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1) Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma

Nivolumab plus ipilimumab produced objective responses in patients with advanced renal-cell carcinoma in a pilot study. This phase 3 trial compared nivolumab plus ipilimumab with sunitinib for previously untreated clear-cell advanced renal-cell carcinoma

We randomly assigned adults in a 1:1 ratio to receive either nivolumab (3 mg per kilogram of body weight) plus ipilimumab (1 mg per kilogram) intravenously every 3 weeks for four doses, followed by nivolumab (3 mg per kilogram) every 2 weeks, or sunitinib (50 mg) orally once daily for 4 weeks (6-week cycle). The coprimary end points were overall survival (alpha level, 0.04), objective response rate (alpha level, 0.001), and progression-free survival (alpha level, 0.009) among patients with intermediate or poor prognostic risk.

A total of 1096 patients were assigned to receive nivolumab plus ipilimumab (550 patients) or sunitinib (546 patients); 425 and 422, respectively, had intermediate or poor risk. At a median follow-up of 25.2 months in intermediate- and poor-risk patients, the 18-month overall survival rate was 75% (95% confidence interval [CI], 70 to 78) with nivolumab plus ipilimumab and 60% (95% CI, 55 to 65) with sunitinib; the median overall survival was not reached with nivolumab plus ipilimumab versus 26.0 months with sunitinib (hazard ratio for death, 0.63; P<0.001). The objective response rate was 42% versus 27% (P<0.001), and the complete response rate was 9% versus 1%. The median progression-free survival was 11.6 months and 8.4 months, respectively (hazard ratio for disease progression or death, 0.82; P=0.03, not significant per the prespecified 0.009 threshold). Treatment-related adverse events occurred in 509 of 547 patients (93%) in the nivolumab-plus-ipilimumab group and 521 of 535 patients (97%) in the sunitinib group; grade 3 or 4 events occurred in 250 patients (46%) and 335 patients (63%), respectively. Treatment-related adverse events leading to discontinuation occurred in 22% and 12% of the patients in the respective groups. The recommended schedule and dose for this combination is nivolumab, 3 mg/kg, followed by ipilimumab, 1 mg/kg, on the same day every 3 weeks for 4 doses, then nivolumab, 240 mg, every 2 weeks or 480 mg every 4 weeks. Overall survival and objective response rates were significantly higher with nivolumab plus ipilimumab than with sunitinib among intermediate- and poor-risk patients with previously untreated advanced renal-cell carcinoma.

On 16 April 2018, the US Food and Drug Administration (FDA) granted approvals to nivolumab and ipilimumab (Opdivo and Yervoy, Bristol-Myers Squibb Co.) in combination for the treatment of intermediate or poor risk, previously untreated advanced renal cell carcinoma (RCC).

2) Cabozantinib versus sunitinib as initial therapy for metastatic renal cell carcinoma of intermediate or poor risk (Alliance A031203 CABOSUN randomised trial): Progression-free survival by independent review and overall survival update

The randomised phase 2 CABOSUN trial comparing cabozantinib with sunitinib as initial therapy for advanced renal cell carcinoma (RCC) of intermediate or poor risk met the primary end-point of improving progression-free survival (PFS) as assessed by investigator. Previously untreated patients with advanced RCC of intermediate or poor risk by IMDC criteria were randomised 1:1 to cabozantinib 60 mg daily or sunitinib 50 mg daily (4 weeks on/2 weeks off).

A total of 157 patients were randomised 1:1 to cabozantinib (n = 79) or sunitinib (n = 78). Median PFS per IRC was 8.6 months (95% confidence interval [CI] 6.8-14.0) versus 5.3 months (95% CI 3.0-8.2) for cabozantinib versus sunitinib (hazard ratio [HR] 0.48 [95% CI 0.31-0.74]; two-sided p = 0.0008), and ORR per IRC was 20% (95% CI 12.0-30.8) versus 9% (95% CI 3.7-17.6), respectively. Subgroup analyses of PFS by stratification factors and MET tumour expression were consistent with results for the overall population. With a median follow-up of 34.5 months, median OS was 26.6 months (95% CI 14.6-not estimable) with cabozantinib and 21.2 months (95% CI 16.3-27.4) with sunitinib (HR 0.80 [95% CI 0.53-1.21]. The incidence of grade 3 or 4 adverse events was 68% for cabozantinib and 65% for sunitinib.

In this phase 2 trial, cabozantinib treatment significantly

prolonged PFS per IRC compared with sunitinib as initial systemic therapy for advanced RCC of poor or intermediate risk.

3) Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC

An earlier analysis in this phase 3 trial showed that durvalumab significantly prolonged progression-free survival, as compared with placebo, among patients with stage III, unresectable non-small-cell lung cancer (NSCLC) who did not have disease progression after concurrent chemoradiotherapy. Here we report the results for the second primary end point of overall survival.

We randomly assigned patients, in a 2:1 ratio, to receive durvalumab intravenously, at a dose of 10 mg per kilogram of body weight, or matching placebo every 2 weeks for up to 12 months. Randomization occurred 1 to 42 days after the patients had received chemoradiotherapy and was stratified according to age, sex, and smoking history. The primary end points were progression-free survival (as assessed by blinded independent central review) and overall survival. Secondary end points included the time to death or distant metastasis, the time to second progression, and safety.

Of the 713 patients who underwent randomization, 709 received the assigned intervention (473 patients received durvalumab and 236 received placebo). As of March 22, 2018, the median follow-up was 25.2 months. The 24-month overall survival rate was 66.3% (95% confidence interval [CI], 61.7 to 70.4) in the durvalumab group, as compared with 55.6% (95% CI, 48.9 to 61.8) in the placebo group (two-sided P=0.005). Durvalumab significantly prolonged overall survival, as compared with placebo (stratified hazard ratio for death, 0.68; 99.73% CI, 0.47 to 0.997; P=0.0025). Updated analyses regarding progression-free survival were similar to those previously reported, with a median duration of 17.2 months in the durvalumab group and 5.6 months in the placebo group (stratified hazard ratio for disease progression or death, 0.51; 95% CI, 0.41 to 0.63). The median time to death or distant metastasis was 28.3 months in the durvalumab group and 16.2 months in the placebo group (stratified hazard ratio, 0.53; 95% CI, 0.41 to 0.68). A total of 30.5% of the patients in the durvalumab group and 26.1% of those in the placebo group had grade 3 or 4 adverse events of any cause; 15.4% and 9.8% of the patients, respectively, discontinued the trial regimen because of adverse events.

Durvalumab therapy resulted in significantly longer overall survival than placebo. No new safety signals were identified.

4) Cancer Risks for PMS2-Associated Lynch Syndrome

Lynch syndrome due to pathogenic variants in the DNA mismatch repair genes MLH1, MSH2, and MSH6 is predominantly associated with colorectal and endometrial cancer, although extracolonic cancers have been described within the Lynch tumor spectrum. However, the age-specific cumulative risk (penetrance) of these cancers is still poorly defined for PMS2-associated Lynch syndrome. Using a large data set from a worldwide collaboration, our aim was to determine accurate penetrance measures of cancers for carriers of heterozygous pathogenic PMS2 variants.

In total, 284 families consisting of 4,878 first- and second-degree family members were included in the analysis. PMS2 mutation carriers were at increased risk for colorectal cancer (cumulative risk to age 80 years of 13% [95% CI, 7.9% to 22%] for males and 12% [95% CI, 6.7% to 21%] for females) and endometrial cancer (13% [95% CI, 7.0%-24%]), compared with the general population (6.6%, 4.7%, and 2.4%, respectively). There was no clear evidence of an increased risk of ovarian, gastric, hepatobiliary, bladder, renal, brain, breast, prostate, or small bowel cancer.

Heterozygous PMS2 mutation carriers were at small increased risk for colorectal and endometrial cancer but not for any other Lynch syndrome-associated cancer. This finding justifies that PMS2-specific screening protocols could be restricted to colonoscopies. The role of risk-reducing hysterectomy and bilateral salpingo-oophorectomy for PMS2 mutation carriers needs further discussion.

5) First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer

Enhancing tumor-specific T-cell immunity by inhibiting programmed death ligand 1 (PD-L1)-programmed death 1 (PD-1) signaling has shown promise in the treatment of extensive-stage small-cell lung cancer. Combining checkpoint inhibition with cytotoxic chemotherapy may have a synergistic effect and improve efficacy.

We conducted this double-blind, placebo-controlled, phase 3 trial to evaluate atezolizumab plus carboplatin and etoposide in patients with extensive-stage small-cell lung cancer who had not previously received treatment. Patients were randomly assigned in a 1:1 ratio to receive carboplatin and etoposide with either atezolizumab or placebo for four 21-day cycles (induction phase), followed by a maintenance phase during which they received either atezolizumab or placebo.The two primary end points were investigator-assessed progression-free survival and overall survival in the intention-to-treat population.

A total of 201 patients randomly assigned to the atezolizumab group, and 202 patients to the placebo group. were At ea mdian follow-up of 13.9 months, the median overall survival was 12.3 months in the atezolizumab group and 10.3 months in the placebo group (hazard ratio for death, 0.70; 95% confidence interval [CI], 0.54 to 0.91; P=0.007). The median progression-free survival was 5.2 months and 4.3 months, respectively (hazard ratio for disease progression

or death, 0.77; 95% CI, 0.62 to 0.96; P=0.02). The safety profile of atezolizumab plus carboplatin and etoposide was consistent with the previously reported safety profile of the individual agents, with no new findings observed. The addition of atezolizumab to chemotherapy in the first-line treatment of extensive-stage small-cell lung cancer resulted in significantly longer overall survival and progression-free survival than chemotherapy alone.

6) Osimertinib versus standard-of-care EGFR-TKI as first-line treatment in patients with EGFRm advanced NSCLC: FLAURA Asian subset

FLAURA a multicentre, international, randomised, double-blind, active-controlled trial conducted in 556 patients with EGFR exon 19 deletion or exon 21 L858R mutation-positive, unresectable or metastatic NSCLC who had not received previous systemic treatment for advanced disease. Patients were randomised (1:1) to receive osimertinib 80 mg orally once daily or standard-of-care (SoC) treatment of gefitinib 250 mg or erlotinib 150 mg orally once daily. Of those randomised to SoC, 20% received osimertinib as the next line of antineoplastic therapy.

The estimated median progression-free survival (PFS) was 18.9 months (95% CI: 15.2, 21.4) in the osimertinib arm and 10.2 months (95% CI: 9.6, 11.1) in the SoC arm (hazard ratio 0.46 (95% CI: 0.37, 0.57), p <0.0001). The confirmed overall response rate was 77% for the osimertinib arm and 69% for the SoC arm. The estimated median response durations for the osimertinib and SoC arms were 17.6 and 9.6 months, respectively. At the time of the primary PFS analysis, there were too few deaths to estimate or compare overall survival.

The most common adverse reactions (occurring in at least 20% of patients treated with osimertinib) were diarrhoea, rash, dry skin, nail toxicity, stomatitis, and decreased appetite. Serious adverse reactions were reported in 4% of patients treated with osimertinib. The most common serious adverse reactions (≥1%) were pneumonia (2.9%), interstitial lung disease/pneumonitis (2.1%), and pulmonary embolism (1.8%). The recommended dose of osimertinib is 80 mg orally once daily, with or without food.

On 18 April 2018, the US Food and Drug Administration (FDA) approved osimertinib (Tagrisso, AstraZeneca Pharmaceuticals LP) for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test.

7) Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050): a randomised, open-label, phase 3 trial

The FDA approved the kinase inhibitor dacomitinib (Vizimpro, Pfizer) for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 19 deletion or exon 21 L858R substitution mutations as detected by an FDA-approved test. The approval was based on a randomized, multicenter, open-label, active-controlled trial (ARCHER 1050) comparing the safety and efficacy of dacomitinib with gefitinib (Iressa, AstraZeneca) in 452 patients with unresectable, metastatic NSCLC. Patients were required to have no prior therapy for metastatic disease or recurrent disease, with a 12-month minimum of disease-free status after completion of systemic non-EGFR tyrosine kinase inhibitor–containing therapy; an ECOG status of 0 or 1 and EGFR exon 19 deletion or exon 21 L858R substitution mutations.

Patients were randomly assigned (1:1) to receive either 45 mg of dacomitinib orally once daily or 250 mg of gefitinib orally once daily until disease progression or unacceptable toxicity.The researchers were looking for a significant improvement in progression-free survival (PFS), no improvement in overall response rate or overall survival. The median PFS, as determined by an independent review committee, was 14.7 and 9.2 months in the dacomitinib and gefitinib arms, respectively (hazard ratio, 0.59; 95% CI, 0.47-0.74; *P* <0.0001).

Of 394 patients who received dacomitinib, serious adverse reactions occurred in 27%. The most common adverse reactions resulting in discontinuation of dacomitinib were diarrhea and ILD. The most common adverse reactions of dacomitinib were diarrhea, rash, paronychia, stomatitis, decreased appetite, dry skin, decreased weight, alopecia, cough and pruritus. "The findings from ARCHER 1050 suggest that Vizimpro should be considered as a new first-line treatment option for patients with EGFR-mutated non-small cell lung cancer exon 19 deletion or exon 21 L858R substitution mutations".