TCB plus atezolizumab, 2 patients (18%) achieved PR, 7 (64%) had SD, 9 (82%) had disease control, and 2 (18%) had PD. Clinical activity in mCRC was observed with CEA-TCB doses ≥60 mg in combination with atezolizumab.

The safety analysis included all enrolled patients. The majority of AEs were grade 1-2 and occurred during the first 2 doses of CEA-TCB. The most common treatment-related AEs were pyrexia (71%), infusion-related reactions (40%), and diarrhoea (56%). In total, 31% of patients experienced grade ≥3 treatment-related AEs. Two patients experienced dose-limiting toxicities, grade 3 transient increase of ALT and grade 3 rash (both observed with CEA-TCB 160mg). There was no evidence of new or additive AEs when CEA-TCB was used in combination with atezolizumab.

4. Future studies with atezolizumab in CRC patients

We have summarized in Table 1. the current atezolizumab development pipeline for the treatment of CRC in different scenarios. It will be several years however, until mature results from these trials can be expected. We would like to draw the reader’s attention especially to the 3 ambitious phase III studies evaluating the efficacy of atezolizumab in combination with chemotherapy in the adjuvant setting for MSI-H stage III CRC (NCT02912559) as well as atezolizumab in combination with both bevacizumab and cobimetinib in the metastatic setting (NCT02997228, NCT02788279). The fact that such a considerable number of trials are being undertaken clearly illustrates that experts and sponsors see a great deal of potential in atezolizumab (alone or in combination with other molecules) for the treatment of CRC and not necessarily only for MSI-H/dMMR tumors.

5. Other checkpoint inhibitors for the treatment of mCRC patients

5.1. Pembrolizumab and nivolumab
Pembrolizumab (Keytruda®, MK-3475, Merck & Co., Inc.) is a humanized IgG4 MAb that binds to PD1 with high affinity, preventing its interaction with PD-L1 and PD-L2 and thus reversing the tumor microenvironment and enhancing the endogenous antitumor immune response[36].

In September 2017 the FDA granted pembrolizumab accelerated approval for the treatment of adult and paediatric patients with unresectable or metastatic refractory MSI-H/dMMR solid tumors including breast, prostate, bladder, endometrial, thyroid and other gastrointestinal cancers. This was the FDA’s first-ever tissue/site-agnostic approval. Pembrolizumab has also been approved for patients with MSI-H/dMMR mCRC following progression on standard chemotherapy agents. These approvals were based on data from 149 patients with MSI-H or dMMR cancers enrolled across 5 single-arm studies[37, 38, 39, 40, 41]. Of those 149, 90 patients had mCRC, while the remaining 59 patients had 1 of 14 other tumor types. The ORR with pembrolizumab was 39.6%, including 7.4% CR and 32.2% PR. Among patients who responded to pembrolizumab, 78% had durable responses for at least 6 months or longer. Among the 90 mCRC patients, the ORR was 36% (95 CI 26–46%) lasting up to almost a year[38]. The accelerated approval for pembrolizumab in this setting is contingent however, on the results of a confirmatory trial.

Nivolumab (Opdivo®, BMS-936558/ MDX-1106/ONO-4538, Bristol-Myers Squibb Co.) is also a fully humanized IgG4 MAb directed against PD1. In August 2017, the FDA granted an accelerated approval to nivolumab for the treatment of refractory MSI-H/ dMMR mCRC. This approval was based on results from the phase II CheckMate-142 trial[42], in which the ORR was 28% in mCRC patients who received prior fluoropyrimidine, oxaliplatin, and irinotecan, including 1 CR and 14 PR. Importantly, 69% of the patients had disease control for 12 weeks or longer. The FDA-recommended dose for nivolumab in this setting is 240mg IV every 2 weeks until disease progression or unacceptable toxicity. The accelerated approval of nivolumab for this indication is again contingent upon the outcomes of confirmatory trials.

Dual immune checkpoint inhibition (nivolumab +/- ipilimumab) is being evaluated in an ongoing phase II study (CheckMate-142, NCT02060188) for the treatment of mCRC (MSI-H and non-MSI-H). Updated results presented at the 2018 ASCO Gastrointestinal Cancers Symposium showed that the combined treatment was associated with encouraging clinical activity and survival, especially in the MSI-H subgroup (12-month PFS rate of 71% and 12-month OS rate of 85%)[43].
5.2. Negative trials for other checkpoint inhibitors in mCRC treatment

Disappointingly, a single agent CTLA-4 inhibitor (tremelimumab, CP-675,206, AstraZeneca) did not show significant clinical benefit for the treatment of refractory mCRC patient[44]. This single-arm, multi-center, phase II trial was conducted in refractory mCRC patients with good PS ECOG and measurable disease. Patients received 15 mg/kg tremelimumab IV every 90 days until progression. The primary end point was ORR. Tremelimumab in combination with other checkpoint inhibitors (for example with an antiPD-L1 – durvalumab, AstraZeneca - NCT02870920) is being evaluated in a phase II clinical trial at present.

Another example, BMS936559 (MDX 1105, Bristol-Myers Squibb Co.), a fully human anti PD-L1 MAb, was tested in a phase I/II study on almost 300 patients with advanced solid tumors (including 19 unselected mCRC patients)[45]. Although a 17% ORR was reported, no response was seen in the CRC group.

However, it should be mentioned that in these two examples there was no break-down by MSI status. If solely the MSI-H mCRC population had been selected, the results might have been different.

6. Expert opinion

Results from early trials using nivolumab and pembrolizumab appear promising, especially in patients with refractory MSI-H/dMMR mCRC. The recent FDA approvals for these immunotherapy agents have led the National Comprehensive Cancer Center Network (NCCN) guidelines to incorporate these checkpoint inhibitors into the therapeutic armamentarium for MSI-H/dMMR mCRC in second- and third-line treatments. The attention of the scientific community will expectedly be drawn both by access to checkpoint inhibitors in current oncology practice and the innumerable recruiting clinical trials involving immunotherapy in mCRC treatment.

However, at this stage immunotherapy is not appropriate for every mCRC patient. As previously discussed, only a small number of CRC patients (those with dMMR/MSI-H tumours, which are between 15–20% in stages II and III CRC and around 5% in mCRC) are most likely to benefit from immunotherapy. In spite of MSI-H statuses, the response rates for checkpoint inhibitors in monotherapy are still quite limited (for nivolumab and pembrolizumab ORR are around just 20-30%).
The identification of immunological biomarkers is of the greatest relevance in this clinical setting, helping to select the best candidates for these costly therapies. A better understanding of genomic features related to MSI-H status could help us to find more selective tools to predict (good and durable) responses to immune checkpoint inhibition. However, while in lung and breast cancers, for instance, the morphological evaluation of tumor-infiltrating lymphocytes (TILs) or the measurements of PD1/PDL-1 immunohistochemistry (IHC) expression are gaining momentum as evidence strengthens for the clinical importance of these predictive markers during immunotherapy, in colorectal tumors research in these particular areas seems slower\textsuperscript{[26, 47]}. We should also mention that recent data has indicated that CRC can be best segregated into four groups called consensus molecular subtypes (CMS1–4), each of which has a unique biology, clinical features and gene expression pattern. Thus, CMS1 tumors (MSI Immune) are characterized by hypermutation, MSI, and strong immune activation. Checkpoint inhibitors may have the greatest success in the treatment of this CRC subtype compared with the other proposed CMS subtypes\textsuperscript{[48]}. However, it is still early days for these hypotheses and further investigations are needed to clarify whether the sole assessment of TILs or PD1/PDL-1 expression together with immune gene signatures evaluation could be used as valid predictive biomarker(s) for the selection of the best CRC patients for immunotherapy.

In order to extend the indication of immune checkpoint inhibitors to more mCRC patients (including MSS tumors), new combination treatments are currently under investigation. As we have described above, clinical trials are currently evaluating the clinical relevance of these strategies using atezolizumab in combination with both bevacizumab and cobimetinib. Results from the recently completed phase III Cotezo study (atezolizumab either as monotherapy or in combination with cobimetinib vs. regorafenib) are awaited. These results may change the third-line treatment scenario for mCRC (currently occupied by regorafenib and TAS-102).

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Declaration of interest
T Price has served on advisory board for Roche. has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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Papers of special note have been highlighted as either of interest (*) or of considerable interest (**) to readers.

* This detailed review provides an understanding of the rationale behind immunotherapy in cancer treatment.


32. Bendell J.C ea. A phase lb study of safety and clinical activity of atezolizumab (A) and cobimetinib (C) in patients (pts) with metastatic colorectal cancer (mCRC). J Clin Oncol 36, 2018 (suppl 4S; abstr 560). 2018. **This phase lb study of atezolizumab in combination with a MEK inhibitor showed promising efficacy in mCRC.
**Recent data on efficacy of a dual immunotherapy strategy in MSI-H mCRC: nivolumab and ipilimumab combination**


**The integrative analysis of distinct intrinsic molecular subtypes in CRC and its clinical implications.**

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Atezolizumab (Tecentriq®, MPDL3280A, F. Hoffmann-La Roche Ltd. / Genentech, Inc)</th>
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<table>
<thead>
<tr>
<th>Phase</th>
<th>For metastatic colorectal cancer treatment only results from early phase (Ib) studies available</th>
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<tr>
<td>Indication</td>
<td>Atezolizumab is currently not FDA-approved for the treatment of CRC. It is currently indicated for the treatment of previously treated metastatic NSCLC and for patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-based chemotherapy.</td>
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<tr>
<td>Pharmacology description</td>
<td>Fc-engineered humanized IgG1 monoclonal antibody that directly binds to PD-L1</td>
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<tr>
<td>Route of administration</td>
<td>Intravenous infusion over 60 minutes</td>
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<tr>
<td>Chemical structure</td>
<td>Non-glycosylated IgG1 kappa immunoglobulin with a calculated molecular mass of 145 kDa.</td>
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<tr>
<td>Pivotal trial(s)</td>
<td>Awaited – See Table 1. Summary of registered ongoing/planned clinical trials with atezolizumab for the treatment of CRC</td>
</tr>
</tbody>
</table>

**Drug Summary Box – Atezolizumab for colorectal cancer treatment**

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Readers are referred to Informa-Pipeline (http://informa-pipeline.citeline.com) and Citeline (http://informa.citeline.com).
Table 1. Summary of registered ongoing/planned clinical trials with atezolizumab for the treatment of CRC
### Atezolizumab in the neoadjuvant rectal cancer setting

<table>
<thead>
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<th>Treatment</th>
<th>Target population</th>
<th>Study phase</th>
<th>Estimated enrolment</th>
<th>Primary endpoint</th>
<th>Status</th>
<th>NCT number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concurrent atezolizumab and standard preoperative radio-chemotherapy</td>
<td>Locally advanced rectal adenocarcinoma</td>
<td>Ib/II</td>
<td>54</td>
<td>Rates of AEs and pCR</td>
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### Atezolizumab in the adjuvant setting for MSI-H colon cancers

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Target population</th>
<th>Study phase</th>
<th>Estimated enrolment</th>
<th>Primary endpoint</th>
<th>Status</th>
<th>NCT number</th>
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</thead>
<tbody>
<tr>
<td>FOLFOX +/- atezolizumab</td>
<td>Resected stage III colon cancer dMMR/MSI-H</td>
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<td>700</td>
<td>DFS</td>
<td>Currently recruiting</td>
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### Atezolizumab for MSI-H mCRC

<table>
<thead>
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<th>Treatment</th>
<th>Target population</th>
<th>Study phase</th>
<th>Estimated enrolment</th>
<th>Primary endpoint</th>
<th>Status</th>
<th>NCT number</th>
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<tbody>
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<td>Atezolizumab + bevacizumab</td>
<td>MSI-like molecular signature refractory mCRC</td>
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<td>58</td>
<td>ORR</td>
<td>Not yet open</td>
<td>NCT02982694</td>
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</tbody>
</table>
| Arm A: FOLFOX + bevacizumab  
Arm B: atezolizumab  
Arm C: FOLFOX + bevacizumab + atezolizumab | MSI-H mCRC (1st line) | III | 439 | PFS | Not yet open | NCT02997228 |
| CPI-444* orally +/- atezolizumab | Advanced refractory malignancies, including MSI-H mCRC treated with >1 but ≤5 prior lines of palliative chemotherapy. | I | 534 | DLTs, ORR, incidence of AEs, AUC and Cmax of CPI-444 | Currently recruiting | NCT02655822 |

### Atezolizumab for mCRC patients with liver metastases

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Target population</th>
<th>Study phase</th>
<th>Estimated enrolment</th>
<th>Primary endpoint</th>
<th>Status</th>
<th>NCT number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intrahepatic injection of talimogene laherparepvec + atezolizumab</td>
<td>TNBC and CRC with liver metastases (2nd or subsequent lines of treatment)</td>
<td>I</td>
<td>36</td>
<td>DLTs and incidence of AEs and relevant laboratory abnormalities</td>
<td>Not yet open</td>
<td>NCT03256344</td>
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</tbody>
</table>

### Atezolizumab for mCRC patients
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</tr>
</thead>
<tbody>
<tr>
<td>Cobimetinib + Bevacizumab + Atezolizumab</td>
<td>Progression on a prior line of therapy that contained a fluoropyrimidine and oxaliplatin or irinotecan for unresectable mCRC</td>
<td>I</td>
<td>33</td>
<td>Percentage of Participants with AEs</td>
<td>Currently recruiting</td>
<td>NCT02876224</td>
</tr>
<tr>
<td>Arm A: Atezolizumab</td>
<td></td>
<td>III</td>
<td>360</td>
<td>OS</td>
<td>Completed – awaiting results</td>
<td>NCT02788279</td>
</tr>
<tr>
<td>Arm B: cobimetinib + Atezolizumab</td>
<td></td>
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<tr>
<td>Arm C: regorafenib</td>
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<tr>
<td>Arm A: atezolizumab</td>
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<tr>
<td>Hypofractionated SABR + atezolizumab</td>
<td>Metastatic solid tumours including refractory mCRC</td>
<td>II</td>
<td>180</td>
<td>PFS</td>
<td>Currently recruiting</td>
<td>NCT02992912</td>
</tr>
</tbody>
</table>
Abbreviations: AEs: adverse events; pCR: pathological complete response; FOLFOX: oxaliplatin, leucovorin, and 5-fluorouracil (5-FU); dMMR: deficiency in mismatch repair; MSI-H: microsatellite instability high; DFS: disease-free survival; mCRC: metastatic colorectal cancer; ORR: overall response rate; PFS: progression-free survival; DLTs: dose-limiting toxicities; AUC: area under the curve; Cmax: plasma maximum concentration; TNBC: triple-negative breast cancer; CRC: colorectal cancer; OS: overall survival; CR: complete response; PR: partial response; SD: stable disease; MTD: maximum tolerated dose; PFTs: pulmonary function tests; Ab: antibodies; imAE: immune-mediated adverse events; SABR: stereotactic ablative radiotherapy.

Mechanism of action of new molecules combined with atezolizumab:

* CPI-444: an oral small molecule targeting the adenosine-A2A receptor on T-lymphocytes and other cells of the immune system.

** Cergutuzumab amunaleukin: an immunocytokine, which consists of a variant of Interleukin 2 (IL 2v), that targets CEA.

*** MOXR0916: a humanized agonist anti-OX40 monoclonal antibody.

$ MTIG7192A: a fully human monoclonal antibody designed to bind to TIGIT (T-Cell Immuno-receptor With Ig and ITIM domains) and prevent its interaction with poliovirus receptor (PVR).

$\S$ RO7009789: a monoclonal antibody and CD40 agonist.

$\SS$ RO7198457: personalized cancer vaccine

& GDC-0919: (also known as NLG919 and RG6078), is an orally available inhibitor of indoleamine 2,3-dioxygenase 1 (IDO1), with potential immune-modulating and antineoplastic activities

&& ALX148: a CD47/SIRPa-blocking agent